UNIVERSITÀ DEGLI STUDI DI PALERMO

Dottorato in Scienze Economiche e Statistiche

Dipartimento di Scienze Economiche, Aziendali e Statistiche

Advances in survival analysis: applications and extensions of the "standard" competing risks model

IL DOTTORE
Salvatore Battaglia

IL COORDINATORE
Andrea Consiglio

IL TUTOR
Massimo Attanasio

IL CO-TUTOR
Marco Enea

CICLO XXXV

ANNO CONSEGUIMENTO TITOLO 2023

"In the end we all die, but not all
for the same reason nor with the same life histories"

R.B. Geskus

Acknowledgements

This work is the main result of my 3-years research activity, during which I had the opportunity to work, be supported, and share experiences with several people.

First, I would like to thank my supervisor, Prof. Massimo Attanasio, who I consider a mentor. He was the first to encourage me to start my studies in Statistics when I was a high school student showing and discussing the graph representing the behavior over time of the number of soldiers in Napoleon's army during the Russian invasion. I still remember what he said looking at the graph: "This is what a Statistician can do" and we always laugh when I remind him of this moment. He is the Professor who made me interested in the Biostatistics topic when I was a master's student and he encouraged me to start the Ph.D. program when I was working elsewhere. He supervised me from the master thesis research project until today and, I hope, he will do the same also in the future. I remember with pleasure how much effort we put into the analysis of COVID-19 hospitalized patients working together for an entire month, almost every day, sharing thoughts, doubts, and considerations at each analysis step. His contribution to my growth is not only professional and statistical but also human. He suggested and encouraged me to perform the period abroad in the Netherlands by contacting Prof. Marta Fiocco and Hein Putter from the University of Leiden when I thought that working with such sacred monsters in Biostatistics was too much for me. An experience that I would never have regretted later. Finally, every conversation I have engaged with him over the years has always left me with something useful.

I would like to thank my co-supervisor as well, Prof. Marco Enea, who held part of the Biostatistics master's course when I was a student, and that made me decide about my future as a statistician. He supervised encomiably most of my works during the Ph.D. program, making me learn a lot of statistical concepts and methods in the medical field. He is probably the person I learned the most from the Biostatistical point of view. That is why I consider him a reference for this topic.

My gratitude goes also to my Ph.D. fellows from the DSEAS of the University of Palermo, whose I consider friends. In particular, I thank Nicoletta for her routine snack times, Ale for his "wired" questions and for forcing all of us to long long walks, Prilli to receive any knee pads from Ale and me, Andri to be my best football rival in the department context, Furio for his ever-wise speeches, and Dani for being my cigar buddy. I am grateful to have shared this experience with them, hoping It will not be the last one.

A great mention goes to all the postdocs, researchers, and Professors from the DSEAS of the University of Palermo. I loved sharing with them the launches in Aula Mineo, where all the topics were allowed but talking about work.

I cannot fail to gratitude to all the people I met at the Mathematical Institute of the University of Leiden during my research period abroad. There, I realized my dream as a biostatistician: to meet, and even work with, all the authors of the tutorial on competing risks in R that I studied for the first time when I was a master's student.

In particular, I would like to thank Prof. Marta Fiocco who did everything possible to make me grow as much as possible in just six months. I could never ask for a better visiting supervisor than her. I also wish to thank Prof. Hein Putter to have supervised my visiting research project giving invaluable advice, continuous support, and to have

shared a lot of "long" coffees. I also thank Prof. R.B. Geskus for showing me his boundless passion for biostatistics, even for just some days.

My gratitude goes also to Professor Mirko Signorelli, who always supported me when things seemed not to be easy, and all Ph.D. students of the Mathematical Institute of the University of Leiden. In particular, I thank Marta, Daniel, Tyron, and Vera to make me feel like a family member when I was just a foreign student (you cannot imagine how much I miss our "Tuesdays", barbecues, lunches and dinners together!)

I would like to thank the members of the Department of Gastroenterology at the University of Palermo for giving me the opportunity to be part of one of the best research teams in the liver diseases topic in Italy and beyond.

It might go without saying to thank my family, who have always supported me, morally and financially, to achieve this goal.

Finally, I would like to partly dedicate this work to my wife, who has always supported me in the most difficult times to continue my studies in statistics, with the hope that the efforts made to complete my Ph.D. will serve our future together.

Contents

List of Figures

List of Tables

List of Abbreviations

ABG	**A**rterial **B**lood **G**as
AFT	**A**ccelerated **F**ailure **T**ime
AUC	**A**rea **U**nder **C**urve
CCI	**C**harlson **C**omorbidity **I**ndex
CIF	**C**umulative **I**ncidence **F**unction
CRP	**C**- **R**eactive **P**rotein
CPAP	**C**ontinous **P**ositive **A**irway **P**ressure
GLM	**G**eneralized **L**inear **M**odel
GLMM	**G**eneralized **L**inear **M**ixed **M**odel
GOT	**G**lutamic **O**xaloacetic **T**ransaminase
GPT	**G**lutamic **P**yruvic **T**ransaminase
HL	**H**ierarchical **L**ikelihood
HR	**H**azard **R**atio
HCQ	**H**ydroxy **C**loro **Q**uine
KM	**K**aplan **M**eier
JVMM	**J**oint **V**ertical **M**ixed **M**odel
ICU	**I**ntensive **C**are **U**nit
INLA	**I**ntegrated **N**ested **L**aplace **A**pproximation
IQR	**I**nter **Q**uartile **R**ange
LDH	**L**actate **D**e **H**ydrogenase **M**odel

mEi	**m**odified **E**lixhauser **i**ndex
MLE	**M**aximum **L**ikelihood **E**stimator
NHF	**N**asal **H**igh **F**low
NIV	**N**on **I**nvasive **V**entilation
OR	**O**dds **R**atio
PL	**P**artial **L**ikelihood
ROC	**R**eceiving **O**perating **C**urve
RT-PCR	**R**eal-**T**ime Reverse Transcriptase **P**olymerase **C**hain **R**eaction
SMACORE	**SMA**tteo **CO**vid19 **RE**gistry
SVMM	**S**eparated **V**ertical **M**ixed **M**odel
WHO	**W**orld **H**ealth **O**rganization

Introduction

0.1 General framework

This work is structured as a collection of 4 applications dealing with competing risks models, a useful tool for the survival analysis of real-world datasets. These applications, included in chapter 2, 3, 4 and 5 are presented in the form of scientific papers. Two of them (see chapter 2 and 3) are already published in two high-impact medical journals, while the others will be submitted soon. In particular, chapter 4 and 5 represent the main core of the dissertation. They include a novel way to analyze overcrowding in Emergency Department by using a frailty competing risks model, and a methodological novelty that aims to extend the Vertical model as an alternative competing risks model (see section 0.2.2 for more details about the structure of the dissertation).

The competing risks topic has been hugely discussed in the literature and has aroused a lot of interest in recent years, especially among biostatisticians [13] and epidemiologists [82]. Competing risks occur, in time-to-event data, when more than one event is of interest. A typical example, when dealing with competing risks, relies on the computation of the risk of death for different causes. If one dies from a cause of death, it is not possible to observe eventual times relied to other causes. The focus of the dissertation is on the application of competing risks methods in healthcare and medical research, but these methods can be applied to any research area. By taking into account a variety of potentially occurring event types that are mutually exclusive, a competing risks model extends the traditional survival setting.

The first traces of competing risks analysis date back to 1760, when Daniel Bernoulli tried to determine the extent to which life expectancy would increase if smallpox were no longer a cause of death. Using differential equations in two subgroups, he determined that, in a population without the disease, life expectancy would be increased by about three years. This result was eventually corroborated by the first vaccine, created by Edward Jenner 40 years later.

The interest in competing risks grew up after the second half of the 20^{th} century, when, Cornfield defined competing risks as "a problem that exists whenever several withdrawals can be subdivided into a set of mutually exclusive classes, and its existence

is no way dependent on how these classes are defined" [36]. He compared the probability of dying from lung cancers in smokers with/without the presence of other causes of death. So, he introduced the concept of non-informative censoring in a competing risks setting. Even though competing risks have been largely developed over the last decades, their use in the clinical community is still marginal. [80]. Fortunately, things evolved quickly.

The first important result was given by Tsiatis in 1975 [139]. He discussed the non-identifiability of the survival times when more than one cause occurs. The main result relied on the inequality of the "crude" survival probabilities (that is, in presence of independence) with the joint survival probabilities (that is, in presence of non-independence). Especially in the clinical setting, the independence assumption of the risks does not often hold. Though assuming independence among events of interest could be not always possible, treating events that preclude the occurrence of other ones of interest is still controversial. In 1997, Di Serio [130], in an application to survival data to Bone Marrow Transplantation, assumed that the lack of independence between the competing failures may cause the *unexpected protectivity* of a covariate. The results have shown that the lack of independence did not cause the protectivity but it may occur according to the degree and the sign of dependence between the frailty factor and the covariate. The concept of frailty, corresponding to the random effects in the GLMs, will be discussed later. The estimation procedure of the parameters in the competing risks follows essentially two alternative approaches: the first one is the cause-specific hazard model [107], and the Fine and Gray model [49].

0.2 "Standard" competing risks models

Much concern regards the choice between the two types of competing risks models, widely discussed in the literature. The usual way to estimate competing risks models is to compute the cause-specific hazard, that is, the hazard function is given by the deaths observations, while the censored observations and the deaths due to other causes are together treated as censored.

In 1999, Fine and Gray [49] defined the sub-distribution hazard function to provide a competing risks model, where the cumulative incidence functions as a regression model. Such model, even if yields valid inference, is based on an awkward construction of the risk set, in which observations dying for a cause of death remain at risk for the other causes. In the last 20 years, the model has been used in medical and healthcare studies to predict the cumulative incidence in a competing risk setting, with little knowledge of its limitations. For example, many researchers interpreted the Hazard ratios estimated

by the Fine and Gray model as a corresponding increase in the cumulative incidence function. This is not completely true [11](see section 1.2 for more details). One of the biggest limitation is that the sub-distribution hazard approach can allow the sum of the probabilities of the individual events to exceed 1 in some risk profiles. This discrepancy can be explained by the fact that at least one of the fitted models will be inaccurate when there are two different sub-distribution hazard models coming from two types of events [21]. This problem can be overcome by fitting all the cause-specific hazard models, one for each event of interest, and combining the estimated cause-specific hazard functions to get subject specific estimates of the risks [15]. Austin et al. [14] discussed deeply the Fine and Gray model limitations but they also argued that model allows to identify the factors associated to higher or lower risk. The cause-specific hazard model is unable to provide this information. Moreover, the sub-distribution hazard model enables computation of subject-specific estimates of absolute risk when the focus is on a single event type. Even though some estimates may be biased, they can be considered better than the results from a single Cox proportional hazards model where the overestimation of the censored observations is certainly wrong. On the contrary, it is preferred using the cause-specific hazard model when all the events are of interest.

To overcome the "uneasy feelings" with the sub-distribution hazard model, Putter et al. [109] explored satisfactorily the link between the Fine and Gray and cause specific approaches, defining the *reduction factor*, which is defined as the ratio between sub-distribution hazard and cause-specific hazard. The relationship between the cause-specific and the sub-distribution hazard, obtained by the computation of the reduction factor, is useful to compute the predicted CIF based on the sub-distribution hazard coefficients starting from a cause-specific hazard model.

In general, the choice of the "right" hazard function relies on the research aim. Lau et al. suggested that the cause-specific hazard model is more appropriate for addressing etiological questions, while the Fine and Gray model is more appropriate for addressing questions around incidence and prognosis [82]. In conclusion, researchers should begin by carefully formulating the research question and then selecting the model that is most appropriate for addressing the formulated question.

A third approach dealing with competing risks analysis is represented by the Vertical model [97]. It is considered an alternative approach to the "standard" competing risks model, especially when the proportionality assumption of the risks is violated or when facing with missing cause of failure [98]. The Vertical model is focused on the estimation of the joint distribution of time to failure T and cause of failure D, denoted as $P(T, D)$, decomposed by the chain rule into two components. The two components are easily obtainable by estimating first the *overall hazard*, that is the risks occurrence to any event, and

then proceeding "vertically" to the estimation of the *relative hazard*, that is the probability of experiencing the event of interest.

Specifically, we consider "standard" and "extended" competing risks models, where: the first ones concern all the models above described including in the first category and the second ones concern the frailty models. The latter models accommodate for a random component to take into account for unobserved heterogeneity aroused in multi-center settings.

0.2.1 Frailty (extended) Models

The concept of frailty was first introduced by Vaupel et al. [143] to account for individual heterogeneity in univariate (independent) survival data. These models can be seen as extensions of the well-known Cox proportional hazards model. The R statistical software is plenty of routines performing different functions to fit frailty survival models [16]. Other approaches to inferentiate frailty models were discussed in the literature. Martinussen et al. [91] proposed the use of the Aalen additive gamma frailty model, which is an extension of the Aalen additive hazard model [2], useful for studying time-dependent covariate effects in such a context. Wienke et al. [150] proposed a bivariate model with compound Poisson frailty, an extension of the compound Poisson frailty model in univariate survival analysis, which yields a subgroup of zero frailty, that is observations that never experience the event under study. This model represents an alternative to cure models in multivariate frailty settings.

The vast majority of published research addressing clustered survival data focus on estimating the parameters of a single type of event at a time, presuming that the censoring mechanism is independent of the event type of interest conditional on the covariates [95, 59, 47]. This assumption is still not valid anymore, though, when different causes of failure occur. There has not been much research on clustered failure time competing risks. Bandeen-Roche and Liang [18] presented statistical techniques for examining multivariate failure times in the presence of competing risks without including covariates and accommodating for multiplicative frailty effect on the hazard. They analyzed the time until the earliest failure from any event such that the overall hazard, which is the total of the type-specific risks, is identical to the conventional frailty model with no competing risks. More recently, several papers considered shared frailty to model the correlation structure within the clusters [4, 83, 147]. Unlikely, the assumption that each cluster has the same effect on the events of interest is strong. Yashin et al. first introduced a correlated gamma frailty model decomposing a twin's frailty into a sum of two independent frailties, relationship of which is shared by the twins [159]. This model overcomes the use

of shared frailty in a multi-center study but considering frailties for different competing events within a center to be independent may be questionable, since they are likely to be correlated. Other authors considered correlated frailty competing risks model with a parametric approach [151], while others a semi-parametric one [123]. In chapter 4, a frailty competing risks model is proposed to model the risk of two competing events, Discharge and Hospitalization, in the Emergency Departments (ED), following the approach described by Do Ha et al. [64], with a random effect for each hospital, in which the two events of interest are correlated (multivariate frailty competing risks model).

Similarly to the "standard" competing risks models, these "extended or frailty" models can accommodate for cause-specific [123] or sub-distribution hazard functions [63, 164]. In chapter 4, an application of a frailty cause-specific competing risks model is presented with the ED data. In chapter 5, a second application of a Vertical model is proposed with the inclusion of a random term in both sub-models' linear predictors, as an alternative to the usual frailty competing risks approach.

Actually, the realm of the "extended" competing risks is wider. As a matter of fact, a cure fraction, that is a proportion of the population for which none of the competing events can occur, can be considered in the competing risks framework. It is interesting to note how several papers considered the cure fraction in presence of competing risks [146, 102, 46] and in the vertical modeling approach [99].

Another "extension" is to include time-dependent covariates in the competing risks model, either in the cause-specific hazard model or in the Fine and Gray model [38, 12].

We showed the results coming from the Separated Vertical Mixed Model (SVMM) assuming no correlation between the overall and the relative hazard (estimated by a Cox frailty hazard model and a mixed logit model), and we also provided the estimation of the Joint Vertical Mixed Model (JVMM), which arises from the assumption that the couple of random effects included in both sub-models linear predictor are correlated. We used R-INLA, an R-Package able to implement Latent Gaussian Model (LGM) analysis [142]. The aims were, to find a fast alternative to the "usual" frailty competing risks model estimation procedures and to extend the SVMM by introducing a correlation coefficient among random effects.

0.2.2 Chapters organization

Figure 1 briefly describes the dissertations' structure and its main contents, distinguishing among data-sets and competing risks models. The description of the Covid-19 data-sets is at the beginning of Chapters 1 and 2, while the description of the data-set ED at the beginning of Chapter 3.

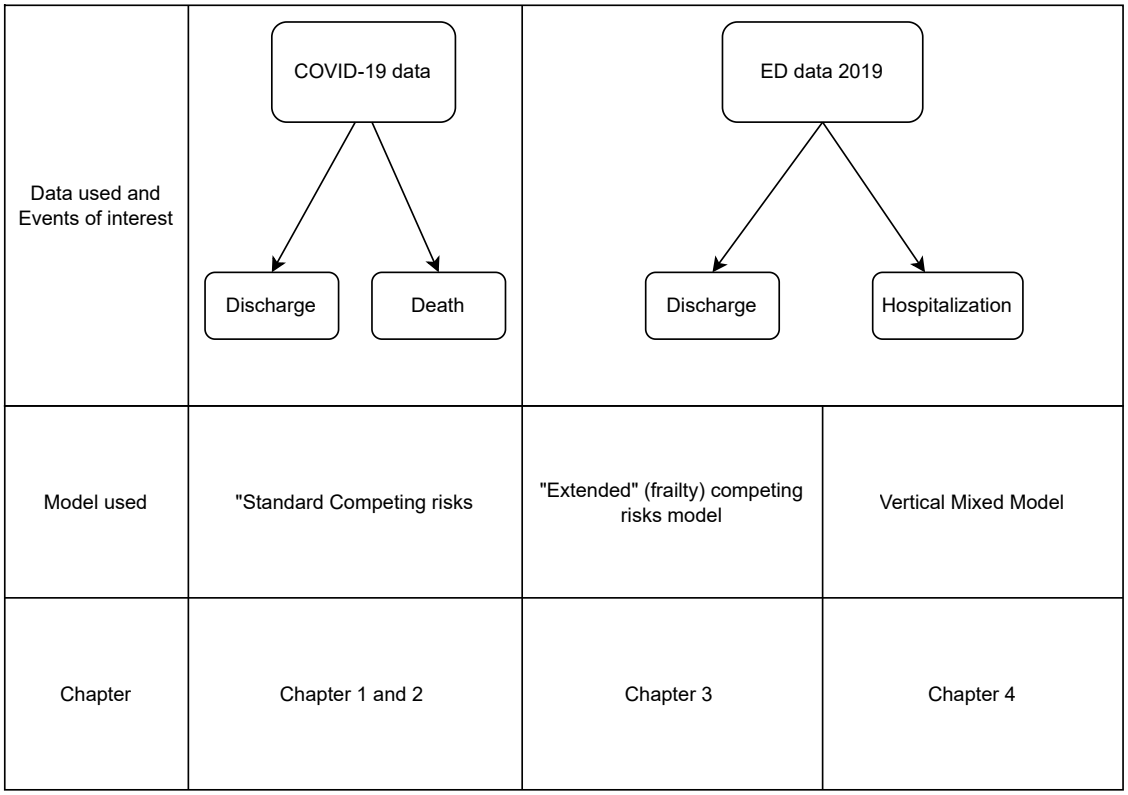


FIGURE 1: Chapters structure and types of competing risks models used in each chapter.

The first two chapters consider two applications on Covid-19 hospitalized patients to analyze In-hospital mortality using "standard" competing risks models. The first chapter's 2 main goal was to identify the factors associated with In-Hospital mortality in a cohort of 426 patients coming from IRCCS Policlinico San Matteo, Pavia, Lombardy, Italy. The second chapter 3 is an extension of the work in chapter 2, with a web app to predict In-hospital mortality according to different patient profiles. To do that, the prediction rule, identified using an internal cohort (including 1810 patients coming from Bergamo and Pavia units), was validated using an external cohort (381 patients from the Rome unit). The third chapter 4 considers the analysis of overcrowding in the Emergency Department in 63 Sicilian hospitals: the database consists of around 1.700.000 records of access to the Emergency Department (EMUR 2019 database). The application regards the development of a frailty competing risks model, modeled by maximizing the Hierarchical Likelihood, which takes into account the unobserved heterogeneity among hospitals. The fourth chapter 5 considers the Vertical model, introduced in 2010 [97] as an alternative approach to the standard competing risks model. The novelty is given by the accommodation into the model of a random effect component. It may be an alternative

to the frailty competing for risks model, which presents long computation times. Data used is the same of the third chapter (EMUR 2019 database).

Chapter 1

Standard and extended competing risks models

This section includes the theoretical definitions useful to carry out the survival analyses performed in the dissertation chapters, starting from the definition of the basic quantities in survival analysis to the definition of competing risks frailty model. Due to his definition of "alternative to the competing risks model", the theoretical definitions behind the Vertical Model are included in chapter 5 and will not be discussed in this section.

We stress that the aim of the work relies on the application of "standard" and "extended" competing risks models. These models are useful to determine the association between risk factors and the occurrence of more than one event of interest. In the "extended" case, the unobserved heterogeneity, which can arise, in particular in biomedical fields, from repeated measurements or multi-center studies, is taken into account.

1.1 Survival analysis principles

Survival data, or more commonly "time-to-event" data, take into account the interval between a certain origin and the occurrence of an event of interest, such as the interval between the diagnosis of a particular illness and death. Although it is common to talk about survival time, the event being considered is not always death. For instance, in chapter 4, we are interested in the waiting time in the Emergency Department from admission to visit one of the leaving types.

There are two key characteristics that set survival data apart. First, it is clear that the time-to-event, commonly abbreviated with T, is a positive continuous random variable. The potential for censorship and truncation, which results in incomplete data, is the second characteristic of survival data. Because of censorship, it is difficult to determine exactly when an event of interest will occur for some study subjects. In a clinical trial, a patient can still be alive at the time of the final follow-up appointment. In that example,

the survival time is said to be right-censored at the date of the final information accessible because we know that the real survival time is longer than the observed survival time. Even if right censoring is more common in such a framework, left censoring, interval censoring and truncation are still possible. We assume the right censoring to analyze the two available survival datasets. To define the basic quantities, we need to first define the distribution function of T as:

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

with density function:

$$f(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P(t \leq T \leq t + \Delta t) \tag{1.1}$$

1.1 is useful to define a more common quantity in survival analysis, the survival function as:

$$S(t) = 1 - F(t) = P(T > t) \tag{1.2}$$

The survival function represents the individual probability to survive beyond time t. It is a strictly decreasing function in [0,1] where at $t = 0$ its value is 1 and at $t = \infty$ its value is 0. The survival function can be defined also in terms of $f(t)$ as the integral of the probability density function:

$$S(t) = \int_t^{\infty} f(t)dt \tag{1.3}$$

and, thus:

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

Even if identifying the failure pattern by looking at the survival curve graphically is difficult, it is still a popular quantity in literature to describe the survival probability and is particularly useful when comparing more than one survival pattern. Two more basic quantities in survival analysis able to describe some aspects of the time-to-event distribution are the hazard function and the cumulative hazard function. They are defined as:

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

and:

$$H(t) = \int_0^t h(t)dt \tag{1.5}$$

The hazard function is useful to determine the mechanism of failure over time. It is a non-negative function, that is $h(t) \geq 0$. The hazard function is also named hazard rate. Indeed, assuming T as continuous, it can be derived from the fractional between the

probability density function and the survival function. In formula:

$$h(t) = \frac{f(t)}{S(t)} = -d\ln[S(t)]$$

from the relationships in 1.5 :

$$H(t) = -\ln[S(t)]$$

and, taking the reversal, the survival function can, again, be defined:

$$S(t) = exp(-\int_0^t h(t)dt) = exp(-H(t)) \tag{1.6}$$

Thus, the knowledge of one of these quantities is sufficient to derive the others. Interestingly, the hazard function and the cumulative hazard function represent, respectively, the instantaneous and cumulative quantification of the event times distribution.

1.1.1 Survival and hazard function estimation approaches

To estimate the basic quantities in survival analysis shown in section 1.1 researchers can choose among parametric, non-parametric, or semi-parametric approaches. In the first case, a parametric distribution for the event times is assumed. Survival data, by definition, have usually asymmetric distribution, thus consider the normal distribution is not appropriate. The most used parametric survival distributions are: the Weibull, Exponential, and Log-Normal. We recommend some books on survival analysis for a deep description of parametric survival distributions [78, 85]. In chapter 5 we implemented a Joint Vertical Mixed model assuming a Log-Normal distribution for the "time to-any-event" inside the Emergency Department setting, useful to estimate the *overall hazard*.

The second case does not concern with the assumption of a time-to-event distribution. Here the data are treated as they are. The parametric estimation assumes that the hazard function follows a deterministic rule, which is rare in practice (due to the presence of censoring). Indeed, even if the true time distribution was continuous, this approach would consider the data comes from a discrete distribution. Thus, the survival function can be estimated just by computing the number of subjects still *alive* from the cause of interest at time t over all the subjects under observation just before t (represented by all the subject that are event-free just before t).

Formally, we denote with $Y = min(T, C)$ the time-to-event in right censoring setting, with observed n times $y_1, y_2, ..., y_n$ and censoring indicators $\delta_1, \delta_2, ..., \delta_n$. Then we denote $y_1, ..., y_r$ the r ordered event times with $d_1, ..., d_r$ the number of events for each event time and $R(y_{(1)}), ..., R(y_{(r)})$ the corresponding risk set. The survival function can be, then,

estimated by the well known Kaplan-Meier estimator [76]:

$$\hat{S}(t) = \prod_{j:y_j \leq t} \left(1 - \frac{d_j}{R(y_{(j)})}\right) \tag{1.7}$$

The Kaplan-Meier estimator has several properties: it is a decreasing function with value 1 at time 0 and will reach 0 if the biggest time observed, $y_{(r)}$, is an event. In the case of uncensored data, the Kaplan-Meier estimator is simply the fraction between subjects who survive at time t over all subjects in the risk set at that time. Moreover, the Greenwood formula [152, 114], available in every Survival analysis book (see for example [78]), is useful to make inference and to compute the survival function confidence intervals.

In practice could be important comparing two subgroups in survival terms. To test whether two survival functions are equal (or not), the log-rank test is the most used. The log-rank test compares the observed number of events with the expected number of events at each event time. The most intuitive way to do that is to compute the sums of the differences between the observed and expected number of events (under the null hypothesis H_0 that the two survival curves are equal). Simplifying the notation we define the U_L statistics as:

$$U_L = \sum_{i=1}^{r} (d_{1i} - e_{1i})$$

and, under H_0:

$$\frac{U_L}{\sqrt{V(U_L)}} \approx N(0,1)$$

Which leads also to:

$$\frac{U_L^2}{V(U_L)} \approx \chi_1^2$$

The log-rank test is powerful when the risks proportionality assumption holds. We recommend [85] to check for some extensions of this test.

1.1.2 Survival Regression models

Survival regression models are used to quantify the effect of some covariates on the event time distribution. Such an approach is useful to determine which factors affect more or less the occurrence of the event of interest over time. For example, in chapter 2 we identified the factors associated with the risk of death, in hospitalized Covid-19 patients, during the time spent inside the Hospital. We used a competing risks model, considering the Discharge to the hospital to prevent death occurrence.

A simpler way to perform a survival regression model relies on the risk evaluation of just one event of interest, as in the case of the Cox proportional hazard model [39] (which considers a semi-parametric approach to estimate the hazard function) or Accelerated Failure Time model (AFT) (which considers a fully parametric approach). The latter will not be discussed later. Let assume $X^t = (X_1, X_2, ..., X_p)$ be the set of covariates with values ${x^t}_i = (x_{i1}, ..., x_{ip})$ which determine the hazard function of individual $i (i = 1, ..., n$ as the product of a baseline hazard function $h_0(t)$ and a factor depending on the value of X. Notice that $h_0(t)$ is a common quantity for each i. The proportional hazards (PH) model considers the exponential of the linear predictor to be the multiplying factor of the baseline hazard. In formulas:

$$h_i(t) = h(t|x_i) = h_0(t)exp(\beta^t x_i) \tag{1.8}$$

where β is the unknown parameters vector.

The main assumption of the model is that the hazards are assumed to be *proportional* which means that the hazard ratio (HR) of two subjects with covariates values x_1 and x_2 is constant over time:

$$\frac{h(t|x_1)}{h(t|x_2)} = \frac{h_0(t)exp(\beta^t x_1)}{h_0(t)exp(\beta^t x_2)} = \frac{exp(\beta^t x_1)}{exp(\beta^t x_2)} = exp\{\beta^t(x_1 - x_2)\} \tag{1.9}$$

This means, also, that the HR does not depend on time. One can make assumptions on the baseline hazard function, assuming a parametric distribution to the event times (AFT) or to be unspecified, leading to a semi-parametric PH model (Cox model).

The estimation procedure is based on the maximization of the partial likelihood (PL) in the case the baseline hazard is set to be unspecified. In the survival regression model framework, the likelihood function is defined as:

$$L(h_0, Y, \beta) = \prod_{i=1}^{n}(h_0(y_i)exp(\beta^t x_i))^{\delta_i} exp(-H_0(y_i)exp(\beta^t x_i)) \tag{1.10}$$

The maximization of 1.10 is not feasible, due to the presence of the nuisance parameter h_0. Hence, to remove such a parameter, the partial likelihood must be maximized. In presence of no ties, the PL is derived as a profile likelihood:

$$L_p(\beta) = \prod_{i=1}^{r} \frac{exp(\beta^t x_i)}{\sum_{l \in R(y_i)} exp(\beta^t x_l)} \tag{1.11}$$

The denominator is referred to all the subjects still at risk. The censored subjects, therefore, contribute to this sum.

Even if the partial likelihood might be not consider a real one, it's been proved that is a valid quantity to provide consistent and asymptotically normally distributed estimators of $\hat{\beta}$. The maximization of PL is performed through the Newton-Raphson algorithm and the variance-covariance matrix of $\hat{\beta}$ is approximated by the inverse of the Fisher information matrix at $\hat{\beta}$ (see [85, 56] for more details about the estimation procedure).

Sometimes researchers forget that the Cox PH model is based on some assumptions that need to be verified. The most important assumption, as already stated, is the proportionality of the hazards. To check for the proportionality of the Cox model, several aspects can be inspected. One approach is based on the log-cumulative hazard plot. Indeed the hazard in 1.8 can be written as:

$$\log(H(t|x_i)) = \log(H_0(t)) + \beta^t x_i$$

and, in terms of the survival function:

$$-\log(-\log(S(t|x_i)) = -\log(-\log(S_0(t)) - \beta^t x_i$$

Thus, one can check for proportionality assumption looking at the $-\log(-\log)$ transformation of the survival function. In that case, proportionality holds if the two curves (one for each value of x_i) are parallel. Another approach, one of the most used, is based on the scaled Schoenfeld residuals [60], which computes the expectation of the i^{th} component of the scaled residuals for the j^{th} covariate, as:

$$E(r_{ji}^{P^*}) \approx \beta_j(y_i) - \hat{\beta}_j$$

with $\beta_j(y_i)$ the time-varying coefficient for X_j. Thus, checking the plot, showing the scaled residuals plus the estimated beta $r_{ji}^{P^*} + \hat{\beta}_j$ versus time, a horizontal line is expected in the case of proportionality.

1.1.3 Frailty models

In survival analysis, frailty models represent an extension of the classical approach, where the population is assumed to be homogeneous. This might be rarely true. Indeed, in some applications is more logical to consider heterogeneous population or grouping of people. Even in such situations, subjects can be exposed to different levels of risk which might depend on unobserved risk factors related to the event of interest. The frailty is the tool to address for the unobserved heterogeneity which can arise by the presence of unobserved (or unmeasured) covariates. In his seminar paper, Vaupel first accounted for this issue

[143]. The idea was to model the unobserved heterogeneity by adding a random component (the so-called frailty) acting multiplicative on the hazard. The univariate frailty model, assuming the censoring to be non- informative conditionally on $U_i = u_i$ denoting the univariate frailty for the i-th subject and the clusters with $j = 1, ..., q$, is defined as:

$$\lambda_{ij}(t|u_i) = \lambda_0(t)exp(\beta^t x_{ij}) \tag{1.12}$$

The most used distribution, assumed for U_i, which is considered as an i.i.d. random variable, is the log-normal (particularly useful to account for correlated frailties) and the gamma. From 1.12 it is noticed that the individual risk depends also on the frailty. Indeed, larger values of u_i correspond to a higher hazard (meaning also a smaller survival probability). On the contrary, smaller values of u_i correspond to a lower hazard (meaning also a higher survival probability).

While several approaches, already briefly discussed in 0.2.1, are used in literature to inferentiate frailty models, we will focus on the Hierarchical likelihood-based approach, following [61].

1.2 Survival analysis and competing risks models

As already discussed in 0.1, competing risks concerns, in survival analysis, the situation in which different types of events can occur and the occurrence of one of them can preclude, or modify, the occurrence of the others. The simplest approach is to perform a classical survival analysis, where the observation failing from other causes can be treated as censored. This can, anyway, remove information on the other causes of occurrence. The interpretation of the results is where such an approach has been largely criticized. Suppose to estimate the probability of failing from cause k using the Kaplan-Meier estimator (that is $\hat{F}_{KM}(t) = 1 - \hat{S}_{KM}(t)$) where the observation failing from a competing event are censored. The so-called *Naive Kaplan-Meier* do not describe anymore the probability of experience cause k at time t, and the sum of the estimated probabilities of all the causes can exceed one [108]. Strictly speaking, the *Naive Kaplan-Meier* is biased. The main reason for this bias relies on the violation of the assumption of independence of the censoring distribution. Indeed, the naive Kaplan-Meier method overestimates the probability of failure because patients that will never fail are treated as though they could fail (they are censored). To make it clearer, we show, in figure 1.1, the comparison between naive and no naive KM computed for covid-19 patients hospitalized in "Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Lazio", between February *22nd* and April *7th*, 2020 (see 3.2 for more details on the data used). The main difference between the two

approaches shown in figure 1.1 is that the Naive KM seems to overestimate the probability of Death and underestimate the probability of Discharge (represented in survival terms as $1 - \hat{F}(t)$).

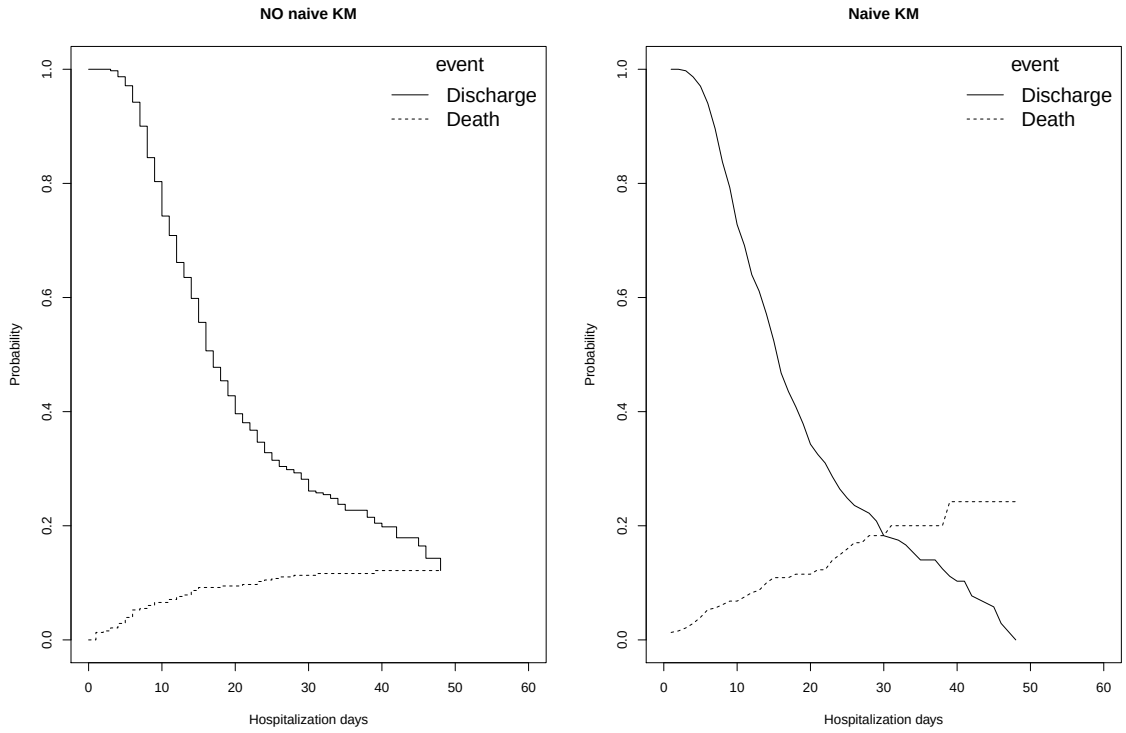


FIGURE 1.1: naive KM vs no naive KM according to death, with discharge as competing event, in covid-19 hospitalized patients.

