Joint modelling of hospitalizations and survival in heart failure patients: a discrete non parametric frailty approach

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Joint modelling of hospitalizations and survival in Heart Failure patients: a discrete non parametric frailty approach

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Abstract

In this work, we propose a novel joint frailty model assuming bivariate discretely-distributed non-parametric frailties, with an unknown finite number of mass points. This approach allows to detect a latent structure among subjects, clustering them in sub-populations where individuals are characterized by a common frailty value. Our method can be interpreted as an unsupervised classification tool and motivates further investigation into the reasons for similarities within the clustered subjects and dissimilarities across the clusters. This work is motivated by a study of patients with Heart Failure (HF) undergoing ACE inhibitors treatment in the Lombardia region of Italy. Recurrent events of interest are hospitalizations due to HF and terminal event is death for any cause.

Keywords: Joint models; Discrete frailties; Recurrent events; EM algorithm; Heart Failure patients.

1. Introduction

Recurrent or *repeated events* are common in many clinical and biomedical studies, as patients usually experience the same event multiple times. In the recurrent event framework, classic survival approaches are not suitable as they discard the correlation between subsequent events in the same subject. A wide literature about recurrent events modelling has hence flourished in past years [2,8]. Among others, *frailty models* handle repeated episodes by introducing a random effect which takes a common value for each group of dependent observations and can be used to describe excess risk or frailty of different individuals [2,8]. The time span of an individual's recurrent process could also depend on another terminal event, e.g., the end of the study, loss to follow-up, or death. To jointly analyse both recurrent and terminal processes over time, joint frailty models can be adopted [5,6]. Joint frailty models capture both the correlation among repeated events and the dependence between repeated and terminal processes by incorporating random effects in the two hazard functions. Last advances in this field regard the work proposed in [6], where the authors considered joint models by conditioning on a shared frailty that does not apply equivalently for the two hazard functions and the one proposed in [5], where a joint frailty model with multivariate Gaussian random effects is developed. In contrast to traditional joint shared-frailty models, the authors in [5] yield a more general model where two sets of random effects are used to account for intra-subject correlation of multivariate recurrent event times and individual differences in

mortality hazard rate. Their method allows for a positive or negative association between recurrent and terminal events, distinguishing the origin of their dependence.

We insert within this literature by proposing a joint frailty model with discrete random effects. In the last few decades, a branch of the literature is focusing on the treatment of discretely-distributed random effects [3,4]. Most of the work in this direction has been done in the context of mixed-effects regression models for continuous responses (both univariate and multivariate) and other types of responses in the exponential family. Recently, this approach has been extended in the survival analysis framework, by the introduction of discretely-distributed frailties [1]. The main advantage of modelling discrete random-effects regards the new type of treatment and interpretation of the units at the highest level of the hierarchy, that are clustered into latent subpopulations. When considering events nested within patients or patients nested within health providers, modelling discrete frailties allows to cluster patients or health providers, identifying, for example, long/short-term survivors or more/less successful health providers.

Motivated by the advantages of a discretely-distributed frailty approach in practice, in this article we propose an original extension of the general joint model in [5] to the discrete-frailty framework. In addition to handling heterogeneous susceptibility to the risk and informative censoring, this novel approach can detect a latent structure among subjects, grouping them in sub-populations where individuals are characterized by a common frailty value. Along with the model, we propose an estimation routine via Expectation-Maximization algorithm.

The approach we develop is motivated by a study on patients with Heart Failure (HF) in the Lombardia region of Italy. We face the problem of joint modelling of hospitalizations and survival of patients affected by Heart Failure, with a focus on the effect that a pharmacological treatment based on ACE Inhibitors has on these two processes. The course of HF disease is usually characterized by recurrent hospital admissions [7]. Re-hospitalization events usually herald a substantial worsening of patient's survival prognosis and are terminated by death. The application of our novel approach to this context is hence of interest.

