Research Article

Statistics in Medicine

Received 12 April 2012, Accepted 15 February 2014 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.6140

A joint frailty model to estimate the recurrence process and the disease-specific mortality process without needing the cause of death

Aurélien Belot,[a,b,c,d,e*†] Virginie Rondeau,[f,g] Laurent Remontet,[a,b,c,d] Roch Giorgi[h,i,j] and the CENSUR working survival group

In chronic diseases, such as cancer, recurrent events (such as relapses) are commonly observed; these could be interrupted by death. With such data, a joint analysis of recurrence and mortality processes is usually conducted with a frailty parameter shared by both processes. We examined a joint modeling of these processes considering death under two aspects: 'death due to the disease under study' and 'death due to other causes', which enables estimating the disease-specific mortality hazard. The excess hazard model was used to overcome the difficulties in determining the causes of deaths (unavailability or unreliability); this model allows estimating the disease-specific mortality hazard without needing the cause of death but using the mortality hazards observed in the general population. We propose an approach to model jointly recurrence and disease-specific mortality processes within a parametric framework. A correlation between the two processes is taken into account through a shared frailty parameter. This approach allows estimating unbiased covariate effects on the hazards of recurrence and disease-specific mortality. The performance of the approach was evaluated by simulations with different scenarios. The method is illustrated by an analysis of a population-based dataset on colon cancer with observations of colon cancer recurrences and deaths. The benefits of the new approach are highlighted by comparison with the 'classical' joint model of recurrence and overall mortality. Moreover, we assessed the goodness of fit of the proposed model. Comparisons between the conditional hazard and the marginal hazard of the disease-specific mortality are shown, and differences in interpretation are discussed.

Keywords: excess hazard; joint model; recurrent events; shared frailty

1. Introduction

The objective of many medical and epidemiological studies is to estimate the hazard of death. For this estimation, patient death is observed and a survival analysis is carried out to model the time-to-death and estimate the impact of prognostic factors on the hazard of death. Many works have been devoted

[a] *Service de Biostatistique, Hospices Civils de Lyon, F-69495 Pierre-Bénite Cedex, France*
[b] *Université de Lyon, F-69000 Lyon, France*
[c] *Université Lyon I, Villeurbanne, F-69622, France*
[d] *CNRS ; UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique Santé, Pierre-Bénite, F-69495, France*
[e] *Département des Maladies Chroniques et Traumatismes, Institut de Veille Sanitaire, Saint-Maurice, F-94415, France*
[f] *Centre INSERM U-897-Epidemiologie-Biostatistique, INSERM, Bordeaux, F-33076, France*
[g] *Université Bordeaux Segalen, Bordeaux, F-33076, France*
[h] *Aix-Marseille Université, UMR_S 912 (SESSTIM), IRD, Marseille, F-13385, France*
[i] *INSERM, UMR_S 912 (SESSTIM), Marseille, F-13284, France*
[j] *APHM, Hôpital Timone, Service Biostatistique et Technologies de l'Information et de la Communication, Marseille, F-13005, France*
**Correspondence to: Aurélien Belot, Service de Biostatistique, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, F-69495 Pierre-Bénite Cedex, France.*
[†] *E-mail: aurelien.belot@chu-lyon.fr*

to various useful approaches within this context [1, 2]. However, in many clinical situations, the subjects may experience repeated or recurrent events before dying. These events may be repeated tumor occurrences, repeated hospitalizations, multiple rejection episodes after organ transplantation, and so on [3]. Furthermore, there is variability between patients in the probability of these recurrent events (some patients are at a low risk and others at a high risk); this variability leads to correlation between recurrent events in the same patient, and this correlation should be taken into account.

Different methodological developments were proposed to analyze recurrent events. Among them, the three mains models are the following: (i) the marginal model of Wei *et al.* [4]; (ii) the conditional model of Prentice *et al.*, [5]; and (iii) the model of Andersen and Gill [6] based on the powerful counting process and martingale theory. Briefly, the marginal model is a Cox proportional hazard (PH) model stratified on the number of events; it assumes that each patient is at risk for each event and may be viewed as a variance-corrected model. When the model's parameters are estimated, the times to the events in each patient are assumed independent, but a variance-covariance matrix, which takes into account the correlation between times to events, is used for inference. The conditional model differs principally by its risk set. It considers that the risk set for the $(k+1)^{\text{th}}$ recurrence is restricted to those individuals who have experienced k recurrences. In the Andersen and Gill model, the hazard of the recurrent process at time t describes the probability of a new recurrence in the very small interval $[t, t+\Delta t]$ given an individual's past history of recurrences up to t. One solution for fitting these models is to create a reorganized dataset that can be further analyzed with any standard statistical software [7]. Many well-written papers that describe clearly the approaches to analyze recurrent event data may be found elsewhere [8–11].

Other models that allow taking into account the correlation between recurrent event times are the frailty models [12]. These correspond to extensions of PH models through inclusion of a frailty term (or random effect), which induces dependence between the multiple times to the events in the same individual. Frailty models have been proposed and successfully used in the analysis of multivariate and correlated failure time data [13–15]. Within the framework of parametric models, the analyst has to choose the shape of the baseline hazard and the distribution of the frailty term. A mathematically convenient choice is then the gamma distribution because the full marginal likelihood has an explicit analytic expression [14]. Maximizing the likelihood is then straightforward using an optimization procedure such as the Newton–Raphson procedure. With other distributions of frailty, one may use the full likelihood based on numerical integration of the conditional likelihood (for example, the Gauss–Hermite quadrature method) [16]. Within the framework of the semi-parametric Cox PH model, the analyst has to choose only the distribution of the frailty, the baseline hazard being treated as a nuisance parameter. A gamma or a lognormal distribution is usually assumed (but other distributions are also usable), and approaches to fit these models are based on the Expectation-Maximization (EM) algorithm [17] or on the maximization of the penalized partial likelihood [7]. Other approaches that assume a smooth spline function for the baseline hazard were proposed; in these approaches, inference is made using the maximum penalized likelihood [18].

