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Hospitalization rate as a proxy for the quality of life evaluation: the case of dilated cardiomiopathy

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Key words

Hospitalization • Quality of life • Dilated cardiomiopathy

Summary

Rationale, aims and objectives. *Some objective indicators like symptoms, toxicity, performance status, rate of hospitalization or re-employment have been already employed in scientific literature as proxies of Quality of Life assessment, and, in spite of the intrinsic limitations of such a measurement, they represent a valuable source of information in all the situations where a formal assessment is impossible, due to budget, time or human resources constrains. We concentrate here on some models for the analysis of frequency of hospitalization data and we discuss an application to the Hearth Muscle Disease Study Group data.*
Methods. *A sample of 235 patients with dilated cardiomyopathy (DCM) prospectively treated at the Department of Cardiology (Trieste, Italy) have been observed during a period of 18 years, from 1978 to 1992 and data regarding hospitalization history were collected. The hospitalization process depends on the time since the last event, and usually is a function of a set of explanatory variables, such as the current state of the patient, treatments he has been receiving and the severity of disease.*
We propose here a semi-Markov representation of the hospitalization process, and we analyze data regarding DCM, implementing Exponential, Weibull, and Cox models; in Cox models we take care also of the stratification according to the duration or to the levels of the state factor.
Results. *The probability of experiencing a second hospitalization within one year after the first one is estimated about 0.50, and within two years about 0.30. After this point the probability remains constant at a 0.10 level. The same pattern is observed for the second hospitalization, while things are getting worse after the third hospitalization, when the probability of not having a subsequent hospitalization is about 0.10 within one year. Betablockers have a strong influence in enlarging the time interval spent between an hospitalization and the other.*
Conclusions. *The hospitalization process can be viewed only as a rough approximation of the good standing of the patient. However, for diseases like DCM can be reasonable, because of the relatively fast increment in the worsening conditions of the patients and the consequently high chances of observing new hospitalizations up to the absorbing state (the death). Moreover a very detailed modeling of the process leads to extract as much information as possible from the data.*

Introduction

Dilated cardiomyopathy (DCM) is a primary myocardial disorder characterized by cardiac enlargement and impaired systolic function of one or both ventricles. Despite conventional therapies the prognosis remains poor, with a mortality rate of 10% [1-3]. Even if the assessment of Quality of Life (QoL) has become a challenging issue in the scientific debate [4], only few studies have evaluated the burden of illness and the impact of the disease natural history on QoL for the individual with DCM.
After the systematization given to the subject of QoL evaluation by Schumacher and Olschewski [5, 6] different modes of assessing the quality of life have been described, distinguishing among: *(i)* First Order, or ascertainment using validated measuring questionnaires; *(ii)* Second Order, or objective measurements (for example sleep dysfunction, general well being, motor functioning); *(iii)* Third Order, where only *proxies* for the quality of life are known, as for example the hospitalization history of the patient.

The analysis of non-fatal recurring events, for example repeated admissions, is appropriate in studies on chronic-degenerative diseases implying that the patient passes from an acute phase to another acute phase or worse. In this case, the patient's hospitalization rate, being associated with a high familiar, social and economic burden, is considered as evidence of the severity of the disease [7, 8]. Thus, the underlying hypothesis is that QoL decreases when the hospitalization rate increases, as typically happens for DCM patients in which clinical picture progresses from asymptomatic left ventricular dysfunction to overt symptomatic heart failure [9, 10]. Studies performed in other clinical setting [11, 12] validated measuring questionnaires in order to evaluate the impact of exacerbation on health status and admission to hospital testify the negative effect of hospitalization on QoL confirming the correctness of assumption on which a third order evaluation is based on.
However, very few models have been proposed in order to assess QoL starting from proxy such as hospitaliza-