In the competing risks setting, all the basic quantities described in 1.1 are extended to take into account more than one event of interest occurrence. For example, the hazard function is computed for each event in the competing risks framework. We define the so-called *cause-specific hazard*, with continuous T, for the k^{th} event, with $k = 1, ..., K$ as:

$$\lambda_k(t) = \lim_{\Lambda_t \to 0} \frac{P(t \leq T < t + \Delta_t, E = k | T \geq t)}{\Delta_t}$$

and, hence, the cumulative cause-specific hazard:

$$\Lambda_k(t) = \int_0^t \lambda_k(s) ds$$

and:

$$S_k(t) = exp(-\Lambda_k(t))$$

An important quantity is represented by the *overall survival function*, which is the survival probability of experiencing any event at time t and it is the sum of $S_k(t)$ for all causes.

$$S(t) = exp\left(-\sum_{k=1}^{K} \Delta_k(t)\right) \tag{1.13}$$

It is useful to define the *cumulative incidence function* (CIF), the probability of failing from a cause before time t.

$$I_k(t) = \int_0^t \lambda_k(s)S(s)ds \tag{1.14}$$

which is different from the Naive KM:

$$1 - S_k(t) = \int_0^t \lambda_k(s)S_k(s)ds$$

It is then clear that the definition of the overall survival function is what corrects for the bias provided by the Naive KM.

In the stochastic process theory of survival analysis [1], Competing risks can be seen as a special case of multi-state models, composed of an initial state and more than one final state (see figure 1.2). The process is useful to understand the computation of the CIF, defined as the probability of experiencing an event from cause k a time s (described by the cause-specific hazard $\lambda_k(s)$) given the probability of surviving to any event at the time just before s (described by the overall survival $S(s)$).

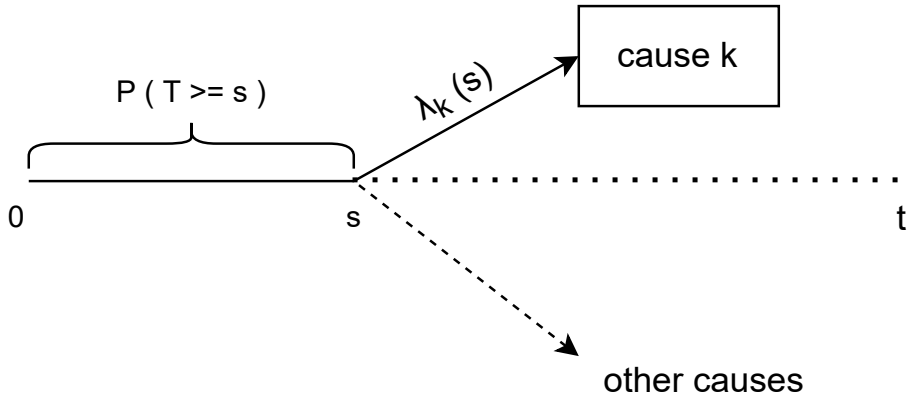


FIGURE 1.2: Competing risks process.

The simplest approach is to fit a standard Cox model for one event of interest censoring the others or to fit separate models, one for each event of interest.

For example, in chapter 2 we fitted two separate regression models using In-hospital covid-19 data: one for In-hospital mortality and one for Discharge. The idea was that

if Discharge occurred, the patient cannot experience anymore death (and, thus, he was censored). This is, obviously, true also in the opposite situation. Formally, the impact of covariates on the cause-specific hazard is modelled via:

$$\lambda_k(t|x_i) = \lambda_{k,0}(t)exp(\beta_k^t x_i) \tag{1.15}$$

with $\lambda_k(t|x_i)$ the cause-specific hazard for cause k at time t for a subject with covariate x_i, $\lambda_{k,0}(t)$ the baseline hazard for cause k and $\beta_k = (\beta_{k1}, ..., \beta_{kp})$ the vector parameter associated with X. Given that 1.15 can be performed through the standard PH Cox model, the estimation procedure is identical to that used in traditional survival analysis with one event of interest. The difference relies on the interpretation of the results due to the fact that 1.15 is referred to the influence of the covariates X on the cause-specific hazard. It is also possible to fit the cause-specific hazard models for each cause at the same time using a data augmentation approach. The most relevant, well described in [108], transforms the dataset in the long format, that is the subjects will have one row for each possible transition in the competing risks process, thus k lines per subject.

TABLE 1.1: Example of long format dataset.

Row	id	from	to	trans	Tstart	Tstop	time	status	Pathology
1	1	1	2	1	0	1,68	1,68	0	Other_symp
2	1	1	3	2	0	1,68	1,68	1	Other_symp
3	2	1	2	1	0	0,25	0,25	1	Dig_dis
4	2	1	3	2	0	0,25	0,25	0	Dig_dis
5	3	1	2	1	0	1,22	1,22	1	Injury
6	3	1	3	2	0	1,22	1,22	0	Injury
7	4	1	2	1	0	2,07	2,07	1	Other_symp
8	4	1	3	2	0	2,07	2,07	0	Other_symp

To better understand Table 1.1 we refer to Figure 4.1 for a graphical description of the process inside the ED. The long format includes columns identifying the transition type for each row (columns *from* stands for the initial state, columns *to* refers to the final state of the competing risks process, that takes value 2 or 3 for subjects, respectively, discharged or hospitalized). The elapsed time (computed as the difference between *Tstop* and *Tstart* is common for the same subject and different transitions). Finally, a failure indicator is represented by *status* (value 0 for discharge, value 1 for hospitalization type). The long format allows to perform two different competing risks models: a stratified model for the event type (which leads to identical results of the separate models approach, and a model that includes the status as covariate. The latter alternative assumes proportional baseline

hazards between event types and can be helpful to quantify the effect of the covariates on the marginal hazard by a single measure.

Moreover, it's been largely discussed that the use of the cause-specific hazard does not provide a one-to-one relationship with the CIF [7], because the cause-specific incidence computation for one event type k involves all cause-specific hazards [14]. This also means that the sign of the regression coefficient $\hat{\beta}_k$, estimated from a competing risks model, might be not matched with a higher/lower CIF.

1.2.1 The Fine and Gray Model

Fine and Gray, in 1999, defined the sub-distribution hazard to make the one-to-one relationship with the CIF [49]. The model appears very similar to the Cox PH model:

$$h_k(t|x_i) = h_{k,0}(t)exp(\beta_k^t x_i) \tag{1.16}$$

Where $h_{k,0}(t)$ is the baseline sub-distribution hazard for event type k. The main difference relies on the definition of the risk set. In a sub-distribution approach, indeed, subjects who fail from a cause k are still at risk of experiencing any other cause. This definition has been largely criticized, due to the unrealistic world such an approach defined (for example, people dying from a cause cannot be at risk for another cause). As expressed in 0.1 the sub-distribution approach seems to solve the issue in the interpretation of the betas, corresponding to a direct increase in the CIF, but looking at 1.16 the occurrence of an event k depends on the baseline sub-distribution hazard and the effect of the covariates on the baseline hazard, but also the baseline hazard and the effect of the covariates on the baseline hazard for the competing events. The estimation procedure, even though still based on the maximization of the partial likeliihood, similarly to 1.11, is more complex, due to the presence of a different definition of the risk set. In the simplest case, that is assuming right censoring distribution, the Fine and Gray partial likelihood is:

$$L_p^{FG} = \prod_{i=1}^{n} \left(\frac{exp(\beta_k^t)}{\sum_{j \in R_{y_i}} exp(\beta_k^t x_j)} \right)^{\delta_i} \tag{1.17}$$

From 1.17, subjects experiencing a competing event are treated as censored, coming back to the main issue on the computation of non-parametric cumulative incidence. To overcome this issue, the event time for these individuals is set to be equal to the end of the study (administrative censoring). We used such methodology to perform a Fine and Gray model, chapter 2 and 3, in covid-19 hospitalized patients, to predict in-hospital mortality considering the Discharge to be a competing event. This model is known to be

more appropriate in a prediction setting, given the one-to-one relationship between the sub-distribution hazard and the CIF. This relationship allowed us to define the different risk profiles for mortality in order to improve the treatments, validate the model using an external cohort, and, finally, decrease the overcrowding faced by the Italian hospitals during the first wave.

1.2.2 H-likelihood

H-likelihood is known in the GLMM theory to overcome the issues aroused from the maximization of the extended likelihood (where the maximum likelihood estimator for the unobservable results useless [61]) to get the joint distribution of (θ, v), where θ is the vector of unknown parameters and v the log transformation of the random effect U. The H-likelihood is still an extended likelihood but it is built under a different scale of v [84].

Supposing to define the likelihood ratio (LR) for θ_1 and θ_2, the pair of values of the vector parameter θ of length p, including a special scale v:

$$\frac{L(\theta_i; y)}{L(\theta_j; y)} = \frac{L(\theta_i; \hat{v}_{\theta_i}, y, v)}{L(\theta_j; \hat{v}_{\theta_j}, y, v)} \tag{1.18}$$

where $\hat{v}_{\theta_i}$ is the MLE of v at $\theta = \theta_i$ with $i, j = 1, .., p$ and $i \neq j$. The H-likelihood is the extended likelihood when the scale of v is canonical, that is the scale satisfying 1.18. It's been proved that the canonical scale is $log(u)$. The log-H-likelihood can be, therefore, defined as:

$$h = l_1(\theta; y|v) + l_2(\theta; v) \tag{1.19}$$

In the frailty model setting, considering the Cox PH model as belonging to the GLM family, the H-likelihood approach is still valid.

Defining with $Y_{ij} = min(T_{ij}, C_{ij})$ the event times for the i-th subject and j-th cluster and $\delta_{ij} = I(T_{ij} \leq C_{ij})$ the event indicator, the H-likelihood for the frailty model is, similarly to 1.19:

$$h(\beta, v, \lambda_0, \alpha) = \sum_{ij} l_{1ij} + \sum_{i} l_{2i} \tag{1.20}$$

where

$$l_{1ij} = (\beta, \lambda_0; y_{ij}, \delta_{ij}|u_i) = \delta_{ij}\{log\lambda_0(y_{ij} + \eta_{ij})\} - \{\Lambda_0(y_{ij})exp(\eta_{ij})\}$$

is the log-likelihood conditionally on $U_i = u_i$ and l_{2i} is the logarithm of the density function of U_i, and:

$$\eta_{ij} = \beta^t x_{ij} + v_i$$

the linear predictor with $v_i = log(u_i)$. In such a setting the dimension of baseline hazard is potentially high when λ_0 is unknown and increases with the number of events [62]. Therefore, given λ_0 is often not of interest, it can be removed by profiling the H-likelihood.

$$h^* = h|_{\lambda_0 = \hat{\lambda}_0}$$

where

$$\hat{\lambda}_{0k}(\beta, v) = \frac{d_{(k)}}{\sum_{ij \in R_{(k)}} exp(\eta_{ij})}$$

obtained computing $\frac{\delta h}{\lambda_{0k}} = 0$. Then, substituting $\hat{\lambda}_{0k}$ in 1.20:

$$h^*(\beta, v, \alpha) = \left\{ \sum_k d_{(k)} log\hat{\lambda}_{0k} + \sum_{ij} \delta_{ij}\eta_{ij} - \sum_k d_{(k)} \right\} + \sum_i l_{2i}$$

The fitting procedure is based on different orders of the Laplace approximations to get fixed and random effects estimates (see [61]). In R, such a procedure is implemented in the *frailtyHL* routine included in *frailtyHL* R package.

1.2.3 Competing risks frailty models

As already stated in 1.2, in the survival framework more than one event of interest may occur and all the quantities, useful to perform such analysis, have to be extended. To do that, suppose the presence of $i = 1, ..., q$ number of clusters with $j = 1, ..., n_i$ observation of each cluster. Let T_{ij} the time of the first event for subject j in cluster i and $\epsilon_{ij} \in 1, ...K$ the corresponding cause of failure. Denote with C_{ij} the censoring time and with U_i the frailty for cluster i. We, therefore, assume that censoring C_{ij} is conditionally independent with the respect of the time-to-event (T_{ij}, ϵ_{ij}) conditionally on U_i and that censoring is also non-informative to (T_{ij}, ϵ_{ij}) conditionally on U_i. Similar to frailty models, we define the cause-specific hazard function conditional on the log-frailty v_i, shared by clusters, for the jth observation in cluster i who failed from cause k, as:

$$\lambda_{ijk}(t|v_i) = \lambda_{0k}(t)exp(x_{ij}^t \beta_k + v_i) \tag{1.21}$$

where v_i represents the random component, from an assumed univariate distribution with parameter θ, acting in a multiplicative way with the respect to the cause-specific-hazard. The so-called "univariate" cause-specific frailty model assumes that the shared frailty v_i affects the event type inside a cluster in the same way, which is unrealistic in situations where people inside a cluster are more or less frail to experience any event than the others. Moreover, the shared frailty assumes only a positive association within

a cluster. This means that, if $v_i > 0$ for all i, the subject in the cluster will experience the event early. To overcome this issues, the multivariate competing risks frailty model can be considered.

$$\lambda_{ijk}(t|v_i) = \lambda_{0k}(t)exp(x_{ij}^t\beta_k + v_{ik}) \tag{1.22}$$

where v_{ik} is the random effect for failure k in cluster i. The multivariate normal distribution is the usual choice for the distribution of v_{ik} with mean 0 and matrix-covariance matrix $K \times K$ (denoted with Σ). In chapter 4 we used a multivariate frailty competing risks model with unstructured Σ_U, to model the risk of discharge and hospitalization (K=2) once the patients were admitted to visit. The distribution of v_{ik} is assumed to be:

$$\begin{pmatrix} v_{i1} \\ v_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & \rho_{12}\sigma_1\sigma_2 \\ \rho_{12}\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}\right)$$

.

The construction of the H-likelihood is similar to 1.20. Denote with $Y_{ij} = min(T_{ij}, C_{ij})$ and $\delta_{ijk} = I(Y_{ij} = T_{ijk})$ the event time and the event indicator respectively, where $\delta_{ijk} = 1$ if cause k occurs first and 0 otherwise. Thus, the conditional likelihood with the respect to v_{ik} is defined as:

$$L_i(\beta, \lambda_0|v_{ik}) = \prod_{k=1}^{K}\prod_{j=1}^{n_i}\left(\lambda_{0k}(y_{ij})exp(x_{ij}^t\beta_k + v_{ik})\right)^{\delta_{ijk}} exp\left(-\Lambda_{0k}(y_{ij})exp(x_{ij}^t\beta_k + v_{ik})\right) \tag{1.23}$$

where $\eta_{ij} = x_{ij}^t\beta_k + z_{ij}^t v_k$ is the linear predictor with $z_{ij} = (z_{ij1}, ..., z_{ijq})$ the $q \times 1$ cluster indicator vector. The H-likelihood for cluster i is therefore the product of the conditional likelihood in 1.23 and the likelihood provided by the joint probability density function of $V_i = (V_{i1}, V_{i2})$:

$$h_i = log\left\{\prod_k\prod_j L_{1ijk}(\beta_k, _{0k}; y_{ij}, \delta_{ijk}|v_{ik})L_{2i}(\theta; v_i)\right\} \tag{1.24}$$

where:

$$L_{1ijk}(\beta_k, _{0k}; y_{ij}, \delta_{ijk}|v_{ik}) = \left\{\lambda_{0k}(y_{ij})exp(\eta_{ij})\right\}^{\delta_{ijk}} exp(-\Lambda_{0k}(y_{ik})exp(\eta_{ij}))$$

and, assuming a bivariate distribution of V_i with mean 0 and variance covariance matrix Σ

$$f_i(v_i; \theta) = |2\pi\Sigma|^{\frac{-1}{2}} exp\left(\frac{-1}{2}v_i^t\Sigma^{-1}v_i\right)$$

Summarizing over the clusters, the log h-likelihood is:

$$h(\beta, \lambda_0, v, \theta) = \sum_i h_i = \sum_{ijk} l_{1ijk}(\beta_k, \lambda_{0k}; y_{ij}, \delta ijk | v_{ik}) + \sum_i l_{2i}(\theta; v_i) \tag{1.25}$$

with:

$$l_{1ijk}(\beta_k, \lambda_{0k}; y_{ij}, \delta ijk | v_{ik}) = \delta_{ijk}(log(\lambda_{0k}(y_{ij})) + \eta_{ij} - \delta_{0k}(y_{ij}) exp(\eta_{ij})$$

and:

$$l_{2i}(\theta; v_i) = -\frac{1}{2} log|2\pi\Sigma| - \frac{1}{2} v_i^t \Sigma^{-1} v_i$$

As discussed in section 1.2.2, the baseline hazard function λ_{0k} must be removed due to its high dimensionality that increases as well as the number of events. The first step is to compute the MHLE for $\hat{\lambda}_{0kr}$ by solving $\frac{\delta h}{\delta \lambda_{0kr}} = 0$

$$\hat{\lambda}_{0kr} = \frac{d_{(kr)}}{\sum_{ij \in R_{(kr)}} exp(\eta_{ij})} \tag{1.26}$$

where $d_{(kr)}$ is the number of events occurred at time $y_{(kr)}$ for cause k. Replacing $\hat{\lambda}_{0kr}$ with λ_{0kr} in 1.25, the h-likelihood is now:

$$h^*(\beta, v, \theta) = \sum_{k=1}^{2} \left[\sum_{r=1}^{D_k} d_{(kr)} log(\hat{\lambda}_{0kr}) + s^t_{x(kr)} \beta_k + s^t_{z(kr)} v_k - \hat{\lambda}_{0kr} \sum_{ij \in R_{(kr)}} exp(\eta_{ij}) \right] + \sum_{i=1}^{q} l_{2i}(\theta; v_i) \tag{1.27}$$

where $s^t_{x(kr)} = \sum_{ij \in D_{(kr)}} x^t_{ij}$ and $s^t_{z(kr)} = \sum_{ij \in D_{(kr)}} z^t_{ij}$.

The estimation is based on the maximization of 1.27 with respect to the regression parameters, through the Laplace approximation. The estimation of the competing risks frailty model in chapter 4, using the R routine *hlike_frailty* of the *frailty_HL* package, is based on 0-order and first-order of the Laplace approximation for, respectively, fixed and dispersion parameters. This choice should perform well in the case the log-normal distribution is assumed for the random effects.

1.2.4 Vertical models

Competing risks in survival analysis occur when multiple events are of interest and the occurrence of one event precludes the others (e.g. in a liver disease process the liver transplant event avoids, clinically, the occurrence of death). In such a setting, the main quantity is the Cumulative Incidence Function (CIF) which represents the cumulative probability of failing from the cause j (denoted by D) up to time T (time to event D) $(F_j = P(T <= t | D = j))$. Another approach to describe the joint distribution of (T, D) is

based on the following decomposition:

$$P(T, D) = P(D|T)P(T)$$

The two quantities $P(T)$ and $P(D|T)$ are connected with one of the main quantities in a competing risk setting, the cause-specific hazard. The first is is the overall hazard $\lambda_.$, that is the hazard of experiencing any event of interest, the latter is the so-called relative cause-specific hazard $\pi_j = \frac{\lambda_j}{\lambda_.}$ with $\sum_{j=1}^{J} \pi_j = 1$.

As described in section 5.1, covariates can be involved estimating a multinomial logistic model for the relative cause-specific hazards π_j (where we included the interaction between a smoothed function of time $B(T)$ and the vector of covariates Z assuming that the effect on π_j of each level of Z is not the same along time t) and a Cox proportional hazard model for the overall hazard $\lambda_.$. In formulas:

$$\pi_j(t) = \frac{exp(\beta_j^T B(t) * Z)}{\sum_{j=1}^{J} exp(\beta_j^T B(t) * Z)}$$

with j=1,..,J
where $B(t)$ is a vector of smoothed functions of time $(B_1(t), B_2(t), ..., B_p(t))^T$,
and:

$$\lambda_.(t) = h_0(t)exp(\beta^T * Z)$$

Vertical Mixed Model

The novelty is to accommodate for a random component in the Vertical Model, taking into account the unobserved heterogeneity that can arise in presence of clustered data or subjects' repeated measurements [123]. The assumption is that the clusters are observations coming from a random distribution that must be assumed. Denote the couple (V_i, U_i) as the random effects for the overall hazard and the relative hazard respectively in the i-th cluster. The Vertical mixed model for the j-th cause and i-th cluster, an extension of the model described in section 1.2.4, is defined as:

$$\pi_j(t) = \frac{exp(\beta_j^T B(t) * Z + u_i)}{\sum_{j=1}^{J} exp(\beta_j^T B(t) * Z + u_i)} \tag{1.28}$$

and:

$$\lambda_.(t) = h_0(t)exp(\beta^T * Z + v_i) \tag{1.29}$$

The regression model for the relative hazard is now a Multinomial mixed model and the model for the overall hazard is a Cox frailty model. The couple (V_i, U_i) act additively in the linear predictors of the two sub-models. Moreover, we assume that they are normally distributed with zero mean and variance-covariance matrix Σ [30].

$$\begin{pmatrix} u_i \\ v_i \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_u^2 & \rho_{u,v}\sigma_u\sigma_v \\ \rho_{u,v}\sigma_u\sigma_v & \sigma_v^2 \end{pmatrix}\right)$$

The correlation coefficient $\rho_{u,v}$ represents the degree of correlation between the two random variables (U, V). In a multicentre framework, this quantity describes how the clusters are related. A positive correlation coefficient $\rho_{u,v}$ would mean that clusters with negative frailty (meaning lower overall hazard) tend to have a positive random effect in the multinomial mixed model(meaning higher probability of experiencing one of the events of interests); on the other hand, clusters with positive frailty (higher overall hazard) tend to have negative random effect in the multinomial mixed model (meaning a lower probability of experiencing one of the events of interests).

According to the assumption on $\rho_{u,v}$ two different Vertical Mixed Model can be performed:

- *JVMM* assuming $\rho_{u,v} = 0$ that is the couple (V_i, U_i) are uncorrelated. The Vertical Mixed Model can be performed estimating separately the overall hazard and the relative hazards as a mixture model.
- *JVMM* assuming $\rho_{u,v} \neq 0$. The overall and the relative hazard, as well as $\rho_{u,v}$, must be estimated integrating them out from the joint likelihood.

Joint Vertical Mixed Model

Denote with i the cluster with random components (V_i, U_i), with j $(j = 0, 1, ..., n_i)$ the j-th event of interest, with δ_{ij} the event indicator variable within a cluster i and $y_{ij} = \{\delta_{ij} = 2\}$ representing the binomial response variable for the event of interest 2. The joint likelihood can be written as:

$$L = \int_0^\infty \int_0^\infty \prod_{i=1}^{n} \prod_{j=1}^{n_i} l_{1ij}(\beta, \lambda_0(t_{ij}), v_i) l_{2ij}(\gamma, B(t_{ij}), u_i) f_\Sigma(u_i, v_i), du_i\, dv_i \tag{1.30}$$

where l_{1ij} and l_{2ij} are the overall and the relative hazard contribution to the joint likelihood, respectively, and f is assumed to be a bivariate normal distribution with mean zero

and variance-covariance matrix Σ.
The two sub-likelihoods are given by:

$$l_{1ij}(\beta, \lambda_0(t_{ij}), v) = (\lambda_0(t_{ij}))exp(\beta^T z_{ij} + v_i))exp(-\Lambda_0(t_{ij})exp(\beta^T z_{ij} + v_i))^{\delta_{ij}>0} \quad (1.31)$$

$$l_{2ij}(\gamma, B(t_{ija}), u_i) = (expit(\gamma^T z_{ij} \nu^T B(t_{ij}) + u_i)^{y_{ij}} expit(\gamma^T z_{ij} \nu^T B(t_{ij}) + u_i)^{1-y_{ij}})^{\delta_{ij}>1} \quad (1.32)$$

where $expit(x) = \frac{exp(x)}{1+exp(x)}$

Direct maximization of the joint likelihood 1.30 is impossible due to the nonparametric component λ_0.

The estimation procedure, considering a EM (*Expectation- Maximization*) approach, would rely on profiling the joint likelihood with e respect to λ_0, that is getting a non-parametric estimation $\hat{\lambda}_0$, substituting $\hat{\lambda_0}$ in 1.30 and then maximize the joint likelihood to get the model parameters [17, 70]. Such a procedure, especially when the number of observations and random effects increases [64], could be computationally heavy.

A bayesian based approach to the JVMM

To overcome the computational issues, regarding the maximization of the joint likelihood explained in section 1.2.4, we considered a bayesian based approach to estimate the JVMM. The assumption is that the model is considered as a Latent Gaussian Model (LGM). Such an approach is based on INLA (Integrated Nested Laplace Approximation) which is able to approximate the joint posterior distribution of the model parameters starting from the selection of a priori distribution.

LGM is a specific subset of hierarchical Bayesian additive models [142]. This class comprises of well-known models such as mixed models, temporal and spatial models. An LGM is defined as a model having a specific hierarchical structure, as follows: the likelihood is conditionally independent based on the likelihood parameters (hyper parameters), θ and the linear predictors, η_i, such that the complete likelihood can be expressed as:

$$\pi(y|\eta, \theta) = \prod_{i=1}^{N} \pi(y_i|\eta(\mathcal{X}), \theta) \quad (1.33)$$

Where: $\eta_i = \beta_0 + \beta^T X_i + u_i(z_i)$
and: $\mathcal{X} \sim N(0, Q^{-1}(\theta))$ with $\mathcal{X}$ the latent gaussian field with sparse precision matrix $Q(\theta_2)$ to ensure efficient computation [120].

The main assumption is that the data, Y is conditionally independent given the partially observed latent field $\mathcal{X}$, and some hyper parameters θ_1. A prior $\pi(\theta)$ for the hyper-parameters can be assumed to get the joint posterior distribution:

$$\pi(\mathcal{X}, \theta) \propto \pi(\theta)\pi(\mathcal{X}|\theta)\prod_i \pi(Y_i|\mathcal{X}, \theta) \tag{1.34}$$

The joint posterior density in 1.34 is then approximated to obtain the marginal posterior densities $\pi(\mathcal{X}_i|\theta)$ $i = 1, 2, ..., n$ and $\pi(\theta|Y)$. Strictly speaking, the distribution a priori assumed for θ is then updated through the data (that is the joint likelihood in 1.30) to get the posterior joint distribution. Moreover, the Laplace approximation is used to approximate possible intractable joint posterior distribution in case of non-Gaussian likelihood [141].

The JVMM proposed will be performed, in chapter 5 using the *inla* function from the R package *INLA*. Estimation of joint models under a bayesian approach is also implemented in *JMBayes* R-package [118].

Chapter 2

Competing risks analysis of coronavirus disease 2019 in-hospital mortality in a Northern Italian centre from SMAtteo COvid19 REgistry (SMACORE)

2.1 Introduction

This chapter represents an already published paper remake, where the clinical parts are removed to make place for statistical definitions and results. My role in this paper, published on Scientific Reports (https://doi.org/10.1038/s41598-020-80679-2) in 2021, was to perform entirely the statistical analysis (represented, beyond the descriptive analysis, by the implementation of the Fine and Gray model, defined from a theoretical point of view in section 1.2.1, and the computation of the CIFs for the different risk profiles) and to write anything dealing with statistical concepts. Nevertheless, the discussion is reported as it was, given it was written in 2020.

To the best of my knowledge, this work represented the first attempt to predict in-hospital mortality and the clinical factors associated with it, in covid-19 hospitalized patients. To be honest, at that time we did not know about other papers, published almost at the same time, using a similar approach (the Fine and Gray model) and similar data structure. In the Italian pandemic context, some authors predicted the risk of secondary infection during the time from admission until discharge or death in patients hospitalized at "IRCCS San Raffaele" Hospital [117]. Outside Italy, other authors used a similar approach to analyze in-hospital mortality covid-19 patients in 5 dutch hospitals [101].

Clearly, we could update the In-hospital mortality issue from Covid-19 after 2020, especially in western countries, but it is not of interest.

Since December 2019 SARS COV 2 disease, defined as a pandemic by the World Health Organization (WHO) on 11 March 2020, has spread rapidly all over the world [53]. Outside China, the first western country to be affected was Italy, where the epidemic began on 21 February 2020 and quickly affected thousands of people, practically overwhelming the capacity of the National Health System to respond to it in terms of availability of the hospital, Intensity Care Unity (ICU) beds and Emergency Room (ER) spaces to receive and manage patients[115].

Although Policlinico San Matteo is one of the largest teaching hospitals (1.300 beds) in Lombardy and the Infectious Diseases division managed to more than double its total capacity of regular beds from 44 to 94, in the first 2 weeks it experienced difficult in allocating patients, because clinical criteria to define the evolution of the disease were missing[9].

At the end of 2019, most of the studies that have extensively reported the clinical and laboratory characteristics of patients infected by COVID-19 have been carried out in China[119]. Data on clinical outcomes and treatment of COVID-19 outside China are lacking and the high heterogeneity in observed case-fatality ratios between and within different countries still remains unexplained. Because COVID-19 shows an array of clinical presentations and the lack of effective treatment makes it difficult to predict its outcome, the identification of risk factors for clinical outcomes, such as death, ICU admission and hospital discharge is crucial in order to improve the organisation of healthcare and to identify patients who may benefit the most from the available treatment strategies. Moreover, in such a complex epidemiological and clinical scenario, competing risks might help in the assessment of the impact of treatment strategies on meaningful clinical endpoints, such as in-hospital death and discharge[108].

The aim of this study was to explore and explain, in a cohort of Lombardy patients with COVID-19 in Pavia, Italy, the heterogeneity of clinical outcomes and to identify predictors of in-hospital mortality and discharge by competing risks analysis.

2.2 Data and Methods

SMatteo COvid19 Registry (SMACORE) is a cohort of patients with a confirmed diagnosis of COVID-19 disease referred to the IRCCS Policlinico San Matteo Hospital of Pavia, Italy from February 2020. Te SMACORE database includes demographic, clinical laboratory tests, treatment, and outcome data. This is a single centre, retrospective, observational cohort study and all patients of SMACORE cohort consecutively admitted to the

Infectious Diseases Unit between 22 February and 30 March 2020, with a diagnosis of COVID-19 were enrolled. ICD-9 CM codes were reviewed, and clinical data were further extracted and reviewed by consulting the medical charts. Patients were followed until 21 April 21 2020. Laboratory confirmation of the SARS COV-2 infection was defined as positive Real-Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) from clinical nasal swab. Demographic, clinical, laboratory, treatment, and outcome data were extracted from medical records using a standardised data collection form. The Charlson comorbidity index (CCI) and the modified Elixhauser index (mEi) were used to assess comorbidity[**charlson1987new**, **fabbian2017modified**]. CCI includes 16 comorbidities, predicting 10-year survival in patients with multiple comorbidities and was used as a measure of the total comorbidity burden.

Lymphocitopenia was defined as lymphocyte count< 1.5×109 /L. CRP was considered elevated above 10 mg/dL. LDH levels were considered elevated above 245 U/L.

Treatment data included the use of lopinavir/ritonavir, hydroxychloroquine, corticosteroids, tocilizumab, and antibiotic drugs. Lopinavir/ritonavir 400/100 mg was administered orally twice daily for 14 days. Hydroxychloroquine (HCQ) 600 mg twice on day 1, then 400 mg daily for 7 days.

Corticosteroid treatment consisted of dexamethasone 20 mg daily for 5 days in patients admitted from 22 February to 20 March and methylprednisolone 1 mg/kg intravenously daily for 5 days from 21 March to the end of follow-up. Tocilizumab 8 mg/kg was given intravenously in 1 or 2 doses from 13 March to the end of follow-up. A second dose was given 8–12 h after the first dose in patients with inadequate response.

Antibiotic therapy consisted of a combination of piperacillin/tazobactam and doxycycline. Low (cannula and simple masks) and high (Venturi and reservoir masks, Nasal High Flow (NHF), helmet continuous positive airway pressure (CPAP)) fow oxygen support was provided when hypoxia was detected. Time to ICU admission was defined as the time from hospitalisation to ICU admission.

The primary disease event was in-hospital mortality. Discharge was analysed as a competing event by competing risks analysis. The criteria for discharge were absence of fever, clinical remission of respiratory symptoms, oxygen saturation greater than 94% and two nasal swab samples negative for SARS-CoV-2 RNA obtained at least 24 h apart.

In-hospital mortality and discharge were evaluated by competing risks analysis, using cumulative incidence function (CIF)[108]. The proportional sub-distribution hazard model by Fine and Gray, widely described in section 1.2.1, was fitted in order to estimate the effect of covariates on CIFs in-hospital death and discharge [49], including ICU admission as a time-dependent discrete factor. We investigated the association between other clinical factors and the occurrence of death and discharge during hospitalization

time, in order to define the risks profiles with the respect the two events of interest, to improve the management of the structure under a critical emergency situation, as those caused by the covid-19 pandemic in Lombardy in 2020, and also the treatment of the patients in future.

2.3 Results

2.3.1 Descriptive Analysis

From 22 February to 30 March 2020, 426 confirmed cases of COVID-19 were observed, 292 (68.5%) were males (Table 2.1). The median age was 68 years (IQR, 56 to 77 years) and 197 (45.8%) patients were older than 70 years of age. 269 (63%) patients had at least one comorbidity, with hypertension and diabetes being the most common (140 (33%) and 63 (15%) patients, respectively). The median score on the Charlson comorbidity index (CCI)6 was 3 (IQR, 1 to 4) while the median score of Modifed Elixhauser score (mEI) was 9.2±7.8. Te first nasal swab test for SARS-COV2 was positive in 365 (86%) patients, while 61 (14%) patients had a negative first nasal swab test and positive repeat nasal swab test.

Laboratory findings on admission are reported in Table 2.1. Lymphocytopenia was present in 398 (93.3%) patients, while platelet count was lower than 150,000/mmc in 100 (23.5%) patients. CRP was increased in 188 (44.0%) patients and LDH was elevated in 369 (87.0%) patients.

Chest radiography revealed the presence of interstitial pneumonia in 301 (71.0%) patients. Data on treatments are reported in Table2.2. Antibiotic therapy was started in 304 (85%) of patients. Corticosteroid treatment was administered to 70 (20%) patients and consisted of dexamethasone 20 mg daily in 13 patients and, starting on 21 March 2020, methylprednisolone 1 mg/kg intravenously daily in 57 patients.

Hydroxychloroquine, 600 mg twice on day 1, then 400 mg daily for 7 days, was administered to 249 (70.3%) patients and was initiated within 72 h following admission. 64 (18.1%) patients did not receive any antiviral drug, while 174 (49.1%) patients received antiviral treatment with Lopinavir/ritonavir 400/100 mg twice daily. 22 (5.2%) patients received Tocilizumab 8 mg/kg from 13 March 2020.

