Computers in Biology and Medicine 69 (2016) 37–43

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Estimating the parameters of multi-state models with time-dependent covariates through likelihood decomposition

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ARTICLE INFO

Article history:
Received 1 September 2015
Accepted 26 November 2015

Keywords:
End-stage renal disease
Transition rates
Markov models
Multi-state models
Time-dependent covariates

ABSTRACT

Background: Multi-state models become complex when the number of states is large, when back and forth transitions between states are allowed, and when time-dependent covariates are inevitable. However, these conditions are sometimes necessary in the context of medical issues. For instance, they were needed for modelling the future treatments of patients with end-stage renal disease according to age and to various treatments.

Methods: The available modelling tools do not allow an easy handling of all issues; we designed thus a specific multi-state model that takes into account the complexity of the research question. Parameter estimation relied on decomposition of the likelihood and separate maximisations of the resulting likelihoods. This was possible because there were no interactions between patient treatment courses and because all exact times of transition from any state to another were known. Poisson likelihoods were calculated using the time spent at risk in each state and the observed transitions between each state and all others. The likelihoods were calculated on short time intervals during which age was considered as constant.

Results: The method was not limited by the number of parameters to estimate; it could be applied to a multi-state model with 10 renal replacement therapies. Supposing the parameters of the model constant over each of seven time intervals, this method was able to estimate one hundred age-dependent transitions.

Conclusions: The method is easy to adapt to any disease with numerous states or grades as long as the disease does not imply interactions between patient courses.

1. Introduction

Multi-state models have already been widely used in medicine. These models are of great interest in studying chronic diseases with several grades and/or treatments [1]. When the number of states is large, when back and forth transitions between states are allowed, and when time-dependent covariates (such as age) have to be taken into account, the resulting model can become quite complex. We faced all these difficulties when we designed a model to describe the successive treatments offered to patients with end-stage renal disease (ESRD).

ESRD is a life-threatening condition but, in the sixties, renal replacement therapies (RRTs) radically changed patients' prognoses and led to longer survivals, especially in renal transplant patients. Currently, ESRD patients may experience several switches between various RRTs [2,3], and, in several countries, registries have been established to collect data on these switches [4–7]. These switches can be described using the rates of transition between different RRTs.

Various solutions have been proposed to solve the specific problems of multi-state models in medical research [1,8,9]. These solutions are extensions of survival data analyses applied to settings with multiple transitions and competing risks [10–16]. In fact, several authors succeeded in using these solutions to analyse

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http://dx.doi.org/10.1016/j.compbiomed.2015.11.016
0010-4825/

ESRD datasets, but their models used small numbers of transitions (only the main RRTs were studied), and they considered only age as a categorical variable (i.e., the estimates of the parameters were made for age classes) [17–19].

In France, 10 different RRT modalities are used and all of them should be considered to model the successive treatments a patient may undergo; this requires the estimation of a high number of transition rates. Moreover, the transitions to renal transplantation or death depend on the patients' age which should be integrated into the model.

The data recorded in the French ESRD registry [4] have two features that helped us overcome these difficulties. First, the patients' treatment courses are independent (that is, the switch of a patient from one treatment to another does not depend on the treatments the other patients are undergoing). Second, the exact times of all transitions from any treatment to another are known. These two features make it possible to decompose a multi-state model into sub-models whose likelihoods can be separately maximised [8,10].

In this paper, we explain the way we solved a complex problem with a simple implementation of likelihood decomposition. This decomposition greatly facilitates the theoretical analysis and the numerical solution. Afterwards, considering short time intervals during which the time-dependent covariates are supposed constant led to the estimation of these covariate effects on the transition rates.

2. Materials and methods

2.1. REIN registry

Several studies on ESRD patients are longitudinal studies with possible state changes [17,18,20]: the RRT may change over time during the disease. The three main RRTs are haemodialysis (HD), peritoneal dialysis (PD), and renal transplantation (TX). These RRTs may be subdivided further according to the technique, the type of facility, the type of assistance, and the type of renal graft.

The French Renal Epidemiology and Information Network (REIN) registry [4] collects data on patients with ESRD who might undergo one to ten different RRTs. REIN registry contains data on patients registered since ESRD onset (incident patients) and data on patients registered late after ESRD onset (but whose date of ESRD onset is available: prevalent patients). At registration, the mean time since ESRD onset in prevalent patients was 6.1 years (SD: 6.2 years). Overall, the dataset studied here includes 67,258 patients, 206,401 person-years of follow-up, and 56,084 transitions (between 10 RRTs+state "death"). Table 1 presents the main characteristics of REIN registry population. The complexity of ESRD data is due to the high number of possible transitions (100 possibilities including back and forth transitions) and to the dataset structure that includes left-truncated, interval-censored, and right-censored observations. One advantage of REIN registry is that, as soon as a patient is registered, all changes in RRT are recorded with the exact time of transition from any state to another.