However, in many clinical situations, the follow-up of recurrent events may stop because of patient death [19]. As death precludes the observation of recurrence, the question is whether this censoring is independent of the recurrent process. Within the context of cancer survival, for example, the terminal event (death, whatever its cause) depends on the recurrent event process (relapses) and creates an informative censoring. When such an informative censoring exists, analyzing a dataset on recurrent events or terminal events separately may lead to biased estimates [20]. To overcome this difficulty, a joint modeling of recurrence and mortality processes was proposed with a frailty term shared by the intensities of the two processes [20–23]. The joint modeling approaches are indeed useful to assess the unbiased covariate effects on both processes as well as the level of their correlation.

To our opinion, this correlation is not meaningful within the framework of population-based studies on cancer because death may be related to cancer itself or to other causes; the expected correlation is here between the recurrence process and the cancer-related mortality process. We believe that death due to cancer is the event that creates an informative censoring and not death whatever its cause. Therefore, knowing the exact cause of death is crucial, but, unfortunately, in many population-based studies, this information is not usually collected. The cause of death may then be obtained from death certificates, but these are often inaccurate [24, 25]; the excess mortality hazard method was developed to overcome this difficulty [26]. Using the population (i.e., the expected) mortality hazard, this method allows estimating an excess mortality hazard that can be interpreted as the disease-specific mortality hazard [26, 27]. The excess mortality hazard method enables us (i) to differentiate the impact of the 'demographic' covariates (such as age or sex) on the disease-specific mortality from their impact on the 'natural'

population mortality, (ii) to estimate the impact of covariates specifically related to the disease, and (iii) to consider as disease-specific deaths those indirectly due to the disease (in addition to those directly due to the disease), such as the deaths due to treatment complications or suicide.

The objective of the present work was to analyze jointly the recurrence process and the disease-specific mortality process using population-based data with no information on the causes of death. The paper is organized as follows: in Section 2, we introduce the 'classical' joint model for recurrence and overall mortality, the excess mortality hazard model, and the new joint model (NJM) we propose to estimate the recurrent event process and the disease-specific mortality process. In Section 3, we summarize the results of simulation studies that evaluate the accuracy of the estimators. In Section 4, we present an illustration using French population-based data on colon cancer, and then we conclude with a discussion concerning the findings of the study and an outline of further developments.

2. Method

2.1. The joint frailty model for recurrence and overall mortality processes

Let C_i and D_i be the times to censoring and death for subject i ($i = 1, \ldots, N$), respectively, $T_i = \min(C_i, D_i)$ the follow-up time, and $\Delta_i = I(D_i \leqslant C_i)$ the failure indicator, equal to 1 if subject i dies and 0 otherwise. Let t_{ij} be the j^{th} time to a recurrence since the study entry for subject i ($j = 1, \ldots, \mathrm{n}_i$) and δ_{ij} the recurrent event indicator at t_{ij}, equal to 1 if a recurrent event is observed and 0 otherwise. According to the model of Liu *et al.* [20], herein called the classical joint model (CJM), the hazards of recurrence $r(t)$ and overall mortality $\lambda(t)$ are

$$\begin{aligned} r_i(t, \mathbf{x}_i, w_i) &= r_0(t) \exp(\boldsymbol{\beta}\mathbf{x}_i + w_i) \\ \lambda_i(t, \mathbf{x}_i, w_i) &= \lambda_0(t) \exp(\boldsymbol{\alpha}\mathbf{x}_i + \gamma w_i) \end{aligned} \tag{1}$$

The effects of covariates $\mathbf{x}_i$ on each hazard are assumed possibly different, equal to $\boldsymbol{\beta}$ and $\boldsymbol{\alpha}$ for recurrence and mortality, respectively, and w_i is the random effect linked to the i^{th} patient. The frailty term is defined as $u_i = \exp(w_i)$ for the i^{th} patient and may be considered as a latent variable that reflects the 'health status' of patient i. The correlation between the times to the recurrent events relative to a given patient i is introduced by the frailty parameter u_i. Moreover, the frailty term u_i is shared by the hazards of recurrence and mortality; it allows taking into account the possible informative censoring of the recurrent event process by death considering that the two processes are interdependent. We assume that the random-effect w_i follows a Normal distribution with mean 0 and variance θ. In this case, frailty u_i follows a lognormal distribution [14].

In the model of Huang and Wang [22], γ was set to one, implying identical effects of frailty on the hazard for recurrences and the hazard for death. In the CJM, parameter γ provides a greater flexibility (versus the Huang and Wang model) because the frailty parameter may have a different impact on each hazard. A parameter γ estimated close to 0 means that the mortality hazard $\lambda(t)$ does not depend on the frailty; thus, death (or another terminal event) is not informative for the recurrent events. In other words, conditional on the covariates, the two hazards $r(t)$ and $\lambda(t)$ are not associated. When $\gamma = 1$, the effect of the frailty is identical for the recurrent events and the terminating event. When γ is estimated greater than zero, recurrence and death hazards are positively correlated; a higher frailty will result in a higher risk of recurrence and a higher risk of death. On the other hand, when γ is negative, the hazards of recurrence and death are negatively correlated. Note that the interpretation of parameter γ makes sense only in presence of heterogeneity, that is, when the variance of the random effects is significantly different from zero. In the CJM, a θ significantly different from zero (by a unilateral Wald test) and a γ nonsignificantly different from 0 (by a classical Wald test) indicate that death and recurrent event processes are independent but that an inter-patient heterogeneity exists, probably because of the recurrent events.

