

Statistical models for hazard functions: a case study of hospitalizations in health failure telemonitoring

Stefano Baraldo, Francesca Ieva, Anna Maria Paganoni and Valeria Vitelli

Abstract Home telemonitoring is gradually spreading as a possible solution for reducing heavy costs associated to the treatment of heart failure patients with usual care. In this work, a very general statistical model for recurrent events is applied to the analysis of cardiovascular hospitalizations in Lombardia region, concerning patients who underwent a period of telemonitoring. The aim of the study is to identify crucial characteristics of these subjects. The model is applied to the whole known patients' history and to the periods pre and post telemonitoring separately, and cumulative hazard functions related to the hospitalization processes are estimated. In particular, hazard functions could be used to perform a classification analysis, treating them as functional data.

Key words: Health service research, Semiparametric statistical methods, Longitudinal data analysis, Data mining, Point processes

1 Introduction

Heart failure is known worldwide as one of the most important causes of hospitalization among the oldest part of the population. This disease is degenerative, so that the frequency of crises grows up along time, causing growing employment of health care resources in terms of money, structures and personnel. The necessity of a cost-effective solution for the care of this and other chronic pathologies has led to the use of telemedicine as a possible solution (see [3], [6] and [12]).

Thanks to development of information technology, the practice of telemonitoring has been experimented in many countries during the last decade, and it is being

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gradually recognized as an effective way of dealing with patients subject to recurrent outbreaks of a chronic disease, remotely keeping track of their vitals by a proper set of devices. The patient resides home during the period of telemonitoring, and is adequately instructed about the use of monitoring instruments, which send the registered information (ECG, body weight, heart frequency, etc.) to the health institution by a network connection. The physician in charge evaluates received data to properly manage the home care program, for example by modifying drug doses and scheduling visits.

Another important practical issue in the study of telemonitoring is availability and use of data. In our case study, we consider patients from Lombardia region who have been subject to telemonitoring in the years 2004–2008. Some information about telemonitoring periods (like duration, number of ECGs transmitted to the hospital, NYHA¹ class of the patient, clinical parameters at starting and ending moments, etc.) is available, but we believe that it is not sufficient alone to get conclusions about care effectiveness. For this reason, we consider Hospital Dismission Forms (*Schede di Dimissione Ospedaliera*, briefly SDO), which gather information about hospitalizations; SDOs were extracted from Public Health Databases in a time window wider than telemonitoring periods, to put them in a context that enables us to operate a multi-period comparison of hospitalization risk.

Many studies have been conducted to analyze the impact of telemonitoring on cost reduction and life quality of patients. Works concentrating on the latter aspect have often found apparently positive but not decisive results, due to the difficulty of finding precise criteria on which judging the care program effectiveness (see the reviews [4], [5] and [8]). Moreover, the characteristics of chronic heart failure, which alternates phases of stability to sudden worsenings of the patient's condition, make an exhaustive statistical description of the phenomenon quite difficult. Here we propose a new approach to the problem of heart failure telemonitoring evaluation, consisting in the use of a counting process (see, for example, [1] for a presentation of the general theory on this subject) to model recurrent hospitalizations. The class of models considered has been introduced by Peña and Hollander in [10], and applied in [11] to the study of intervention effects after cancer relapse. This class of models is very general, and allows us to take into account many aspects that influence hospitalization risk.

At present time, a retrospective control group is not available, neither it is possible to design a randomized study to prove telemonitoring effectiveness. For this reason, the results of the analysis here conducted are mainly intended to describe the phenomenon, and to introduce the use of the class of models described in Section 2 to this real problem. Dependence between different periods pre and post telemonitoring will not be taken into account, nonetheless it will be an important object of study in future works.

Section 2 introduces the class of models and some remarks about its characteristics. Section 3 presents the dataset and its composition methodology. Section 4

¹ The New York Heart Association (NYHA) classification divides in four classes the extent of heart failure.

deals with the results obtained by the application of these models. Finally, Section 5 contains some concluding remarks.