tion rate. Generally, the hospital history of the patient is considered as a "follow-up" and the subject becomes the protagonist of a Markov process at the finished states, whose transitions between states correspond to the occurrence of one or more events of interest [13]. Multistate models that exploit the properties of Markov chains are widely used in medical research because they have a methodological framework useful to describe complex outcomes which are dependent on time [14]. The earlier applications of multi-state model have been done with homogeneous Markov models, which assume that the transition intensities do not depend on time [15]. A slightly more general model is to consider that the transitions depend, in addition to time, on the time spent in the present state, which makes sense in QoL since the length of hospitalization is an evidence of the inability to conduct a satisfactory life, which defines a Semi-Markov model.
A first discussion has been given by Andersen [16] who proposed a class of Semi-Markov models to analyze the hospitalization rate. The advantage of using Semi-Markov models relies on the fact they allow for a hospitalization rate, which varies depending on the time (a non constant intensity of the process moving from one state to another). Nevertheless they can be reduced to constant intensity Markov model when the rate does not vary within transitions.
In the present paper the application of Semi-Markov models to describe the hospitalization process, as proxy of the QoL, in individuals affected by DCM, is proposed. Hospitalization rates are estimated considering treatments patients have been receiving, giving thus some insight to investigate their influence on the intensity (duration) of the process. A short introduction to Semi-Markov models, both in parametric and semi-parametric form, is given and their application to the DCM patients is discussed.

Methods

Data collection

The HMSDG (Hearth Muscle Disease Study Group) dataset is a Hospital Registry, which enrolled 235 patients affected by the dilated cardiomiopathy. The patients have been observed during a period of 15 years, from 1 Janauary 1978 to 31 December 1992, at Maggiore Hospital, Department of Cardiology, in Trieste (Italy). The end points of follow up were heart transplantation or death. The follow up data were obtained by regular hospital visits [17].
Only in the very last years a systematic collection of data about QoL has been undertaken using mainly the Minnesota Living with Heart Failure Questionnaire [18], whereas for earlier years the only data available on QoL are based on the patients' history of hospitalization. Data regarding pharmacological treatment were also collected, including pharmacotherapic choice (Betablockers, ACE-inhibitors) and time at first assumption.

Duration models

In analogy to irreversible illness-death models, a Markov model can be assumed for modeling multistate phenomenon such as hospitalization histories. Given the maximum number of observed hospitalizations in a cohort of patients, the process of hospital admission can be viewed as a forward-moving Markov Chain, in which the only possible transitions from the actual state (the progressive number of hospitalization) are to a new hospitalization or to the absorbing state (the death). However, modeling hospitalization histories is more complex than modeling a simple point-process as that described above, since the risk of being hospitalized is not only dependent on the time (duration) but also on other factors, such as the current state of the patient, treatments he has been receiving and the severity of disease. Furthermore, in some cases also the risk may depend on the time.
In this setting, patient's hospitalization history can be assumed to result from Semi-Markov process, i.e. the time-dependent state transition probability from one state (one hospitalization) to another depends only on its previous state. Based on this assumption, the Cox's proportional hazard-model [19, 20] can be applied to estimate the time dependent state transition probability.
In the Cox's proportional hazard-model is usally written in term of the *hazard,* or *intensity,* function *h(t),* which represents the instantaneous changing rate of state at time *t,* i.e the risk to experience a hospitalization given survival up to time *t.* Following McCullagh [19], *h(t)* can be modeled as functions of a set of predictor variables **x** and the time *t* and can be specified as:

$$h(t;\mathbf{x}) = \lambda(\mathrm{t})\exp[\beta^{\mathrm{T}}\mathbf{x}] \qquad (1)$$

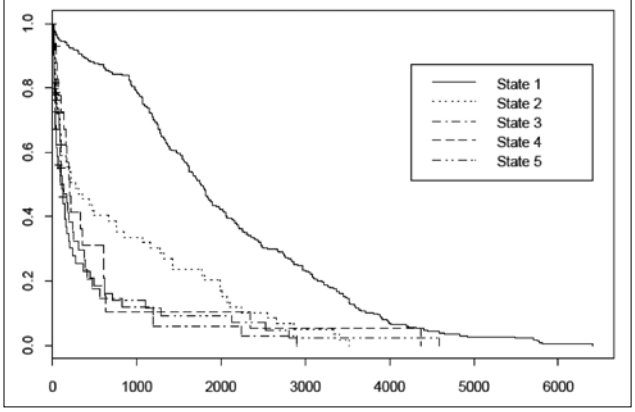
The model (1) belongs to the class of the intensity-based models, with an intensity function not constant over the time. Given the nature of *h(t)*, the model could be parametric or semi-parametric. In the parametric setting, the Weibull and the Exponential distribution can be used to define the form of the hazard function *h(t)*. The main difference between these models relies on the definition of *h(t)*. In the Exponential model the intensity is constant over time, while it is assumed as a power function of the time in the Weibull model.
On the contrary, the Cox Proportional Hazard Model does not specify any form of the hazard function *h(t)* and this property makes Cox models semi-parametric models.
In our setting, the intensity function can be supposed joined with a treatment factor for a global effect within each state. Thus the hazard function can be stratified according to the patient's state. This assumption is equal to assume, that the time dependent term $\lambda(t)$, and thus the hazard function, is different in each stratum [20].
In the following analysis, we considered Exponential, Weibull, Cox models and stratified Cox Model to assess the hospitalization rate of patients affected by the dilated cardiomiopathy. The transition hazard rates between different states were estimated with respect to treatments. The estimated coefficients of treatments provided useful