On 21 April 2020, 141 (33.1%) patients died. The median time from symptoms onset to death and from hospitalisation to death was 11 days (IQR 3–19) and 6 days (IQR 3–11), respectively. 41 (9.6%) patients had been transferred to ICU. The median time from hospitalisation to ICU admission was 4 days (IQR 2–6). 239 (56%) patients had been discharged and 46 (10.7%) patients were still hospitalised (17 of whom were still in ICU). Median time from hospitalisation to discharge was 10 days (IQR 5–18).

TABLE 2.1: Demographic, clinical and laboratory characteristic of patients on admission. Data are expressed as median (interquartile range) or n (%). P-values are calculated on the basis of two sample T-test for categorical variables and Wilcoxon test for continous variables at a 0.05 significance level.

	Overall (n=426)	Death (n=141)	Survivor (n=285)	p-value
Age (years)	68(56-77)	77(71-83)	61(50-72)	<0.001
<50	72(16.9%)	1(0.7%)	71(24.9%)	<0.001
50-59	64(15%)	8(5.7%)	56(19.6%)	0.003
60-69	95(22.3%)	21(14.9%)	74(25.9%)	0.014
70-79	125(29.3%)	66(46.8%)	59(20.7%)	<0.001
>80	70(16.4%)	45(31.9%)	25(8.8%)	<0.001
Male sex	292(68.5%)	103(73%)	189(66.3%)	0.194
Comorbidity	269(63.1%)	116(82.2%)	153(53.7%)	<0.001
Hypertension	140(32.8%)	52(36.8%)	88(30.9%)	0.256
Diabetes	63(14.8%)	28(19.9%)	35(12.3%)	0.074
Atrial fibrillation	37(8.7%)	21(14.9%)	16(5.6%)	0.002
Coronary heart disease	36(8.5%)	25(17.7%)	11(3.9%)	<0.001
Obesity	26(6.1%)	10(7.1%)	16(5.6%)	0.636
Chronic kindey disease	25(5.9%)	16(11.3%)	9(3.2%)	<0.001
Chronic heart failure	21(4.9%)	12(8.5%)	9(3.2%)	0.027
Chronic liver disease	21(4.9%)	11(7.8%)	10(3.5%)	0.085
Chronic obstructive lung disease	20(4.7%)	9(6.4%)	11(3.9%)	0.342
History of malignancy	18(4.2%)	4(2.8%)	14(14.9%)	0.467
Active malignancy	16(3.8%)	8(5.7%)	8(2.8%)	0.182
Dementia	12(2.8%)	9(6.3%)	3(1.1%)	0.005
Charlson comorbidity index	3(1-4)	4(3-5)	2(1-3)	<0.001
Modified Elixhauser index	9.2±7.8	15±7.9	6.4±5.9	<0.001
Number of comorbidities				<0.001
0	155(36.3%)	25(17.7%)	130(45.6%)	
1	145(34%)	52(36.9%)	93(32.6%)	
2	73(17.1%)	34(24.1%)	39(13.7%)	
>3	53(12.4%)	31(22%)	22(7.7%)	
Median time from symptoms onset to Hospitalization	7(3-10)	6(3-8)	8(4-11)	0.037
Time of hospital admission				0.025
From February. 21 to March. 3	137(32.2%)	36(25.5%)	101(35.4%)	
From March. 4 to March. 16	165(38.7%)	67(40.6%)	98(34.3%)	
From March. 17 to March. 30	124 (29.1%)	38(27%)	86(30.2%)	
Glutamuc oxaloacetic transaminase. U/L	41(28-64)	44(29-70)	40(27-57)	0.117
Glutamic pyruvic transaminase U/L	32(21-48)	34(23-53)	31(21-44)	0.258
C-reactive protein. mg/dL	8.23 (4.14-14.75)	10.4(5.85-15)	7.64(3.62-14.54)	0.008
C-reactive protein $> 10^9$ mg/dL	188(44.1%)	83(58.9%)	105(36.8%)	<0.001
Creatinine. mg/dL	0.89(0.72-1.11)	0.90(0.75-1.16)	0.87(0.71-1.09)	0.132
Lactate dehydrogenase. U/L	365 (304-446)	380(325-455)	365(294-446)	0.075
Lactate dehydrogenase>245. U/L	369(86.6%)	129(91.5%)	240(84.2%)	0.054
Troponine. ng/L	26(10-108)	21(10-55)	37(11-119)	0.103
White cell blood count. x $> 10^9$ per L	6.73(5.18-9.15)	7.02(4.95-8.9)	6.65(5.35-9.3)	0.423
Lymphocyte count. x $> 10^9$ per L	0.8(0.6-1)	0.74(0.6-0.97)	0.8(0.6-1.01)	0.087
Lymphocyte count< 1.5 x $> 10^9$ per L	398(93.3%)	135(95.7%)	263(92.3%)	0.25
Neutrophil count. x $> 10^9$ per L	5.27(3.9-7.72)	5.5(3.61-7.68)	5.2(3.94-7.75)	0.455
Platelet count. x $> 10^9$ per L	204(152-287)	201(144-263)	207(154-296)	0.184
Platelet count <150 x $> 10^9$ per L	100 (23.5%)	39(27.7%)	61(21.4%)	0.236
Pneumonia at chest X-ray	301(70.7%)	130(92.2%)	171(60%)	<0.001

TABLE 2.2: Treatments and outcomes of patients. Data are expressed as median (interquartile range) or n (%).

	N=426
Treatments	
Lopinavir/ritonavir	174/354 (49.1%)
Hydroxychloroquine	249/354 (70.3%)
Corticosteroids	70/349(20%)
Antibiotics	304/358 (84.9%)
Tocilizumab	22(5.2%)
Outcomes	
Death	141 (33.1%)
Median time from symptoms to death (days)	11(3-19)
Median time from hospitalization to death (days)	6 (3-11)
Admission to ICU	41 (9.6%)
Median time from symptoms to ICU admission (days)	11 (8-13)
Median time from hospitalization to ICU admission (days)	4 (2-6)
Discharge	239(56.1%)
Median time from symptoms to discharge (days)	19 (9-24)
Median time from hospitalization to discharge (days)	10 (5-16)
Respiratory failure	245 (57.5%)
Acute kidney injury	26 (6.1%)
Acute caridac injury	14 (3.3%)
Thromboembolic events	7 (1.6%)

The outcomes of patients who were still hospitalised have been updated as of 30 May, 2020: among these 46 patients, 5 (10.9%) had died, 8 (17.4%) were still in ICU, 12 (26.1%) were transferred to lower intensity care units and 21 (45.7%) were discharged.

Patients who died were older, had higher CCI and higher mEI score, higher CRP and LDH levels and lower lymphocyte count compared to survivor patients (Table 2.1).

Hydroxychloroquine and antibiotics were used more frequently in patients who died compared to those who did not. The frequency of complications, such as respiratory failure, acute kidney injury, acute cardiac injury and septic shock was significantly higher in patients who died as compared to survivors. (Table 2.3). Area Under the Curve (AUC) for in-hospital mortality prediction was 0.80 (0.75–0.83) for CCI and 0.81 (0.76–0.85) for mEI (p-value for comparison=0.468).

TABLE 2.3: Treatments and outcomes of patients stratified according to death.

	Death (n=141)	Survivor (n=285)	p-value
Treatments			
Lopinavir/ritonavir	66/119(55.5%)	108/235(46%)	0.115
Hydroxychloroquine	92/119(77.3%)	157/232(67.7%)	0.079
Corticosteroids	21/119(17.6%)	49/230(21.3%)	0.504
Antibiotics	109/120(90.8%)	195/238(81.9%)	0.039
Tocilizumab	8(5.7%)	14(4.9%)	0.919
Outcomes			
Admission to ICU	22(15.6%)	19(6.7%)	0.006
Median time (days) from hospitalization to ICU admission	4(2-6)	3(2-6)	0.854
Respiratory Failure	119(84.4%)	126(44.2%)	<0.001
Acute kidney injury	20(14.2%)	6(2.1%)	<0.001
Acute cardiac injury	11(7.8%)	3(1%)	0.007
Septic Shock	7(4.9%)	0(0)	0.007
Thromboembolic events	2(1.4%)	5(1.8%)	0.882

2.3.2 Competing risks analysis results

The CIF for in-hospital mortality is shown in Figure 2.1. The estimated probability of in-hospital death was 24.4% during the first 10 days from hospitalization, 31.0% during the first 20 days and 33.7% at the end of follow-up. Using the Fine and Gray model-to-model mortality, older age (70–79 years: HR 4.42, 95% CI 2.59–7.39, $p < 0.001$. Over 79 years: HR 7.75, 95% CI 4.39–13.74, p<0.001), male sex (HR 1.85, 95%CI 1.22–2.89, p=0.003), number of comorbidities higher than 3 (HR 3.63, $p = 0.03$), and time of hospital admission (between 4 and 16 March: HR 2.32, 95%CI 1.45–3.71, p=0.001; between 17 and 30 March: HR 1.68, 95%CI 1.03–2.75, p=0.04) were independently associated with higher in-hospital

mortality, while time to ICU admission longer than 7 days (HR 0.19, 95%CI 0.05–0.67, p = 0.01) were independently associated with lower in-hospital mortality (Table 2.4). The CIFs for in-hospital mortality performed using the parameter estimates of the Fine and Gray model for each of these covariates are shown in Appendix A.

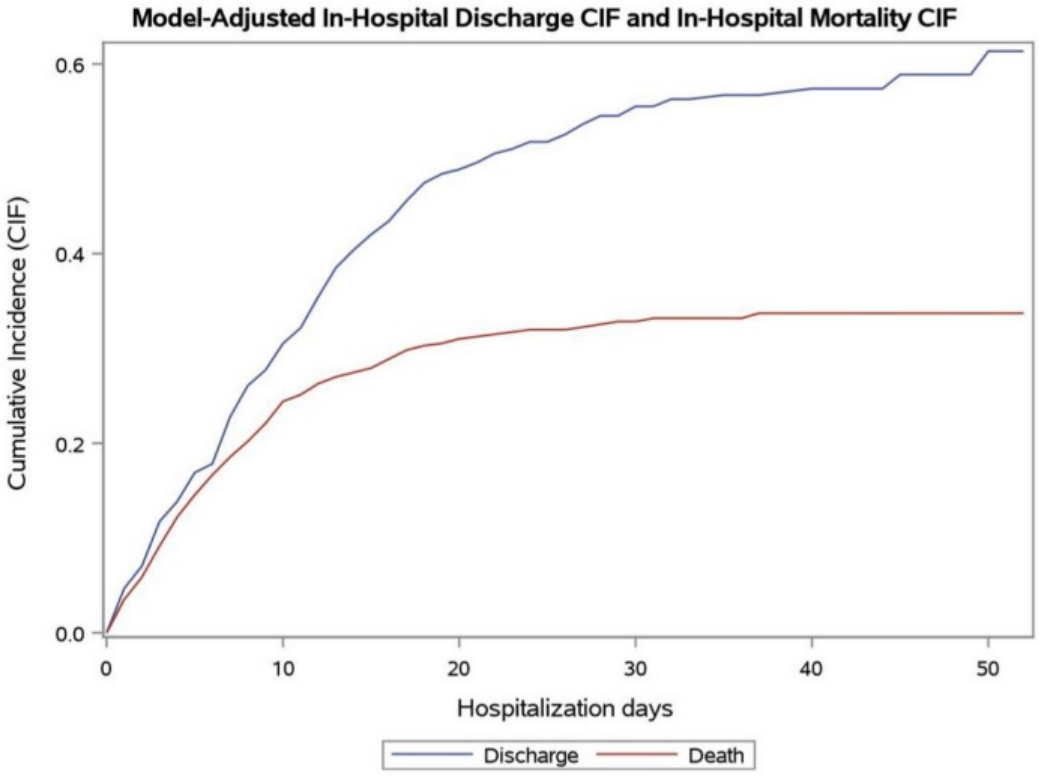
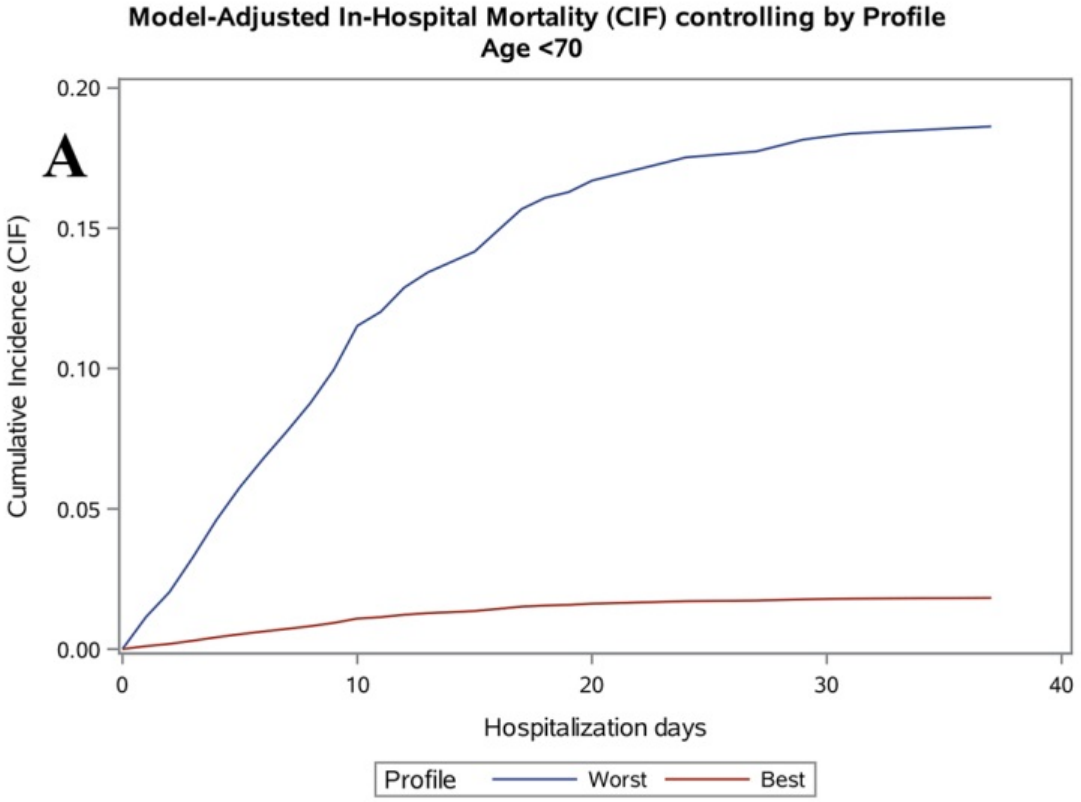
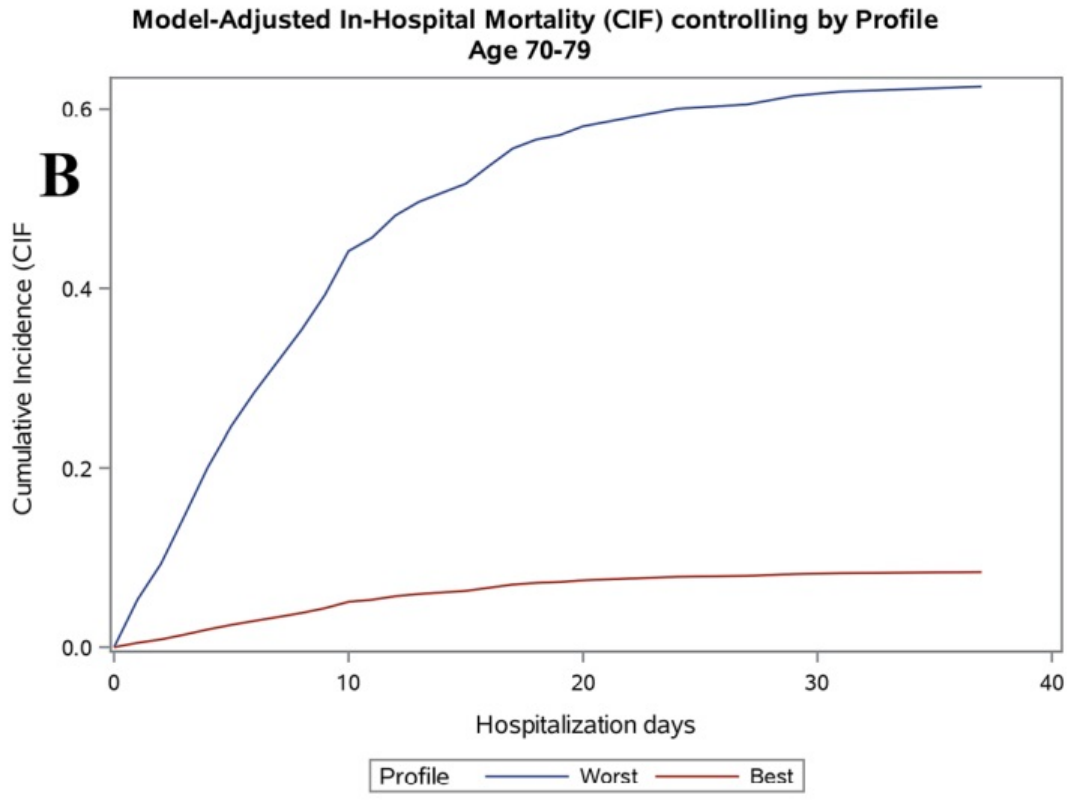


FIGURE 2.1: Cumulative incidence functions for in-hospital mortality and discharge of patients with Coronavirus Disease-19.

These risk factors were then used to construct a model encompassing all patients grouped into a "best" and a "worst" class according to the presence or not of these factors. CIFs for the best class (female patients with less than 3 comorbidities, admitted between February, 21 and March, 3) and for the worst class (male patients with more than 3 comorbidities, hospitalized between 4 and 16 March) stratified by age group are showed in Figure 1.2.

At the end of follow-up, the probability of in-hospital death in patients younger than 70 years was 1.8% in the best class and 18.6% in the worst class. In patients with 70–79 years, the probability of in-hospital death at the end of follow-up was 8.3% in the best class and 62.5% in the worst class. In patients older than 80 years, the probability of in-hospital death at the end of follow-up was 13.7% in the best class and 80.8% in the worst


Model-Adjusted In-Hospital Mortality (CIF) controlling by Profile
Age <70
A
Cumulative Incidence (CIF)
0.20
0.15
0.10
0.05
0.00
0
10
20
30
40
Hospitalization days
Profile
Worst
Best


Model-Adjusted In-Hospital Mortality (CIF) controlling by Profile
Age 70-79
B
Cumulative Incidence (CIF
0.6
0.4
0.2
0.0
0
10
20
30
40
Hospitalization days
Profile
Worst
Best

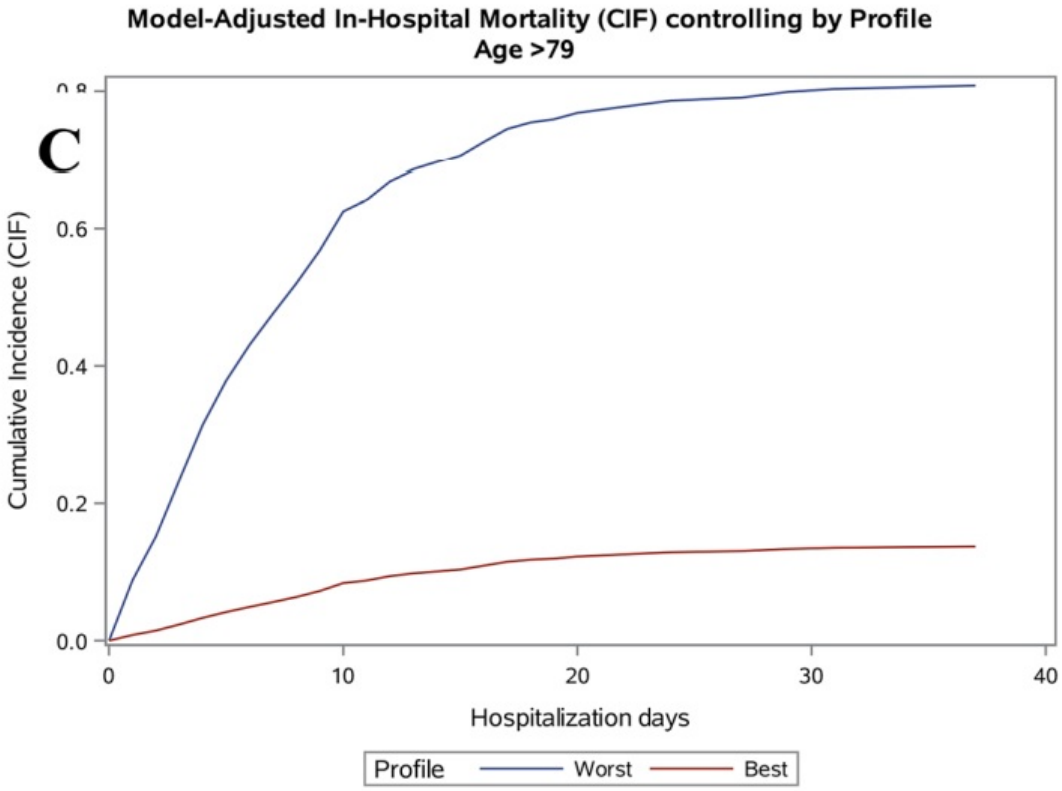


FIGURE 2.2: Cumulative incidence functions for in-hospital mortality performed using the parameter estimates of the Fine and Gray model and considering the best patient profile (female sex, number of comorbidities lower than 3 admitted between 21 February to 3 March 2020) and the worst patient profile (male sex, number of comorbidities higher than 3, admitted between 4 and 16 March 2020) according to age groups. (A) Age lower than 70 years. (B) Age between 70 and 79 years. (C) Age higher than 79 years.

class.

The CIF for discharge is showed in Fig. 1. The estimated probability of discharge was 30.5% during the first 10 days from hospitalization, 48.8% during the first 20 days and 61.4% at the end of follow-up Tocilizumab use was significantly associated with a lower probability to be discharged at univariate analysis, however it was not included in the multivariate model because only 22 patients received Tocilizumab.

Using the Fine and Gray model, we observed that lymphocytes count (HR 1.13, 95% CI 1.06–1.19, p=0.001) was independently associated with higher probability to be discharged, while older age (70–79 years: HR 0.39, 95%CI 0.27–0.55, p<0.001. Over 79 years: HR 0.27, 95% CI 0.16–0.44 p<0.001), number of comorbidities higher than 3 (HR 0.08, p<0.001), and time of hospital admission (between March, 4 and March, 16: HR 0.66, 95% CI 0.47–0.92, p=0.02; between 17 and 30 March: HR 0.68, 95%CI 0.50–0.93, p=0.02) were independently associated with lower probability to be discharged. (Table 2.4). The CIFs for discharge performed using the parameter estimates of the Fine and Gray model for each of these covariates are showed in Figures S5–S9.

The CIFs for the best class and for the worst class according to age are showed in Figures S10–S12. At the end of follow-up, the probability of discharge in patients younger than 70 years was 99.5% in the best class and 31.5in the worst class. In patients with 70–79 years, the probability of discharge at the end of follow-up was 84.6% in the best class and 12.6% in the worst class. In patients older than 80 years, the probability of discharge at the end of follow-up was 75.3% in the best class and 9.6% in the worst class.

TABLE 2.4: Competing risk analysis by Fine and Gray model for in-hospital mortality and discharge. *Three comorbidities or more versus no comorbidities. Hazard ratio was 2.36 for two comorbidities versus no comorbidities and 1.54 for one comorbidity versus no comorbidity. **Tree comorbidities or more versus no comorbidities. Hazard ratio was 0.19 for two comorbidities versus no comorbidities and 0.44 for one comorbidity versus no comorbidity

	Fine and Gray model							
	In-hospital mortality				Discharge			
	Beta	Standard error	Hazard ratio	P-value	Beta	Standard error	Hazard ratio	P-value
Age 70-79	1.49	0.27	4.42	<0.001	-0.95	0.19	0.39	<0.001
Age >80 years	2.05	0.29	7.75	<0.001	-1.31	0.25	0.27	<0.001
Male sex	0.64	0.22	1.89	0.003	-0.66	0.14	0.52	<0.001
Number of comorbidities	0.52	0.25	3.63	0.038	-0.62	0.21	0.08	0.003
Admission between March. 4 and March. 16	0.84	0.23	2.32	0.001	-0.42	0.17	0.66	0.015
Admission between March. 17 and March. 30	0.52	0.25	1.68	0.048	-0.39	0.16	0.68	0.017
Lymphocyte count. count x 10^9 per L	-0.22	0.22	0.8	0.316	0.12	0.03	1.13	0.001
Hydroxycloroquine	-0.13	0.27	0.88	0.639	-0.27	0.16	0.76	0.76
No ICU admission	0.34	0.45	1.41	0.449				
Time to ICU admission lower than 3 days					-0.61	0.32	0.54	0.056
Time to ICU admission between 4 and 6 days	-0.61	0.63	0.54	0.33	-0.02	0.27	0.98	0.955
Time to ICU admission > 7 days	-1.67	0.65	0.19	0.01	-0.01	0.01	0.99	0.996

2.4 Discussion

This report, is the first large retrospective study assessing competing risks in hospitalised patients with confirmed COVID-19 in Europe. Older age, male sex, comorbidities and hospital admission subsequent to March, 4 were significantly associated with a higher in-hospital death, by competing risk multivariate analysis.

When comparing our cohort with those described in the literature we noted that mortality was higher than that observed in other studies both in and outside China[165, 145, 124]. The median age in our cohort was 68 years and 77 years in patients who died, which is higher than that observed in other studies. In-hospital mortality assessed by competing risks analysis was significantly higher in patients aged between 70 and 79 years and in those over 79, compared with patients younger than 70 years. By contrast, the probability of discharge was similar between patients of 70–79 years and those older than 79 years. The association between age and in-hospital mortality could be explained by the lower cardiopulmonary reserve, by the enhanced susceptibility to infections and by the inadequate control of anti-inflammatory mechanisms.

In our cohort, the median Charlson comorbidity index was 3 and modifed Elixhauser Index was 9.2. While the prevalence of comorbidities in our cohort was similar to that reported in the USA[124], it was higher than that observed in Chinese cohorts[165]. Our results are in line with those of the Italian National Institute of Health, showing that approximately 61% of deceased Italian patients with COVID-19 had more than 3 comorbidities, while only 3.6% of patients who died had no comorbidity[54]. It is well known that COVID-19 patients with comorbidities are at high risk to develop a worst outcome.

Several meta-analyses shown that comorbidities (specifically hypertension, respiratory system disease, cardiovascular disease, and chronic kidney disease) are associated with a higher risk of development of severe COVID-19[163, 156, 48]. Different comorbidity scores have been evaluated in COVID-19 patients, such as CCI[124] and mEI score[41]. Our analysis showed that these two scores had a similar accuracy by AUC for the prediction of in-hospital death.

Male sex was an independent risk factor for in-hospital mortality and a lower probability of discharge. The association between gender and worst outcomes in COVID-19 is not fully understood. It has been proposed that female sex could be associated with lower susceptibility to viral infections, with sex hormones playing a relevant role in innate and adaptive immune response[73]. A different expression of ACE 2 receptor has also been suggested as an explanation of the gender-associated mortality in COVID-19 patients[27]. Conversely, it has been suggested that males could be more prone to being

affected by COVID-19 due to the higher smoking rate and higher prevalence of cardiovascular comorbidities[25]. However, our multivariate model suggested that sex was an independent predictor of mortality, and discharge regardless of comorbidities and evidence supporting smoking as a predisposing factor in men with COVID-19 are lacking. Unfortunately, we were unable to evaluate the association between smoking and clinical outcomes in COVID-19.

Patients who were admitted during the first weeks of the emergency had a significantly lower in-hospital mortality and a higher likelihood of discharge compared to those who were admitted during subsequent weeks, with the worst outcomes observed from 4 to 16 March 2020. One factor that many reports have addressed is the sequence of phases into which the disease has been divided, each corresponding to a different pattern of viral and immunological factors. Patient presentation in late phase may also have occurred, leading to the admission of an exceptionally large number of patients who needed hospitalisation in a short time span, resulting in a critical overload in the Policlinico San Matteo, in both triage and the management of the disease. These findings may be explained by also taking into consideration that during the first week many admissions were made for epidemiological reasons, leading to the hospitalisation of patients with few symptoms or mild disease.

Although ICU admission after 7 days from hospitalisation was independently and significantly associated with a lower risk of in-hospital mortality, the rapidity with which patients entered the ICU often concurrently with initiating other treatments makes the benefit of this treatment difficult to assess. Moreover, results from observational studies of drug effects should be interpreted with caution as they may be biased by survivor treatment selection bias, including time-related biases[136, 57].

In the literature, the use of composite endpoints (i.e. death or ICU admission) and, on the other hand, the implementation of traditional survival and Cox models are not appropriate in a disaster medicine setting such as that of COVID-19. The first assumption considers ICU and death to be equal, which is not true, while the traditional Cox model neglects to model discharge as an alternative endpoint. Competing risks analysis may provide further insights into the effect of interventions on the separate endpoint components [153]. We overcame this issue by performing a competing risks analysis taking into account two events (in-hospital death and discharge) and including ICU admission as a time-dependent covariate [109]. We suggest the use of a standardised methodology to assess treatment effects in observational studies in the complex clinical scenario of COVID-19. It should be underlined that COVID-19 case fatality ratio requires a dynamic assessment[72] and that it decreased dramatically in Italy during the months that followed our study. This could be due to the improvements of the supportive treatments, as

well as the general organization and bed occupancy. The competing risks model adopted is able to recognize effective and noneffective predictors, as, for instance, our model excluded treatments since the very beginning. Nevertheless, we are aware that unknown risk factors are still incumbent in all the statistical analyses conducted till now, so frailty survival models can be applied in order to capture the eventual and unknown source of variability.

The main limitation of our study is the retrospective design. Retrospective studies have many problems that reduce their internal and external validity. When assessing retrospective cohort studies, the most important bias is the likelihood of the inappropriate selection of patients, which can lead to incorrect results and spurious associations. However, we included only consecutive patients with confirmed COVID-19, therefore we believe that selection bias was not relevant. Moreover, some potential confounders associated with the severity of COVID-19 (i.e. P/F ratio or circulating cytokine levels) and not available for this modeling, could affect our results. Thus, we performed multivariate competing risks analysis to overcome this issue. Other limitations are the generalisability of our results to different populations and settings, particularly regarding the demographic structure of our country, including European elderly patients with a high prevalence of comorbidities. Finally, mortality was limited to in-hospital death, and discharged patients were assumed to still be alive during the study period.

2.5 Conclusion

The findings indicate that in a Lombardy cohort of elderly hospitalized patients, for the most part male with a high prevalence of comorbidities, COVID-19 is characterized by high in-hospital mortality. Older age, male sex, comorbidities and time of admission were found to be significant risk factors for in-hospital mortality and associated with a lower probability of being discharged.

The dataset included data coming from a single northern Italian centre, which can avoid the possibility to generalize the findings by performing an external validation in presence of competing risks. To do that, data coming from other centers, inside and outside Lombardy, are needed.

The urgency to create novel therapeutic approaches (in a context where the vaccines were not available yet) brought on by the global COVID-19 illness outbreak was unprecedented, and the "rush to COVID-19" provided controversial findings. We, therefore, decided to provide a statistical model in which treatments, in particular hydroxychloroquine, are included even though not associated significantly with any event of interest. This work was also one of the first to assess the ineffectiveness of hydroxychloroquine to

improve from covid-19 survival, at least in this cohort, in contrast to what some authors stated in some prestigious journal [8]. The most important findings, in terms of treatment effectiveness, are related to the protective effect of RAASi [31].

Even if the statistical methodology can be still valid in future, this findings cannot be considered at all with more recent data, and, thanks to the introduction of vaccination, either in Italy and all over the world, in-hospital mortality faced a huge decrease after the first wave. [19]

Chapter 3

Predicting in-hospital mortality from Coronavirus Disease 2019: A simple validated app for clinical use

3.1 Introduction

This chapter is based on a published paper and can be considered as a consecutive work that extends the work in chapter 2. My role in this paper, published on PLOS ONE (https://doi.org/10.1371/journal.pone.0245281) in 2021, was to perform entirely the statistical analysis, by the imputation of missing data through the *hot deck* procedure, the implementation of the Fine and Gray model, defined from a theoretical point of view in section **??**, the computation of the CIFs for the different risk profiles, the validation of the model using an external cohort, the building of the shiny app, helpful for clinicians to predict in-hospital mortality by inserting clinical factor obtainable immediately after the patients came to the hospital, and the definition of any statistical concept or quantity. As in chapter 2, the discussion is reported as it was written dating back to 2020.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in China in December 2019 and has since spread rapidly all over the world [53]. Outside China, Italy was the first western country to be involved and the first case was diagnosed on February, 21. During the initial weeks of the pandemic, the rapid increase in cases overwhelmed the capacity of the National Health System to receive and manage patients and to respond in terms of availability of health resources[115].

In the context of triaging patients in emergency departments or in special clinics set up during an acute outbreak, the lack of clinical criteria to identify the most severe cases and to define the evolution of the disease has made the management of the pandemic even more difficult.

A risk stratification of COVID-19 patients is crucial in order to improve the health-care organization and to best manage a new potential second wave of the epidemic in the coming winter. In this complex epidemiological and clinical scenario, a competing risks model is a robust statistical method to predict patients risk profile when more than one competing event, such as in-hospital mortality and discharge, is present [108]. The aims of this retrospective multicenter study are 1) to derive a simple clinical prediction rule capable of promptly identifying risk factors for in-hospital mortality and discharge in hospitalized patients with COVID-19 by competing risks analysis; 2) to validate this prediction rule in an external validation cohort; 3)to design a free web-app for calculating the risk of in-hospital mortality (COVID-CALC).

3.2 Data structure and Methods

We analyzed an integrated database that contained clinical, laboratory and treatment data from all hospitalized patients with a diagnosis of COVID-19 at three Italian referral tertiary centers, two in Lombardy (the "eye of the SARS-COV-2 storm" in Italy) (Bergamo and Pavia) and one in Lazio (Rome): 1) Hospital Papa Giovanni XXIII, Bergamo, Lombardy; 2) Fondazione IRCCS Policlinico San Matteo, Pavia, Lombardy; 3) Fondazione Policlinico Univerisitario A. Gemelli IRCCS, Rome, Lazio. All consecutive patients admitted between February 22*nd* and April 7*th*, 2020 were enrolled and were followed up until April 30*th*, 2020. Information on the history and physical examination of hospitalized patients with COVID-19 were abstracted from chart reviews by medical officers at each hospital. Variables collected through standardized recording forms included age, sex, comorbidities, smoking status, time of symptoms onset and time of hospital admission. Additional variables were the presence of fever (defined as axillary temperature of at least 37.5C), dyspnea, cough, and diarrhea.

Laboratory confirmation of the SARS COV-2 infection was defined as positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) from nasal and pharyngeal swab; samples were prospectively collected and analyzed at the Molecular Virology Units of each center according to the WHO guidelines and Corman et al. protocols[37, 35].

The primary event was in-hospital mortality. Discharge was analyzed as a competing event in the competing risks survival analysis. The competing risks model proposed by Fine and Gray was applied[49]. The criteria for discharge were absence of fever, resolution of respiratory symptoms, oxygen saturation higher than 94% and two consecutive nasal swab negative for SARS-CoV-2 obtained at least 24 hours apart.