2. ACE Inhibitors Dataset

We consider data coming from an administrative database of Regione Lombardia, which records clinical courses and pharmacological prescriptions of subjects affected by Heart Failure. We focus on patients who undergo an ACE inhibitors treatment in the period from January 1st, 2006 to December 31st, 2012. For each patient, the index date coincides with the discharge after the first hospitalization due to Heart Failure. We adopt a *gap times* timescale, i.e. each patients clinical history is declined in repeated observations, characterized by a time-to-event variable **GapEvent** which expresses the days elapsed from the previous patient's hospitalization to the next one. The last gap time of each patient expresses the time elapsed from the last known hospitalization to the terminal event, which may be death or censoring. The nature of each event is kept track of through two dummy variables, respectively **Event** and **Death**.

To assess the effect of the considered ACE inhibitors treatment on survival and hospitalizations, we design a time dependent binary classifier for adherent subjects (variable **Adherent**). At each event in a patient's history, we compute the proportion of days covered by prescriptions of ACE inhibitors since the patient index date; then, if this proportion exceeds a threshold of 80% the patient is considered adherent to treatment, otherwise not. The other three variables we consider in the model are the patient gender (**Sex**) and time-dependent variables, **AgeEvent** and **Comorbidity**, which respectively indicate the age and the number of known comorbidities of a patient at the beginning of the corresponding gap time.

Table **??** reports as an example the data table of a patient in the ACE inhibitors dataset.

3. Methods

In the proposed joint model with discrete frailty, we express the hospitalization and death hazards for each patient $i, i = 1, ...N$, as follows

ID	Sex	Adherent	AgeEvent	Comorbidity	GapEvent	Event	Death
10003004	F	0	75	5	229	1	
10003004	F	1	75	6	131	1	
10003004	F	0	76	6	168	1	
10003004	F	0	77	7	353	1	
10003004	F	1	79	7	1,153	0	1

Table 1: Data table of patient 10003004.

$$\begin{cases} h_i^R(t|u_i, \boldsymbol{x}_i^R(t)) = h_0^R(t) \exp\{u_i + \boldsymbol{\beta}^T \boldsymbol{x}_i^R(t)\} \\ h_i^D(t|v_i, \boldsymbol{x}_i^D(t)) = h_0^D(t) \exp\{v_i + \boldsymbol{\gamma}^T \boldsymbol{x}_i^D(t)\} \end{cases} \tag{1}$$

where t refers to a gap time with respect to the last known hospitalization event; h_0^R and h_0^D are the hospitalization and death baseline hazard functions, respectively; $\boldsymbol{x}_i^R(t)$ and $\boldsymbol{x}_i^D(t)$ are the observed covariates at time t; $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ are the estimated coefficients of the two models; u_i and v_i are patient-specific additive frailties. According to our formulation, random effects u_i and v_i are distributed according to a bivariate discrete distribution P^* on $\mathbb{R}^2$

$$[u, v]_i \overset{iid}{\sim} P^* \quad \forall i = 1, \ldots, N. \tag{2}$$

Such discrete and with a finite support measure can be characterized by a vector of points in $\mathbb{R}^2$, $\boldsymbol{P}$, and a vector of weights, $\boldsymbol{w}$. Notice that each weight expresses the probability of a patient to be assigned to a certain point l, $l = 1, ..., L$ and thus the sum of the weights is constrained to be unitary. Moreover, the number of points constituting the support of the distribution, L, is assumed to be unknown a priori. By considering L as fixed, we can write each patient's contribution to the likelihood of the model as a mixture of L components. Each component coincides with the product of the individual contributions, $\mathcal{L}_i$, to the full loglikelihood $\mathcal{L}$ of two independent Cox models with fixed intercept, modelling respectively the recurrent and terminal event process