insight to investigate their influence on state and duration on the state.
In all these models we did not consider the potential correlation among observations given by the *subject* effect i.e.: the fact that we have more than one transition (at least potentially) for each subject due to repeated admissions. Several methods have been proposed to take into account the dependencies in the data such as frailty models [21] or marginal hazard methods [22, 23]. In this study we considered a marginal hazard approch in order to adjust the standard errors of the estimates for the dependency in the data applying the Wei-Lin-Weissfeld method [23].

Results

Out of the total of the patients, 48 experienced only one hospitalization, 66, 43 and 22 patients had respectively 2, 3 and 4 hospitalizations. Finally 56 patients had more than or exactly 5 hospitalizations (the actual maximum number of hospitalizations is 13 which was observed in one patient).
In Figure 1, Kaplan-Meier curves of new hospitalization were obtained separately for each state. The estimates of the transition probabilities give some indications on the frequency and rate at which one hospitalization follows the previous one. The probability of experiencing a second hospitalization within one year after the first one is estimated about 0.50, and within two years about 0.30. After this point the probability remains constant at a 0.10 level (State 2 curve). The same pattern is observed after the second hospitalization (State 3 curve), where the probability of not having another hospitalization within one year is about 0.50, remaining constant for the subsequent years. Things are getting worse only after the third hospitalization (State 4 and State 5 curves), where the probability of not having a subsequent hospitalization is about 0.10 within one year.
The results are presented as follow: (i) a measure to compare the goodness of fit for the different models is reported in Table I; (ii) coefficients of explanatory variables estimated by models are given in Table II and Table III; (iii) standard error to assess statistical significance of coefficients are also reported; for Cox models stratified robust standard error have been computed too.
In Table I, the log-likelihood for the different models is shown. Log-likelihood is a pragmatic measure to compare models (the larger the value is, the better the model is). Exponential and Weibull have almost the same log-likelihood, giving the suggestion that the exponential or the Weibull models, which have a constant intensity function, could be adequate to represent the process.

Fig. 1. Time in a State before a new hospitalization (in days). The State 1 curve depicts the probability of the first admission to the hospital in patients with DCM. The State 2, the State 3, the State 4 and the State 5 curves depict the probability of experiencing a hospitalization after the first, the second, the third and the fourth one, respectively.



Explanatory variables coefficients for these parametric models are shown in (Tab. II). The Cox model stratified by states performs better than the analogous stratified by duration, which correspond to a non-constant intensity Markov process (Tab. I).
Treatment effect for Cox model stratified by state is always significant (Tab. III), meaning they influence the duration in a state. Betablockers in particular have a stronger influence in enlarging the time interval spent between a hospitalization and the other. Their positive effect is twice as bigger in the most critical regions in the state-space: the third and fourth hospitalization, where the patient overcomes a threshold, which usually drives him into a worsening condition (Fig. 1). Standard errors obtained for the proportional hazard model stratified by state using normal approximation and robust estimation are given in Table III. The robustified standard errors are about 20% more conservative than those based on independence assumptions. However, this does not change our conclusions about treatment effect.

Discussion

Studies that illuminate the complex relationships among disease status and global quality of life can inform a broad range of topic, including those involving the scope and focus of clinical care, the access to care, and health care policies [24]. However, the possibility to implement this kind of studies is limited in all the situations where a formal assessment is impossible, due to budget, time or human resources constrains. On the other hand,

Tab. I. Log-likelihoods for Exponential, Weibull, Cox models and Cox stratified (by state and by duration) models. The larger the value of the log-likelihood is, the better the model is.

Model	Exp.	Weibull	Cox	Cox (State)	Cox (Duration)
Null	-754.24	-739.46	-998.82	-763.03	-837.5
(BETA+ACE)	-739.21	-729.07	-959.70	-748.19	-826.37
(BETA+ACE)*State	-659.38	-659.38	-949.97	-	-796.52

Tab. II. Coefficients and Standard Errors (SE) for the parametric models.