2 Notation and model specification

Let $(\mathcal{F}_s)_{s \in I}$ be a filtration associated to the probability space $(\Omega, \mathcal{F}, \mathbb{P})$, with $I = [0, \tau]$. We define the counting process $(N(s))_{s \in I}$ adapted to $(\mathcal{F}_s)_{s \in I}$ as follows:

$$N(s) = \sum_{j=0}^{\infty} I\{S_j \leq s, S_j \leq \tau\} \quad (1)$$

where S_j represents the calendar time of the j -th occurrence of the observed event (in our case, the hospitalization); time τ represents a random censoring time for the process.

Since N is a submartingale such that, for every stopping time T , $N(T)$ is uniformly integrable, the Doob-Meyer decomposition theorem (see, for example, [1]) states that there exists a unique predictable, non decreasing, cadlag and integrable compensator (or cumulative hazard) process $(\Lambda(s))_{s \in I}$ such that

$$M = N - \Lambda \quad (2)$$

is a zero-mean, uniformly integrable martingale. Hence, thanks to this theorem, the distribution of event times is completely characterized by the knowledge of process Λ , on which modeling efforts should be focused. We assume that

$$\Lambda(s) = \int_0^s Y(w) \lambda(w) dw, \quad (3)$$

where $Y(s) = I\{s \leq \tau\}$ is the *at-risk process*, and $(\lambda(s))_{s \in I}$ is called *hazard function*, or *intensity process*.

For a subject with covariate vector $X(s) = (X_1(s), \dots, X_q(s))^T$ (possibly time-dependent), the Peña and Hollander model for $\lambda(s)$ is defined as follows

$$\lambda(s|X, Z) = Z \lambda_0[\mathcal{E}(s)] \rho[N(s^-); \alpha] \psi[\beta^T X(s)], \quad (4)$$

where Z is an unobservable nonnegative random variable, $\lambda_0(\cdot)$ is an unknown baseline hazard function, $\rho : \mathbb{N} \rightarrow \mathbb{R}^+$ is a monotone function with $\rho(0) = 1$ (dependent on the parameter α), $\psi : \mathbb{R} \rightarrow \mathbb{R}^+$ is a nonnegative function and $\beta = (\beta_1, \dots, \beta_q)^T$ a vector of real coefficients. $(\mathcal{E}(s))_{s \in I}$ is an observable predictable process, almost surely positive, called *effective age process*, such that $\mathcal{E}(0) = e_0 > 0$ a.s. and $\mathcal{E}(s)$ is a.s. monotone and differentiable with first derivative in $(0, 1]$, for $s \in [S_{(j-1)}, S_j]$. We shall now analyze the meaning of the factors which model $\lambda(s|X(s), Z)$. The variable Z , called *frailty*, represents an unobservable source of variability for the risk of rehospitalization in the considered population; Z is assumed to have a para-

metric distribution (for example from the Gamma family), the parameters of which are determined by an EM algorithm. The baseline intensity $\lambda_0(s)ds$ represents the instantaneous probability of first event occurrence with null covariates and constant frailty, and is estimated non parametrically in the implementation used. The functions ρ and ψ represent, respectively, the effect of process state and subject covariates on intensity. Finally, effective age process represents the effects on the patient's state of the intervention performed during hospitalization. As limit cases, we can observe that $\mathcal{E}(s) = s$ means that the risk state of patients after hospitalization is the same as just before the event (a situation usually described as *minimal repair* in reliability theory), while $\mathcal{E}(s) = s - S_{N(s^-)}$ indicates a perfect restoring of health status after intervention (*perfect repair*). These components of intensity contribute to the definition of a very general model, which embodies various important aspects that influence the hospitalization process.