$$\mathcal{L}(\boldsymbol{\Omega}; data|z_{il}) = \prod_{l=1}^{L} \prod_{i=1}^{N} \left[\mathcal{L}_i(\boldsymbol{\Omega}; data|[u, v]_i = P_l)\right]^{z_{il}}. \tag{3}$$

where $\boldsymbol{\Omega} = [\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{w}, \boldsymbol{P}, h_0^R(t), h_0^D(t)]$. The abscissa and ordinata of each point $\boldsymbol{P}_l$ specify, respectively, the fixed intercept of the recurrent and terminal event Cox models, while z_{il} are a set of binary auxiliary random variables indicating if a patient i is assigned to the point l. In order to obtain estimates for $\boldsymbol{\Omega}$, we design a specific EM algorithm, in which at each iteration the model likelihood is firstly averaged with respect to the z_{il} variables and then maximized.
The EM algorithm is then generalized to cope with an a priori unknown number of support points L through its integration into a wrapper support reduction procedure. The first step consists in the definition of a grid of points in $\mathbb{R}^2$, which ideally covers the region in which the support of the discrete distribution is believed to lie. We evaluate two initialization procedures: the former involves sampling a high number of points from a bivariate Normal distribution, whose parameters are set according to previous knowledge (e.g., looking at the estimates of the model proposed in [5]), and initializing their weights according to the corresponding Normal density; the latter consists in defining a uniform distribution over a rectangle in $\mathbb{R}^2$, whose boundaries are set still according to available knowledge. At each iteration, we merge the couple of points with minimum distance in the actual grid whose Euclidean distance is less than a discretional threshold (*MinDist*), until convergence.

4. Results

We fit the nonparametric joint model with discrete frailty by consdiering both the gaussian and uniform initializations and we compare the results with the ones of a disjoint model and the joint models pro-

Variables	Estimate	StdDev	HR	95% CI	pvalue
Recurrent Events					
Sex [M]	0.039	0.019	1.039	[1.003,1.079]	0.034
Adherent [1]	-0.259	0.019	0.771	[0.743,0.800]	<2e-16
AgeEvent	-0.015	0.001	0.985	[0.984,0.987]	<2e-16
Comorbidity	0.123	0.005	1.131	[1.119,1.143]	<2e-16
Recurrent Events					
Sex [M]	0.169	0.073	1.184	[1.025,1.366]	0.021
Adherent [1]	-0.407	0.078	0.665	[0.571,0.755]	1.7e-07
AgeEvent	0.039	0.004	1.041	[1.032,1.049]	<2e-16
Comorbidity	0.429	0.020	1.535	[1.476,1.597]	<2e-16

Frailty	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**
u	-0.466	-0.194	0.079	0.231	0.468	0.679
v	-1.872	-0.859	-0.090	1.166	2.277	3.088
w	0.208	0.234	0.206	0.217	0.071	0.063

Table 2: Summary of the Nonparametric Discrete Frailty model with uniform initialization. For categorical variables, the considered stratum is indicated between brackets. Points of the identified frailty discrete distribution are characterized through their abscissa (u), ordinata (v) and weight (w).

posed in [5,6]. For all models, we consider the following set of covariates: **Sex**, **Adherence**, **AgeEvent** and **Comorbidity**. The nonparametric discrete frailty models are fitted using a *MinDist* value of 0.25, which is initially believed to be suitable to spot significantly different fragility classes of patients. The trained models are compared from two perspectives: coefficients' estimation and random effects' characterization. Table **??** reports the estimates for the nonparametric discrete frailty model with uniform initialization[1] while Figure **??** displays the Hazard Ratio estimates and their respective 95% confidence of all compared models.