	Weibull		Exponential	
Term	Coeff.	SE	Coeff.	*SE*
Int.	7.94	0.11	7.95	0.11
BETA	-0.23	0.15	-0.24	0.15
ACE	-0.42	0.16	-0.41	0.15
State 2	-0.92	0.22	-0.91	0.21
State 3	-2.07	0.32	-2.04	0.30
State 4	-1.24	0.41	-1.21	0.39
State 5	-1.80	0.33	-1.75	0.32
BETA.State 2	-0.29	0.36	-0.28	0.35
BETA.State 3	1.21	0.45	1.22	0.44
BETA.State 4	1.35	0.60	1.37	0.57
BETA.State 5	0.38	0.43	0.39	0.41
ACE.State 2	-0.10	0.32	-0.10	0.31
ACE.State 3	-0.12	0.44	-0.14	0.42
ACE.State 4	-0.96	0.60	-0.99	0.57
ACE.State 5	0.27	0.40	0.237	0.39
Log(scale)	0.03	0.03		

Tab. III. Coefficients, odds ratio (OR), native and robust Standard Errors (SE) for the Cox model stratified by State. Robust SE have been estimated adjusting for repeated observation on the same subject. 95% Confidence Interval (CI) for OR were calculated base on robust SE.

Treatment	coef	OR (95% CI)	Native SE	robust SE
BETA	0.409	1.51 (1.17; 1.94)	0.126	0.131
ACE	0.596	1.81 (1.28; 2.57)	0.132	0.178

even when only *proxies* for the quality of life are known, an adequate modeling choice could be able to give an estimate of diseases burden and point out major issues in clinical management.

The application of Semi-Markov models to describe the dynamic of quality of life in DCM patients in long-term follow-up has been shown to be a flexible and a realistic choice. In particular, the detailed modeling of the hospitalization process, whether considered a proxy of the quality of life, could be useful to detect impact of therapy in reducing hospitalizations, or in describing the natural history of the disease form a broader perspective. In our setting, according to the log-likelihood, semi-parametric Cox model stratified by states and the parametric Exponential and Weibull models seems to be similarly adequate to modeling the process. On the contrary, Cox model stratified by duration appears to be a poorer model, suggesting that constant intensity transitions are adequate in modeling the process and that they do not depend on events of the history of the process.

The natural history of DCM, as depicted by the hospitalization rate, seems to consist in a highly progressive worsening scenario. The probability of being re-hospitalized within one-year is about 90% after the third hospitalization, indicating a highly severe prognosis in this class of patients. Moreover, such a high re-hospitalization probability is most likely indicating a poor chance of having an independent life and a normal professional activity for these patients. High hospitalization episodes could also leads to have or exacerbates psychological symptoms such as depression and anxiety. These psychological symptoms and the stressful experience of frequent re-hospitalizations, in turn, can initiate a spiraling decline in physical and psychological well-being and can affect also the course of the cardiac disease [25, 26].

Our results stress the key role of a timely diagnosis and of a well-planned, pharmacotherapic management program: treatment seems in fact to be fundamental to reduce the burden of illness. Neurohormonal antagonists like Aceinihibitors and Betablockers were showed to improve prognosis in heart failure [27] and, as expected, were always significant in present analysis. Betablockers in particular, cause a dramatical improvement of the left ventricular function [28]. The strong influence of metoprolol in enlarging the effects of sympathetic activation in patients with more severe heart failure [29] may explain the fact that treatment effect is twice as bigger in the third and fourth hospitalization, and may suggest a greater effect of Betablockers in more severe patients; even if a possible confounding due to the fact that the drug could be evolved during the long time of observation of the study could be considered.

Indeed, the limitation of the data does not allow getting more insight into this process. The hospitalization history can be, in fact, viewed only as a rough approximation of the good standing of the patient. For diseases like DCM can be reasonable, because of the relatively fast increment in the worsening conditions of the patients and the consequently high chances of observing new hospitalizations up to the absorbing state (the death). More generally, this kind of approach is the only one feasible in the analysis of long term open trials, hospital registry data, where usually *ad hoc* QoL assessment covers only a small portion of the total registry population. Moreover even if, deeper observation using questionnaires or *ad hoc* subjective and objective measurements should be used whenever possible, when such information is not available, a very detailed modeling of the process leads to extract as much information as possible from the data.

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