A semiparametric method for estimation of this class of models is described in [11], and it has been implemented in the R package `gcmrec` [7]. The implemented model assumes, for patients $i = 1, \dots, n$, the following form for cumulative hazard:

$$\Lambda_i(s|X_i, Z_i) = \int_0^s Y_i(w) Z_i \lambda_0[\mathcal{E}_i(w)] \alpha^{N_i(w^-)} \exp[\beta^T X_i(w)] dw, \quad (5)$$

where $Y_i(s) = I\{s \leq \tau_i\}$ (i.e., subjects have different censoring times, assumed to be mutually independent).

3 Data presentation

In Lombardia region an experimentation of heart failure telemonitoring was started in 2003, involving 34 health care institutions (see [9] for an overview of program and protocols). The enrollment protocol adopted during the period 2004–2008 includes adult citizens of Lombardia with a NYHA class of III or IV who have experienced at least one hospitalization for heart failure during the 6 months preceding the beginning of telemonitoring, for a total of 1177 subjects. The telemonitoring period is planned for a 180 days duration, with possible re-enrollment under particular conditions. If a hospitalization lasting more than 8 days occurs during the telemonitoring period, telemonitoring is interrupted.

Information about telemonitoring periods has been collected, under prior informed consent, in four studies (*Criteria*, *Piano Urbano*, *Nuove Reti Sanitarie* and *Telemaco*), and gathered in a comprehensive database. Each record of this database refers to a telemonitoring period, and contains anagraphic data of the involved patient, number of ECGs transmitted, NYHA class, number of hospitalizations occurred and other clinical relevant quantities.

Since data regarding telemonitoring periods are not sufficient to operate a retrospective study about effectiveness of this care strategy, we requested an interrogation of regional administrative databases, to obtain SDOs stored during the five years of interest. Each one of these records contains extensive information about a single

hospitalization, like date, duration, DRG², drugs received and other data of clinical and economic interest. The subjects contained in the telemonitoring database have been identified by codes derived from anonymizing procedure applied to their fiscal codes. The codes have been used to retrieve from the SDO database the hospitalization histories of these patients in period 2004–2008.

Before proceeding to the analyses, a consistency test was carried out on available data, to check accordance between the two databases and birth-death coherence. Among the subjects of the telemonitoring database, 85 codes did not find match in the SDO database and 1 patient had a date of decease incoherent with SDO data. The final selected sample included 1091 patients (787 males and 304 females), for a total amount of 1099 telemonitoring periods.

The mean age of selected subjects is 69.37 years old, and a Mann-Whitney hypothesis test shows that women are significantly older than men, providing a p-value of $6.766 \cdot 10^{-9}$ (with mean age for females 73.93, versus 69.87 for males). Conversely, a Mann-Whitney test shows that men present a significantly higher number of hospitalizations, providing a p-value of $2.268 \cdot 10^{-6}$ (the mean number is 4.59 for men and 3.55 for women). Of the 1099 total periods of telemonitoring, 1033 were concluded, 43 patients died during the period for cardiovascular causes and 14 for non-cardiovascular causes, while 49 died during a hospitalization outside the period of telemonitoring; there were 9 drop-outs and 6 interruptions for unavailable causes.

4 Results

In the described models, deaths will be taken into account as censoring times, while the chosen covariates X_1 and X_2 are respectively sex (0 for female, 1 for male) and age. Tests on coefficients are conducted under the assumption of normality, following asymptotic properties of maximum likelihood estimators.