By looking at the hazard ratios of the covariates, we observe that male subjects are more prone to risk of hospitalization (HR=1.035) and death (HR=1.197). The covariate **Adherent** results statistically significant at any level for the two processes in all trained models. Being adherent yields a 22.9% decrease in the risk of a new hospitalization (HR=0.771) and a 33.5% decrease in the risk of death. From a clinical point of view, such results finally endorse the efficacy of the ACE inhibitors treatment for heart failure. The covariate **AgeEvent** results, for both processes, statistically significant at all levels. Its effect on the hospitalization hazard is a 1.5% reduction of the risk of hospitalization per year (HR=0.985), while on the death hazard it yields an increase of the risk of 4.1% (HR=1.040). Clinically speaking this can be explained by the fact that part of the risk of experiencing a new hospitalization is replaced by the risk to die when patients get older. The covariate **Comorbidity** results to be in all models statistically significant for both the processes. It yields an increase of 13.1% in the risk of hospitalization and a very high increase of 53.5% in the risk of death per comorbidity registered.

From the frailties characterization point of view, the nonparametric frailty model identifies the discrete distribution reported in Table **??** and visualized in the left-side panel of Figure **??**. The estimated discrete distribution consists in six points disposed in a diagonal pattern and show left skewness: point **P1** and **P2**, associated with a probability of 21% and 23%, identify respectively a *Highly Protected* and a *Protected* subpopulation; Point **P3** is related to a subpopulation *Neutral* to random effects, with almost a 20% probability for a patient to belong to it; Point **P4** identifies a relevant group of patients (*At Risk*) slightly more prone to the risk of a new hospitalization and death, with a probability of 20.5%. Point **P5** and **P6** identify two outlier subpopulations of *Fragile* and *Very Fragile* patients, associated with small probabilities (respectively, 7% and 6%). The effect of these estimated frailties can be appreciated by looking at the induced stratified baseline survival curves. As an example, right-side panel of Figure **??** reports the terminal event process induced stratified baselines.

[1]For the sake of brevity, we report results for the solely uniform initialization case.