In the CJM, it is assumed that death prevents the observation of new recurrences, but on the contrary, censoring (such as loss of follow-up) does not interrupt the occurrence of recurrence; these recurrences are simply not observed. In other words, the intensity functions at time t for both recurrent and terminal event processes are modeled given that the individual is still alive at that time $D_i \geqslant t$. This assumption is different from that of Ghosh and Lin or that of Huang and Wang [22, 28]; in the latter approaches, the authors assume that recurrence is a latent process (analogous to latent failure times within the context of competing risks) that continues to increment even if the patient dies.

However, informative censoring is more probably due to the disease-specific mortality process than to the overall (i.e., all-cause) mortality process. In our example, as in many population-based studies,

the cause of death is unknown; this is why a proper analysis requires the use of the excess mortality hazard approach.

2.2. *The excess mortality hazard approach*

In this approach, the overall mortality hazard, λ, is split into an excess mortality hazard, λ_+, and a population (or expected) hazard, λ_P

$$\lambda(t, a_i, \mathbf{x}_i, \mathbf{z}_i) = \lambda_+(t, \mathbf{x}_i) + \lambda_P(a_i + t, \mathbf{z}_i) \tag{2}$$

where t is the time elapsed since diagnosis, a_i the age at diagnosis of patient i, $\mathbf{x}_i$ a vector of covariates, and $\mathbf{z}_i$ a vector of population characteristics [26, 29]. The population hazard $\lambda_P(a_i + t, \mathbf{z}_i)$ in Equation (2) is assumed known; it is usually quantified on the basis of vector $\mathbf{z}_i$ (generally age, sex, place of residence, etc.) and may be obtained from national statistics institutes. In the seminal paper of Estève *and others*, the excess mortality hazard was modeled by a PH model: $\lambda_+(t, \mathbf{x}_i) = \lambda_0(t)\exp(\boldsymbol{\beta}\mathbf{x}_i)$, with $\lambda_0(t)$ constant within pre-specified intervals of follow-up [26]; this model will be referred to hereafter as the 'marginal model' (MM).

2.3. *A joint frailty model for recurrence and disease-specific mortality processes*

2.3.1. The new joint model. The parametric NJM we propose combines the CJM (Equation 1) and the excess hazard approach (Equation 2). It may be written as

$$\begin{aligned} r_i(t, \mathbf{x}_i, w_i) &= r_0(t)\exp(\boldsymbol{\beta}\mathbf{x}_i + w_i) \\ \lambda_i(t, \mathbf{x}_i, w_i, a_i) &= \lambda_0(t)\exp(\boldsymbol{\alpha}\mathbf{x}_i + \gamma w_i) + \lambda_P(a_i + t, \mathbf{z}_i) \end{aligned} \tag{3}$$

In this model, $\lambda_0(t)\exp(\boldsymbol{\alpha}\mathbf{x}_i + \gamma w_i)$ represents the excess mortality hazard that may be interpreted as the disease-specific mortality hazard. We assume that the correlation induced by the shared random effect w_i is here between the recurrence process and the disease-specific mortality process (e.g., cancer-related mortality when the work is on a particular cancer). As in the CJM, parameter γ allows a great flexibility, and we assume that w_i follows a Normal distribution with mean 0 and variance θ.

2.3.2. The estimation procedure. The likelihood of the NJM may be written as the product of two terms, one for recurrence $\left(l_i^R\right)$ and one for death $\left(l_i^D\right)$. Denoting $\Theta = (r_0(.), \lambda_0(.), \boldsymbol{\alpha}, \boldsymbol{\beta}, \gamma, \theta)$ the unknown parameters and $f_\theta(w_i)$ the distribution of the frailty, the contribution of patient i to the likelihood is

$$L_i(\Theta) = \int l_i^R l_i^D f_\theta(w_i) dw_i \tag{4}$$

where

$$l_i^R = \prod_{j=1}^{n_i} \{r_0(t_{ij})\exp(\boldsymbol{\beta}\mathbf{x}_i + w_i)\}^{\delta_{ij}} \exp\left[-\int_0^{T_i} r_0(s)\exp(\boldsymbol{\beta}\mathbf{x}_i + w_i) ds\right]$$

$$l_i^D = \{\lambda_0(T_i)\exp(\boldsymbol{\alpha}\mathbf{x}_i + \gamma w_i) + \lambda_P(a + T_i, \mathbf{z}_i)\}^{\Delta_i} \exp\left[-\int_0^{T_i} \{\lambda_0(s)\exp(\boldsymbol{\alpha}\mathbf{x}_i + \gamma w_i) + \lambda_P(a + s, \mathbf{z}_i)\} ds\right]$$

The full likelihood is then expressed as the product of the individual contributions to the likelihood: $L(\Theta) = \prod_{i=1}^{N} L_i(\Theta)$. The last term in l_i^D $\left(\text{i.e., } \exp\left[-\int_0^{T_i} \lambda_P(a + s, \mathbf{z}_i) ds\right]\right)$ does not depend on the unknown parameters; thus, it can be omitted from the full likelihood.

As detailed in Equation (4), when the baseline hazards of recurrence and disease-specific mortality are left unspecified (e.g., in a semi-parametric setting), the contribution of each individual to the likelihood does not take a simple form. However, the estimation procedure is greatly simplified by assuming parametric forms for the baseline hazards $r_0(t)$ and $\lambda_0(t)$, for example, piecewise constant functions [30]. In our approach, in order to use continuous functions instead of piecewise constant functions, we modeled the log of the baseline hazards using cubic B-splines. A cubic regression spline is a smooth piecewise