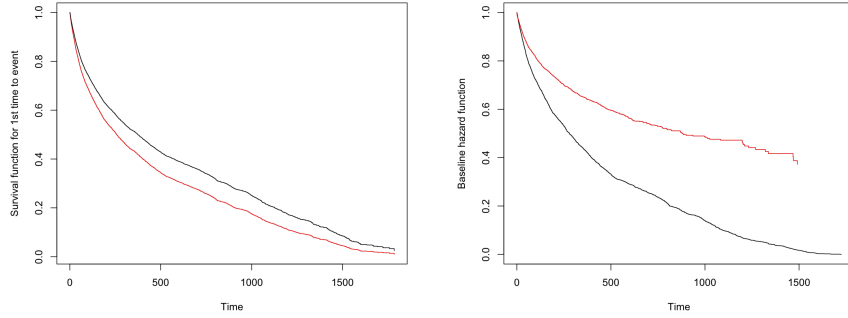
The first considered model is aimed to describe the whole hospitalization process in the five years period, and it assumes effective age of perfect repair type and equal for all patients, and constant frailty variables $Z_i = 1 \forall i = 1, \dots, 1091$. The date 1st January 2004 is taken as the origin of calendar time, while all the processes are censored at 31st December 2008 (if not censored before). The resulting estimates are shown in Table 1. Note that all parameters are significant, and in particular $\alpha > 1$ implies that globally a new hospitalization indicates a worsening in the patient's status, increasing the risk of future hospitalizations. Figure 1a represents a comparison between two estimated survival functions³ for time to first event, associated respectively to a male and a female subject with age equal to the sample mean of the corresponding gender. We can notice that the average male subject, for every time

² Diagnosis Related Group is a system for the classification of patients discharged from hospital, based on the type of resources used during the stay.

³ With the term *survival function* we refer to the function $1 - F_X(x)$, where $F_X(x)$ is the cumulative distribution function of a random variable X .

Table 1: Output of model estimates for the five years period. The p-value for α refers to a test with null hypothesis $\alpha = 1$.

Parameter	Estimate	Std. Err.	p-value
β_1	0.20917	0.03578	5.0e-09
β_2	0.00482	0.00138	4.5e-04
α	1.09	0.00484	~ 0



(a) Survival functions for time to first event on the whole observation period. The red curve refers to a male, the black one to a female, with age equal to the corresponding gender sample mean.

(b) Baseline survival functions for the periods preceding (black) and following (red) telemonitoring.

Fig. 1

instance, has a higher probability of time to first event, so a higher risk of being hospitalized.

Aim of the second analysis is a description of hospitalization histories in periods pre and post telemonitoring, with the same assumptions used in the first model, treating them as different processes. For each patient, estimates are carried out considering two periods: from 1st January 2004 to the beginning date of telemonitoring and from the end of telemonitoring to 31st December 2008 (if not censored). The results are presented in Table 2. Comparing the values of the estimates obtained for the two periods, we observe remarkable variations in regression coefficients. In particular, the estimate of β_2 changes in sign while passing from the pre to the post telemonitoring period, and is no still significant at level 5%. We can also observe that parameter α is lower in the last period, since a p-value near 0 is observed in a test with equality of parameter α in the two periods as null hypothesis.

A remarkable difference can be found also between estimated baseline survival functions (Figure 1b). In fact, we clearly see that the curve associated to the last period is uniformly higher, implying a lower risk of rehospitalization.

Table 2: Output of model estimates for the periods pre (left) and post (right) telemonitoring

Parameter	Estimate	Std. Err.	p-value	Estimate	Std. Err.	p-value
β_1	0.12303	0.04619	0.0077	0.3185	0.07399	1.7e-05
β_2	-0.00306	0.00181	0.0900	0.0029	0.00265	2.7e-01
α	1.21	0.00925	~ 0	1.14	0.0162	~ 0

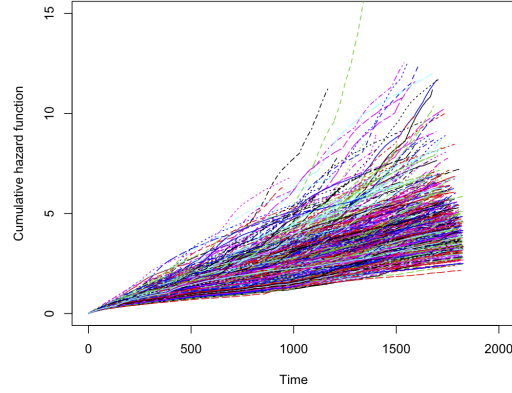


Fig. 2: Estimated cumulative hazard functions for the 1091 subjects.