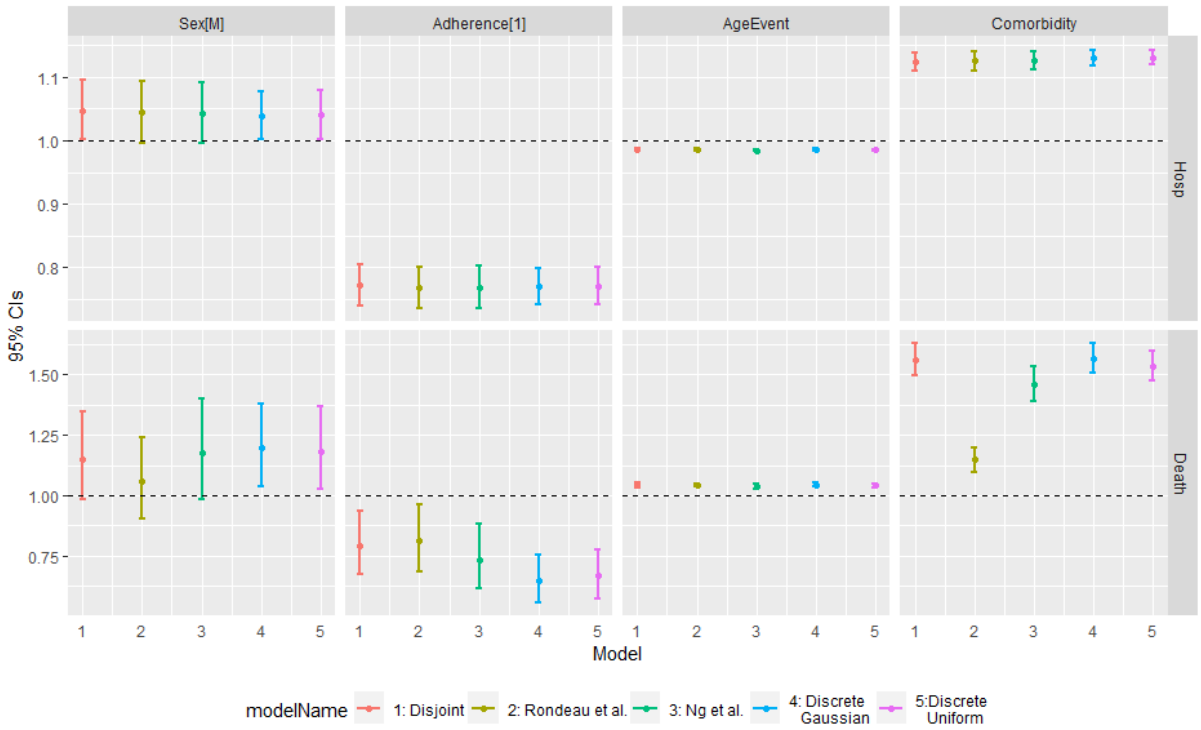

Figure 1: Comparison of estimated hazard ratios and their 95% CI in the trained models. Considered models are: disjoint (pink), Rondeau et al. (pistachio green), Ng et al. (teal), Discrete Nonparametric Frailty with Gaussian Initialization (light blue) and Discrete Nonparametric Frailty with uniform Initialization (purple).

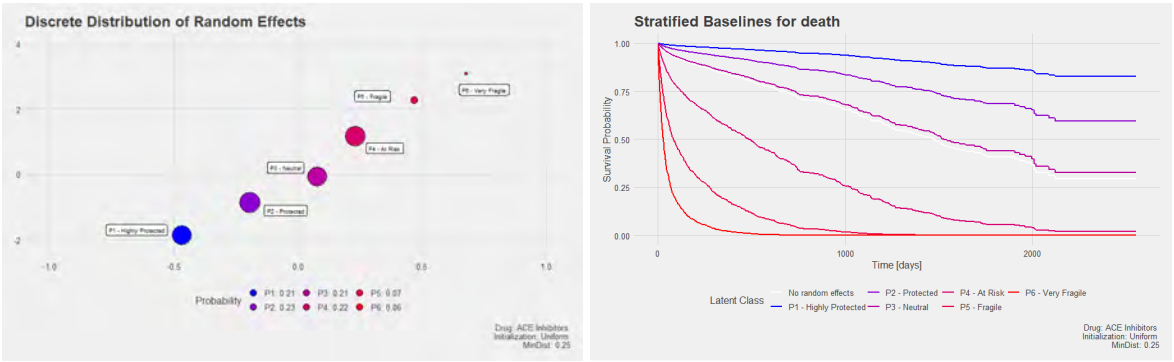

Figure 2: Left-side panel reports the estimated bivariate discrete distribution of random effects, obtained by adopting the uniform initialization case. The color of points ranges from blue (strong subjects) to red (weak subjects), while their size is proportional to the weight. Right-side panel reports the stratified survival probability baseline curves of the terminal event process.

A sensitivity analysis on the *MinDist* threshold is also conducted in order to drive the choice of this important tuning parameter.

5. Conclusions

In this work, we propose a methodology to jointly model two dependent longitudinal processes, the first being a recurrent events process, informative for the second, which instead involves events classified as terminal. In our case, the two processes are represented by hospitalizations and departure of patients affected by heart failure who undergo ACE inhibitors therapy. The work actually stems from the idea of expanding previous analyses developed in the field of pharmacoepidemiology, centered on the effect that adherence to drug prescriptions has on the survival outcome of patients, to include in the modelling the recurrent hospitalizations of a patient, in view of the renewed necessity of a proper managing of hospital beds. In this perspective, the proposed joint model with discrete random effects results to be an effective inferential tool. With respect to its counterpart methods in the literature, it yields consistent fixed-effects coefficients estimates, while providing an easy to understand but richer frailty characterization. The identification of classes of patients standing on their fragility level allows for a deeper characterization of patients' profiles. The identified profiles can be further investigated in terms of collateral patients' information.

From a methodological point of view, future work will be dedicated to the definition of a tool for driving the choice of the important tuning parameter *MinDist*.

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