polynomial function, which is continuous and has continuous first two derivatives throughout its finite support interval, including at the knots, where the adjacent polynomial pieces join each other [31, 32]. We used one knot located at 1 year, but the degree of the splines and the number and positions of the knots can be easily changed. Indeed, the user can either choose another knot location, on the basis of substantive knowledge about the disease process being modeled or, in the absence of such knowledge, may locate the interior(s) knot(s) at the quantile(s) of the sample distribution of uncensored event times [31, 32]. The cumulative baseline hazards $R_0(t) = \int_0^t r_0(x)dx$ and $\Lambda_0(t) = \int_0^t \lambda_0(x)dx$ can be derived by splitting the follow-up time into small intervals and using Cavalieri-Simpson approximation [27, 33]. The first expression in (4) involves also an integral with respect to the random effect w_i that greatly complicates the derivation of its analytical form and implies the use of numerical methods to approximate it. When a Normal distribution for w_i is considered, this approximation can be made using the adaptative Gaussian quadrature. The estimated covariance matrix of the parameter estimates was computed as the inverse Hessian matrix. The implementation of the adaptative Gaussian quadrature is incorporated in procedure *proc nlmixed* of (SAS) software; an example of the (SAS) code that fits the NJM is supplied in Appendix A.

3. Simulation studies

3.1. Data generation, simulation designs, and analysis of the simulated data

We performed simulation studies to evaluate the performance of the NJM and compare it with the CJM under different scenarios. Briefly, in each scenario, the data were simulated using the NJM with a continuous covariate x_1 (e.g., age, uniform between 50 and 90 years), a binary covariate x_2 (e.g., sex, coded 0 or 1, each with probability 0.5), and constant baseline hazards equal to 0.5 and 0.2 for $r_0(t)$ and $\lambda_0(t)$, respectively. We assumed no effect of x_1 (β_1 and α_1 equal to 0) but an effect of x_2 (β_2 and α_2 equal to 1) on both hazards, $r_0(t)$ and $\lambda_0(t)$, respectively. We generated w_i from a Normal distribution with mean 0 and variance θ. The differences between scenarios were linked to different values of parameters (γ, θ) assumed to be equal to (0,1), (0.5,1), (1,1), or (1,2). In an additional scenario, we simulated an 'older population', with an age distribution following a uniform law between 70 and 90 years and (γ, θ) equal to (1,1).

The recurrence gap times and the disease-specific times to death were generated using the inverse transform method [34]. The recurrence calendar times are then deduced from the simulated gap times [23]. The expected time to death was simulated assuming a yearly piecewise exponential law obtained

Table I. Mean of the estimates, coverage probability (CP), empirical standard errors (SE), and mean of the standard errors (mean SE) in two scenarios using the new joint model and the classical joint model.

	New joint model				Classical joint model			
Parameter (True value)	Mean	CP (%)	Empirical SE	Mean SE	Mean	CP (%)	Empirical SE	Mean SE
Scenario 1								
$\beta_1(0)$	−0.010	93.4	0.059	0.057	0.007	93.8	0.058	0.056
$\beta_2(1)$	1.001	93.8	0.143	0.136	0.995	94.2	0.141	0.134
$\alpha_1(0)$	−0.030	92.6	0.082	0.078	0.073	79.8	0.071	0.067
$\alpha_2(1)$	1.019	95.6	0.188	0.193	0.974	94.6	0.164	0.170
$\gamma(1)$	1.058	97.0	0.167	0.174	0.961	92.4	0.149	0.157
$\theta(1)$	0.993	94.2	0.152	0.151	0.963	92.4	0.146	0.145
Scenario 2								
$\beta_1(0)$	−0.013	95.2	0.114	0.115	0.024	94.4	0.111	0.113
$\beta_2(1)$	0.995	93.0	0.144	0.137	0.982	93.4	0.141	0.135
$\alpha_1(0)$	−0.078	93.0	0.174	0.165	0.155	77.0	0.139	0.131
$\alpha_2(1)$	1.023	95.0	0.212	0.204	0.917	90.8	0.170	0.163
$\gamma(1)$	1.065	96.6	0.191	0.181	0.903	83.4	0.160	0.151
$\theta(1)$	0.999	92.2	0.166	0.153	0.950	89.6	0.154	0.143

Scenarios 1 and 2 simulate age distributions 50–90 and 70–90 years, respectively.

from the life table of the general population for each patient of age x_1 and sex x_2. The final time to death was then obtained as the minimum between the censoring time (fixed at 5), the time to ''death due to cancer', and the expected time to death. The corresponding failure indicator Δ_i equals 1 in case of death of subject i (whatever the cause) or 0 otherwise. For each scenario, we generated 500 independent random samples with 500 patients each.

Each simulated sample was analyzed with the NJM and the CJM using cubic B-splines for the baseline hazards of recurrence and mortality processes.

3.2. Simulation results

We report here the results of only two scenarios where the parameters (γ, θ) are equal to (1,1), but the age distributions of the populations are different (between 50 and 90 years for scenario 1 and between 70 and 90 years for scenario 2) (Table I). The results of the other scenarios are given in Appendix B.

The approach that used the NJM had good performances in each scenario, with a very small bias and a coverage probability (CP) close to 95% for each parameter (Table I and Appendix B). The mean of the standard errors (SEs) was also close to the empirical SE of each parameter. However, when we did not take into account the population mortality and used the CJM, we observed that the parameter estimates for the mortality hazard were biased, especially in scenario 2 (lower part of Table I), and that the CPs were less than 95%. The estimates of parameters γ and θ were also biased, and the CP was far from 95%. As expected, the parameter estimates associated with the recurrence process were well estimated with either the CJM or the NJM.

4. Application

4.1. Description of the dataset and model assumptions

To illustrate our approach, we present the results obtained with population-based data on colon cancer patients from FRANCIM, the French network of cancer registries. The dataset we used stems from a 'high-resolution study' of nine French cancer registries and consists of 290 stage 3 colon cancers diagnosed in 1995. All the patients had undergone curative surgery and were followed-up for 5 years at which end they were censored if still alive. The covariates used were sex and age at diagnosis. The population mortality hazards λ_P by sex, age, year, and *Département* (French administrative area) were obtained from the *Institut National de la Statistique et des Études Économiques*.