As we did in chapter 2, the Fine and Gray model (see section 1.2.1 for the model description) was chosen to determine the association between covariates and the CIFs in-hospital mortality with discharge considered as competing event. [49]. Competing risks analyses were performed in SAS version 9.4. Hot-deck missing imputation data and the assessment of discrimination and calibration and were performed in R Core Team (2019). The hot deck procedure was performed in the derivation cohort for those variables with less than 20% missing data. Variables with more than 20% missings were not considered to be included in the Fine and Gray model. We used the *hot.deck* function from hot.deck library in R 3.8.0

Risk factors for in-hospital mortality and discharge identified by competing risks multivariate analysis in the derivation set were used to generate a prediction rule. The probability of dying or of being discharged within 40 days after hospital admission was computed for a hypothetical patient identified by a combination of prognostic factors. The prediction accuracy of the fitted models was assessed by discrimination and calibration both in the derivation (internal validation) and validation cohorts (external validation)[162]. Discrimination of the models was assessed by the area under the receiver operating characteristic curve (AUC or C-index)[129].

Calibration was evaluated by comparing the predicted probability with the observed probability at a certain time point by a calibration plot. Finally, the Brier score, which takes into account both the discrimination and the calibration at the same time, was also calculated. It is defined as the expected squared distance between the observed status at that time and the predicted probability[55]. Thus, a smaller value of the Brier score indicates a better model. To assess the internal validity of the prediction rule, the derivation set was randomly split into a training set (70%) and a test set (30%)[44]. The external validation of the prediction rule was carried out with data from an external validation cohort, represented by the Rome unit, in terms of discrimination, calibration and the Brier score. The prediction rule has been translated into a web-app that is freely available to the public (COVID-CALC: `https://sites.google.com/community.unipa.it/covid-19riskpredictions/c19-rp`).

3.3 Results

From February 22nd to April 7th, 2020, a total of 2191 consecutive confirmed cases of COVID-19 were observed.

Baseline characteristics of patients stratified according to derivation (n = 1810) and validation cohort (n = 381) are shown in Table 3.1. Median age was 67 years (IQR, 56–77 years) and 45% of patients were 70 years or older. Sixty-nine percent of patients were

male. In 27.5% of patients, at least one comorbidity was present, with hypertension and diabetes being the most common (43% and 17% of patients, respectively). Median time from symptoms onset to hospital admission was 8 days (IQR 5–11 days). At hospital admission, fever was present in 85%, dyspnoea in 56% and cough in 44% of patients. Lymphocyte count lower than 1000/mmc was observed in 77% of the patients, and platelet count was lower than 150000/mmc in 37.5% of patients. CRP was increased in 83% of patients, and LDH resulted elevated in 88% of patients.

In the derivation cohort, male sex, hypertension and obesity were significantly more frequent and the prevalence of chronic kidney disease, chronic obstructive lung disease and malignancies was significantly lower in comparison with the validation set. Patients in the derivation set had higher median GPT, CRP, LDH, and D-dimer levels, higher lymphocyte count and lower P/F ratio, in comparison with patients in the validation set.

Data on treatments and outcomes according to derivation and validation cohorts are reported in Table 3.2. Corticosteroid treatment was administered to 129 patients (11%. Data available in 1164 patients). Enoxaparin was given to 254 patients (21%. Data available in 1218 patients). Hydroxychloroquine was administered to 931 patients (80%. Data available in 1163 patients). Seven-hundred seventy-nine patients (49%) received antiviral treatment with Lopinavir-ritonavir and 242 with Darunavir-ritonavir (15%) (Data available in 1593 patients). Tocilizumab was administered in 112 patients (9%) and Sarilumab in 51 patients (13%) (Data available in 1233 patients). One-hundred sixty-four patients (9%) received non-invasive ventilation (Data available in 1765 patients).

TABLE 3.1: Demographic, clinical and laboratory characteristics of patients with Coronavirus Disease-19 on hospital admission in the derivation and the validations cohorts. P-values are calculated on the basis of two sample T-test for categorical variables and Wilcoxon test for continous variables at a 0.05 significance level.

	Overall (n = 2191)	Derivation cohort (n = 1810)	Validation cohort (n = 381)	p-value
Age (years)	67 (56–77)	67 (55–78)	68 (57–77)	0.960
<50	293 (13.4%)	239 (13.2%)	54 (14.2%)	
50–59	394 (18.0%)	312 (17.2%)	82 (21.5%)	
60–69	511 (23.3%)	437 (24.1%)	74 (19.4%)	
70–79	594 (27.1%)	510 (28.2%)	84 (22.0%)	
>80	399 (18.2%)	312 (17.2%)	87 (22.8%)	
Male sex	1521 (69.4%)	1280 (70.7%)	241 (63.3%)	0.006
Median duration of symptoms before hospital admission	8 (5–11)	8(2–10)	7(5–11)	<0.001
Duration of symptoms before hospital admission shorter than 10 days	1473 (67.2%)	1193 (65.9%)	280 (73.5%)	0.004
Fever	1866 (85.2%)	1495 (82.6%)	371 (97.4%)	<0.001
Dyspnea	1235 (56.4%)	1070 (59.1%)	165 (43.3%)	<0.001
Cough	969 (44.2%)	742 (41.0%)	227 (59.5%)	<0.001
Diarrhea	164 (7.5%)	127 (7.0%)	37 (9.7%)	0.810
Number of comorbidities				0.250
0	1506 (71.4%)	1233 (71.3%)	273 (71.7%)	
1	446 (21.1%)	372 (21.5%)	74 (19.4%)	
2	157 (7.4%)	123 (7.1%)	34 (8.9%)	
Comorbidity				
Hypertension	952 (43.4%)	825 (45.6%)	127 (33.3%)	<0.001
Diabetes	372 (17.0%)	311 (17.1%)	61 (16.0%)	0.370
Obesity	320 (14.6%)	265 (14.6%)	54 (14.1%)	0.014
Coronary Heart Disease	209 (9.5%)	159 (8.8%)	43 (11.2%)	0.230
Chronic kidney disease	164 (7.5%)	124 (6.8%)	40 (10.5%)	0.047
Chronic obstructive lung disease	148 (6.8%)	102 (5.6%)	46 (12.1%)	0.001
Malignancy	98 (4.5%)	66 (3.6%)	32 (8.4%)	0.002
Chronic Liver disease	45 (2.0%)	42 (2.3%)	3 (0.7%)	0.005
Current smoker	87 (4.0%)	63 (3.5%)	24 (6.3%)	0.011
Glutamic pyruvic transaminase, U/L	54(108.61)	57(120.05)	44(57.04)	0.003
C-reactive protein, mg/dL	11.5 (10.01)	11.9 (10.33)	10.1 (8.68)	0.001
C-reactive protein>10 mg/dL	1438/1733 (83.0%)	1145/1359 (84.3%)	293/374 (78.3%)	0.100
Lactate dehydrogenase, U/L	441 (323)	462 (343)	343 (173)	<0.001
Lactate dehydrogenase>250 U/L	1931 (88.1%)	1648 (91.0%)	273 (71.7%)	0.007
Creatine kinase, U/L	875 (2288)	2834 (3850)	198 (403)	<0.001
D-dimer, U/L	7680 (26055)	10059 (13667)	5835 (32479)	0.049
9White Cell Blood Count, $\times 10^9$ per L	7.82 (5.93)	7.94 (4.66)	7.42 (8.94)	0.270
Lymphocyte Count, $\times 10^9$ per L	1.04 (1.84)	1.12 (2.14)	0.86(0.52)	0.001
Lymphocyte Count<1.0 $\times 10^9$ per L	1678 (76.6%)	1484 (82.0%)	194 (50.9%)	<0.001
Platelet Count, $\times 10^9$ per L	142 (98)	141 (97)	146 (100)	0.410
Platelet Count < 150 $\times 10^9$ per L	823 (37.5%)	675 (37.3%)	148 (38.8%)	0.480
P/F ratio	238 (117)	203(116)	406 (68)	<0.001

TABLE 3.2: Treatments and outcomes of patients with Coronavirus Disease-19 in the derivation and the validation cohorts.

	Overall (n = 2191)	Derivation cohort (n = 1810)	Validation cohort (n = 381)	p-value
Treatments				
Corticosteroids	129/1164 (11.1%)	112/783 (14.3%)	17 (4.5%)	<0,001
Dexamethasone	69/129 (53.5%)	60/112 (53.6%)	9 (52.9%)	0.99
Methylprednisolone	60/129 (46.5%)	52/112 (46.5%)	8 (47.1%)	0.999
Enoxaparin	254/1218 (20.9%)	67/837 (8.0%)	187 (49.1%)	<0,001
Hydroxychloroquine	931/1163 (80.0%)	577/784 (73.6%)	354 (92.9%)	<0,001
Lopinavir-ritonavir	779/1593 (48.9%)	670/1212 (55.3%)	109 (28.6%)	<0,001
Darunavir-ritonavir	242/1593 (15.2%)	0/1212 (0)	242 (63.5%)	-
Tocilizumab	112/1233 (9.1%)	31/852 (3.6%)	81 (21.3%)	<0,001
Sarilumab	51/1233 (4.1%)	0/852 (0)	51 (13.4%)	-
Non-invasive ventilation	164/1765 (9.2%)	108/1384 (7.8%)	56 (14.7%)	0,001
Outcomes				
Death	540 (24.6%)	495 (27.3%)	45 (11.8%)	<0,001
Median time from symptoms onset to death (days)	13 (9–19)	13 (9–18)	12 (7–21)	0,6
Median time from hospital admission to death (days)	5 (3–10)	5 (3–9)	8 (5–15)	0,003
Admission to ICU	302 (13.8%)	242 (13.4%)	60 (15.7%)	0,308
Median time from symptoms onset to ICU admission (days)	11 (8–16)	11 (8–16)	18 (7–14)	0,71
Median time from hospital admission to ICU admission (days)	3.5 (1–6)	3.5 (1–6)	3.5 (1–6)	
Discharge	1358 (62.0%)	1057 (58.4%)	301 (79%)	<0,001
Median time from symptoms onset to discharge (days)	19 (14–26)	19 (13–25)	21 (16–27)	0,01
Median time from hospital admission to discharge (days)	10 (6–16)	8 (5–15)	14 (10–16)	<0,001

3.4 Clinical Outcomes

At the end of follow-up, 540 patients had died (24.6%), 302 (13.7%) had been transferred to ICU, 1358 patients (62.0%) had been discharged and 258 were still hospitalized. Median time from symptoms onset to death and from hospital admission to death were 13 days (IQR 9–19) and 5 days (IQR 3–10), respectively. Median time from hospital admission to ICU admission was 3.5 days (IQR 1–6). Median time from hospital admission to discharge was 10 days (IQR 6–16).

The CIFs for in-hospital mortality and discharge in the derivation and validation cohorts are shown in Figure 3.1. In-hospital mortality at 7 and 21 days was 16% and 26% in the derivation cohort and 5% and 10% in the validation cohort, respectively. Discharge rates at 7 and 21 days were 22% and 52% in the derivation cohort and 6% and 62% in the validation cohort, respectively.

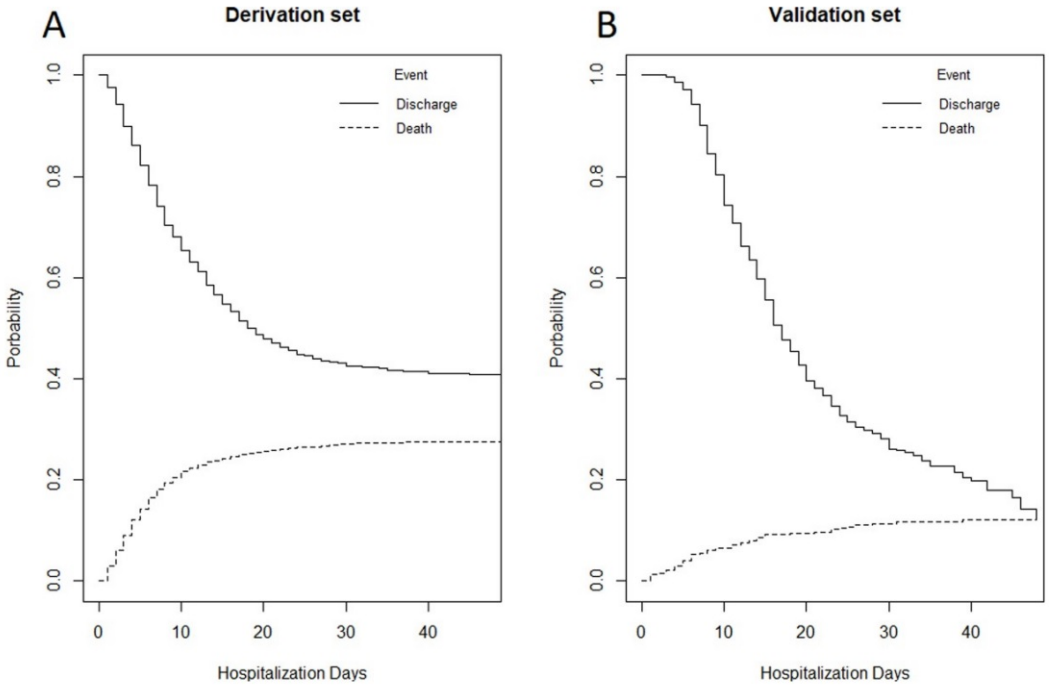


FIGURE 3.1: Cumulative incidence functions (CIFs) for in-hospital mortality and discharge of patients with Coronavirus Disease-19 in the derivation (1A) and validation cohorts (1B).

3.5 Risk factors for in-hospital mortality

Seven variables were independently associated with in-hospital mortality in the Fine and Gray model: age (HR 1.08, 95% CI 1.07–1.09, p<0.001), male sex (HR 1.62, 95% CI 1.30–2.00, p<0.001), duration of symptoms before hospital admission shorter than 10 days (HR 1.72, 95% CI 1.39–2.12, p<0.001), type 2 diabetes (HR 1.21, 95% CI 1.02–1.45, p = 0.044), coronary heart disease (HR 1.40, 95% CI 1.09–1.80, p = 0.009), chronic liver disease (HR 1.78, 95% CI 1.16–2.72, p = 0.008), and LDH levels (HR 1.0003, 95% CI 1.0002–1.0005, p<0.001) (Table 3.3). The same variables were independently associated with Discharge, but with opposite sign of the coefficients (Table 3).

TABLE 3.3: Risk factors for in-hospital mortality and discharge of patients with Coronavirus Disease-19 in the derivation cohort.

	Derivation Cohort							
	In-hospital mortality				Discharge			
	Beta	Standard Error	HR(95% CI)	p-value	Beta	standard Error	HR (95% CI)	p-value
Age (years)	0.074	0,004	1,08(1,07-1,09)	<0,001	-0,027	0,002	0,97(0,96-0,98)	<0,001
Male sex	0.481	0,111	1,62(1,30-2,00)	<0,001	-0,206	0,068	0,81(0,71-0,93)	0,002
Duration of symptoms before hospital admission shorter than 10 days	0.542	0,108	1,72(1,39-2,12)	<0,00	-0,063	0,063	0,76(0,67-0,85)	<0,001
Type 2 diabetes	0.194	0,09	1,21(1,02-1,45)	0,044	-0,087	0,087	0,73(0,62-0,86)	0,003
Coronary heart disease	0.335	0,129	1,4(1,09-1,8)	0,009	-0,129	0,129	0,72(0,56-0,93)	0,013
Chronic liver disease	0.576	0,217	1,78(1,19-2,72)	0,008	-0,271	0,271	0,54(0,32-0,92)	0,024
Lactate dehydrogenase, U/L	0.0004	0,00008	1,0003(1,0002-1,0005)	<0,001	-0,0002	0,0002	0,998(0,997-0,999)	<0,001

These risk factors were used to construct a model encompassing patients grouped into "best", "intermediate" and "worst" profiles. CIFs for the best (60 years old, female, duration of symptoms before hospital admission longer than 10 days, no comorbidities, and LDH levels of 250 U/L), the intermediate (70 years old, male, duration of symptoms before hospital admission shorter than 10 days, chronic liver disease, LDH levels of 300 U/L) and the worst profiles (80 years old, male, duration of symptoms before hospital admission shorter than 10 days, coronary heart disease, chronic liver disease, diabetes, LDH levels of 400 U/L) are shown in Figure 3.2. In the best profile, 7- and 21-day in-hospital mortality was 5% and 8%, respectively; in the intermediate profile, 7- and 21-day in-hospital mortality was 18% and 28%, respectively; in the worst profile, 7- and 21-day in-hospital mortality was 52% and 70%, respectively.

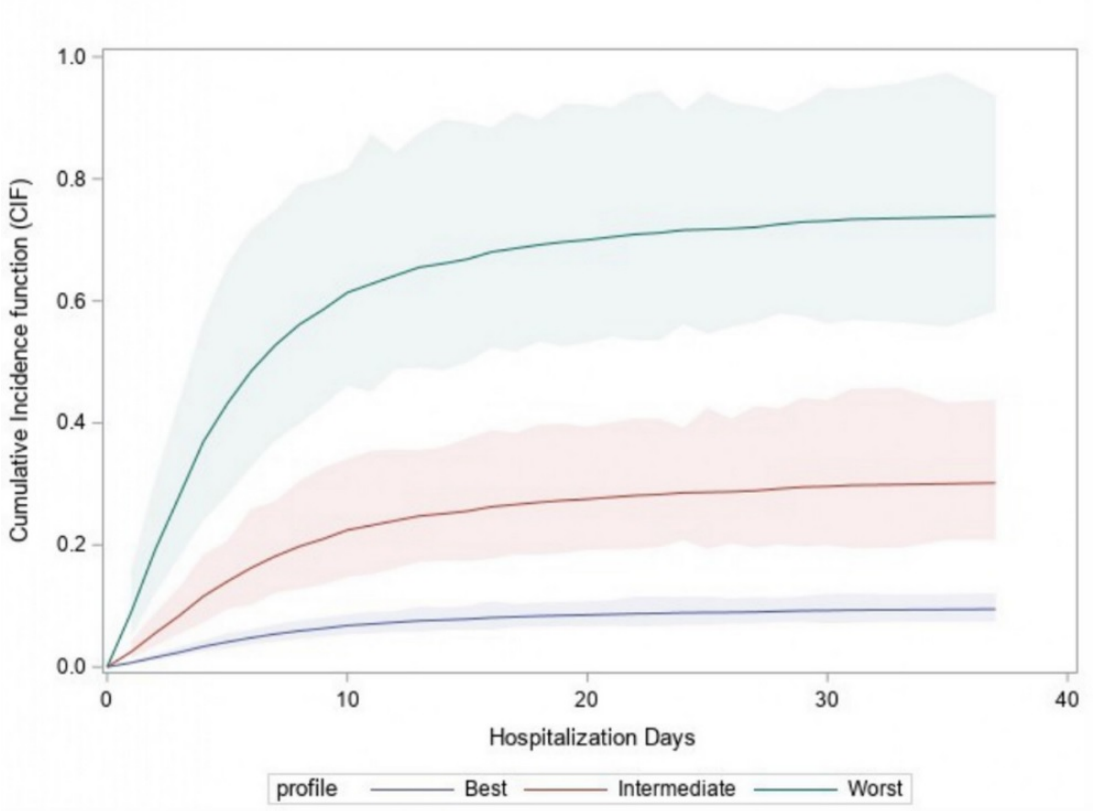


FIGURE 3.2: Cumulative Incidence Functions (CIFs) for in-hospital mortality of patients with Coronavirus Disease-19 according to three different patient profiles. **A**: best profile (60 years old, female sex, duration of symptoms before hospital admission longer than 10 days, no comorbidities, and LDH levels of 250 U/L). **B**: intermediate profile (70 years old, male sex, duration of symptoms before hospital admission shorter than 10 days, chronic liver disease, LDH levels of 300 U/L.) **C**: worst profile (80 years old, male sex, duration of symptoms before hospital admission shorter than 10 days, coronary heart disease, chronic liver disease, diabetes, LDH levels of 400 U/L).

3.6 Validation of the prediction rule

By internal validation, the AUC based on the data from the derivation cohort was good (AUC = 0.822, 95% CI 0.722–0.922). The accuracy in the validation cohort was similar to that of the derivation cohort (AUC = 0.820, 95% CI 0.724–0.920). Figure B.1 shows the calibration plot of the model for in-hospital mortality. The Brier score was 14.3 in the derivation cohort and 16.9 in the validation cohort. Similar results were obtained for discharge model (See Appendix B). The prediction for in-hospital mortality has been translated into a web-based app (COV-ID-CALC) to obtain both the CIF for in-hospital mortality (predicted curve) and confidence intervals for the CIF at 7, 14 and 21 days (https://sites.google.com/community.unipa.it/covid-19riskpredictions/c19-rp).

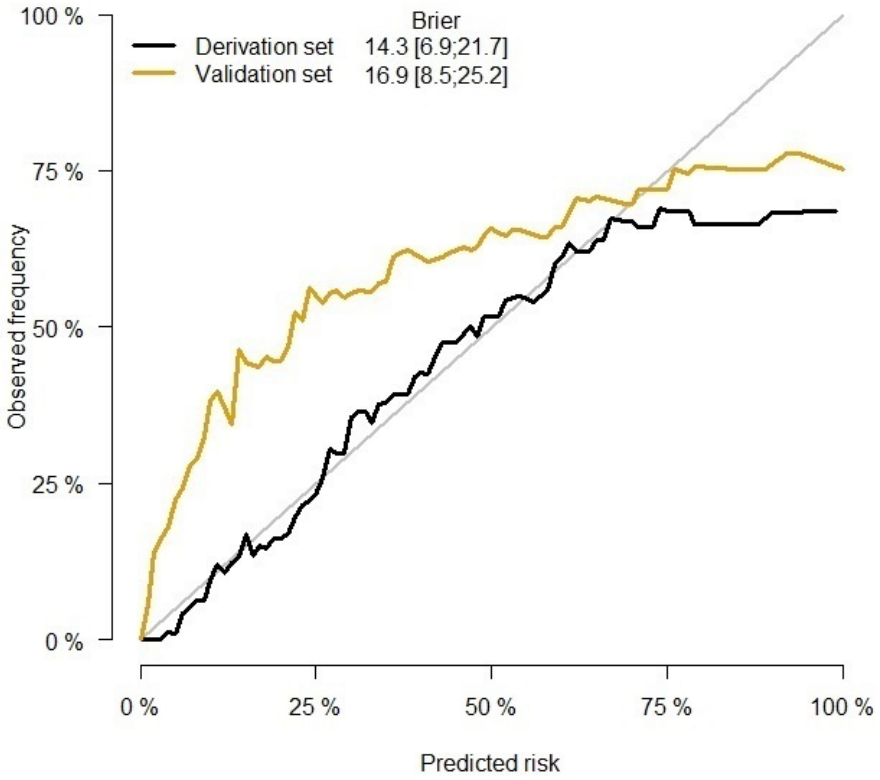


FIGURE 3.3: Calibration curves for predicting in-hospital mortality of patients with Coronavirus Disease-19 in the derivation and validation cohorts.

3.7 Discussion

In this study we developed and validated a simple clinical prediction rule able to predict in-hospital mortality of hospitalized patients with COVID-19, considering discharge as a competing risk. In our analysis, seven variables (older age, male sex, shorter duration of symptoms before hospital admission, diabetes, coronary heart disease, chronic liver disease, and LDH levels) were independent risk factors for in-hospital death, as shown by a competing risks multivariate analysis.

External validation of this prediction rule showed good discrimination and calibration. To support clinicians in the risk stratification, a web-based app was developed.

From a practical point of view, our prediction rule could help physicians to improve the allocation of medical resources, potentially reducing the overcrowding that we have witnessed in healthcare systems which significantly impacted mortality worldwide during the COVID-19 pandemic. Several prediction models have been previously published aiming to stratify the risk of in-hospital mortality in patients with COVID-19, in both Western and Eastern countries[79, 86, 155, 50, 154, 92]. Particularly, the 4C Mortality score[79], including age, sex, number of comorbidities, respiratory rate, oxygen saturation, level of consciousness, urea and CRP levels, was developed in a cohort of more than 35,000 European patients, showing a good discrimination for mortality (AUC = 0.79). Moreover, a 10-item risk score predicting the occurrence of critical illness, defined as a composite of ICU admission, invasive ventilation, or death, was recently validated in a Chinese cohort, showing an AUC of 0.88[86]. However, our methodological approach was quite different to those used in the above quoted studies. It should be noted that the use of a composite endpoint considers ICU and death to be equal, which may not be true. Moreover, the traditional logistic regression model neglects to model discharge as a competing endpoint. Our competing risks analysis may provide further insights into the effect of clinical covariates on the separate endpoint components[153, 109].

Results of our analyses confirmed those of previous reports from China and the USA[165, 145, 124], showing older age as the most important risk factor for in-hospital death in COVID-19. However, we found higher in-hospital mortality in comparison to other studies[165, 145]. The demographic structure of the Italian population could be a reason for this finding. In 2019, Italy resulted as being the European country with the highest proportion of elderly people, with about a quarter of the population aged older than 65 years [131]. Not surprisingly, the median age in our cohort was 67 years, that is higher if compared with that observed in other studies.

Interestingly, in our analysis comorbidities were associated with in-hospital death independently from age and other covariates. In our study the prevalence of comorbidities

was similar to that reported in other Western countries [21], but it was higher when compared to Chinese patients[165, 145], with cardiovascular comorbidities, including coronary heart disease, resulting as the most common. Regarding chronic liver disease, our findings are also in line with the results of two international reporting registries of 152 patients (103 of them with cirrhosis), showing a mortality of about 40% [93].

A shorter duration of the symptoms before hospital admission was independently associated with higher in-hospital mortality. This is a novel finding, and it could be argued that patients with the most severe disease were hospitalized shortly after symptoms onset, while those who were hospitalized after a longer duration of symptoms were those with milder disease.

LDH levels resulted as being independently associated with a higher risk of in-hospital death. LDH is released from cells upon damage of cytoplasmic membrane and its levels might reflect tissue necrosis related to immune hyperactivity, which thus relates to poor outcome [140]. The prognostic role of LDH has also been reported in other Chinese reports[29, 157] and in studies conducted on other coronaviruses [**al2016treatment**].

Our study suffers from several limitations. Retrospective studies have many problems that reduce their internal and external validity and selection bias can lead to incorrect results and spurious associations. However, we believe that selection bias could not be relevant as only consecutive patients with COVID-19 were included.

A limitation of any prediction rule is the generalizability of results to different populations and settings. However, we performed an external validation that showed good calibration and discrimination.

Our derivation and validation cohorts showed significant baseline clinical differences, probably because data were collected in two different settings (Northern vs Central Italy) with different degrees of overcrowding for healthcare systems. However, it should be underlined that hospitalization criteria were similar among participating centres.

Patients in our cohort were collected during the early phase of the spread of the infection locally, therefore it may not fit during different epidemic periods. Whether this prediction rule will also apply to patients observed at a later phase of the pandemic remains to be tested.

Mortality was limited to in-hospital death, and we assumed discharged patients to still be alive during the study period. Moreover, the sample size of our validation cohort was relatively small, probably reflecting the differences in disease burden between Northern and Central Italy.

The high number of missing data on treatments, particularly regarding corticosteroids use, hampered their inclusion in the prediction rule. However, it should be underlined that the effects of most drug interventions are currently highly uncertain, particularly

for the timing of steroids use and the optimal dosage of hydroxychloroquine[43], and no definitive evidence exists that therapies could result in important benefits and harms for any outcomes, as recently reported in a network meta-analysis [133].

LDH was included in our prediction rule, although LDH levels may be not always available. In order to accommodate for possible LDH missings in the app, we implemented two different prediction rules: the first one based on the final model including LDH values when available, the second one based on a model estimated including all the risk factors of the final model but LDH. Moreover, in the latter case the app will warn that the prediction rule is not accurate as the first one.

3.8 Conclusions

We developed and validated a simple prediction rule capable of accurately predicting the risk for in-hospital mortality and discharge of patients with COVID-19. Even if the data collected in 3 different Italian centers until April 30, 2020 might not reflect the more recent in-hospital mortality rates, that, thanks to the improvements in the treatments and the administration of vaccines to the great part of the western population, rapidly decreased, our prediction rule could improve the triage and management of patients with COVID-19 in different epidemiological and healthcare organization settings, especially in those health systems still in the pandemic emergency.

This chapter, together with chapter 2, concludes the work carried out for around 6 months of my first-year PhD program, in which I had the opportunity to be part, as a statistician, of an important and motivated research group aimed to make clearer what was happening in Lombardy, the first Italian region to be hit by COVID-19, in a period where all our lives, dramatically for some people, changed.

Chapter 4

Overcrowding at Emergency Department in the pre-COVID-19 era: a frailty competing risk analysis

4.1 Introduction

The Emergency Department (ED) overcrowding has become more and more prevalent throughout the nation in recent years. Several definitions of overcrowding in ED are largely present in literature. In a review article [158] overcrowding is defined as "the situation in which ED function is impeded primarily because of the excessive number of patients waiting to be seen, undergoing assessment and treatment, or waiting for departure compared to the physical or staffing capacity of the ED." Overcrowding can be also defined as a situation during which the function of an emergency department is compromised primarily due to excessive patient numbers waiting for consultation, diagnostics, treatment, transfer or discharge, exceeding the present resources[87]. In general, overcrowding is due to the imbalance of the need for emergency care and the hospital's capacity to provide the service. Another definition states that overcrowding refers to the condition leading to the dysfunction of the emergency department due to the fact that the number of patients (awaiting visit, awaiting transfer, or undergoing diagnosis and treatment) exceeds either the physical or staffing capacity of the ED [127].

Overcrowding reduces or, in extreme cases, cancels the ability of the ED to carry out its own function. It is therefore clear it is a topic of primary importance, characterized by a high degree of complexity. Although it is a theme now extensively treated in the literature, it is still a challenging topic in which researchers try to contribute in analyzing the phenomenon in its different aspects. It is therefore crucial to detect the determinants of overcrowding to provide understanding of the phenomenon. Rastelli et al. [112] found that the increase of overcrowding is probably due to the reduction of the number

of hospitals and the number of beds. Other authors found that severe overcrowding was usually associated to insufficient ED personnel and lack of beds in the hospital wards. Both issues negatively affect patient care outcomes, including increased length of stay (LoS) at EDs, number of patients who left without being seen, and other factors [104]. In addition, some studies have identified the effect of high ED occupancy (above 90%) and access block as causes of adverse patient outcomes, treatment delays, high mortality rates (20%–30%), prolonged inpatient length of stay (LoS), and hospital readmission [144, 160].

In the Italian setting, though the health ministry published the main policies directions that every Italian hospital must respect (for example that "the measurement of overcrowding must be addressed by the use of the indexes NEDOCS, CEDOCS, SONET, recorded homogeneously by all the hospitals and, at least, every 24 hours"), the health system is regionally dislocated. However, in the last decades, also due to the increasing number of elderly people, the country have been faced with an increased demand for health services, which did not match with an equal improvement of the territorial services. As a matter of fact, unpublished data from SIMEU (Italian Society of Emergency Medicine) from July 2010 show that ED visits have grown by 5% to 6% per year, with 30 million ED visits in 2009 [105]. Moreover, in Sicily, the 26% of people went to an ED in 2019 was older than 65). Different papers, dealing with overcrowding in Italy, are present in literature. Di Bella et al.[42] identified clinical and socio-demographic risk-factors connected to different levels of ED utilisation and highlighted the influential role played by chronic conditions. Strada et al. [135] analyzed the NEDOCS, comparing objective scores with healthcare personnel's perception of overcrowding, just for the accesses at the ED at the University Hospital of Ferrara in 2018. Amodio et al.[6] tried to explore the association between overcrowding and the Italian population characteristics, using data from the regional health system including all ED admissions of patients present in two Italian provinces (Lecco and Monza e Brianza). They found that the high health impact of winter is associated with an increase in ED admissions, especially for older and critical/very critical patients (yellow and red triage codes).

Others authors observed influenza can increase ED admissions as well, rising the risk of absenteeism among healthcare personnel and incrementing the burden of diseases in intensive care units as well as in other wards [5, 138].

The outbreak of Covid-19 pandemic starting from the beginning of 2020 has changed completely the ED management. Gormeli et al. [58] found a significant drop of emergency admissions during Covid-19 pandemic compared with the pre-Covid-19 pandemic period. In turn, this would have increased the rate of deaths occurring at home, and led emergency services to be overcrowded by patients with worse outcomes and higher

mortality rates. Bouillon et al. [22] stated that it appeared that the lockdown could be considered the gold standard for patient care in emergency departments, without any problem for them to find a bed for those needing to be hospitalized.

Nonetheless, we argue that, using recent data to analyze overcrowding at ED, for example just before the beginning of the COVID-19 pandemic, can be useful to better understand the future ED accesses flows, once the pandemic situation will slightly return to "normality".

One of the criteria useful to understand the causes of overcrowding relies on the classification of the variables, that can affect overcrowding, in input, throughput, and output factors[127]. These factors are independent from each other, but they are interconnected and influenced by underlying contributors, making the phenomenon of overcrowding a multifactorial and complex one [125, 110, 40].

The input–throughput–output model therefore appears useful for understanding the factors that regulate the flow and capacity of the ED, but also represents a guideline for conceptualizing the same factors in both the entire hospital setting and the health care system[10, 113, 69]. Strictly speaking, overcrowding is characterized by an imbalance between supply and demand.

Input, throughput, and output factors can be defined as follows:

Input factors: they are represented by factors determining patient access to the ED. They include the waiting time, the number of patients who arrived in the ED, as well as their severity and complexity. Input factors constitute one of the causes of crowding, but the least important [96, 34, 71]. Information such as the Triage, time of arrival in ED, and other accesses characteristics are included in the data we used to analyze overcrowding (see section 4.2 for a detailed description of the EMUR database).

Throughput factors (internal factors): they are represented by the process time, meaning the time between taking charge of the patient and the outcome (diagnosis and decision: discharge, hospitalization, and transfer). They include all the complementary exams that are performed in the ED (laboratory analysis and imaging). These factors are also affected by the healthcare personnel (in terms of quality of work, shift work, burnout, drop in performance, respect for shifts, and holidays)[125, 128, 106, 116]. Throughput factors have a key role in our analysis. We will, indeed, analyze the risk of being discharged or hospitalized during LoS in a survival setting (see section 4.2 for a description of the EDs' process and section 4.3 for a description of the statistical model we used).

Output factors: they include patients boarding in the ED, availability of hospital beds, and the delay of transport (both internal and external) to leave the ED. The lack of hospital beds appears to be a fundamental cause of overcrowding, but so is the lack of home care. The reduction of beds (which in some realities have decreased by more than 50%

in the last 20 years) is a worldwide phenomenon that has led to exit block (that occurs when 'patients in the ED requiring inpatient care are unable to gain access to appropriate hospital beds), as well as to the collapse of the possibility of hospitalizing patients. Considering output factors, it is therefore evident that overcrowding is influenced by the fact that patients who should go to the ward are stationed in the emergency room and must continue to be assisted from a medical point of view[127, 106, 116]. Among the different factors, patient boarding was found to be one of the most significant[110]. Boarding is the practice of keeping patients admitted to the ED for prolonged periods due to inadequate capacity of inpatient wards. Unfortunately the EMUR database doesn't include information about the number of beds or the delay of transport.

Given its multifactoriality and complexity, different aspects must be accounted to solve overcrowding. One possible solution could be to include an increase in transitional beds and better working conditions for hospital staff. Considering that overcrowding is a mismatch between supply and demand, one might think that an increase in supply can solve easily the problem. In some cases [94], this did not lead to an improvement in overcrowding but, on the contrary, to a worsening of the situation. Other authors suggested to act at medical and bureaucratic level. These can be divided into two levels: microlevel (ED point of view) and macrolevel (Hospital point of view)[126, 127].