Table 1
Main characteristics of the population in REIN registry.

	Incident patients	Prevalent patients	Total
Characteristic	$n=33{,}271$	$n=33{,}987$	$n=67{,}258$
Age at ESRD onset			
Mean (SD) (yrs)	67.35 (15.33)	54.56 (17.73)	60.89 (17.78)
18–44 year (%)	3235 (9.72%)	10,578 (31.12%)	13,813 (20.54%)
45–69 year (%)	12,495 (37.56%)	15,452 (45.46%)	27,947 (41.55%)
≥ 70 year (%)	17,541 (52.72%)	7957 (23.41%)	25,498 (37.91%)
Sex (%)			
Males	20,677 (62.15%)	20,513 (60.36%)	41,190 (61.24%)
Females	12,594 (37.85%)	13,474 (39.64%)	26,068 (38.76%)
Diabetes (%)			
Yes	12,037 (36.18%)	6888 (20.27%)	18,925 (28.14%)
No	21,234 (63.82%)	27,099 (79.73%)	48,333 (71.86%)

2.2. The multi-state model used with the French ESRD data

From ESRD onset to death, the patients may undergo several of 10 different RRTs. A multi-state model may then be used to describe the transitions between RRTs and between each RRT and death. This leads to a model with 20 different states: 10 for the RRTs and 10 to indicate the RRT at patient death. No impossible transition between RRTs was considered, including back and forth transitions. Being in a given treatment, a patient may be switched to any other treatment whatever the treatments he/she had previously undergone. Here, for simplicity, the figures and equations present a model with one state for peritoneal dialysis instead of four, one state for haemodialysis instead of four, one state for transplantation instead of two, and three states for death instead of 10 (Fig. 1).

The time of interest was the time since ESRD onset in each patient because the transition rates from one state to another depends on the time elapsed since ESRD onset.

Formally, this multi-state model may be written in terms of rates of transition between states. The process of patients moving between states was assumed to be Markovian: i.e., any change for a given patient depends only on the current state, not on the time spent in the current state. A proportional hazard model was chosen to take into account various covariates. Thus, the rate of transition from a given state i to another state j at time t (the delay since ESRD onset) for all patients whose characteristics are $\mathbf{Z(t)}$ at time t may be written [14]:

$$\lambda_{ij}(t, Z(t)) = \lambda_{ij,0}(t) * \exp(\beta_{ij}^T Z(t))$$

where $\lambda_{ij,0}(t)$ represents the baseline transition rate between states i and j at time t and $\boldsymbol{\beta}_{\mathbf{ij}}$ the vector of regression parameters that represents the effect of characteristics $\mathbf{Z(t)}$ on the transition rate. A

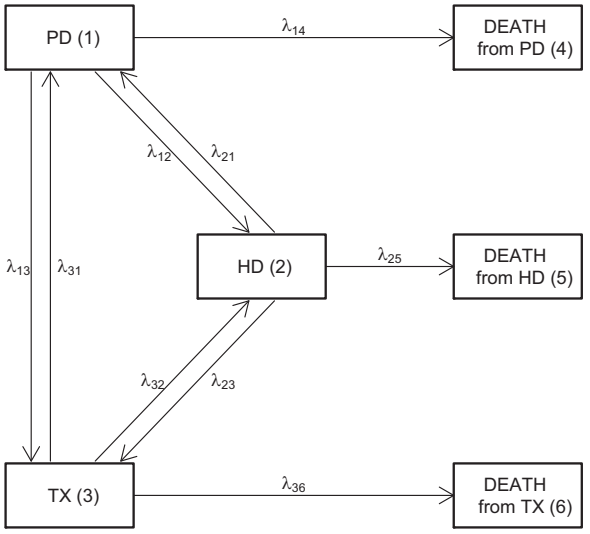

Fig. 1. The simplified multi-state model used to describe the transitions of ESRD patients between renal replacement therapy states and between these states and the absorbing state "death". Only three main RRT states are considered: PD: Peritoneal Dialysis, HD: Haemodialysis, and TX: Transplantation. The boxes and the arrows represent the theoretical model. λ_{ij} is the transition rate from any state i to another state j; here, $i=1$–3 and $j=1$–6.