In this dataset, there were as many men as women and nearly half of the patients were 75 years old or more (Table II). Over 5 years of follow-up, there were 158 deaths and 138 recurrences occurred in 106 patients. On average, the recurrences occurred more frequently in men than in women. The overall survival at 5 years after diagnosis was the same in men and women, about 45%. There were marked differences between age classes; the recurrences were more frequent among the youngest than among the oldest patients (on average, 0.55 vs. 0.36), and the overall survival was 80% in the youngest age class versus 33% in the oldest age class (Table II). Over the 5 years of follow-up, the incidence rate of recurrence was the highest in patients aged 55 to 65 years (21.64 per 100 person-years), but it decreased thereafter to reach 13.14 per 100 person-years in patients aged 75 years and older.

Table II. Description of the data on colon cancer patients.

Covariates	*N* (%)	Average number of recurrences (min–max)	Overall survival at 5 years (standard error)*	Number of recurrences	Person-years	Annual incidence rate of recurrence (per 100 person-years)
Sex						
Men	145 (50%)	0.52 (0–4)	0.44 (0.04)	75	483	15.53
Women	145 (50%)	0.43 (0–3)	0.45 (0.04)	63	458	13.76
Age (years)						
15–45	11 (4%)	0.55 (0–3)	0.80 (0.13)	6	47	12.77
45–55	18 (6%)	0.33 (0–2)	0.78 (0.22)	6	81	7.41
55–65	45 (16%)	0.82 (0–4)	0.57 (0.07)	37	171	21.64
65–75	80 (28%)	0.50 (0–2)	0.44 (0.06)	40	269	14.87
75 and older	136 (47%)	0.36 (0–2)	0.33 (0.04)	49	373	13.14

*Using the Kaplan–Meier method.

In the models fitted here, we modeled the baseline hazards for recurrence and death using cubic B-splines with one knot fixed at 1 year after diagnosis. This choice was guided by the fact that more recurrent events are usually expected during the first years of follow-up than during the other periods, and also more deaths are mainly due to post-surgical mortality [35]. For the frailty distribution, we assumed that w_i follows a Normal distribution with mean 0 and variance θ. We used SAS software with procedure *proc nlmixed*, and the adaptative Gaussian quadrature was run with 100 quadrature points.

To test whether the variance of the random effect was different from zero, that is, $H_0 : \theta = 0$ vs. $H_1 : \theta > 0$, the p-value from a Wald test was used. Because zero is the lower bound of θ, a unilateral Wald test was used, which is equivalent to a square Wald test with a half-half mixture of zero and chi-square with 1 degree of freedom [36].

4.2. Results

The estimated parameters (with the corresponding p-values) obtained with the NJM are shown in Table III (second and third column). Covariate sex had no significant prognostic effect on the hazards of recurrence and disease-specific mortality, whereas age had an important prognostic effect on both

Table III. Parameter estimates relative to the recurrence hazard and the disease-specific or overall mortality hazard for colon cancer patients using the new joint model, the classical joint model, and the marginal model.

	New joint model for recurrence and disease-specific mortality processes		Classical joint model for recurrence and overall mortality processes		Marginal model	
Covariates	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Recurrence						
Men	0.04 (0.39)	0.92	0.12 (0.37)	0.74	—	—
Age	0.053 (0.018)	<0.01	0.067 (0.018)	<0.01	—	—
Disease-specific mortality						
Men	−0.01 (1.10)	0.99	—	—	0.03 (0.22)	0.93
Age	0.242 (0.061)	<0.01	—	—	0.032 (0.010)	<0.01
Overall mortality						
Men	—	—	0.42 (1.17)	0.72	—	—
Age	—	—	0.365 (0.109)	<0.01	—	—
θ	6.98 (1.51)	<0.01	6.73 (1.43)	<0.01	—	—
γ	2.86 (0.47)	<0.01	3.40 (0.93)	<0.01	—	—

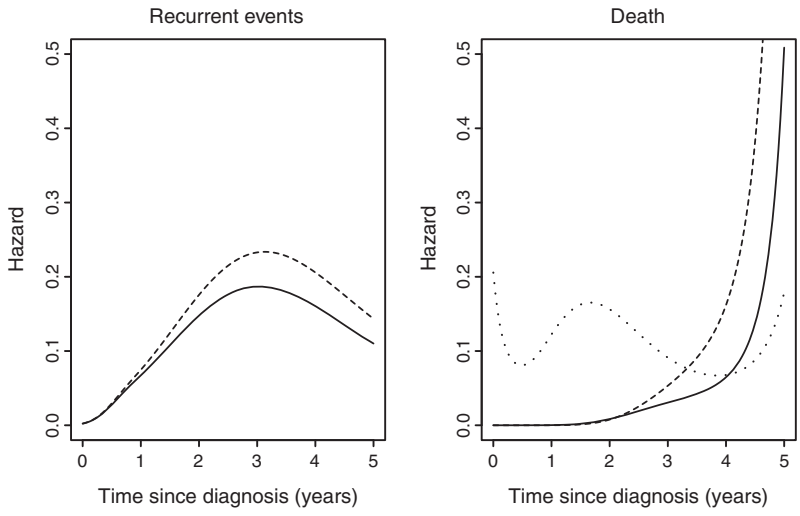

Figure 1. Hazards for women aged 70 years with the frailty parameter w_i equal to 0 for the recurrence process (left panel) and for the mortality process (right panel) using the classical joint model (dashed lines) or the new joint model (bold lines). Notice that the bold line in the right panel corresponds to the excess mortality hazard obtained with the new joint model. The marginal disease-specific baseline mortality hazard that corresponds to women aged 70 years (using the marginal model) is plotted in the right panel (dotted line).

hazards, younger people having better prognoses. The variance of the frailty parameter θ was highly significant using a unilateral Wald test ($p < 0.01$), and parameter γ was estimated at 2.86, which implies that the recurrence process and the disease-specific mortality process were positively associated.