From a methodological point of view, there are two main approaches to analyze overcrowding in ED. The first concerns the use of indexes that measure the degree of crowding inside the ED. In USA, the NEDOCS (National Emergency Department Overcrowding Score) is an extensively studied and validated measure of emergency department crowding and one of the most used index in literature to measure overcrowding [71, 149]. The NEDOCS score is computed considering seven variables recorded at a single point in time [23]. It includes variables related to input (ability of ambulances to offload patients, patients who leave without being seen or treated or time to Triage) throughput (ED occupancy rate , patients' total length of stay in the ED and the time until a physician first sees the patient) and output factors (ED boarding time and number of patients boarding in the ED). Recently, even if it has been used in many EDs over the years, especially in USA, NEDOCS was found to overestimate the ED overcrowding [135]. Other authors compared the predictive performance of NEDOCS with the EDWIN model [20] (which highly depends on the number of the patients in a Triage category), demonstrating a "superiority of the NEDOCS when compared with the EDWIN in measuring overcrowding" [148]. In order to reduce the overcrowding, the Sicilian health institution published, in 2018, the health policy directions suggesting the use of new indexes (K1,K2,K3) to measure overcrowding by taking into account the number of people inside the ED at different intervals of time [132].

The second approach uses statistical models to predict overcrowding or determine factors associated with it or with the type of exiting from ED. In the literature there are few papers using the statistical model approach to analyze overcrowding. A multivariate logistic regression was used to predict hospital admission using factors easily obtainable at the time of triage, to reduce the ED flow burden [24]. Sprivulis et al. [134] used the Cox regression models was to determine the association between hospital and ED occupancy and mortality after emergency admission. Harris et al.[67] used a parametric survival model for the time spent in the ED from the first visit by a treating doctor to admission, to analyze the association between the length of stay and bed access block factors. Others approaches are based on linear regression [75, 45]; machine learning [77, 111] and time-series forecasting [74, 26], to predict demand emergency services.

When accounting for more than one type of leaving from ED, a competing risks model can be the best choice to model the length of stay (LoS). Unfortunately, the literature is poor. Few papers considered a similar approach in ED's overcrowding but the analysis setting is limited to a single hospital. Some authors used an accelerated failure time model to evaluate the dependence of ED LOS on relevant covariates, such as Age, Triage acuity level, transfer, patient entity and arrival time, considering 3 final fates for ED patients: discharge, admission to the hospital, or expiring in the ED [28]. Others identified predictors for LoS considering Death and Discharge as competing events in patients with burn injuries, performing a cause-specific hazard analysis with burn size Age and inhalation injury as covariates [137].

Piecewise exponential models was used to determine the risk of being dead, considering discharge as a competing event, in seriously injured or ill patients [32].

By using a competing risks model, this work focuses on detecting the determinants of overcrowding at EDs, and on the identification of risk profiles that are at "risk" to be discharged or hospitalized during LoS (in particular the so-called bottlenecks) according to different accesses characteristics (input factors), especially the pathology assigned at the ED and the role fo the season and the level of ED utilization. The knowledge of such determinants and risk profiles can help the EDs' management to act properly to reduce overcrowding. We used the *EMergenze - URgenze* (EMUR) dataset, which includes the accesses from 63 Sicilian EDs in 2019, to perform such analysis. Because we are in a multi-centre setting, to take into account the unobserved heterogeneity due to the hospitals, a frailty component is used.

The aim is to exploit the information on the pre-pandemic setting to provide "good" quantitative information to the EDs' heads and policymakers in order to develop processes able to systematically address high ED volumes in a post Covid-19 pandemic setting. Indeed, over the past two years, hospitals have faced difficulties brought by

the SARS-CoV-2 pandemic, and its effects have provided a completely different setting, which is beyond our scope.

The chapter is divided as follows: first, we introduce the definition of overcrowding, the factor associated with it and the statistical methods used, in literature, to analyze the overcrowding in ED. Section 4.2 includes the description of the data used to analyze overcrowding in the sicilian EDs the EMUR database. In Section 4.3 details on the survival methods, used to predict the risk of two event of interest (Discharge and Hospitalization), are described followed by the results in section 4.4. The results obtained are discussed in section 4.5.

4.2 Data

The EMUR database is a national informative system collecting data from EDs containing information on all the accesses to the Italian EDs. This archive aims at monitoring all the medical emergencies in the public hospitals to favor an effectiveness of the intervention, as well as guaranteeing the continuity of care for the benefit of the patient.

Our database is the Sicilian 2019 EMUR consisting of 1,724,758 records coming from 63 Sicilian EDs. Each record is an access, so repeated accesses of the same patient can be considered by a unique patient ID.

Each record includes information on the demographic characteristics of the patient (age, gender) and several pieces of information connected to the access (e.g. time of arrival, time of first visit and dismissal, urgency level according to the triage system, Pathology, means of arrival).

Following official documents [52], we also divided the Sicilian EDs according to their size (as in Table 4.1) which depends on the number of accesses in 2019. The most important variable in this work is the pathology. Our hypothesis is that the risks of Discharge and Hospitalization, once the patients are admitted, are different across pathologies, thus, its knowledge can allow the EDs' staff to predict patients exiting and to make policies appropriately. In the EMUR database, the pathology is defined through the International Classification of Diseases, Clinical Modification (ICD9-CM) coding system. Due to a large number of different diagnosis codes, we aggregated, thanks to the indications of an ED manager, the ICD9 codes appropriately into 9 macro-categories as in Table 4.2.

TABLE 4.1: Number of Sicilian EDs by size.

EDs size	**# Accesses in 2019**	**# EDs**
Biggest	>40.000	12
Big - Medium	25.000-40.000	16
Small-Medium	10.000-25.000	18
Small	<10.0000	18

TABLE 4.2: ICD9 codes aggregation according to homogeneous diseases categories.

ICD9 Diagnostic codes	Description	Aggregated ICD9 codes	Label
001-139	Infectious And Parasitic Diseases	001-139	Inf_Dis
140-239	Neoplasms	140-239	Neoplasms
240-279 280-289	Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders Diseases Of The Blood And Blood-Forming Organs	240-289	Blood_Dis
290-319 320-389	Mental Disorders Diseases Of The Nervous System And Sense Organs	290-389	Nerv_Dis
390-459 460-519	Diseases Of The Circulatory System Diseases Of The Respiratory System	390-519	Circ&Resp_Dis
520-579 580-629	Diseases Of The Digestive System Diseases Of The Genitourinary System	520-629	Dig_Dis
630-679	Complications Of Pregnancy, Childbirth, And The Puerperium	630-679	Preg_Comp
680-709 710-739	Diseases Of The Skin And Subcutaneous Tissue Diseases Of The Musculoskeletal System And Connective Tissue	680-739	Skin&Musc_Dis
740-759 760-779	Congenital Anomalies Certain Conditions Originating In The Perinatal Period	740-779	Cong_Anom
780-799 V01-V91	Symptoms, Signs, And Ill-Defined Conditions Supplementary Classification Of Factors Influencing Health Status And Contact With Health Services	780-799 + V	Other_Symp
800-999 E000-E999	Injury And Poisoning Supplementary Classification Of External Causes Of Injury And Poisoning	800-999 + E	Inj&Pois

4.2.1 Data cleaning

In Italy, as in the rest of the World, there exist women's and children's Hospitals. We did not consider such hospitals in our analysis because the aim is to compare similar hospitals. We, therefore, excluded, a priori, all the accesses less than 15 years old. We also restricted our analysis to multispeciality hospitals selecting the biggest sixteen EDs (638,748 accesses in total) located in 7 Sicilian cities (Agrigento, Caltagirone, Catania, Messina, Palermo, Siracusa, Vittoria). The EDs located in the other Sicilian little cities are therefore excluded because of the lack of wards. Therefore, it is important to include multispeciality hospitals to analyze the Length of Stay (LoS) in the EDs before transferring to an appropriate medical ward. Our sample is represented by 12 "Biggest" and 4 "Big-Medium" Hospitals (see Table 4.1). The included EDs are shown in Table 4.3.
Numerically, we excluded the following not appropriate records: 87,941 records with patients aged less than 15 years; 1,644 unidentifiable records; 2,194 repeated accesses within 4 hours.

TABLE 4.3: Sicilian EDs included in the analysis.

EDs	**# Accesses**
Ospedale San Giovanni di Dio (Agrigento)	32.022
Presidio Ospedaliero Gravina e Santo Pietro (Caltagirone)	25.188
Ospedale Garibaldi (Catania)	31.692
Ospedale Cannizzaro (Catania)	18.867
Presidio Ospedaliero Gaspare Rodolico (Catania)	26.374
Ospedale Vittorio Emanuele (Gela)	27.276
Policlinico Gaetano Martino (Messina)	18.687
Azienda Ospedaliera Papardo (Messina)	15.756
Ospedali Riuniti Villa Sofia- Cervello (Palermo)	14.870
A.R.N.A.S. Ospedali Civico Di Cristina Benfratelli (Palermo)	36.355
Policlinico "Paolo Giaccone" (Palermo)	31.137
Ospedale Buccheri La Ferla (Palermo)	30.732
Presidio Villa Sofia (Palermo)	25.712
Ospedale Ingrassia (Palermo)	18.454
Ospedale Umberto I (Siracusa)	37.204
Ospedale Guzzardi (Vittoria)	19.807
Total	410.133

Some Pathologies may be not useful to explain overcrowding because they represent accesses that should be filtered by territorial services. Therefore, we considered them not appropriated to be included in the analysis. We excluded 136.836 accesses coming from:

-*Mental disorders* (ICD-9 [290-319]), *diseases of the Nervous system and sense organs* (ICD-9 [320-389]). We found that these accesses (60.956 in total), in particular in the Health Italian System, are rapidly discharged. They represent people who should not go directly to the ED but consult the family doctor.

-*Complications of Pregnancy, Childbirth, And the Puerperium* (ICD-9 [630-679]), *Congenital Anomalies and Certain conditions originating in the perinatal period* (ICD-9 [740-779]). These accesses (42.816 in total) are rapidly Hospitalized, thus they rarely have prolonged EDs LoS.

-*Neoplasms* (ICD-9 [140-239]). These accesses might be potentially effective on overcrowding caused by prolonged LoS but they should go directly to the Oncology ward. Furthermore, they represent the least frequent Pathology, at least in our data (2.224 accesses).

4.2.2 Description of the ED process

The admission steps at EDs are described as follows: the first step is the triage assignment, which is a color assigned to each patient right after they access the ED, assigned by the ED personnel, according to their severity conditions. The second step is represented by the time during which the patients wait in the Emergency room until they are admitted to visit. We called this interval of time $T1$. The third step is the time interval ($T2$) between the admission and the leaving from ED according to the decision of the physicians. The patients, indeed, can be Hospitalized or Discharged after being visited. The entire process in Figure 4.1 would recall the use of a multi-state model with the admission state as transient. We simplified the analysis considering the process with ED admission as starting state and Discharge and Hospitalization as absorbing states, that, with the time of interest $T2$ recalls the typical competing risks setting. Then, we deleted the patients' records ended up with deaths and leaves. Deaths were excluded because they are rare (0.11%), while leaves, usually of two types "leave before treatment" and "leave without being seen", because the leaving times were not recorded for both types. The knowledge of the leaving times could allow us to consider an even more complicated multi-state process that might be able to predict the leavings and the factors associated with it.

4.3 Statistical Analysis

In order to identify the factors associated with two events of interest (Discharge and Hospitalization), we first calculated the quartiles of LoS. Differences in the quartiles of

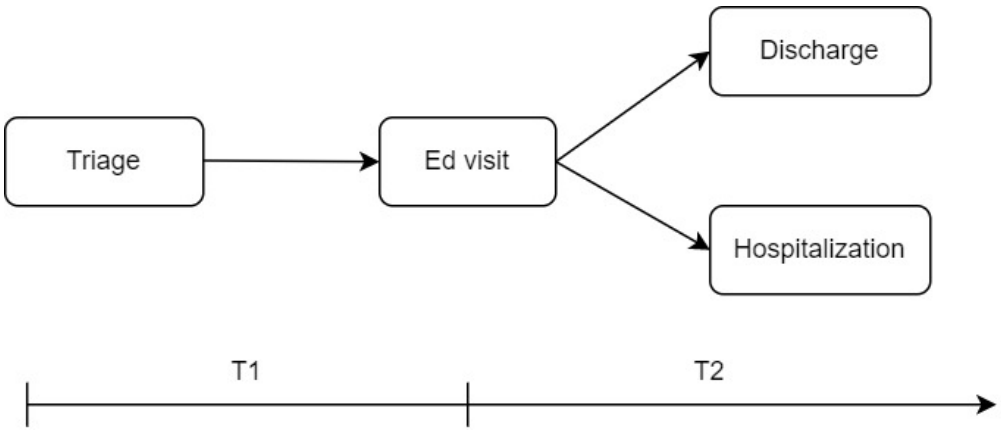


FIGURE 4.1: Emergency department admission process.

Los among categories might provide useful descriptive information about overcrowding to the ED's heads.

Predicting the probability of Discharge or Hospitalization, once a patient was admitted, is crucial to detect the so called bottlenecks which generate overcrowding[3]. We therefore applied a competing risks model for the LoS. The Hazard ratios are estimated using the cause-specific Hazard Function, as both outcomes are of interest.

To quantify the unobserved heterogeneity among EDs (the assumption is that each Hospital effect the risk of Discharge or Hospitalization) we considered the frailty competing risks model 1.12 described in section 1.2:

$$\lambda_{ijk}(t|v_i) = \lambda_{0k}(t)exp(X_{ij}^T\beta_k + v_{ik})$$

Where $\lambda_{ijk}(t|v_i)$ is the cause-specific hazard function conditional for the j^{th} observation who failed from cause k $(k = 1, 2)$ on the log-frailty v_{ik} (i.e. the random effect for type event k and cluster i with $i = 1, .., 16$) and T the time spent from Admission to one of the events (LoS).

To perform the competing risks frailty model avoiding large computational times, we sampled sistematically 15.191 rows from the population of interest, one every 27 rows.

The estimation procedure was conducted under the framework of the H-likelihood that allows to overcome the computational issues by using the marginal likelihood approach in presence of the frailty component [64]. Other possible approaches to estimate the unobserved frailties, were proposed by Rueten et al.. [123] who used the EM algorithm approach. In addition, such algorithm provides empirical Bayes estimates for each center's frailty.

Model estimation was performed by using the frailtyHL R package. On the basis of the competing risks model we computed the predicted Cumulative Incidence Functions

(CIFs) for each event of interest according to the most important covariates. Given that this package does not include routines to compute the predicted CIF, we created the R codes to compute them. (See Appendix C)

4.4 Results

Descriptive analysis of LoS

Accesses with prolonged length of stay are considered the most relevant in terms of overcrowding. We therefore calculated the quartiles of LoS (measured in hours) at ED according to several access characteristics (Table 4.4). A number of 410.133 accesses were recorded in 16 Sicilian Hospitals in 2019 (76% Discharged and 24% Hospitalized). The number of accesses included in the descriptive analysis is much greater than the sample used for modelling purposes. When considering Discharge as outcome of interest, the median LoS (time occurred from Admission to Discharge) was 1.88 hours. Females and males have similar median LoS (1.97h vs 1.82h).The oldest patients stayed, in median, 3.28 hours. Pathologies with the highest median LoS before being discharged are Blood related diseases (6.49h), Circulatory and Respiratory diseases (2.6 h), and Other Symptoms accesses (2.43h). Accesses occurred in Winter show the greatest LoS in median (1.97). Accesses occurred in the first half of the week do not register large differences with those occurred in the weekend (1.92h vs 1.87h) and those occurred from 06AM to 18PM are similar, in median, with those occurred from 18 PM to 06 AM (2.03h vs 1.83h). People arrived at hospital autonomously show much lower median LoS than people arrived through Ambulance (1.7h vs 3.15h). Repeated accesses have similar median time of LoS of unique accesses (1.97h vs 1.83h).

When considering Hospitalization as outcome of interest, the median LoS (the time occurred from Admission to Hospitalization) was 4.05 hours. Females stayed inside the ED, in median, equal than males (4.02h vs 4.07h), Oldest patient stayed, in median, 5.35 hours. Pathologies with the highest median LoS before Hospitalization are Blood diseases (6.53h) , Circulatory and Respiratory Diseases (5.15h) and Digestive Diseases (4.08h). Accesses occurred in Winter show the greatest LoS in median (4.37). Accesses occurred in the first half of the week do not register large differences with those occurred in the weekend (4.13h vs 3.9h respectively) and those occurred from 06AM to 18PM are longer of almost a hour, in median, with those occurred from 18PM to 06AM (4.5h vs 3.8h). People arrived at hospital autonomously show much lower median LoS than people arrived through Ambulance (3.52h vs 5.12h). Repeated accesses show similar median LoS with the respect to unique accesses (4.18h vs 3.92)

TABLE 4.4: Quartiles of length of stay (hours) at ED, considering 16 Sicilian hospitals as a whole, with respect to Discharge or Hospitalization as competing events, in 2019.

	Discharge				Hospitalization			
	p25	p50	p75	# of accesses	p25	p50	p75	# of accesses
Gender								
Male	0.72	1.82	3.62	158.893	1.82	4.07	12.68	51.103
Female	0.83	1.97	3.72	154.312	1.82	4.02	12.77	45.819
Age								
<30	0.55	1.50	2.77	68.539	0.52	1.15	2.7	8.720
30-50	0.53	1.6	3.07	94.073	1.37	3	6.75	15.140
50-80	0.97	2.18	4.35	125.516	1.88	4.32	13.98	49.736
>80	1.62	3.28	7.58	25.083	2.38	5.35	20.03	23.326
Pathology								
Inf_Dis	0.55	1.73	3.37	9.141	1.87	4.08	15.58	2.262
Blood_Dis	2.6	6.49	16.12	4.608	2.58	6.53	23.47	3.401
Circ&Resp_Dis	1.25	2.6	5.42	29.546	1.92	5.15	20.37	27.171
Dig_Dis	0.68	2.02	3.95	55.273	1.92	4.1	10.23	19.522
Skin&Musc_Dis	0.63	1.55	2.98	42.214	1.87	3.85	7.37	5.207
Other_Symp	1.2	2.43	4.48	85.094	1.82	3.68	8.93	22.836
Inj&Pois	0.47	1.33	2.52	87.335	1.52	3.22	10.5	16.523
Season								
Winter	0.83	1.97	3.85	72.501	1.93	4.37	14.92	24.635
Spring	0.78	1.9	3.7	79.079	1.78	4.02	12.97	24.532
Summer	0.7	1.82	3.53	83.477	1.7	3.78	10.8	23.576
Fall	0.77	1.88	3.65	78.154	1.83	4.03	12.23	24.179
Weekdays								
Mon - Thu	0.78	1.92	3.72	186.220	1.82	4.13	13.08	57.740
Fri - Sun	0.75	1.87	3.62	126.991	1.8	3.9	12.13	39.182
Arrival hour								
06 am - 18 pm	0.83	2.03	3.88	103.846	2.08	4.5	9.35	30.142
18 pm - 06 am	0.73	1.83	3.55	209.365	1.72	3.8	14.42	66.780
Arrival Mode								
Ambulance	1.6	3.15	6.93	51.334	2.25	5.12	18.42	39.469
Autonomous	0.65	1.7	3.27	261.877	1.55	3.52	9.07	57.453
Repeated Access								
No	0.75	1.83	3.52	172.509	1.77	3.92	12.43	50.760
Yes	0.78	1.97	3.9	140.702	1.87	4.18	13.02	46.162
total	0.77	1.88	3.67	313.211	1.82	4.05	12.72	96.922

Even though Triage is known in the literature to be associated with LoS [65, 51], we decided, looking at the data, to not include such a variable as a covariate in the competing risks frailty model. Our choice depends on the different criteria hospitals assign such a code to patients. In other words, there is too much variability, among Hospitals, on the conditional probability of Hospitalization and Discharge according to the Triage levels (see details in Table 4.5).

TABLE 4.5: Distribution of Triage for each Hospital (number of cases and percentage) according to Discharge and Hospitalization.

	Discharge				Hospitalization				
Hospital	W (%)	G (%)	Y (%)	R (%)	W (%)	G (%)	Y (%)	R (%)	Total
1	862(3,6)	13.923(60)	8.287(36)	98(0,4)	18(0,2)	2.274(25,5)	6.110(69)	450(5)	32.022(8)
2	28(0,1)	14.308(62)	8.387(36)	433(1,9)	1(0,001)	1.926(25)	4.693(62)	956(13)	30.732(7)
3	293(1,6)	12.033(67)	5.484(31)	35(0,4)	15(0,2)	2.275(30,8)	4.797(65)	256(4)	25.188(6)
4	112(0,8)	7.673(56)	5.625(41)	172(1,2)	7(0,4)	1.289(7,6)	3.295(76)	694(16)	18.867(5)
5	967(4)	11.851(54)	9.028(41)	278(1)	5(0,01)	2.098(22)	6514(68)	951(9,9)	31.692(8)
6	295(1)	11.447(53)	9.375(45)	255(1)	14(0,3)	884(17,7)	3.537(71)	567(11)	26.374(6)
7	5.010(21)	12.149(50)	6.857(28)	178(1)	158(5)	903(29)	1.803(58)	218(8)	27.276(7)
8	288(2,5)	7.752(68)	3.426(29,5)	0(0)	2(0,04)	297(7)	3.644(85)	347(8)	15.756(4)
9	618(5)	5.479(47)	5.440(47)	24(1)	32(0,4)	522(7)	5.422(76)	1.150(16,6)	18.687(4)
10	169(1,6))	4.365(42)	4.896(47)	999(9,4)	7(0,2)	619(14)	2.458(55)	1.357(30,8)	14.870(4)
11	3.670(13)	16.202(58)	7.667(27)	504(2)	107(1)	1671(20)	4.966(60)	1.568(19)	36.355(9)
12	1.735(11)	9.786(63)	3.783(25)	168(1)	46(1,5)	657(22)	1.816(60,5)	463(16)	18.454(4)
13	2.830(12)	12.767(52)	8.654(35)	127(1)	35(0,5)	1.143(17)	4.979(73,5)	602(9)	31.137(8)
14	5.737(28)	7.541(37)	5.997(29)	1.357(6)	355(7)	476(9)	2.539(50)	1.710(34)	25.712(6)
15	1.012(3,4)	22.896(77)	5.666(19)	93(0,6)	16(0,2)	3.254(43)	3.808(50,8)	459(6)	37.204(9)
16	768(4,99)	13.192(82)	2.148(13)	12(0,01)	19(0,5)	1.489(40,5)	2.057(56)	122(3)	19.807(5)
Total	24.394(7,5)	183.364(58)	100.720(32)	4.733(1,5)	837(0,8)	21.777(22)	62.438(64)	11.870(12,2)	410.133

4.4.1 Competing risks frailty model estimates

Table 4.6 provides the hazard ratios estimated by the cause-specific competing risk frailty model. Risk factors associated with Discharge and Hospitalization regard patient level covariates (Pathology, Age, Arrival mode), and ED-level covariates (Season, Arrival hour and Repeated Access).

In a cause-specific hazard framework, interpretation of the model coefficients (or in terms of hazard ratios) relies just on the sign and does not reflect a direct magnitude on the cumulative incidence function.

In our analysis the most important information, useful to predict the LoS, are provided by the pathology. The other covariates included in the model can be considered as correction factors for the pathologies. Among them, accesses with Skin & Musculoskeletal diseases have the highest risk of Discharge (HR [Skin&Musc_Dis] = 1.88) while accesses with Circulatory & Respiratory Diseases and Digestive Diseases have the highest risk of Hospitalization (HR [Circ&RespDis] = 1.48, HR[Dig_Dis]= 1.26). Risk factor as Age (0.99), Arrival Mode (HR [Ambulance]=0.5) , accesses occurred between 06 AM to 18 PM (HR = 0.98) and accesses of frequent users (HR = 0.93) are related with Discharge Correction factors associated with risk of Hospitalization are Age (HR=1.002) accesses occurred between 06 AM to 18 PM (HR = 0.91), and arrival mode (HR = 1.11).

TABLE 4.6: Estimates from the Cause-specific frailty model. Baseline category of Access: Pathology Other_Symp, Median Age (54), Arrival Hour from 18 PM to 6 AM, Unique Access.

	Event of interest							
	Discharge				Hospitalization			
Pathology	HR	Estimate	SE(beta)	p-value	HR	Beta	SE(beta)	p-value
Circ&RespDis	0.68	-0.39	0.036	<0.001	1.48	0.39	0.051	<0.001
Dig_Dis	0.98	-0.02	0.031	0.59	1.26	0.23	0.057	0.001
Inf_Dis	1.08	0.07	0.058	0.2	0.82	-0.2	0.13	0.12
Skin&Musc_Dis	1.88	0.63	0.033	<0.001	0.87	-0.14	0.088	0.12
Blood_Dis	0.52	-0.65	0.083	<0.001	0.94	-0.06	0.103	0.5
Inj&Pois	1.60	0.47	0.026	<0.001	1.2	0.18	0.056	0.001
Age	0.99	-0.014	0.0004	<0.001	1.002	0.003	0.001	0.007
Arrival Hour								
06 AM - 06 PM	0.98	-0.03	0.02	0.02	0.91	-0.1	0.038	0.001
Arrival Mode								
Ambulance	0.5	-0.69	0.026	<0.001	1.11	0.11	0.038	0.006
Repeated Accesses								
Yes	0.93	-0.07	0.019	<0.001	1.04	0.04	0.035	0.29

4.4.2 Predicted Cumulative Incidence Functions.

The cumulative incidence functions were predicted from the competing risks frailty model in order to obtain the probability, during the LoS, of being Discharged or Hospitalized. We used as a stratification factor the pathology, which represents, in our data, the most important variable affecting overcrowding. While the others covariates values are fixed at the baseline category values. Given that the statistical framework concerns the presence of a hospital effect in our model, we provide the predicted CIFs of a hospital median effect in Figure 4.2, that is the CIFs computed without considering any random effect ($\nu_{ik} = 0$).

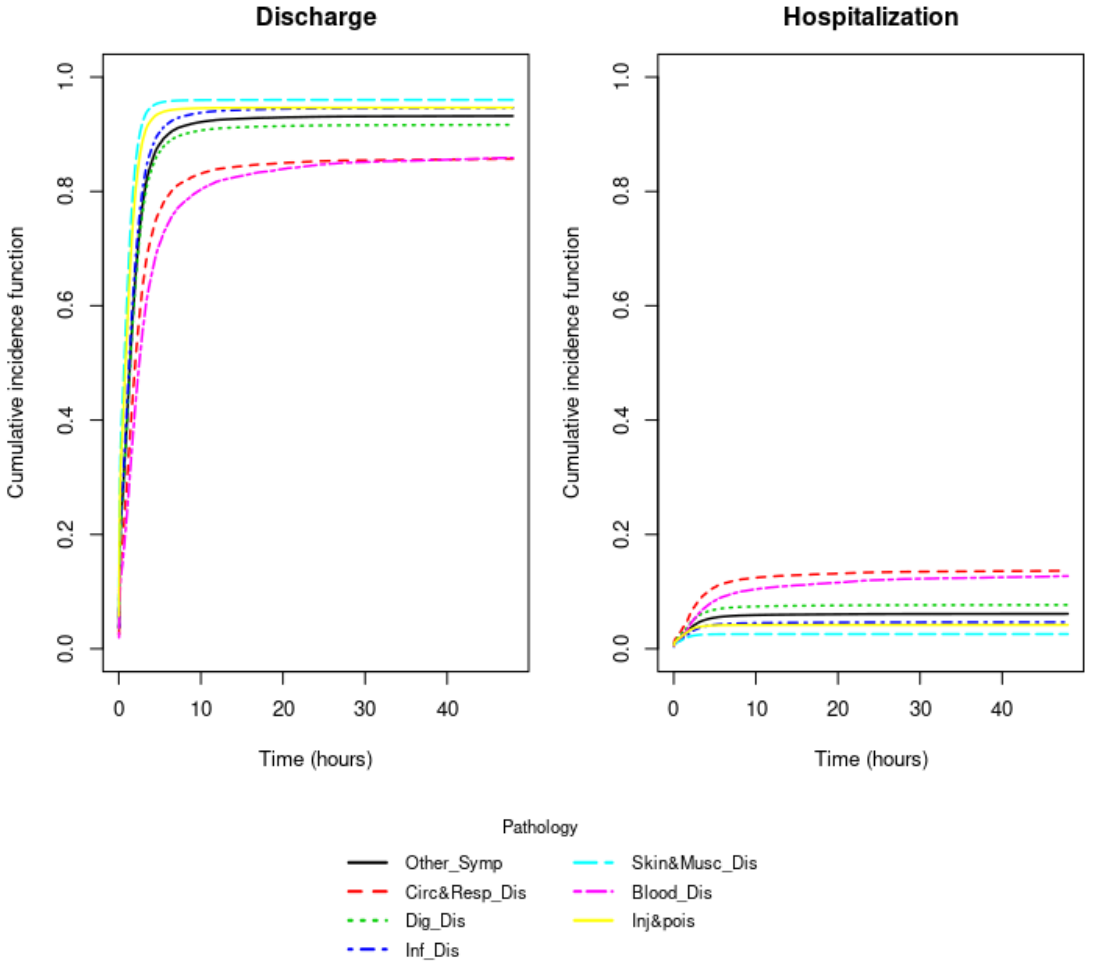


FIGURE 4.2: CIFs by pathology, predicted from the cause specific model, with respect to the length of stay at ED of a hospital median effect and two competing events: discharge and hospitalization.

Pathologies with lower probability of discharge could affect more overcrowding. On the other side, pathologies with higher probability of Hospitalization could affect more

the overcrowding. It's also important to consider which pathologies have prolonged times. This can be assessed looking at the rapidity by which the CIF reaches its maximum.

Even though there is no direct relationship between model coefficient and predicted CIF in such a context, the behaviour of the latter seems to confirm what obtained in the model estimation. In terms of crude probability pathologies such as Skin&Musc_Dis, Other_Symp and Dig_Dis are the highest CIFs for Discharge, while Circ&Resp_Dis and Blood_Dis and Dig_Dis are the highest CIFs for Hospitalization.

Moreover, pathologies such as Circ&Resp_Dis and Blood_Dis have prolonged times, either for Discharge and Hospitalization, with the respect to the others. This could suggest that these access categories stayed more inside the ED before taking any decision.

The CIFs for any centre effect, fixing a pathology, provide information either on unobserved heterogeneity and on the comparison among hospitals in terms of probability of being discharge and hospitalized for a specific profile. Figure 4.3 shows the CIFs for accesses with Blood Diseases according to the minimum and maximum centre effect. The huge distance between the CIFs computed at the minimum and maximum centre effect suggests the presence of heterogeneity, in particular in case of Hospitalization (the probability of being Hospitalized at 48h, since admission, of the largest centre effect ED is 0.5, while of the lowest centre effect ED is 0.2). Instead, concerning the Discharge, the CIFs computed the minimum and maximum centre effect appear closer (respectively 0.59 against 0.64 at 48h since admission).

4.4.3 Testing the unobserved heterogeneity

The test on the frailty parameter, was used to determine whether it needs to be included in the model or not. We performed the test graphically, computing the 95% Confidence intervals for each random effect and checked if they included the 0, and empirically, based on the null mixture $\chi^2_{1,0.1}$ distribution [64]. Figure 4.4 shows the random effects estimates and their CI 95% according to Discharge and Hospitalization.

In both events of interest, 9 random effects significantly diverge from 0. Investigating the characteristics of the Hospitals with significant random effects could detect part of the source of the unobserved heterogeneity. In such a context, apparently, those hospitals do not present any peculiar characteristics.

The graphical test is not sufficient to determine if the frailty component is statistically significant. Given that the value of the statistics $\chi^2_{1,0.1}$ is equal to 1,275.785, we can conclude that the frailty component in the model is needed (p-value <0.001 at 5% significance level).

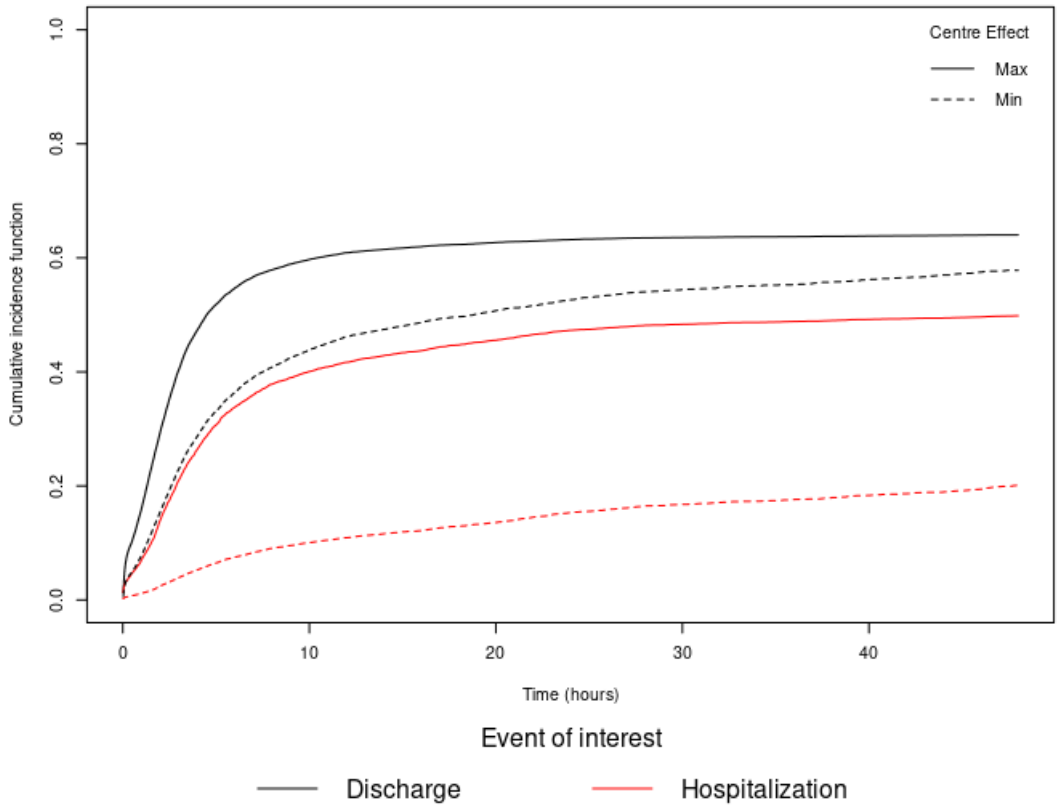


FIGURE 4.3: CIFs by minimum (dashed lines) and maximum (solid lines) centre effect, predicted from the competing risks frailty model, considering accesses with Blood Diseases (Blood_Dis) computed for discharge (red lines) and hospitalization (black lines).

4.5 Discussion

Overcrowding in emergency department is a multi-factorial phenomenon. For this reason, there is no complete agreement on what determines the overcrowding in literature. Several authors tried to identify the causes of overcrowding analyzing different aspects of the process.