Estimation of parameters and baseline hazard function allows us to reconstruct cumulative hazard functions for each patient. Figure 2 shows estimates of compensator process trajectories $\Lambda_i(s)$ for $i = 1, \dots, 1091$. These curves can be treated as functional data and classified using a proper functional clustering algorithm (see [13] for details on the implementation of functional k-means) to detect possible relations between their shape and other factors (for example, sex, age class, reference health institution, etc.). This aspect of the study will be developed in [2] (work in progress).

5 Conclusions

The model we presented in this work is very general, and the estimated parameters and hazard functions provide important results of clear interpretation. The use of the Public Health Database allows to acquire data about different periods in patients' hospitalization histories, providing information that can be decisive in characterizing the effectiveness of telemonitoring. On the other hand, cluster analysis on hazard

functions could be an effective method to determine factors that increase the risk of hospitalization.

Nonetheless, model details like the choice of covariates should in the future be more finely tuned, with the help of expert medical advice. The assumption of perfect repair is indeed too restrictive, and methods for estimating more complex effective age formulations (i.e. a combination of minimal and perfect repair) should be explored. Moreover, a model formulation able to describe correlation between periods pre and post is under study. Finally, estimates on the model with frailties could provide a more accurate description of the sample, and could be used for prediction.

Future works will concern the above aspects, and improve upon the analysis of cumulative hazard functions as functional data. Finally, setting this model in a Bayesian non parametric framework for the estimation of frailties could be a very challenging line of research to be explored.

References

1. Andersen, P. K., Borgan, Ø., Gill, R. D. and Keiding, N.: Statistical Models Based on Counting Processes. Springer-Verlag, New York (1993)
2. Baraldo, S., Paganoni, A. M., Ieva, F., Vitelli, F.: Clustering of hazard functions in hospitalizations of patients with heart failure. Work in progress (2010)
3. Capomolla, S. et al.: Heart failure case disease management program: a pilot study of home telemonitoring versus usual care. *Eur. Heart J. Suppl.*, **6** (Supplement F), F91–F98 (2004)
4. Chaudhry, S. I. et al.: Telemonitoring for patients with chronic heart failure: A systematic review. *J. Card. Fail.*, **13**(1), 56–62 (2007)
5. Clark, R. A. et al.: Telemonitoring or structured telephone support programmes for patients with chronic heart failure: Systematic review and meta-analysis. *Int. J. Cardiol.* (2008) doi: 10.1136/bmj.39156.536968.55
6. Giordano, A. et al.: Multicenter randomised trial on home-based telemanagement to prevent hospital readmission of patients with chronic heart failure. *J. Statist. Plann. Inference.* **131**(2), 192–199 (2008)
7. González J. R., Slate, E. H. Peña E. A.: gcmrec: General class of models for recurrent event data (2009). R package version 1.0-3
8. Holland, R. et al.: Systematic review of multidisciplinary interventions in heart failure. *Heart* **91**, 899–906 (2005)
9. Nuove Reti Sanitarie, <http://ftp.cefriel.it/nrs/>
10. Peña, E. A., Hollander, M.: Models for recurrent events in reliability and survival analyses. In: Soyer, R., Mazzocchi, T., Singpurwalla, N. (eds.) *Mathematical Reliability: an Expository Perspective*, pp. 105–123. Kluwer Academic Publishers (2004)
11. Peña, E. A., Slate, E. H., González, J.R.: Semiparametric inference for a general class of models for recurrent events. *J. Statist. Plann. Inference.* **137**, 1727–1747 (2006)
12. Scalvini, S. et al.: A pilot study of nurse-led, home-based telecardiology for patients with chronic heart failure. *J. Telemed. Telecare.* **10**, 113–117 (2004)
13. Tarpey, T., Kinatader, K. K. J.: Clustering functional data. *J. Classif.* **20**, 93–114 (2003)