Figure 1 shows the baseline hazards of recurrence and disease-specific mortality in women aged 70 years with w_i equal to zero. According to the NJM (bold line), the baseline hazard for recurrence reached a maximum between 2 and 4 years after cancer diagnosis, whereas the baseline hazard for disease-specific mortality increased with the time elapsed since diagnosis.

We also fitted the NJM assuming a gamma distribution for the frailty parameter u_i (detailed results not shown). When a gamma distribution is assumed, Liu *et al.* suggest to adapt the estimation procedure described earlier by reformulating the likelihood [37]. The estimated parameters for the covariate effects were quite close to each other (results not shown). The variance of the frailty parameter θ and parameter γ were also highly significant ($p < 0.01$ for each one). These comparisons underline the robustness of the method against misspecification of the frailty distribution.

4.2.1. Comparison between the classical and the new joint models for recurrence and mortality processes. The results of fitting the CJM are shown in Table III (fourth and fifth column) and Figure 1. As with the NJM, covariate sex had no significant prognostic effect on either process, but age had an important prognostic impact on both (Table III). The NJM reduced the impact of age on disease-specific mortality because we took into account the mortality due to other causes, which increases with increasing age. Concerning the shared frailty parameter, we observed a slightly higher variance θ with NJM than with CJM (θ =6.98 vs. 6.73 with the CJM); a better modeling of the mortality hazard at the individual level has apparently led to a better distinction between individuals. This indicates a higher correlation between recurrence and disease-specific mortality than between recurrence and overall mortality. As expected, the overall mortality (obtained with the CJM) was higher than the disease-specific mortality obtained with the NJM (Figure 1, right panel).

4.2.2. Marginal versus conditional estimates of the hazard of disease-specific mortality. It is important to underline that the estimated baseline hazards and the covariate hazard ratios derived from the NJM are *conditional* estimates (conditional on the frailty parameter) as opposed to those obtained with the MM (*population-averaged*). Thus, their interpretation will be clearly different. To enlighten this point, we fitted the MM to the colon cancer data. For this analysis, only death or censoring times were considered (the times to recurrence were not), and the baseline hazard was modeled using a cubic B-spline with one knot at 1 year. The marginal hazard ratios (Table III, sixth and seventh column) for men (versus women) were estimated to 0.03 (SE = 0.22) and to 0.032 for a 1-year increment in age (SE = 0.01). The marginal disease-specific baseline mortality hazard is shown in Figure 1 (right panel.)

4.2.2.1. Differences in interpretation of the estimates

The marginal baseline hazard of the disease-specific mortality obtained with the MM was far different from the conditional baseline hazard of the disease-specific mortality obtained with the NJM. This fact is well known and may be explained by a 'selection phenomenon' over time [38, 39]; patients with high frailties are more prone to early death, whereas robust patients will still be alive at end of the follow-up. In other words, with ongoing time, the marginal (or *population-averaged*) hazard will approach the hazard of the robust subgroup of patients.

The interpretation of the parameters associated with the covariates will also be different between the NJM and the MM. In the NJM, assuming constant over time, the conditional hazard ratio for each covariate does not mean assuming constant the marginal hazard ratio derived from the conditional model [14, 39]; the assumption of a PH ratio at the individual level leads to a marginal time-dependent hazard ratio.

4.2.2.2. Comparison between the marginal disease-specific survivals obtained with the marginal model and the new joint model

We compared the marginal disease-specific survival obtained with the MM with the one obtained with the NJM by integrating out the frailty. In women aged 70 years, the marginal disease-specific survival obtained with the NJM is defined by $\int_{-\infty}^{+\infty} \exp\left[-w\Lambda_0(t)\right] f_\theta(w)dw$. However, no simple analytical form of this expression can be derived when f_θ is the normal density. Thus, we used the Monte Carlo inte-

Table IV. Marginal disease-specific survivals for colon cancer patients at 1, 3, and 5 years as derived from the marginal model and the new joint model.

	Marginal model			New joint model		
Subgroup	1 year	3 years	5 years	1 year	3 years	5 years
Women, 60 years old	92.9	76.1	67.3	94.2	77.1	66.5
Men, 60 years old	92.7	75.7	66.8	94.3	76.9	66.5
Women, 70 years old	90.1	68.2	57.4	89.6	66.4	54.3
Men, 70 years old	89.9	67.7	56.8	89.8	66.2	54.3
Women, 80 years old	86.4	58.5	45.9	82.9	54.5	41.7
Men, 80 years old	86.2	57.9	45.2	82.8	54.5	41.7

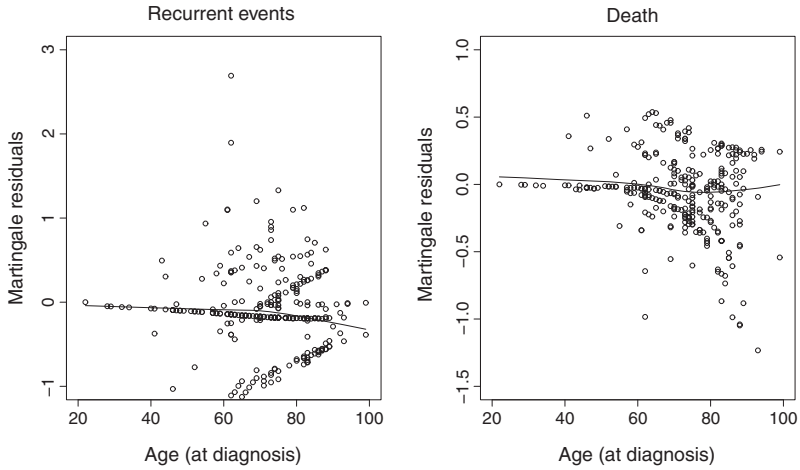

Figure 2. Martingale residuals of the new joint model for recurrence (left panel) and excess mortality (right panel). The solid lines correspond to lowess estimates.

gration method [40] with 100,000 values for the random effect w_i generated from a normal distribution with mean 0 and variance 6.98 (i.e., the estimated variance θ of w_i, see Table III). The results for different subgroups are shown in Table IV (fifth to seventh column). The marginal disease-specific survival estimates at 1, 3, and 5 years obtained with the MM were close to the ones obtained with the NJM (Table IV). This indicates a good agreement between the MM and the NJM on these colon cancer data.