This work focused on the identification of the factors associated with the risk of Discharge and Hospitalization in order to identify the so-called bottlenecks. We used a competing risks analysis including 7 pathologies (made by aggregating ICD-9 codes appropriately) as covariates and correction factors such as Age, time of arrival at ED, season

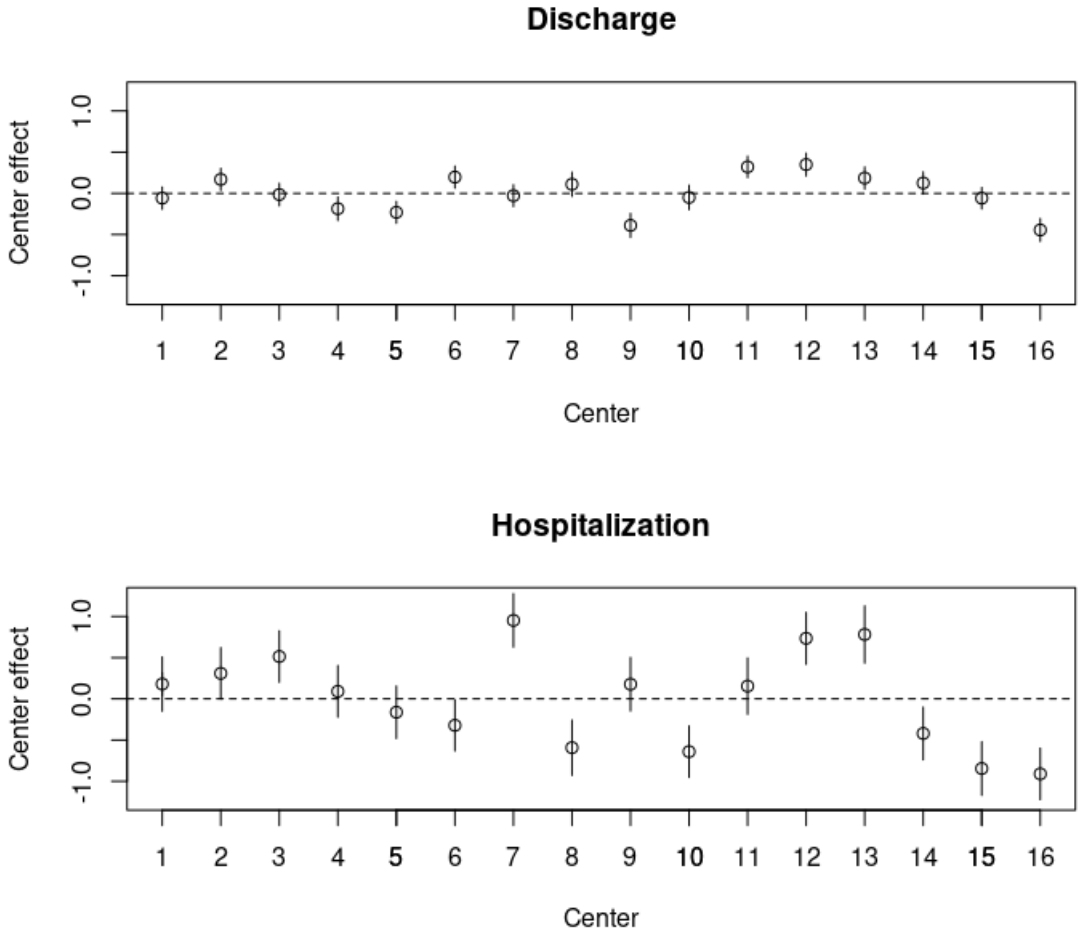


FIGURE 4.4: Centres effect estimates and CI 95% extracted from the Cause-specific frailty model according to the event of interests (Discharge and Hospitalization).

and type of arrival and repeated accesses.

The main assumption is that, among 16 hospital in Sicily, there is an amount of heterogeneity that cannot be observed. To assess for this amount we add an extra frailty component in the competing risks model.

We found that the pathology is an important factor affecting overcrowding. We are able to detect which pathologies have prolonged LoS with the respect to two endpoints: Discharge and Hospitalization (we didn't consider the Death because is a rare event); moreover, other factors, such Age and arrival mode and repeated accesses are associated with their risk occurrence. Despite the definition of a frequent user in the literature is still not clear [81], some papers [66, 88] defined them as patients who have made four or more visits during the previous 12 months. Repeated accesses, in this work, were defined as such if at least the second access occurred later than 4 hours from the first and before the end of the year 2019, thus, following one of the definitions provided in the literature for the repeated accesses could improve the competing risks model performance.

The estimated hazard ratios (HRs) provide further information to the ED's heads, indicating whether that characteristic affects positively or negatively the risk occurrence of the event. In particular, accesses with higher risk of Discharge or higher risk of Hospitalization should improve the ED management process (increasing the number of available beds in that specific ward, the number of medical personnel, ICU capacity, arranging admission or Discharge immediately after valuation or developing disease-specific protocols[28]).

In general, the information provided by the model coefficients (Table 4.6), predicted CIFs (Figure 4.2) and random effects estimates (Figure 4.4) should allow ED's heads to conduct appropriate policy making.

This work has several limitations. The competing risks framework allows to estimate the cause-specific hazards considering an initial state (Admission in ED) and more than one absorbing state (Discharge and Hospitalization). A multi-state model would consider the entire process inside ED considering admission as intermediate state and the Triage as initial (like in Figure 4.1).

Due to large computational times, we reduced the sample size to 410.133 to 15.191 extracted from 16 EDs out of 63 to consider only multi-speciality hospitals. Using a modeling approach allowing to exploit more data could improve the estimates precision and the predictive performance of the competing risks model, even though we found that the estimation procedure implemented in the *frailtyHL* R package requires larger computational times anyway. Finally, some important factors, assumed to be useful to analyze overcrowding, were not included in the EMUR dataset (for example the number of beds inside the wards).

The cause-specific model is useful to identify the factors associated with the occurrence of the events of interest, but there is no direct relationship between the model coefficient and a "direct" effect on the CIFs. Thus, in a situation where the aim is the prediction, estimating the sub-distribution hazard can be preferred.

Even if the statistical methodology used is valid in helping physicians to detect bottlenecks inside ED, the data used in this work do not represent the actual ED's dynamics. In one hand, using ED data during Covid-19 pandemic could be not useful to identify factors associated with Discharge and Hospitalization. Early reports from different countries suggested that, as the number of persons hospitalized with COVID-19 increased, sharp drops in the numbers of persons seeking emergency medical care for other reasons, [103]. On the other hand, we may face Covid-19 pandemic affection on overcrowding in ED still in future.

4.6 Conclusions

Overcrowding in ED is a worldwide issue. With the spread of Covid-19 pandemic, this issue becomes even more cumbersome to face. Our results aim to help ED's managers to act properly to reduce overcrowding, identifying the characteristics of bottlenecks.

Our findings provide quantitative and timely information to the EDs in order to analyze the bottlenecks causing overcrowding. An important risk factor for overcrowding is the pathology, as the CIFs associated to the seven ICD-9 macro categories show very different patterns.

From a statistical point of view we believe that competing risks analysis is a valid tool to describe the process and to predict LoS starting from admission in ED. The reduction to a small sample size, due to large computational times, suggests further research on the identification of statistical tools able to address for more data in reasonable computational times.

Chapter 5

Vertical Model in presence of random effects using R-INLA: an alternative approach to the competing risks frailty model

5.1 Introduction

Vertical model is considered a valid alternative to the competing risks approach. The focus is on the joint probability of time to failure T and the cause of failure D (denoted as $P(T, D)$). These two components are observed, namely relative hazard and overall hazard, and can be easily estimated through a multinomial regression model and a cox proportional hazard model when accounting for covariates.

The Vertical Model has been implemented as an alternative to the competing risks model especially when the proportionality assumption is relaxed[97] or in presence of a missing cause of failure [98]. In this work, we extended the standard Vertical Model including a random component (V_i, U_i) inside the model to take into account the unobserved heterogeneity that can arise in presence of clustered data. We used the EMUR (EMergenze-URgenze) database, which includes Emergency Department accesses from 63 Sicilian EDs, to analyze the risk of being Hospitalized or Discharged during the Length of Stay (LoS), once admitted to Hospital, in a multi-center setting.

Assuming a correlation degree between the couple (V_i, U_i) we considered a JVMM. The value of (V_i, U_i) can provide insights from a single Hospital point of view. Moreover, the correlation coefficient of (V_i, U_i) provides information from a multicentre perspective.

Due to the large computational times, that occurred considering a frequentist approach, we decided to implement a JVMM using R-INLA, which uses a Bayesian approach to approximate the posterior distribution of the hyperparameters.

In the last decades, interest in approaching the frailty models from a Bayesian point of view has grown. The first discussion on frailty model with Bayesian inference date back to 1991 [33]. More recently, several papers introduced the frailty competing risks model with a Bayesian approach. To carry out such analysis, the specification of a prior distribution for the vector of parameters is needed to get the posterior distribution through the observed data, expressed by the likelihood function. Due to the complexity of the frailty model likelihood, obtaining the posterior distribution is not simple. Zhang et.al. [161] developed a Gibbs sampling algorithm to sample from the posterior distribution, in order to carry out posterior inference. A similar approach has been conducted by other authors to estimate the posterior probability of dying from gastroenterological diseases in different Iranian regions [68]. In the Bayesian setting, interest has grown in applying *INLA* (Integrated Nested Laplace Approximation) in the last five years on censored data. Such an approach is based on the INLA methodology developed by Rue et al. [121], and provides computational efficiency by using sparse representations of high dimensional matrices used in latent Gaussian models (LGM). The main advantage of using INLA is represented by the lower computational times to obtain the posterior distribution of the parameters. Indeed, the Laplace approximation is used to approximate the intractable joint posterior density that can arise in case of non-Gaussian likelihood. Recently, INLA has been hugely used to estimate survival joint models, as a fast and efficient alternative to Markov Chain Montecarlo (MCMC) approach, to account for multivariate longitudinal outcomes and competing risks.

We applied the JVMM using the *inla* function from *R-INLA* package to approximate the posterior distribution of the parameters (such as the pathology) and the correlation coefficient ρ_{u_i,v_i} among 63 Sicilian hospitals.

To date, this is the first attempt at dealing with Vertical Model using INLA. As a matter of fact, INLA is applied more to estimations of joint models for longitudinal and survival parts [90, 122, 120, 141]. Within the realm of joint longitudinal-survival models, users have a choice of various computational approaches. The *joineR* library in R is widely used to fit joint models from a frequentist point of view whereas the *JMBayes* library facilitates Bayesian estimation of joint models. The *joineR* library can even accomodate competing events in the survival submodel. Others used *R-INLA* to deal with joint competing risks model [100]. In terms of partially linear joint models the *JointModel* library was developed to fit non-linear covariate effects in the longitudinal submodel using B-splines with a sieve approximation. The *bamlss* library can also be used to fit a

partially linear joint model using a Markov Chain Monte Carlo (MCMC) approach.

5.2 Data and computational issues

The data used come from the EMUR *(EMergenze-URgenze)* database (see section 4.2 for a brief description of the data). Differently from chapter 4, we included all 63 Sicilian Hospitals in our analysis. This chapter has different aims: first, we wanted to assess whether a correlation degree of the couple of random effects (V_i, U_i), included inside the Vertical Model, is present among hospitals, even if they have different characteristics (in terms of number of accesses, age or location). Second, we wanted to overcome the computational issues faced by implementing a frailty competing risks model (we reduced the sample size to around 10.000 of accesses coming from 16 EDs. See chapter 4 for more details. We first tried to compute a separate Vertical model including all the accesses in 2019 in Sicily but we faced large computational times (the Logit Mixed Model for the relative hazard took 72 hours to run with more than 1 million of rows). We, therefore, sampled systematically 154.055 accesses from the population of interest (k=8). We excluded 18.307 not appropriate accesses (17.194 accesses with Mental Disorders and 393 with Neoplasms).

To implement the JVMM we estimated separately the relative and overall hazard using, respectively, the *glmer* R function from *lme4* (the estimation of the relative hazard for Hospitalization took 2 hours) and the *coxme* R function from *coxme* (the frailty cox model took a few minutes to run).

To reduce again the computational time we considered a bayesian approach, based on INLA, which approximates the posterior distribution of the parameter (the JVMM using the *inla* routine from *R-INLA* package took 20 minutes).

5.3 Results from the separate Vertical Mixed Model

As explained in section 1.2.4, the SVMM can be performed assuming no correlation between the random effects (V_i, U_i), that is the random effects included in the two submodels (1.28 and 1.29). Such a model was already implemented, without considering a random component, either as an alternative to the standard competing risk model [97], especially when the proportionality assumption of the risks doesn't hold, and as a valid approach when missing cause of failures occurred [98].

The following results come from the estimation of the SVMM using a sample of 135.748 accesses from 63 Sicilian EDs to determine the probability of being Hospitalized (or Discharged) during the LoS once the patients are admitted to Hospital (see Figure 4.1). The model included the pathology, consisting of seven different macro-diagnoses

identified aggregating the ICD9 codes appropriately (see Table 4.2), the age and the arrival mode of the patients (by ambulance or by themselves) at the ED, as covariates. The latter represent correction factors for the pathology.

As we assumed that the effect of each pathology on the probability of being hospitalized (or discharged) is different during LoS, we included an interaction term between a smoothed function of LoS and the pathology in the model for the relative hazards. In particular, we've chosen a cubic spline with 5 knots that interpolates the relative hazard at the 5 quantiles of LoS (1%, 10%, 50%, 90% and 99%). The choice of the quantiles depends on the fact that the greatest part of the events occurred 1 hour until experience one of the events. Furthermore, we decided to include 5 knots to avoid computational increased times.

TABLE 5.1: Fixed coefficient estimates from the separated Vertical Mixed Model.

	Relative hazard estimates			Overall hazard estimates		
	lower (95%)	OR	upper (95%)	lower (95%)	HR	upper (95%)
Intercept	0,53	0,69	0,90			
Digestive Diseases	0,25	0,34	0,46	1,01	1,04	1,06
Infectious	0,21	0,35	0,58	0,97	1,01	1,05
Skin	0,05	0,08	0,12	1,60	1,65	1,69
Blood	0,33	0,87	2,32	0,71	0,74	0,78
Other_Symptoms	0,25	0,33	0,43	0,99	1,01	1,03
Injuries	0,08	0,10	0,14	1,53	1,56	1,59
Age	1,013	1,014	1,015	0,989	0,989	0,989
Arrival mode	2,56	2,65	2,75	0,64	0,65	0,66

For reason of an easier interpretation, we show, in Table 5.1, the fixed coefficient estimates, and their confidence interval at 95% significance level, of the SVMM with Hospitalization as event of interest. Concerning the pathology, Circulatory and Respiratory accesses (which is in the model the baseline characteristic) seem to have the highest probability of being hospitalized given admission to Hospital (all the other pathology's Odds Ratios are lower than 1). Accesses with Skin Diseases have the lowest probability of hospitalization (92% less than Circulatory and Respiratory). Furthermore, the older the patients the higher the probability of being hospitalized (1.4% per year), and accesses arrived through ambulance have higher probability of hospitalization (more than 2.5 times the accesses arrived by own means).

Further information can be provided by the overall hazard beta estimates. For example, accesses with skin diseases are the most likely to be admitted to Hospital (HR = 1.65), which also means to experience one of the events; on the contrary, accesses with blood diseases are the least likely to be admitted to Hospital (HR=0.74).

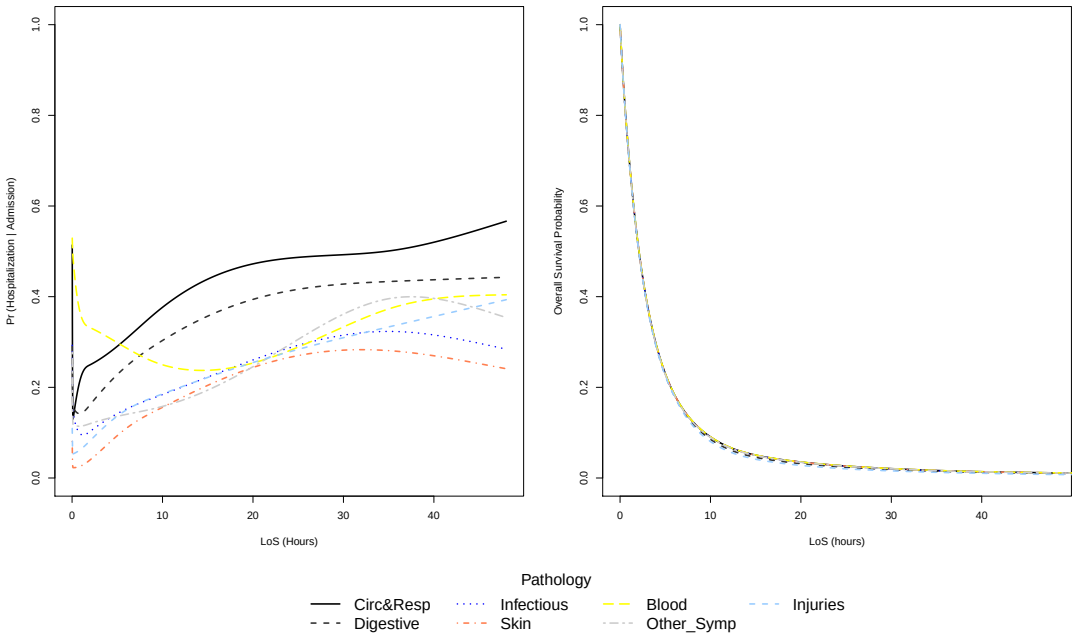


FIGURE 5.1: Predicted probability of being hospitalized given being admitted to Hospital during LoS, or relative hazards (left) and survival probability of being admitted to hospital, or overall hazard (right), according to pathology.

On the basis of the SVMM, the predicted relative hazard and the overall survival probability (obtained from the overall hazard function), for each pathology, can be computed (see Figure 5.1). From an interpretational point of view, the relative hazard and overall survival are complementary. In particular, the first (left panel in Figure 5.1) describes the behavior of the probability of being hospitalized, given being admitted to Hospital, during LoS, and the second, either in terms of a hazard or survival scale (right panel in Figure 5.1), describes, somehow, the intensity of the relative hazard during LoS (that is how many accesses remain at risk at a specific LoS time and how many are expired).

In such a context the overall survival probability is the same across pathologies with low median time (2 hours of LoS). This means that the 50% of accesses, whatever the pathology, are admitted to hospital since 2 hours of LoS. Going vertically to the relative hazard, a huge amount of those accesses are hospitalized (described by the big jumps of the smoothed curves in the first minutes of LoS). In ED's terms, those accesses should be the least severe and the decision to discharge them is immediate. On the contrary, the most severe accesses need to be visited, increasing the LoS and the probability of being

hospitalized. This is true for almost all the pathologies included in the model. Some of them, instead, show a sinusoidal pattern (Blood diseases and Symptoms). Table 5.2 shows the relative hazard value for the selected quantiles of LoS.

TABLE 5.2: relative hazard according to quantiles of LoS by pathology.

	quantiles of LoS (hours)				
	0,02	0,12	1,92	9,13	35,25
Circ & Resp	0,51	0,13	0,25	0,36	0,5
Digestive Diseases	0,29	0,15	0,16	0,29	0,43
Infectious	0,08	0,02	0,04	0,15	0,28
Skin	0,29	0,14	0,1	0,18	0,32
Blood	0,53	0,48	0,33	0,26	0,37
Other_Symptoms	0,28	0,12	0,12	0,15	0,39
Injuries	0,11	0,05	0,08	0,18	0,33

As mentioned in section 1.2.4, the cause-specific hazard can be computed by the reversal of $\pi_j = \frac{\lambda_j}{\lambda_.}$, thus the Cumulative Incidence Function (CIF) can be obtained as the product between the cause-specific hazard and the overall survival. Figure 5.2 compares the "median effect" CIFs by pathology according to Hospitalization and Discharge. The CIFs confirm that the great part of the accesses experiment an event in the first hours (the CIFs are flat after 10 hours of LoS). Comparing the CIFs by the different pathologies, we can state that accesses with Blood and Circulatory and Respiratory diseases have the highest probabilities of being hospitalized and lowest of being discharged. Finally, it seems, from a graphical point of view, that the CIFs are proportional, in contrast to those obtained in 4, Figure 4.2, highlighting one of the advantages of using the Vertical Model.

The couple of random effects (V_i, U_i) estimated from the SVMM are shown in Figure 5.3. The scatterplot, which includes each Hospital effect on the two sub-models, confirms that the Vertical model is under an uncorrelation assumption between the random effects $(\rho = 0.09)$. This assumption is confirmed by a non deterministic pattern of the couple of random effects inside the scatterplot as well.

The interpretation of each Hospital effect is not straightforward. For a single Hospital, negative values for both (V_i, U_i) would mean that the Hospital experiences one of the possible event slowly (given by a lower overall hazard) with a lower probability of hospitalization (given by a lower relative hazard). On the contrary, positive values for both (V_i, U_i) would mean that the Hospital experiences quickly one of the events (meaning a higher overall hazard), with a higher probability of hospitalization (meaning a higher relative hazard).

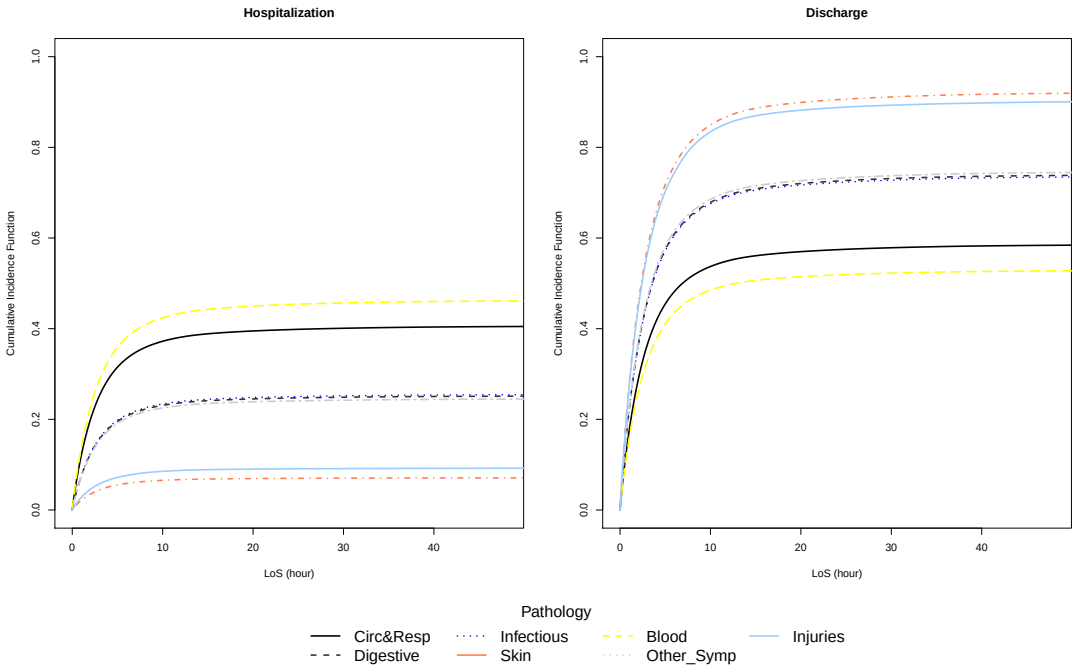


FIGURE 5.2: Cumulative incidence function by pathology predicted by the SVMM.

5.4 Results from the JVMM using R-INLA

Differently from section 5.3, we estimated a JVMM assuming a correlation degree between the random effects (V_i, U_i) included in the two sub-models. To do that, we considered the model as a LGM (See section 1.2.4). The binomial distribution was chosen to model the probability of being hospitalized given admission to Hospital (relative hazard in the Vertical Model), the log-normal distribution for the survival times (overall hazard in the Vertical Model). The latter is implemented in *R-INLA* package under the parametric hazard function assumption. We chose a non-informative prior distribution (Wishart) for the precision matrix hyperparameters (See Appendix D for more details about the prior distributions considered in the model). In terms of covariates included, the JVMM is identical to its separate version in section 5.3. We again considered to include the interaction term between the pathology and a smoothed function of LoS in the relative hazard's sub-model. In this case we have chosen different quantile knots (that are 1%, 16%, 33%, 50% 66% and 88%) because those used in the separate VM provided to much large standard errors.

Table 5.3 includes the fixed effects coefficients (either for the relative and the overall hazard) estimated by INLA.

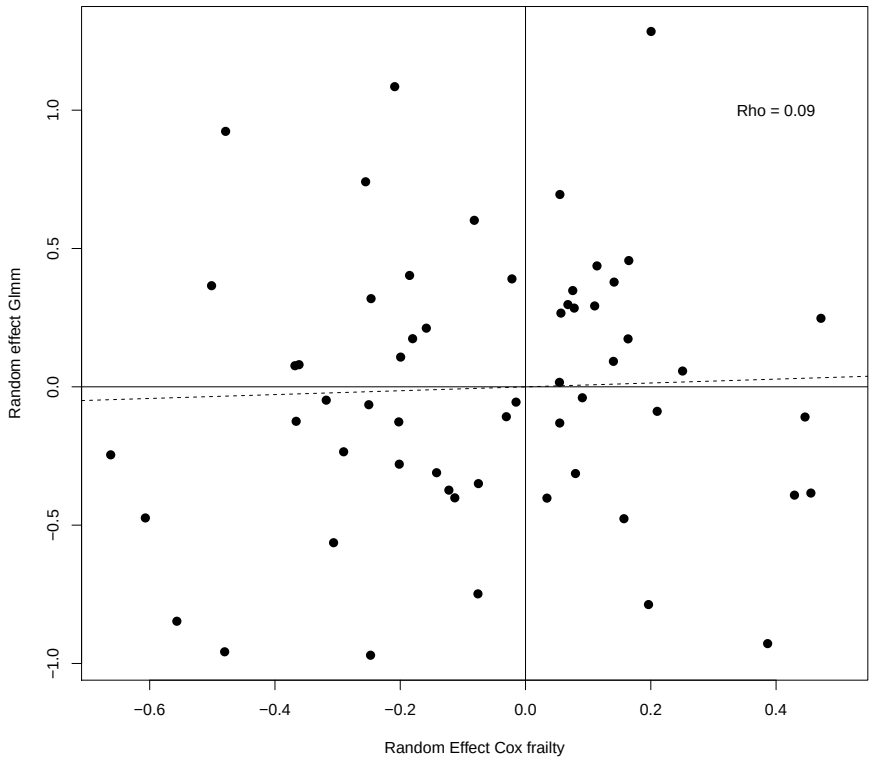


FIGURE 5.3: Scatterplot of the random effects (V_i, U_i) from the SVMM.

TABLE 5.3: Estimate coefficients of the Joint Vertical Mixed Model by INLA.

	Relative hazard estimates			Overall hazard estimates		
	0,025 q	mean	0,975 q	0,025 q	mean	0,975 q
Intercept	0,14	0,17	0,21	0,57	0,73	0,93
Digestive Diseases	0,63	0,75	0,89	0,93	0,97	1
Infectious	0,53	0,72	0,96	0,88	0,93	0,98
Skin	0,10	0,14	0,18	0,51	0,53	0,55
Blood	1,95	3,06	4,81	1,61	1,73	1,86
Other_Symptoms	0,53	0,62	0,72	1,05	1,08	1,11
Injuries	0,21	0,25	0,29	0,58	0,59	0,61
Age	2,54	2,64	2,73	1,94	1,99	2,03
Arrival mode	1,01	1,01	1,02	1,02	1,02	1,02

As noticed, the model returns the posterior distribution for each parameter included in the model, that is the mean (or the mode) and the credible interval quantiles (0,025 and 0,975) of the distribution. The mean of the posterior distribution can be compared with the estimates of the separate Vertical Model in Table 5.1. It is noticed that INLA provides quite different OR and HR coefficients than the previous method. For example, in terms of relative hazard accesses with blood diseases have 3 times the probability of being hospitalized than the reference category (0.87 in the separate VM). Coefficient differences between the two methods are present also in terms of overall hazards. Again, INLA estimated an overall hazard mean for Blood diseases accesses of 1.73 against 0.73 in the SVMM.

As already stated, INLA approximate the posterior distribution of the model parameters and hyperparameters.That is why we need to explore such a distribution to get summary statistics of the parameters. Figure 5.4 shows the posterior distribution, with the credible interval indicated by the blue line), of Digestive diseases in both sub-models. The negative sign in both sub-models indicates that those accesses have a lower risk of being admitted to Hospital and a higher probability to be hospitalized than the reference category (represented by Circulatory and Respiratory diseases).

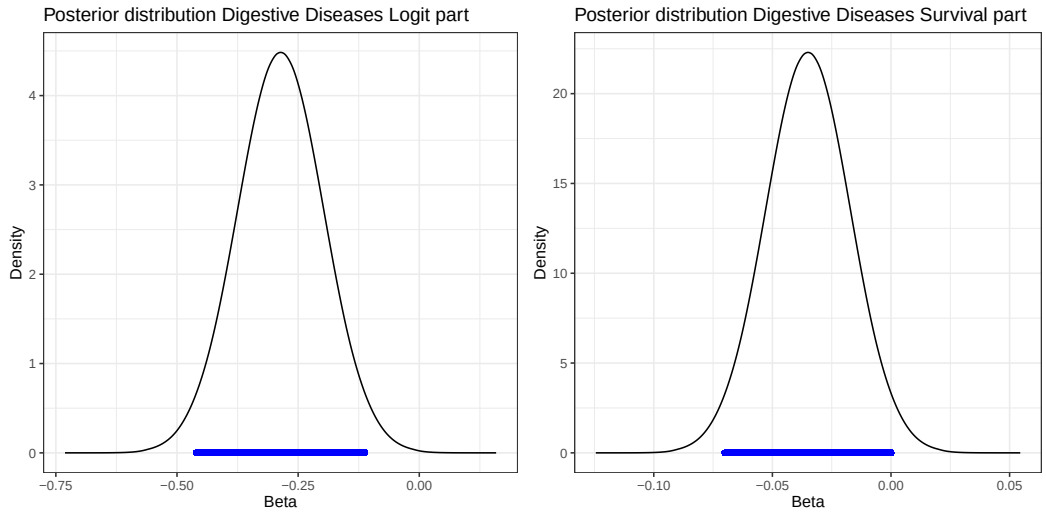


FIGURE 5.4: Posterior distribution of digestive disease parameter for the GLMM model part (left) and the Survival model part (right).

The relative and overall hazard according to pathology predicted by INLA are shown in Figure 5.5. The biggest difference with 5.1 relies on a general lower probability of hospitalization given admission to Hospital ,over LoS, for all the pathologies, and on the fact that patholgies have different overall survival probabilities. For example, accesses with skin related diseases have the lowest probability of hospitalization and the highest

probability of survive to admission to Hospital. From a ED's point of view, these accesses experience prolonged times inside the Emergency Room before admission to Hospital, to be, then, discharged with high probability.

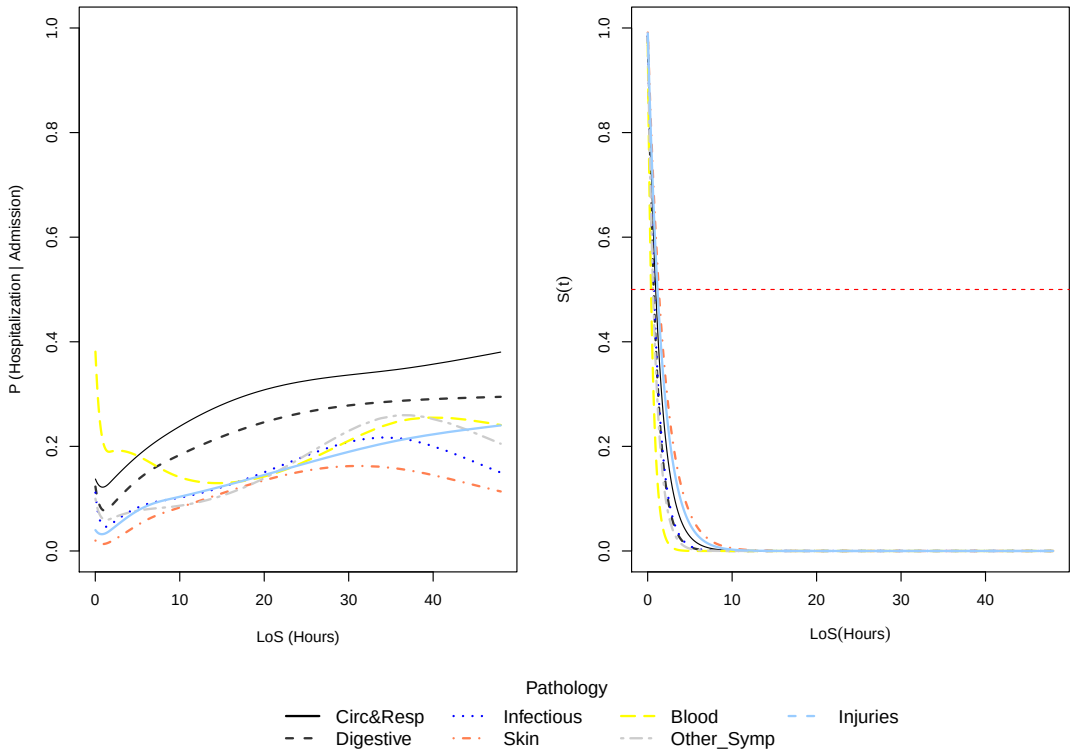


FIGURE 5.5: Predicted probability of being hospitalized given being admitted to Hospital during LoS, or relative hazards (left) and survival probability of being admitted to hospital, or overall hazard (right), according to pathology.

The CIFs shown in Figure 5.6 describe a different pattern than its separate version (Figure 5.2). Apparently, hospitalized accesses have lower LoS after admission to Hospital than discharges. Skin diseases related accesses confirm to have the lowest probability of hospitalization and the highest of discharge; while, on the contrary, Blood diseases confirm to have the highest probability of hospitalization. Differently from Figure 5.6, accesses with Circulatory and Respiratory diseases are not among the pathologies with the highest hospitalization probabilities during LoS.

As expected, the posterior distribution of $\tilde{\rho}_{u_i v_i}$, shown in Figure 5.7, is asymmetric and the credible interval lies in the negative realm (the posterior distribution mean is -0.84 (credible interval = [-0.92;-0.63]), meaning that negative centre effects in the binomial

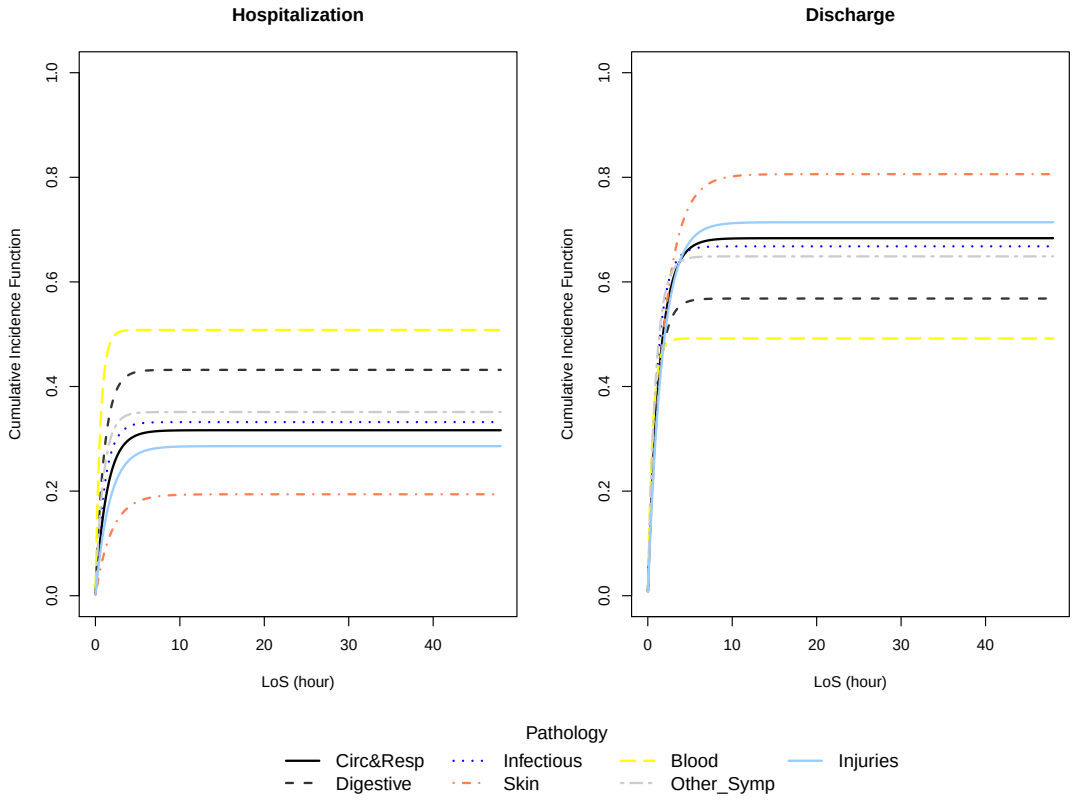


FIGURE 5.6: Cumulative incidence function by pathology predicted by the JVMM.

part tend to have positive frailty in the survival one or that positive centre effects in the binomial part tend to have a negative frailty.

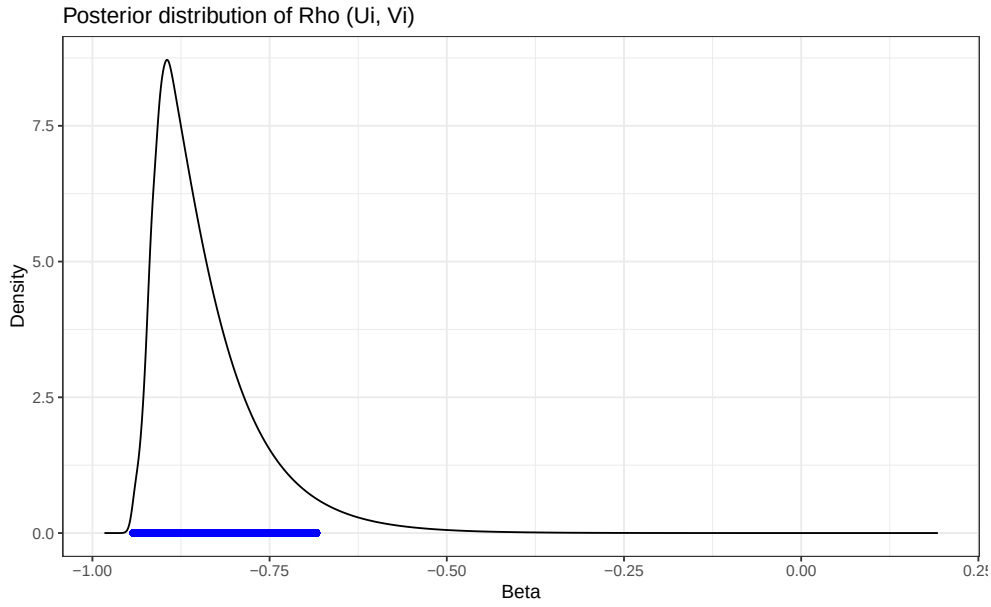


FIGURE 5.7: Posterior distribution of the Rho parameter estimated by INLA.

Figure 5.8 shows the scatterplot of the couple of random effects (V_i, U_i) estimated by INLA. It is noticed that there is a negative relationships between the random binomial part and its survival counterpart, confirming the negative value of ρ_{v_i,u_i}. This means that in hospitals with negative frailty the admission in Hospital occurs quickly and they are more likely to hospitalize (due to a positive random effects in the binomial part) and means that in hospitals with negative frailty the admission in Hospital occurs slowly with a corresponding lower probability of hospitalization.

5.5 Discussion

We have proposed a novel approach for conducting competing risks analysis that incorporates a random component to account for unobserved heterogeneity. The frailty competing risks model, commonly used for this purpose, can be computationally demanding, requiring either an EM-algorithm [123] or maximizing the H-likelihood [64]. However, the extended time needed to compute this model motivated us to seek a faster alternative that can handle larger datasets. Thus, we developed the Vertical model, which offers improved computational efficiency and scalability to accommodate more data. In general, the Vertical model is particularly useful when missing cause of failure occurs

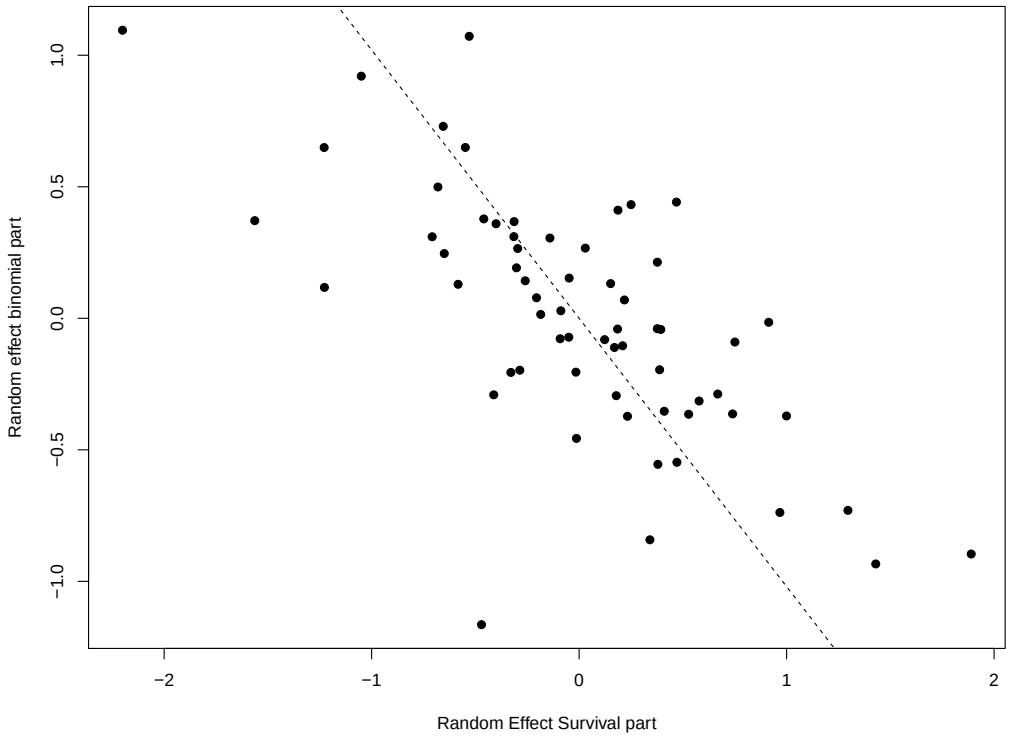


FIGURE 5.8: Scatterplot of the random effects (V_i, U_i) from the JVMM.

or when the proportionality assumption has to be relaxed. We applied a Vertical Model which accommodates for a random component using Sicilian EDs' accesses, included in the EMUR database, to predict the probability of being Hospitalized vertically by predicting, first, the risk of being admitted to Hospital. The random component is represented by the 63 Sicilian Hospitals.

Two ways to compute a Vertical mixed model are proposed. First, the SVMM, assuming that the two random variables, one for each sub-model, are not related. To perform a SVMM, a model for the relative hazard (a GLMM with a binomial response) and for the overall hazard (a frailty Survival regression model considering the events of interest as one) are necessary. We first tried to perform such a model with all the rows included in the EMUR database but the GLMM took 3 days to run. We then decreased the sample size to 135.748 rows sistematically extracted from the population. This model took around 2 hours to run.

Second, the JVMM, assuming a correlation degree between the couple (V_i, U_i). We proposed a fast Bayesian-based approximation approach to estimate the hyperparameters of the joint likelihood (composed by a binomial part and a survival one) using R-INLA. INLA took around 20 minutes to obtain the parameter posterior distributions.

From a comparison point of view between the SVMM and the JVMM, the results may change because of some differences: first, the survival sub-models are different. While we used a semi-parametric frailty model performed by the *coxme* routine in the *coxme* R-package in the SVMM Vertical Mixed Model we considered a parametric survival model, in the JVMM, assuming a lognormal distribution for the time of interest. We tried to perform a semi-parametric survival model but the *inla* routine from *R-INLA* crashed.

Second, given INLA provided large standard errors including the same knots to construct the splines as in the SVMM, we considered different spline knots in the JVMM.

Third, the two model estimation procedures are different. In particular, in order to obtain the parameter estimates in a SVMM, maximizing the two sub-model likelihoods independently is needed. On the contrary, the implementation of a JVMM involves an approximation of the posterior hyper-parameters distribution, considering a joint likelihood and a prior distribution.

Thus, the fact that the two models' estimates are quite different should not be surprising (See Table 5.1 and 5.3). The differences in the beta coefficients are reflected in the predicted quantities we computed on the basis of the two models. In particular, accesses with Circulatory and Respiratory Diseases have the highest probability of Hospitalization given being admitted to Hospital (see Figure 5.1 and one of the highest CIF among the other pathologies (see Figure 5.2) in the SVMM. The same does not hold in the JVMM (See Figure 5.5 and 5.6). This mismatch between the two models must be further assessed.

The estimation of ρ_{v_i,u_i} is crucial. From a statistical point of view, it represents the degree of correlation between the two sub-models. From a healthcare point of view, it provides key information about the centers. In particular, we estimated a negative ρ_{v_i,u_i} meaning that hospitals, which admit to Hospital quickly, tend to hospitalize less likely and that hospitals, which admit to Hospital slowly, tend to hospitalize more likely. Even though the results are attractive, care needs to be done when dealing with INLA, which is often defined as a black box [89]. That is why a simulation study would be helpful to verify the goodness of the model. Further analysis would also regard the presence of association between the value of the couple (V_i, U_i) and some specific type of hospital (in terms of size, number of available beds, and location). Moreover, the knowledge of (V_i, U_i) for the single hospital could be used for comparison purposes with the others.

5.6 Conclusions

The Vertical Model is a useful tool that can be used alternatively to the "standard" competing risks approach, depending on the research aim. When accounting for random effects and a large sample size, the Joint Vertical Mixed Model using INLA represents a fast alternative to the well-known competing risks frailty models, even though it is based on an approximation approach. In order to understand the performance of INLA with the respect to the maximizing likelihood approaches, further analysis should be employed.

The estimation of ρ_{v_i,u_i} represents the main result of this work. Using the Sicilian EDs database we found a negative value of ρ_{v_i,u_i} but care needs to be done about the goodness of the model performed with R-INLA. Finally, applying the JVMM to data coming from other Italian regions or even from another European country could provide more insights on the phenomenon.

Conclusions

This work focuses on the application of competing risks models in healthcare and clinical data analysis. These models extend the classical survival analysis approach by considering studies where more than one event of interest may occur. We discuss three approaches to competing risks modeling: cause-specific, sub-distribution hazard model, and Vertical model. While there have been debates in the literature about which approach is best, it is now commonly accepted that the choice of approach should depend on the research goals and objectives. The first approach is a direct extension of the Cox regression model, where subjects who do not experience the event of interest are considered censored. This method is more suitable for investigating the association between risk factors and the occurrence of outcomes. The second approach involves an unnatural construction of the risk set and is more appropriate for prediction purposes, as there is a one-to-one relationship between the estimated coefficients and CIF. The third approach is an alternative to the first two models, used particularly when the proportionality assumption is violated or when there are missing causes of failures. The latter approach is known as the Vertical model. In addition to the three main approaches to competing risks modeling, this work also introduced a distinction between the "standard" and "extended" competing risks models.The standard model adjusts only for fixed effects, while the extended model incorporates a random component to appropriately account for unobserved heterogeneity, particularly in multi-center studies.

The first two chapters of this work (Chapter 2 and Chapter 3) focused on applications of the standard competing risks model, while Chapters **??** and **??** discussed extensions of the model.

In Chapter 2, we presented a Fine and Gray model to identify the risk profiles for in-hospital mortality in COVID-19 patients, considering discharge as a competing event. The analysis was based on data from a center located in Lombardy, the first Italian region to face the pandemic emergency.

The results of the study have significant implications for clinical decision-making in the management of COVID-19 patients. By identifying the factors associated with in-hospital mortality, our findings can support clinicians in identifying patients at higher risk of adverse outcomes and tailoring their treatment accordingly.

Moreover, our study sheds light on the effectiveness of certain treatments, such as hydroxychloroquine, during the early stages of the pandemic when vaccines were not yet available. This information can inform future treatment protocols and help clinicians make evidence-based decisions in the management of COVID-19 patients.

Overall, our study highlights the importance of applying competing risks models to healthcare data to improve our understanding of complex clinical outcomes and inform evidence-based decision-making in clinical practice.

Chapter 3 represents a continuation of the work described in chapter 2, where we investigated the risk factors associated with in-hospital mortality in COVID-19 patients using data from a single center in Lombardy. In chapter 3, we expanded our analysis to include data from three centers, two located in Lombardy and one in Latium.

Using a Fine and Gray model, we developed a prediction rule for in-hospital mortality based on factors easily obtainable at admission. We validated the prediction rule using an external cohort from a hospital located in Latium. Furthermore, we developed a web application based on a prediction rule, which can support clinicians and hospital managers in predicting in-hospital mortality in different clinical contexts during the first wave of the COVID-19 pandemic.

Our work in chapter 3 represents an important step forward in the application of competing risks models to healthcare data. By developing a prediction rule for in-hospital mortality in COVID-19 patients, we can assist clinicians in making evidence-based decisions and allocate resources more efficiently in the management of the pandemic.

In chapter 4, we applied a cause-specific frailty model to investigate the overcrowding issue in 16 emergency departments (EDs) in Sicily. Our analysis showed that the type of diagnosis or pathology, classified into 7 macro categories, is significantly associated with the risk of hospitalization and discharge. Specifically, we found that patients with circulatory, respiratory, and blood diseases had the highest risk of hospitalization during their length of stay (LoS) and the lowest risk of discharge. These findings, adjusted for covariates such as age, time of arrival, arrival mode, and repeated accesses, provide valuable insights for ED managers to allocate resources effectively and reduce overcrowding. However, due to the large computational time required, we had to reduce the sample size from 410,133 to 15,191 accesses. Addressing this issue by developing statistical models with shorter computational times remains a problem.

In chapter 5, we introduced a novel approach called the Vertical mixed model as an alternative method for analyzing ED access data. This model is an extension of the Vertical model. We applied this model to analyze nearly 1 million accesses from 63 Sicilian EDs. The model converges into a solution in 72 hours. To reduce computational time, we reduced the sample size to 154,055 accesses. First, it estimates the overall and relative

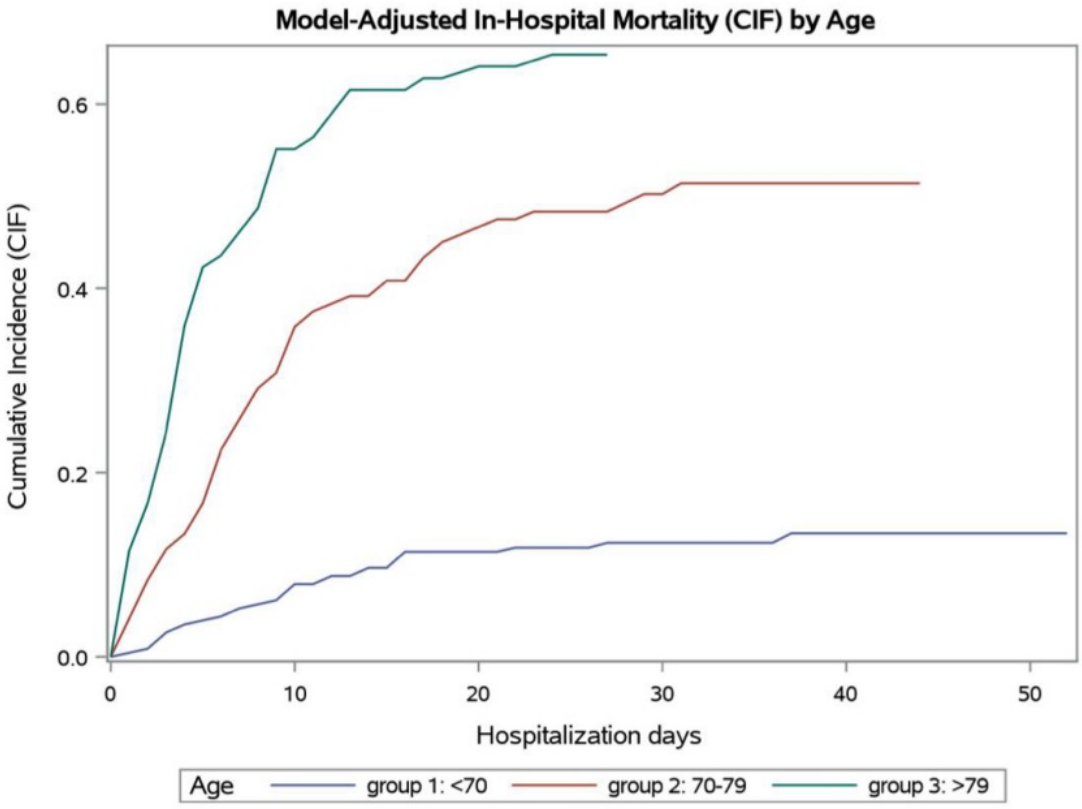
hazards separately (SVMM). Second, to address the correlation among the sub-models' random effects, we developed the Joint Vertical Mixed Model (JVMM). The Bayesian approach, which utilized the Integrated Nested Laplace approximation to obtain the posterior distribution of the hyperparameters, provided a fast procedure for estimating the JVMM.

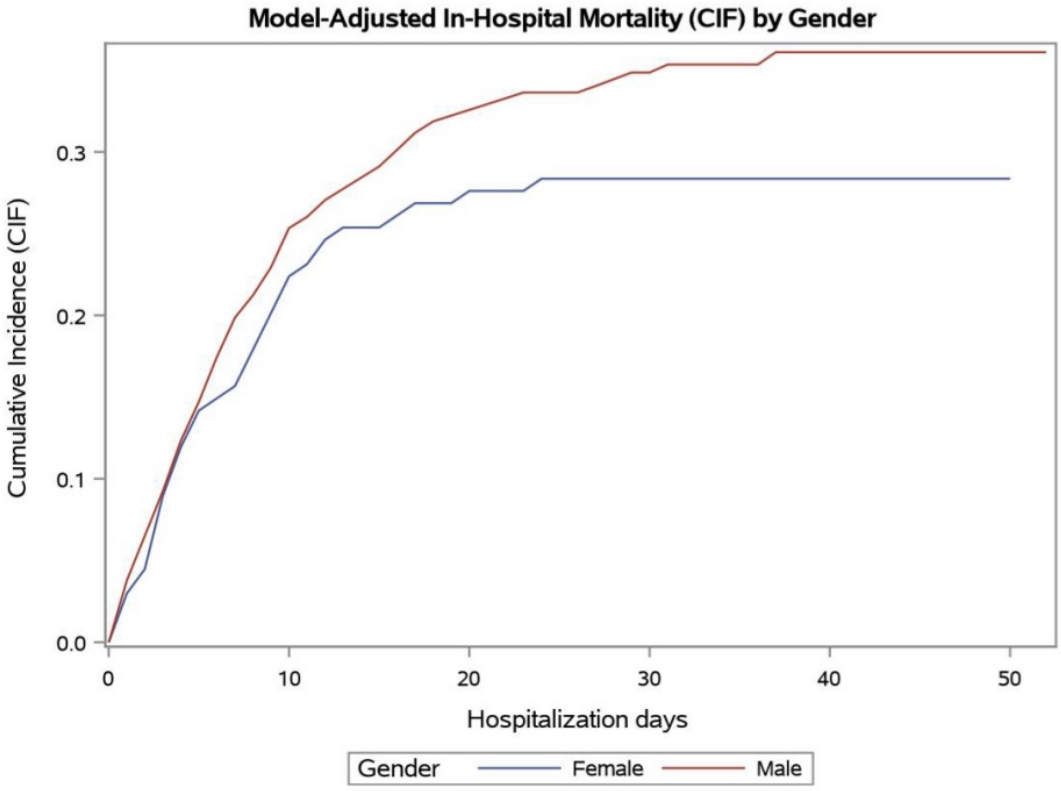
As expected, the JVMM's results coming from the reduced sample were similar to those obtained in chapter 4. The JVMM provided an additional advantage in the estimation of ρ, which indicated how the random effects of EDs were related. We found that hospitals with higher risks of exit from their EDs were less likely to hospitalize patients, whereas hospitals with lower risks of exit from their EDs were more likely to hospitalize patients.

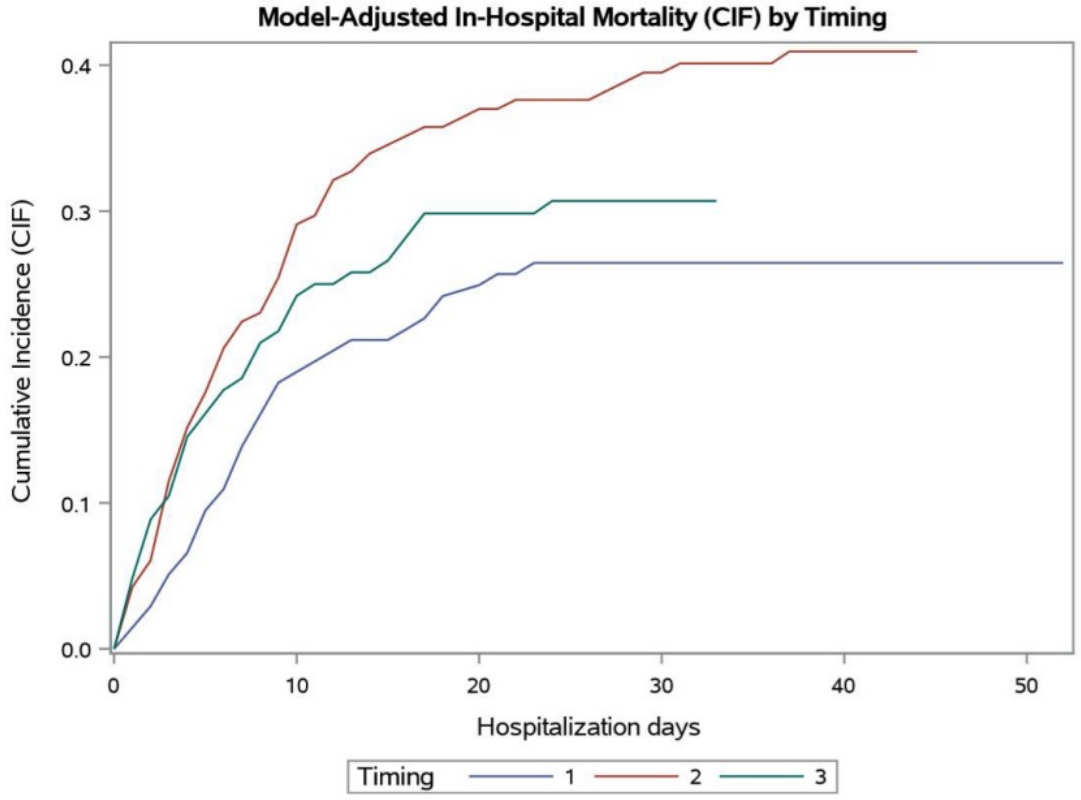
Our approach, the JVMM, is estimated using *INLA* and provides fast coefficient estimates, despite being based on an approximation approach of the posterior distribution. The novelty of this approach consists of an alternative to the usual frailty competing risks approach. We believe that the Vertical Model and its developments are a promising alternative to the open problems present in the Cox and Fine-Gray approaches. However, it is important to acknowledge that the "extended" version of the Vertical Model is both a novelty and a limitation, as it has not yet been completely validated in other settings and applications.

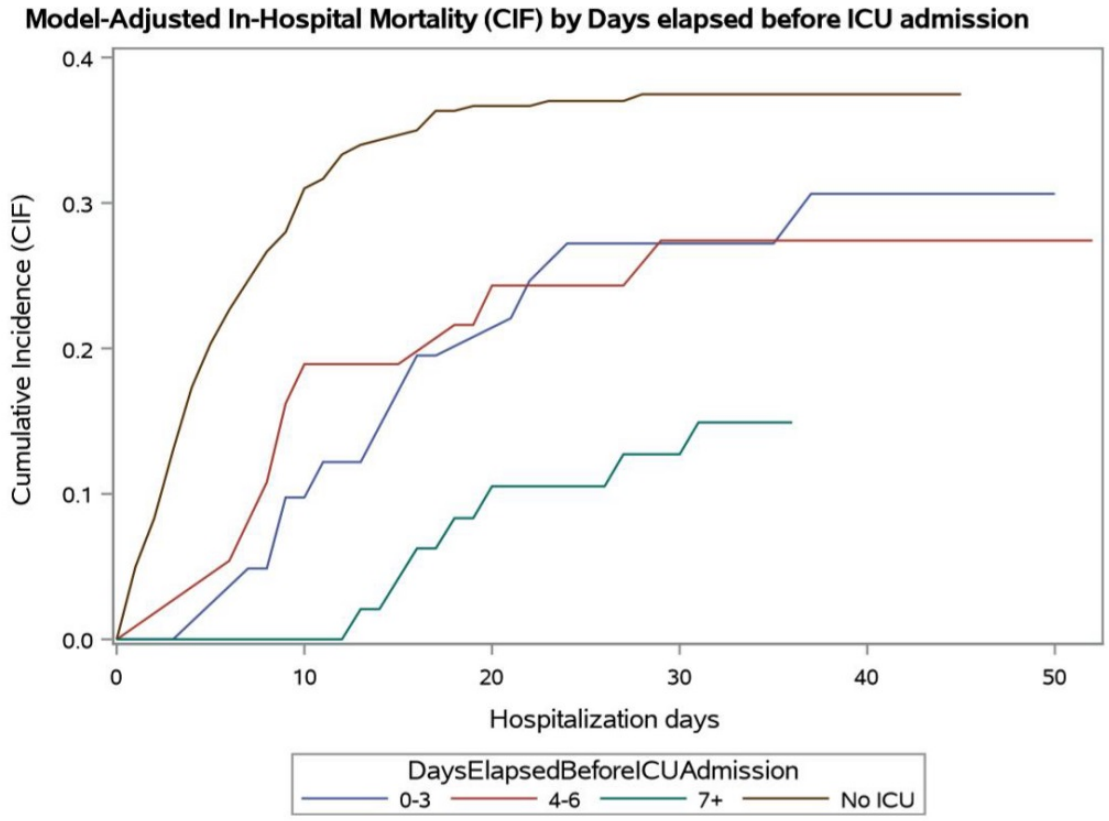
Appendix A

Supplementary material of Chap.2




Model-Adjusted In-Hospital Mortality (CIF) by Gender
Cumulative Incidence (CIF)
0.0
0.1
0.2
0.3
0
10
20
30
40
50
Hospitalization days
Gender
Female
Male


Model-Adjusted In-Hospital Mortality (CIF) by Timing
Cumulative Incidence (CIF)
0.0
0.1
0.2
0.3
0.4
0
10
20
30
40
50
Hospitalization days
Timing
1
2
3


Model-Adjusted In-Hospital Mortality (CIF) by Days elapsed before ICU admission
Cumulative Incidence (CIF)
0.0
0.1
0.2
0.3
0.4
0
10
20
30
40
50
Hospitalization days
DaysElapsedBeforeICUAdmission
0-3
4-6
7+
No ICU

Appendix B

Supplementary material of Chap.3

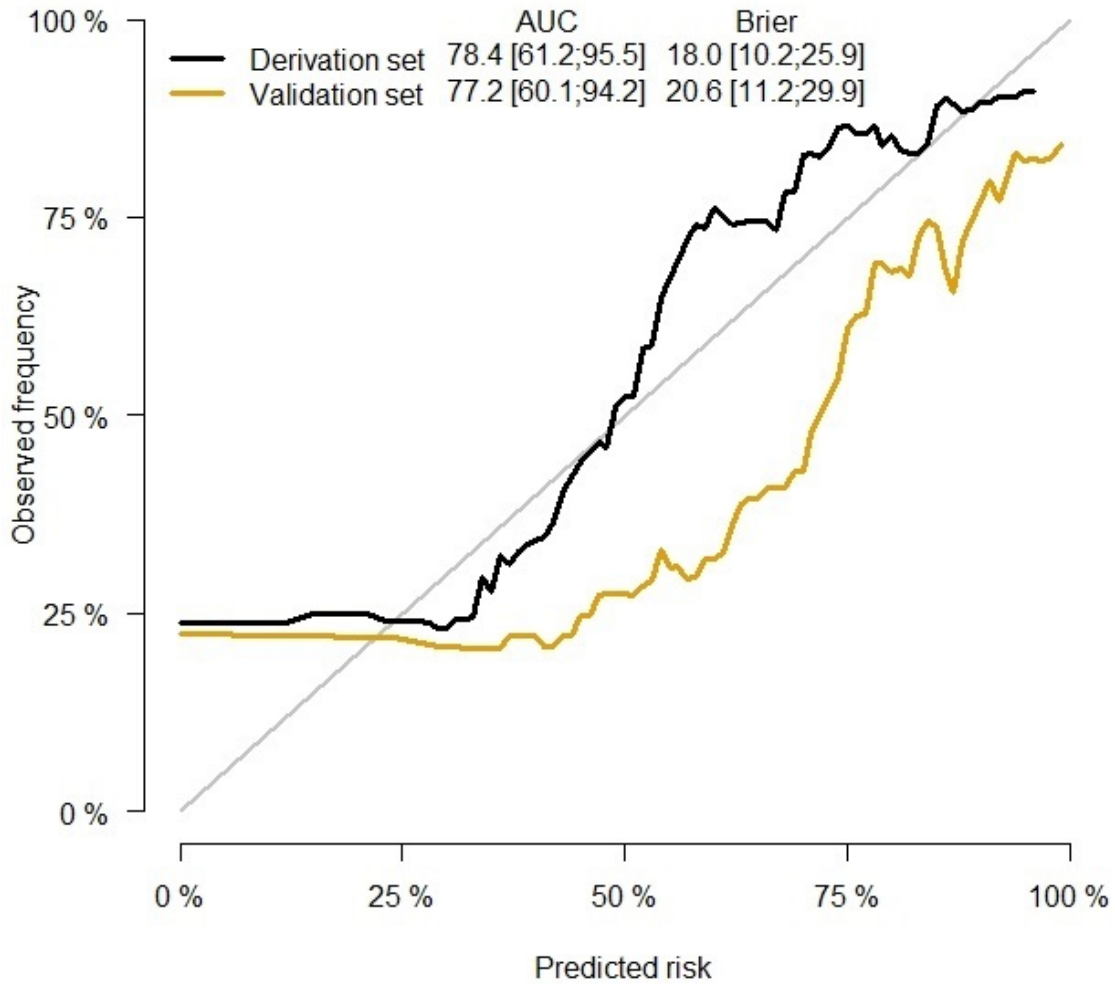


FIGURE B.1: Calibration curves for predicting Discharge in patients with Coronavirus Disease-19 in the derivation and validation cohorts.

Appendix C

Supplementary information of chapter 4

C.1 Computation of the predicted CIF from a hlike.frailty R object

```
## hlike_obj is the hlike.frailty object which includes
##all the quantities estimated by the model
## the baseline cause-specific hazard "lam1" and "lam2" and the time-to-event
#"TIME" are picked up from the model
lam1<-hlike_obj$lambda.0[[1]]
lam2<-hlike_obj$lambda.0[[2]]
TIME<-sort(unique(c(unlist(hlike_obj$time))))

## time-to-discharge "t1" and time-to-hospitalization "t2" are computed
t1<-TIME %in% hlike_obj$time[[1]]
t2<-TIME %in% hlike_obj$time[[2]]

## the cause-specific hazard wtr the two events "lambda1" and "lambda2"
lambda1<-rep(0,length(TIME))
lambda2<-rep(0,length(TIME))
lambda1[t1]<-lam1
lambda2[t2]<-lam2

## cumulative hazards
LAMBDA1<-cumsum(lambda1)
LAMBDA2<-cumsum(lambda2)

## overall cumulative hazard as the sum of
```

```
##the cumulative cause-specific hazards
LAMBDA=cumsum(lambda1)+cumsum(lambda2)

## from the survival analysis theory we got the overall survival "SURV0"
SURV0=exp(-LAMBDA)
tab_new<-data.frame(TIME,lambda1,lambda2,LAMBDA1,LAMBDA2,LAMBDA,SURV0)
## The cause-specific CIF is computed by the ##product of the overall
survival and the cause-specific hazard
tab_new$CIF_dim<-cumsum(SURV0*lambda1)
tab_new$CIF_ric<-cumsum(SURV0*lambda2)

## marginal CIF for Discharge and Hospitalization
plot(tab_new$TIME,tab_new$CIF_dim, type="s",ylim=c(0,1),xlim=c(0,50))
lines(tab_new$TIME,tab_new$CIF_ric, lty=2)

## 1) function fix_CIF computes the predicted CIF
## for different levels of the covariates
## 2) It needs the tab_new data frame constructed above, the estimated
## coefficient from the model for each event of interest
## "BETA1" and "BETA2" and a profile indicator vector "X"
## 3) The procedure is similar to the computation of the marginal CIF,
## but the covariates are included in the linear predictors
## "exp_effect1" and "exp_effect2"
## 4) the fuction fix_CIF provides i dataframes,
## inside a list, one for each level of the covariates
fix_CIF<-function(CIF0=tab_new,X=X_f,BETA1=beta_discharge,

        BETA2=beta_hospitalization)
{
  CIF<-vector("list",length(X))
  for(i in 1:length(X)){
    WCIF<-CIF0
    exp_effect1<-exp(drop(crossprod(X[i],BETA1[i])))
    exp_effect2<-exp(drop(crossprod(X[i],BETA2[i])))
    WCIF$lambda1<-WCIF$lambda1*exp_effect1
    WCIF$lambda2<-WCIF$lambda2*exp_effect2
    WCIF$LAMBDA1<-CIF0$LAMBDA1*exp_effect1
    WCIF$LAMBDA2<-CIF0$LAMBDA2*exp_effect2

    WCIF$LAMBDA<-WCIF$LAMBDA1+WCIF$LAMBDA2
    WCIF$SURV0<-exp(-(WCIF$LAMBDA1+WCIF$LAMBDA2))
    WCIF$CIF_dim<-cumsum(WCIF$SURV0*WCIF$lambda1)
```

```
    WCIF$CIF_ric<-cumsum(WCIF$SURV0*WCIF$lambda2)

    CIF[[i]]<-WCIF

  }
  return(CIF)
}

## profile vector indicator
X_f<-c(c(1,1,1,1,1,1),rep(54,1),rep(1,1),rep(1,1),rep(1,1))


f_CIF<-fix_CIF(CIF0=tab_new,X=X_f,BETA1=beta_discharge,

        BETA2=beta_hospitalization)


#fixed CIF for each pathology
layout(matrix(c(1,2,3,3), ncol=2, byrow=TRUE), heights=c(5, 1))

par(mar=c(5, 4, 3, 1) + 0.1)
plot(tab_new$TIME, tab_new$CIF_dim, type="s", xlim=c(0,48), ylim=c(0,1),
     xlab="Time␣(hours)", ylab="Cumulative␣incidence␣function",lty=1,
     lwd=1.5, main="Discharge")
for( i in 1:6){
  lines(f_CIF[[i]]$TIME, f_CIF[[i]]$CIF_dim, type="s",lty=i+1,
  col=i+1, lwd=1.5)
}
plot(tab_new$TIME, tab_new$CIF_ric, type="s", xlim=c(0,48), ylim=c(0,1),
     xlab="Time␣(hours)", ylab="Cumulative␣incidence␣function",lty=1,
     lwd=1.5, main="Hospitalization")
for( i in 1:6){
  lines(f_CIF[[i]]$TIME, f_CIF[[i]]$CIF_ric, type="s",lty=i+1,
  col=i+1,lwd=1.5)
}
par(mai=c(0,0,0,0))
plot.new()
legend(0.28,1, ncol=2,legend=c("Other_Symp","Circ&Resp_Dis", "Dig_Dis",
      "Inf_Dis","Skin&Musc_Dis","Blood_Dis",  "Inj&pois"),
       col=seq(1:7), title="Pathology",title.adj = 0.45, bty="n", lty=1:7,
       lwd=rep(2,9), cex=0.85)
```

Appendix D

Supplementary information of chapter 5

D.1 The Wishart prior distribution

Parametrization

The two-dimensional Wishart model is used if one want to define the model for the linear predictor η as:

$$\eta = a + b$$

where a and b are correlated

$$\begin{pmatrix} a \\ b \end{pmatrix} \sim N\left(0 \quad ,\mathrm{W}^{-1}\right)$$

with covariance matrix $W^{-1} = \begin{pmatrix} 1/\tau_b & \rho\sqrt{\tau_a\tau_b} \\ \rho\sqrt{\tau_a\tau_b} & 1/\tau_b \end{pmatrix}$

and τ_a, τ_b and ρ are the hyperparameters. In this case the following model is implemented for the precision matrix W

$$W \sim Wishart_p\left(\mathrm{r} \quad ,\mathrm{R}^{-1}\right), p = 2$$

where the Wishart distribution has density

$$\pi(W) = c^{-1}|W|^{(r-(p+1))/2} exp\left\{-\frac{1}{2}Trace(WR)\right\}, r > p+1$$

Hyperparameters

The hyperparameters are

$$\theta = (\log \tau_a, \log \tau_b, \tilde{\rho})$$

where

$$\rho = 2\frac{exp(\tilde{\rho})}{exp(\tilde{\rho}) + 1} - 1$$

See the R-INLA documentation https://inla.r-inla-download.org/r-inla.org/doc/latent/wishard.pdf for more details on the Wishart distribution.