4.2.3. Assessment of the goodness of fit. To assess the goodness of fit of the NJM, we used Martingale residuals. Martingale residuals may be easily calculated by the 'predict' statement of *proc nlmixed* in SAS, the empirical Bayes estimates being provided for the random effects. Using the NJM with time-independent covariates, the martingale residuals of the recurrence process are defined as $M_i^R = \delta_i^R - \hat{R}\left(T_i, \mathbf{x}_i, \hat{\boldsymbol{\beta}}, \hat{w}_i\right)$, where δ_i^R represents the total number of recurrent events for patient i and $\hat{R}\left(T_i, \mathbf{x}_i, \hat{\boldsymbol{\beta}}, \hat{w}_i\right)$ the estimated cumulative hazard of recurrence. For the mortality process, the martingale residuals are defined as $M_i^D = \Delta_i - \hat{\Lambda}\left(T_i, \mathbf{x}_i, \hat{\boldsymbol{\alpha}}, \hat{w}_i, \hat{\gamma}\right)$ [41]. The particularity of the NJM is that a component of the estimated cumulative mortality hazard, $\hat{\Lambda}\left(T_i, \mathbf{x}_i, \hat{\boldsymbol{\alpha}}, \hat{w}_i, \hat{\gamma}\right)$, is constrained to be equal to the expected mortality of the population, $\Lambda_P(a_i + T_i, \mathbf{z}_i)$ [42]. The martingale residuals with respect to age are shown in Figure 2; there is no clear pattern regarding age at diagnosis for recurrence and excess mortality hazards as derived from the NJM.

5. Discussion

The NJM makes it possible to estimate jointly the hazard of recurrence and the hazard of disease-specific mortality without needing the cause of death. This model provides more accurate parameter estimations than the CJM by taking into account the expected mortality included in the overall mortality and allows separating the covariate effects on the disease-specific mortality from their effects on the expected mor-

tality. The correlation between the hazard of recurrence and the hazard of disease-specific mortality is introduced through a shared frailty parameter that follows a lognormal distribution. We checked the robustness of the estimated covariate effects with a gamma distribution of frailty; the estimated effects of the covariates on recurrence and disease-specific mortality were close to each other (results not shown). Within the context of joint modeling for longitudinal processes (such as the change over time of a biomarker) and survival, some approaches have been proposed to model jointly the two processes in the presence of competing risks, when the cause of death is known [43,44]. The approach proposed here makes it possible to use the excess hazard method to estimate the hazard of disease-specific mortality when the cause of death is unknown (or badly reported). Moreover, the NJM gives new insights into disease-specific mortality; at the population level, the hazard of disease-specific mortality is the result of (i) an increasing hazard of disease-specific mortality at the individual level and (ii) a selection of robust patients over time.

For identifiability reasons, the analyst must use a restriction on the parameters of the distribution of the random effect w_i or on the parameters of the distribution of frailty u_i. We used the restriction $E(w_i) = 0$, and in this case, because $E(\exp(w_i)) \neq \exp(E(w_i))$, the baseline hazard is not the 'mean hazard'; it should be interpreted as the hazard of a patient with $w_i = 0$. Another possibility would be to use a restriction on the mean of frailty u_i, $E(u_i) = 1$. This would have the advantages that the baseline hazard will correspond to the mean hazard and that the results will be directly comparable with those obtained with other shared frailty models (e.g., the shared gamma frailty model). However, we have chosen the parameterization $E(w_i) = 0$. With this choice, it is assumed that the random effects have a Gaussian distribution and that they act on the linear predictor as in the generalized linear mixed models. Because of its similarity with the 'classical' mixed models, this parameterization is more easily understandable by the researchers who are not familiar with survival analyses and frailty models. Note that this restriction choice has no impact on the estimated parameters [45].

The estimation step was performed with procedure *proc nlmixed* in SAS software, and the numerical integration method chosen was the adaptative Gaussian quadrature with 100 quadrature points. Some authors suggested that 5 to 10 quadrature points are sufficient to obtain accurate parameter estimates with the adaptative Gaussian quadrature method [30, 46]. In the present work, we used nevertheless 100 quadrature points. This was because the log likelihood increased importantly between 10 and 20 quadrature points and continued to increase up to about 60 quadrature points before stabilizing. With 100 quadrature points on a dataset of 290 patients and using a computer with Pentium CPU dual-core of 2.6 GHz each, the algorithm took about 10 min to converge.

The time scale used to analyze recurrent events may be the gap times between consecutive events or the times to the events since the study started (calendar time). The choice of the scale depends on the objective. The gap timescale is based on the idea that the clock restarts after each event. In this work, we used the calendar timescale to obtain information on the progression of the process over time since diagnosis of cancer [47], but the NJM can be easily adapted to a gap timescale.