Bibliography

[1] Odd Aalen, Ornulf Borgan, and Hakon Gjessing. *Survival and event history analysis: a process point of view*. Springer Science & Business Media, 2008.

[2] Odd O Aalen. "A model for nonparametric regression analysis of counting processes". In: *Lecture notes in statistics* 2.1 (1980), p. 25.

[3] Andrew Affleck et al. "Emergency department overcrowding and access block". In: *Canadian Journal of Emergency Medicine* 15.6 (2013), pp. 359–370.

[4] Marco Pollo Almeida et al. "Bayesian non-parametric frailty model for dependent competing risks in a repairable systems framework". In: *Reliability Engineering & System Safety* 204 (2020), p. 107145.

[5] Emanuele Amodio et al. "Diagnosis of influenza: only a problem of coding?" In: *Medical Principles and Practice* 23.6 (2014), pp. 568–573.

[6] Emanuele Amodio et al. "Emergency department performances during overcrowding: the experience of the health protection agency of Brianza". In: *AIMS public health* 5.3 (2018), p. 217.

[7] Per Kragh Andersen et al. "Competing risks in epidemiology: possibilities and pitfalls". In: *International journal of epidemiology* 41.3 (2012), pp. 861–870.

[8] Samia Arshad et al. "Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19". In: *International journal of infectious diseases* 97 (2020), pp. 396–403.

[9] E Asperges et al. "The COVID19 IRCCS San Matteo Pavia Task Force, rapid response to COVID-19 outbreak in Northern Italy: how to convert a classic infectious disease ward into a COVID-19 response centre". In: *J Hosp Infect* 105 (2020), pp. 477–479.

[10] Brent R Asplin et al. "A conceptual model of emergency department crowding". In: *Annals of emergency medicine* 42.2 (2003), pp. 173–180.

[11] Peter C Austin and Jason P Fine. "Practical recommendations for reporting f ine-g ray model analyses for competing risk data". In: *Statistics in medicine* 36.27 (2017), pp. 4391–4400.

[12] Peter C Austin, Aurélien Latouche, and Jason P Fine. "A review of the use of time-varying covariates in the Fine-Gray subdistribution hazard competing risk regression model". In: *Statistics in medicine* 39.2 (2020), pp. 103–113.

[13] Peter C Austin, Douglas S Lee, and Jason P Fine. "Introduction to the analysis of survival data in the presence of competing risks". In: *Circulation* 133.6 (2016), pp. 601–609.

[14] Peter C Austin, Ewout W Steyerberg, and Hein Putter. "Fine-Gray subdistribution hazard models to simultaneously estimate the absolute risk of different event types: cumulative total failure probability may exceed 1". In: *Statistics in Medicine* 40.19 (2021), pp. 4200–4212.

[15] Peter C Austin et al. "Estimation of the Absolute Risk of Cardiovascular Disease and Other Events: Issues With the Use of Multiple Fine-Gray Subdistribution Hazard Models". In: *Circulation: Cardiovascular Quality and Outcomes* 15.2 (2022), e008368.

[16] Theodor A Balan and Hein Putter. "A tutorial on frailty models". In: *Statistical methods in medical research* 29.11 (2020), pp. 3424–3454.

[17] Theodor Adrian Balan and Hein Putter. "frailtyEM: An R package for estimating semiparametric shared frailty models". In: *Journal of Statistical Software* 90 (2019), pp. 1–29.

[18] Karen Bandeen-Roche and Kung-Yee Liang. "Modelling multivariate failure time associations in the presence of a competing risk". In: *Biometrika* 89.2 (2002), pp. 299–314.

[19] Jamie Lopez Bernal et al. "Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study". In: *bmj* 373 (2021).

[20] Steven L Bernstein et al. "Development and validation of a new index to measure emergency department crowding". In: *Academic Emergency Medicine* 10.9 (2003), pp. 938–942.

[21] Jan Beyersmann, Arthur Allignol, and Martin Schumacher. *Competing risks and multistate models with R*. Springer Science & Business Media, 2011.

[22] Jean-Baptiste Bouillon-Minois et al. "Emergency department and overcrowding during COVID-19 outbreak; a letter to editor". In: *Archives of Academic Emergency Medicine* 9.1 (2021).

[23] Adrian Boyle et al. "Comparison of the International Crowding Measure in Emergency Departments (ICMED) and the National Emergency Department Overcrowding Score (NEDOCS) to measure emergency department crowding: pilot study". In: *Emergency Medicine Journal* 33.5 (2016), pp. 307–312.

[24] Justin Boyle et al. "Predicting emergency department admissions". In: *Emergency Medicine Journal* 29.5 (2012), pp. 358–365.

[25] Hua Cai. "Sex difference and smoking predisposition in patients with COVID-19". In: *The Lancet Respiratory Medicine* 8.4 (2020), e20.

[26] Rafael Calegari et al. "Forecasting daily volume and acuity of patients in the emergency department". In: *Computational and mathematical methods in medicine* 2016 (2016).

[27] Yanan Cao et al. "Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations". In: *Cell discovery* 6.1 (2020), pp. 1–4.

[28] Chung-Hsien Chaou et al. "Analyzing factors affecting emergency department length of stay—using a competing risk-accelerated failure time model". In: *Medicine* 95.14 (2016).

[29] Nanshan Chen et al. "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". In: *The lancet* 395.10223 (2020), pp. 507–513.

[30] Nicholas J Christian, Il Do Ha, and Jong-Hyeon Jeong. "Hierarchical likelihood inference on clustered competing risks data". In: *Statistics in medicine* 35.2 (2016), pp. 251–267.

[31] Pietro E Cippà et al. "A data-driven approach to identify risk profiles and protective drugs in COVID-19". In: *Proceedings of the National Academy of Sciences* 118.1 (2021), e2016877118.

[32] David E Clark and Louise M Ryan. "Concurrent prediction of hospital mortality and length of stay from risk factors on admission". In: *Health services research* 37.3 (2002), pp. 631–645.

[33] David G Clayton. "A Monte Carlo method for Bayesian inference in frailty models". In: *Biometrics* (1991), pp. 467–485.

[34] Helene Colineaux et al. "Why are people increasingly attending the emergency department? A study of the French healthcare system". In: *Emergency Medicine Journal* 36.9 (2019), pp. 548–553.

[35] Victor M Corman et al. "Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR". In: *Eurosurveillance* 25.3 (2020), p. 2000045.

[36] Jerome Cornfield. "Estimation of the probability of developing a disease in the presence of competing risks". In: *American Journal of Public Health and the Nations Health* 47.5 (1957), pp. 601–607.

[37] *Coronavirus disease (COVID-19) technical guidance: Laboratory testing for 2019-nCoV in humans*. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory^guidance. 2020.

[38] Giuliana Cortese and Per K Andersen. "Competing risks and time-dependent covariates". In: *Biometrical Journal* 52.1 (2010), pp. 138–158.

[39] David R Cox. "Regression models and life-tables". In: *Journal of the Royal Statistical Society: Series B (Methodological)* 34.2 (1972), pp. 187–202.

[40] Marcia Crosse. *Hospital emergency departments: crowding continues to occur, and some patients wait longer than recommended time frames*. Diane Publishing, 2010.

[41] A De Giorgi et al. "Prediction of in-hospital mortality of patients with SARS-CoV-2 infection by comorbidity indexes: an Italian internal medicine single center study". In: *Eur Rev Med Pharmacol Sci* 24.19 (2020), pp. 10258–10266.

[42] E Di Bella et al. "Frequent use of emergency departments and chronic conditions in ageing societies: a retrospective analysis based in Italy". In: *Population Health Metrics* 18.1 (Nov. 2020), p. 29. ISSN: 1478-7954. DOI: 10.1186/s12963-020-00237-w. URL: https://doi.org/10.1186/s12963-020-00237-w.

[43] Augusto Di Castelnuovo et al. "Low dose hydroxychloroquine is associated with lower mortality in COVID-19: a meta-analysis of 26 studies and 44,521 patients". In: *MedRxiv* (2020).

[44] Kevin K Dobbin and Richard M Simon. "Optimally splitting cases for training and testing high dimensional classifiers". In: *BMC medical genomics* 4.1 (2011), pp. 1–8.

[45] Andreas Ekström et al. "Forecasting emergency department visits using internet data". In: *Annals of emergency medicine* 65.4 (2015), pp. 436–442.

[46] Sandra Eloranta et al. "The application of cure models in the presence of competing risks: a tool for improved risk communication in population-based cancer patient survival". In: *Epidemiology* (2014), pp. 742–748.

[47] Jianqing Fan and Runze Li. "Variable selection for Cox's proportional hazards model and frailty model". In: *The Annals of Statistics* 30.1 (2002), pp. 74–99.

[48] Xiaoyu Fang et al. "Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis". In: *Aging (albany NY)* 12.13 (2020), p. 12493.

[49] Jason P Fine and Robert J Gray. "A proportional hazards model for the subdistribution of a competing risk". In: *Journal of the American statistical association* 94.446 (1999), pp. 496–509.

[50] Carlo Fumagalli et al. "Clinical risk score to predict in-hospital mortality in COVID-19 patients: a retrospective cohort study". In: *BMJ open* 10.9 (2020), e040729.

[51] Rebekah L Gardner et al. "Factors associated with longer ED lengths of stay". In: *The American journal of emergency medicine* 25.6 (2007), pp. 643–650.

[52] Gazzetta Ufficiale della Regione Siciliana del 21-9-2018 Parte I n. 41. *Approvazione delle "Linee di indirizzo per la gestione del sovraffollamento nelle strutture di pronto soccorso della Regione Sicilia"*. 2018. URL: http://www.gurs.regione.sicilia.it/Gazzette/g18-41/g18-41.pdf.

[53] *General opening remarks at the middle briefing on covid-19, 11-march-2020*. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. 2020.

[54] *General opening remarks at the middle briefing on covid-19, 11-march-2020*. https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-analysis-of-deaths. 2020.

[55] Thomas A Gerds, Per K Andersen, and Michael W Kattan. "Calibration plots for risk prediction models in the presence of competing risks". In: *Statistics in medicine* 33.18 (2014), pp. 3191–3203.

[56] Ronald Bertus Geskus. *Data analysis with competing risks and intermediate states*. CRC Press Boca Raton, 2016.

[57] Marshall J MD Glesby and Donald R Hoover. "Survivor treatment selection bias in observational studies: examples from the AIDS literature". In: *Annals of internal medicine* 124.11 (1996), pp. 999–1005.

[58] Nazli Gormeli Kurt and Celal Gunes. "How has Covid-19 pandemic affected crowded emergency services?" In: *International Journal of Clinical Practice* 74.12 (2020), e13624.

[59] Usha S Govindarajulu et al. "Frailty models: applications to biomedical and genetic studies". In: *Statistics in medicine* 30.22 (2011), pp. 2754–2764.

[60] Patricia M Grambsch and Terry M Therneau. "Proportional hazards tests and diagnostics based on weighted residuals". In: *Biometrika* 81.3 (1994), pp. 515–526.

[61] Il Do Ha, Jong-Hyeon Jeong, and Youngjo Lee. "Competing Risks Frailty Models". In: *Statistical Modelling of Survival Data with Random Effects*. Springer, 2017, pp. 125–171.

[62] Il Do Ha, Maengseok Noh, and Youngjo Lee. "Bias reduction of likelihood estimators in semiparametric frailty models". In: *Scandinavian Journal of Statistics* 37.2 (2010), pp. 307–320.

[63] Il Do Ha et al. "Analysis of clustered competing risks data using subdistribution hazard models with multivariate frailties". In: *Statistical methods in medical research* 25.6 (2016), pp. 2488–2505.

[64] Il Do Ha et al. "Frailty modelling for survival data from multi-centre clinical trials". In: *Statistics in medicine* 30.17 (2011), pp. 2144–2159.

[65] Jin H Han et al. "The effect of physician triage on emergency department length of stay". In: *The Journal of emergency medicine* 39.2 (2010), pp. 227–233.

[66] Helen Hansagi, Olof Edhag, and Peter Allebeck. "High consumers of health care in emergency units: how to improve their quality of care". In: *International Journal for Quality in Health Care* 3.1 (1991), pp. 51–62.

[67] Anthony Harris and Anurag Sharma. "Access block and overcrowding in emergency departments: an empirical analysis". In: *Emergency Medicine Journal* 27.7 (2010), pp. 508–511.

[68] Saeed Hesam et al. "A cause-specific hazard spatial frailty model for competing risks data". In: *Spatial Statistics* 26 (2018), pp. 101–124.

[69] Nathan R Hoot and Dominik Aronsky. "Systematic review of emergency department crowding: causes, effects, and solutions". In: *Annals of emergency medicine* 52.2 (2008), pp. 126–136.

[70] Fushing Hsieh, Yi-Kuan Tseng, and Jane-Ling Wang. "Joint modeling of survival and longitudinal data: likelihood approach revisited". In: *Biometrics* 62.4 (2006), pp. 1037–1043.

[71] Ula Hwang et al. "Measures of crowding in the emergency department: a systematic review". In: *Academic Emergency Medicine* 18.5 (2011), pp. 527–538.

[72] Marco Iosa, Stefano Paolucci, and Giovanni Morone. "Covid-19: a dynamic analysis of fatality risk in Italy". In: *Frontiers in Medicine* 7 (2020), p. 185.

[73] Sébastien Jaillon, Kevin Berthenet, and Cecilia Garlanda. "Sexual dimorphism in innate immunity". In: *Clinical reviews in allergy & immunology* 56.3 (2019), pp. 308–321.

[74] Mehdi Jalalpour, Yulia Gel, and Scott Levin. "Forecasting demand for health services: Development of a publicly available toolbox". In: *Operations research for health care* 5 (2015), pp. 1–9.

[75] Spencer S Jones et al. "Forecasting daily patient volumes in the emergency department". In: *Academic Emergency Medicine* 15.2 (2008), pp. 159–170.

[76] Edward L Kaplan and Paul Meier. "Nonparametric estimation from incomplete observations". In: *Journal of the American statistical association* 53.282 (1958), pp. 457–481.

[77] Krishan L Khatri and Lakshman S Tamil. "Early detection of peak demand days of chronic respiratory diseases emergency department visits using artificial neural networks". In: *IEEE journal of biomedical and health informatics* 22.1 (2017), pp. 285–290.

[78] John P Klein and Melvin L Moeschberger. *Survival analysis: techniques for censored and truncated data*. Vol. 1230. Springer, 2003.

[79] Stephen R Knight et al. "Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score". In: *bmj* 370 (2020).

[80] Michael T Koller et al. "Competing risks and the clinical community: irrelevance or ignorance?" In: *Statistics in medicine* 31.11-12 (2012), pp. 1089–1097.

[81] Eduardo LaCalle and Elaine Rabin. "Frequent users of emergency departments: the myths, the data, and the policy implications". In: *Annals of emergency medicine* 56.1 (2010), pp. 42–48.

[82] Bryan Lau, Stephen R Cole, and Stephen J Gange. "Competing risk regression models for epidemiologic data". In: *American journal of epidemiology* 170.2 (2009), pp. 244–256.

[83] Minjung Lee, Il Do Ha, and Youngjo Lee. "Frailty modeling for clustered competing risks data with missing cause of failure". In: *Statistical methods in medical research* 26.1 (2017), pp. 356–373.

[84] Youngjo Lee and John A Nelder. "Hierarchical generalized linear models". In: *Journal of the Royal Statistical Society: Series B (Methodological)* 58.4 (1996), pp. 619–656.

[85] Catherine Legrand. *Advanced survival models*. Chapman and Hall/CRC, 2021.

[86] Wenhua Liang et al. "Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19". In: *JAMA internal medicine* 180.8 (2020), pp. 1081–1089.

[87] Gregor Lindner and Bertram K Woitok. "Emergency department overcrowding". In: *Wiener Klinische Wochenschrift* 133.5 (2021), pp. 229–233.

[88] Raymond H Lucas and Sandra M Sanford. "An analysis of frequent users of emergency care at an urban university hospital". In: *Annals of emergency medicine* 32.5 (1998), pp. 563–568.

[89] Sara Martino and Håvard Rue. "Case studies in Bayesian computation using INLA". In: *Complex data modeling and computationally intensive statistical methods* (2010), pp. 99–114.

[90] Thiago G Martins et al. "Bayesian computing with INLA: new features". In: *Computational Statistics & Data Analysis* 67 (2013), pp. 68–83.

[91] Torben Martinussen, Thomas H Scheike, and David M Zucker. "The Aalen additive gamma frailty hazards model". In: *Biometrika* 98.4 (2011), pp. 831–843.

[92] Arthur Eumann Mesas et al. "Predictors of in-hospital COVID-19 mortality: A comprehensive systematic review and meta-analysis exploring differences by age, sex and health conditions". In: *PloS one* 15.11 (2020), e0241742.

[93] Andrew M Moon et al. "High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: preliminary results from an international registry". In: *Journal of hepatology* 73.3 (2020), pp. 705–708.

[94] Bryn E Mumma et al. "Effects of emergency department expansion on emergency department patient flow". In: *Academic Emergency Medicine* 21.5 (2014), pp. 504–509.

[95] Susan A Murphy. "Asymptotic theory for the frailty model". In: *The annals of statistics* (1995), pp. 182–198.

[96] Yusuf Nagree, Tor NO Ercleve, and Peter C Sprivulis. "After-hours general practice clinics are unlikely to reduce low acuity patient attendances to metropolitan Perth emergency departments". In: *Australian Health Review* 28.3 (2004), pp. 285–291.

[97] MA Nicolaie, Hans C van Houwelingen, and Hein Putter. "Vertical modeling: a pattern mixture approach for competing risks modeling". In: *Statistics in medicine* 29.11 (2010), pp. 1190–1205.

[98] MA Nicolaie, HC van Houwelingen, and H Putter. "Vertical modelling: Analysis of competing risks data with missing causes of failure". In: *Statistical methods in medical research* 24.6 (2015), pp. 891–908.

[99] Mioara Alina Nicolaie, Jeremy MG Taylor, and Catherine Legrand. "Vertical modeling: analysis of competing risks data with a cure fraction". In: *Lifetime data analysis* 25.1 (2019), pp. 1–25.

[100] Janet van Niekerk, Haakon Bakka, and Håvard Rue. "Competing risks joint models using R-INLA". In: *Statistical Modelling* 21.1-2 (2021), pp. 56–71.

[101] Gerine Nijman et al. "Risk factors for in-hospital mortality in laboratory-confirmed COVID-19 patients in the Netherlands: A competing risk survival analysis". In: *PloS one* 16.3 (2021), e0249231.

[102] Suvra Pal. "A simplified stochastic EM algorithm for cure rate model with negative binomial competing risks: An application to breast cancer data". In: *Statistics in Medicine* 40.28 (2021), pp. 6387–6409.

[103] Marco Pellegrini et al. "The impact of COVID-19 pandemic on ophthalmological emergency department visits". In: *Acta ophthalmologica* (2020).

[104] J. Laureano Phillips et al. "Overcrowding and Its Association With Patient Outcomes in a Median-Low Volume Emergency Department". eng. In: *Journal of clinical medicine research* 9.11 (Nov. 2017). 29038668[pmid], pp. 911–916. ISSN: 1918-3003. URL: https://pubmed.ncbi.nlm.nih.gov/29038668.

[105] Jesse M Pines et al. "International perspectives on emergency department crowding". In: *Academic Emergency Medicine* 18.12 (2011), pp. 1358–1370.

[106] Stephen R Pitts et al. "National trends in emergency department occupancy, 2001 to 2008: effect of inpatient admissions versus emergency department practice intensity". In: *Annals of emergency medicine* 60.6 (2012), pp. 679–686.

[107] Ross L Prentice et al. "The analysis of failure times in the presence of competing risks". In: *Biometrics* (1978), pp. 541–554.

[108] Hein Putter, Marta Fiocco, and Ronald B Geskus. "Tutorial in biostatistics: competing risks and multi-state models". In: *Statistics in medicine* 26.11 (2007), pp. 2389–2430.

[109] Hein Putter, Martin Schumacher, and Hans C van Houwelingen. "On the relation between the cause-specific hazard and the subdistribution rate for competing risks data: The Fine–Gray model revisited". In: *Biometrical Journal* 62.3 (2020), pp. 790–807.

[110] Elaine Rabin et al. "Solutions to emergency department 'boarding'and crowding are underused and may need to be legislated". In: *Health Affairs* 31.8 (2012), pp. 1757–1766.

[111] Fatemeh Rahimian et al. "Predicting the risk of emergency admission with machine learning: Development and validation using linked electronic health records". In: *PLoS medicine* 15.11 (2018), e1002695.

[112] Gianni Rastelli, Mario Cavazza, and Gianfranco Cervellin. "Sovraffollamento in Pronto Soccorso". In: *Emergency Care Journal* 4.2 (2010), pp. 25–35.

[113] Niels K Rathlev et al. "Time series analysis of variables associated with daily mean emergency department length of stay". In: *Annals of emergency medicine* 49.3 (2007), pp. 265–271.

[114] Nancy Reid. "Estimating the median survival time". In: *Biometrika* 68.3 (1981), pp. 601–608.

[115] Andrea Remuzzi and Giuseppe Remuzzi. "COVID-19 and Italy: what next?" In: *The lancet* 395.10231 (2020), pp. 1225–1228.

[116] Drew B Richardson and David Mountain. "Myths versus facts in emergency department overcrowding and hospital access block". In: *Medical Journal of Australia* 190.7 (2009), pp. 369–374.

[117] Marco Ripa et al. "Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors". In: *Clinical Microbiology and Infection* 27.3 (2021), pp. 451–457.

[118] Dimitris Rizopoulos. "The R package JMbayes for fitting joint models for longitudinal and time-to-event data using MCMC". In: *arXiv preprint arXiv:1404.7625* (2014).

[119] Alfonso J Rodriguez-Morales et al. "Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis". In: *Travel medicine and infectious disease* 34 (2020), p. 101623.

[120] Havard Rue and Leonhard Held. *Gaussian Markov random fields: theory and applications*. Chapman and Hall/CRC, 2005.

[121] Håvard Rue, Sara Martino, and Nicolas Chopin. "Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations". In: *Journal of the royal statistical society: Series b (statistical methodology)* 71.2 (2009), pp. 319–392.

[122] Håvard Rue et al. "Bayesian computing with INLA: a review". In: *Annual Review of Statistics and Its Application* 4 (2017), pp. 395–421.

[123] Anja J Rueten-Budde, Hein Putter, and Marta Fiocco. "Investigating hospital heterogeneity with a competing risks frailty model". In: *Statistics in medicine* 38.2 (2019), pp. 269–288.

[124] Richardson Safiya et al. "karina W. Davidson, and the northwell COVID-19 research Consortium, presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area". In: *J. Am. Med. Assoc* 323 (2020), pp. 2052–2059.

[125] RJ Salway et al. "Emergency department (ED) overcrowding: evidence-based answers to frequently asked questions". In: *Revista Médica Clınica Las Condes* 28.2 (2017), pp. 213–219.

[126] Marina Sartini et al. "Overcrowding in Emergency Department: Causes, Consequences, and Solutions—A Narrative Review". In: *Healthcare*. Vol. 10. 9. MDPI. 2022, p. 1625.

[127] Gabriele Savioli et al. "Emergency department overcrowding: Understanding the factors to find corresponding solutions". In: *Journal of Personalized Medicine* 12.2 (2022), p. 279.

[128] Gabriele Savioli et al. "How the coronavirus disease 2019 pandemic changed the patterns of healthcare utilization by geriatric patients and the crowding: A call to action for effective solutions to the access block". In: *Internal and emergency medicine* 17.2 (2022), pp. 503–514.

[129] Rotraut Schoop et al. "Quantifying the predictive accuracy of time-to-event models in the presence of competing risks". In: *Biometrical Journal* 53.1 (2011), pp. 88–112.

[130] Clelia Di Serio. "The protective impact of a covariate on competing failures with an example from a bone marrow transplantation study". In: *Lifetime data analysis* 3.2 (1997), pp. 99–122.

[131] *Share of population that are aged 65 years and older in European countries in 2019. March, 2020.* https://www.statista.com/statistics/1105835/share-of-elderly-population-in-europe-by-country/. 2020.

[132] Regione Siciliana. "LINEE DI INDIRIZZO PER LA GESTIONE DEL SOVRAFFOLLAMENTO NELLE STRUTTURE DI PRONTO SOCCORSO DELLA REGIONE SICILIA". In: ().

[133] Reed Ac Siemieniuk et al. "Drug treatments for COVID-19: living systematic review and network meta-analysis". In: *BMJ* 373 (2021), n967.

[134] Peter C Sprivulis et al. "The association between hospital overcrowding and mortality among patients admitted via Western Australian emergency departments". In: *Medical Journal of Australia* 184.5 (2006), pp. 208–212.

[135] Andrea Strada et al. "Do health care professionals' perceptions help to measure the degree of overcrowding in the emergency department? A pilot study in an Italian University hospital". In: *BMC Emergency Medicine* 19.1 (2019), pp. 1–9.

[136] Samy Suissa and Laurent Azoulay. "Metformin and the risk of cancer: time-related biases in observational studies". In: *Diabetes care* 35.12 (2012), pp. 2665–2673.

[137] Sandra L Taylor et al. "A competing risk analysis for hospital length of stay in patients with burns". In: *JAMA surgery* 150.5 (2015), pp. 450–456.

[138] Fabio Tramuto et al. "Burden and viral aetiology of influenza-like illness and acute respiratory infection in intensive care units". In: *Microbes and infection* 18.4 (2016), pp. 270–276.

[139] Anastasios A Tsiatis. "An example of nonldeutifiability in competing risks". In: *Scandinavian Actuarial Journal* 1978.4 (1978), pp. 235–239.

[140] Ping Tim Tsui et al. "Severe acute respiratory syndrome: clinical outcome and prognostic correlates". In: *Emerging infectious diseases* 9.9 (2003), p. 1064.

[141] Janet Van Niekerk, Haakon Bakka, and Haavard Rue. "Joint models as latent gaussian models-not reinventing the wheel". In: *arXiv preprint arXiv:1901.09365* (2019).

[142] Janet Van Niekerk et al. "New frontiers in Bayesian modeling using the INLA package in R". In: *arXiv preprint arXiv:1907.10426* (2019).

[143] James W Vaupel, Kenneth G Manton, and Eric Stallard. "The impact of heterogeneity in individual frailty on the dynamics of mortality". In: *Demography* 16.3 (1979), pp. 439–454.

[144] P Walley. "Designing the accident and emergency system: lessons from manufacturing". In: *Emergency Medicine Journal* 20.2 (2003), pp. 126–130.

[145] Dawei Wang et al. "Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China". In: *Jama* 323.11 (2020), pp. 1061–1069.

[146] Yijun Wang et al. "Semiparametric estimation for proportional hazards mixture cure model allowing non-curable competing risk". In: *Journal of Statistical Planning and Inference* 211 (2021), pp. 171–189.

[147] Yin-Chen Wang et al. "Likelihood-based inference for a frailty-copula model based on competing risks failure time data". In: *Quality and Reliability Engineering International* 36.5 (2020), pp. 1622–1638.

[148] Steven J Weiss, Amy A Ernst, and Todd G Nick. "Comparison of the national emergency department overcrowding scale and the emergency department work index for quantifying emergency department crowding". In: *Academic Emergency Medicine* 13.5 (2006), pp. 513–518.

[149] Steven J Weiss et al. "Estimating the degree of emergency department overcrowding in academic medical centers: results of the National ED Overcrowding Study (NEDOCS)". In: *Academic emergency medicine* 11.1 (2004), pp. 38–50.

[150] Andreas Wienke et al. "A bivariate survival model with compound Poisson frailty". In: *Statistics in Medicine* 29.2 (2010), pp. 275–283.

[151] Andreas Wienke et al. "The heritability of mortality due to heart diseases: a correlated frailty model applied to Danish twins". In: *Twin Research and Human Genetics* 4.4 (2001), pp. 266–274.

[152] Rick L Williams. "Product-limit survival functions with correlated survival times". In: *Lifetime data analysis* 1.2 (1995), pp. 171–186.

[153] Marcel Wolbers et al. "Competing risks analyses: objectives and approaches". In: *European heart journal* 35.42 (2014), pp. 2936–2941.

[154] Laure Wynants et al. "Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal". In: *bmj* 369 (2020).

[155] Arjun S Yadaw et al. "Clinical features of COVID-19 mortality: development and validation of a clinical prediction model". In: *The Lancet Digital Health* 2.10 (2020), e516–e525.

[156] Jing Yang et al. "Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis". In: *International journal of infectious diseases* 94 (2020), pp. 91–95.

[157] Xiaobo Yang et al. "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study". In: *The Lancet Respiratory Medicine* 8.5 (2020), pp. 475–481.

[158] Mohammad H Yarmohammadian et al. "Overcrowding in emergency departments: a review of strategies to decrease future challenges". In: *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences* 22 (2017).

[159] Anatoli I Yashin, James W Vaupel, and Ivan A Iachine. "Correlated individual frailty: an advantageous approach to survival analysis of bivariate data". In: *Mathematical population studies* 5.2 (1995), pp. 145–159.

[160] Philip Yoon, Ivan Steiner, and Gilles Reinhardt. "Analysis of factors influencing length of stay in the emergency department". In: *Canadian Journal of Emergency Medicine* 5.3 (2003), pp. 155–161.

[161] Yuanye Zhang et al. "Bayesian gamma frailty models for survival data with semi-competing risks and treatment switching". In: *Lifetime data analysis* 20.1 (2014), pp. 76–105.

[162] Zhongheng Zhang et al. "Overview of model validation for survival regression model with competing risks using melanoma study data". In: *Annals of translational medicine* 6.16 (2018).

[163] Zhaohai Zheng et al. "Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis". In: *Journal of infection* 81.2 (2020), e16–e25.

[164] Bingqing Zhou et al. "Competing risks regression for clustered data". In: *Biostatistics* 13.3 (2012), pp. 371–383.

[165] Fei Zhou et al. "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study". In: *The lancet* 395.10229 (2020), pp. 1054–1062.

CRediT Author Statement

Chapters 2 and 3 show the outcomes of collaboration with clinicians. However, for the thesis proposal's authorship statement, only the statisticians' contributions will be acknowledged.

- **Chapter 1 - Salvatore Battaglia:** methodology, investigation, writing , visualization. **Marta Fiocco:** methodology, supervision. **Hein Putter:** methodology, supervision. **Massimo Attanasio:** methodology, supervision. **Marco Enea:** methodology, supervision.

- **Chapter 2 - Salvatore Battaglia:** methodology, software, formal analysis, investigation, data curation, writing - original draft, visualization. **Massimo Attanasio:** formal analysis, investigation, supervision. **Marco Enea:** formal analysis, supervision, writing - review and editing.

- **Chapter 3 - Salvatore Battaglia:** methodology, software, formal analysis, investigation, data curation, writing - original draft, visualization. **Massimo Attanasio:** conceptualization, formal analysis, investigation, supervision. **Marco Enea:** formal analysis, writing - review and editing. **Vincenzo Giuseppe Genova:** software and construction of the R-shiny app.

- **Chapter 4 - Salvatore Battaglia:** methodology, software, formal analysis, investigation, data curation, writing - original draft, visualization. **Massimo Attanasio:** conceptualization, formal analysis, investigation, supervision. **Marco Enea:** formal analysis, writing - review and editing.

- **Chapter 5 - Salvatore Battaglia:** methodology, software, formal analysis, investigation, data curation, writing - original draft, visualization. **Marta Fiocco:** conceptualization, formal analysis, investigation, supervision. **Hein Putter:** conceptualization, methodology, formal analysis, investigation, supervision. **Goergy Gomon:** software, formal analysis.

Ph.D. output research

During my Ph.D. program, I co-authored, beyond the published papers mentioned in chapter 2 and 3, the following papers, being part, as a statistician, of the research group from the Gastroenterology department of the University of Palermo:

- Cabibbo G., Celsa C., Enea M., Battaglia S. et al.(2020) *Optimizing Sequential Systemic Therapies for Advanced Hepatocellular Carcinoma: A decision Analysis.* Cancers, 2020, 12.8: 2132.

- Celsa C., Cabibbo G., Enea M., Battaglia S. et al.(2020). *Progression-free survival is a robust surrogate endpoint of overall survival in immunotherapy trials of hepatocellular carcinoma*.Digestive and Liver Disease 53 (2021): S35

- Magro B., Battaglia S. et al. *Consequences of ESBLE and MRSA carriage in awaiting liver transplant patients".* Liver Transplantation. 2020 Sep 21. DOI: 10.1002.

- Cabibbo G, Reig M., Celsa C, Battaglia S, et al. (2021). *First-Line Immune Checkpoint Inhibitor-based Sequential Therapies for Advanced Hepatocellular Carcinoma: Rationale for future Trials*. Liver Cancer.

- Celsa C., Cabibbo G., Enea M., Battaglia S. et al.(2021). *Are Radiology-based endpoints robust surrogate outcomes of overall survival in hepatocellular carcinoma patients treated with transarterial chemoembolization?*. Liver International 41.5 (2021): 1105-1116.

- Calvaruso V., Battaglia S. et al.(2021). *Liver and cardiovascular mortality after hepatitis C virus eradication by DAA: Data from RESIST-HCV cohort.* Journal of Viral Hepatitis.

- Pennisi G., Petta S., Enea M., Battaglia S., et al. (2021). *GEMS, a GEnetic and Metabolic Staging Predicting the Outcome of Non-Alcoholic Fatty Liver Disease*. Hepatology Communications.

- Cabibbo G., Battaglia S. et al. *"First-line immune checkpoint inhibitor-based sequential therapies for advanced hepatocellular carcinoma: rationale for future trials."* Liver cancer 11.1 (2022): 75-84.

- Vizzutti F., Battaglia S. et al. *"Mortality after transjugular intrahepatic portosystemic shunt in older adult patients with cirrhosis: a validated prediction model."* Hepatology (2022).