In the present work, we have chosen the context of intensity-based models to analyze recurrent events. Intensity at a given time t describes the probability of a new event within an infinitesimal interval $[t, t + \Delta t[$, given an individual's history of events [1, 48]. Other authors have proposed approaches based on the rate function of a Poisson process, which can be interpreted as the average risk in the population without conditioning on the history of the events [19, 49, 50]. In case a terminal event precludes further recurrence, some authors proposed quantities derived from the rate function that model the recurrent event process after the terminal event [19, 51]. For example, the adjusted rate function quantifies the expected number of events before the time of death; otherwise, the survivor rate function quantifies the expected number of events among those subjects who have not experienced the terminal event. Although these quantities give useful indicators to help in resource use (estimates of the total number of events experienced in a patient's lifetime), they are not recommended when the focus of the study is the covariate effects (e.g., treatment) [19,52].

The statistical inference based on the joint models presented in the present article leads to problems related to inference in the presence of a nuisance parameter [53]. When the gamma parameter equals zero, there is no relationship between the disease-specific mortality process and the recurrence process. Moreover, the interpretation of the gamma parameter is possible only when the variance of the random effect is different from zero, that is, gamma vanishes when the variance of the random effect is zero. As a consequence, the gamma parameter and the variance of the random effect cannot be separated from each other, and the statistical inference should take this particularity into account. Several approaches have been proposed to solve this problem. Conniffe has proposed a score test after replacing the nuisance

parameter by its maximum likelihood estimate under the alternative hypothesis [54]. Hansen has used a transformation based on a conditional probability measure and simulation to determine the critical values of the test [55]. Davies has proposed to maximize the statistics of the test over the possible values of the nuisance parameter [56, 57]. This specific problem is beyond the scope of this article but future works should be carried out to propose a valid statistical test for the joint models detailed here.

In our analysis, an independent random patient effect was assumed constant over the follow-up for each patient. However, in some cases, this assumption seemed too restrictive; more realistic were models with time-varying frailties [58]. Frailties may be modeled as time series with a correlation described by an autoregressive structure [59, 60]. However, these models may be cumbersome to calculate and difficult to fit.

Another interesting extension would be to fit the NJM using a penalized likelihood to have smooth estimations of the baseline hazards. The R-package frailtypack was developed to analyse recurrent events and overall mortality [23, 61, 62]; extending this approach to the context of disease-specific mortality (rather than overall mortality) would be interesting. Because the number and the positions of the knots are an issue in the NJM, this extension will highlight the benefit of the penalized-likelihood approach. To test the sensitivity of our results to the model specifications, we performed supplementary analyses using B-splines with various number and locations of the knots for the baseline hazards of recurrence and excess mortality. These supplementary NJMs were used with the real data and with the simulated data. The details of this sensitivity analysis are presented in Appendix B. The analysis showed that the results are robust to different choices of knots. This sensitivity analysis does not provide a general guideline for choosing the number and the locations of the knots for B-spline functions. One may use some tools such as cross-validation or Akaike information criterion to select the more parsimonious model. However, it should be noted that a cubic B-spline with one interior knot allows for up to three inflection points, offering sufficient flexibility for most real-life applications while limiting the risk of serious over-fit bias [32, 35, 63].

The main limitation of the shared frailty model is that it cannot account for two heterogeneous but independent processes. A more general model is needed, and one possibility would be to use a correlated frailty model in which two random effects are used to correlate the recurrence and the mortality excess hazards [43, 45, 64]. A bivariate normal distribution may be used for these random effects with a correlation parameter that takes into account the correlation between the two processes. When the two processes are heterogeneous but independent, this correlation parameter should be estimated close to zero. However, fitting correlated frailty models is challenging and may lead to identifiability and computational problems, in particular when there are no repeated observations in one of the processes (here, the mortality process). With our real data, we tried to fit a correlated frailty model where the hazard of recurrence was defined by $r_i(t, \mathbf{x}_i, w_i) = r_0(t)\exp(\boldsymbol{\beta}\mathbf{x}_i + w_{1i})$ and the mortality hazard by $\lambda_i(t, \mathbf{x}_i, w_i, a_i) = \lambda_0(t)\exp(\boldsymbol{\alpha}\mathbf{x}_i + w_{2i}) + \lambda_P(a_i + t, \mathbf{z}_i)$. In this model, the parameters (w_1, w_2) were assumed to follow a bivariate normal distribution with mean (0,0) and variance-covariance matrix $\Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$. To avoid computational problems, we followed some hints detailed in a publication by Kiernan *et al.* [65]. The initial values used for the covariate parameters and baseline hazards were obtained from a simpler model assuming no correlation (parameter $\rho = 0$), the initial values for the parameters of the variance-covariance matrix were obtained using a grid search, and the variance-covariance matrix was reparameterized using the Cholesky root. We checked our estimation procedure with a short simulation study (data not shown) and observed that most of the parameters were estimated with a very small bias and with a coverage rate close to 95%, except for the correlation parameter, which was estimated equal to 0.55 on average (true value 0.5) and had a coverage rate equal to 79%. Unfortunately, we never reached convergence with the real data because the correlation parameter was always estimated at the boundary of the parameter space. In a slightly different context, this problem was also encountered by Zahl [66] who decided to fix the correlation parameter and then re-estimated the parameters. We report in Appendix C such an exploration on the real data using a correlated frailty model and fixed correlation parameters at different values. Interestingly, the log likelihood decreased when the correlation increased, which can be interpreted as a better fit of the correlated frailty model when the correlation is fixed at a high level ($\rho = 0.8$). However, this is clearly unsatisfactory because the other parameter estimates change (Appendix C), and further research is needed. This convergence problem was not always reported by the researchers who used correlated frailty models because, in many cases, the studies concerned data on twins and it is then natural to assume that the two frailties of each pair have the same variance ($\sigma_1 = \sigma_2$), which simplifies the estimation procedure [15, 45, 67]. The modified EM

algorithm proposed by Xue and Brookmeyer seems to work well within the context of semi-parametric models (no computational problems reported by the authors) [68]. Thus, more research should be carried out to propose a modified EM algorithm within the context of correlated frailty models using B-splines. Another interesting direction would be to evaluate the Monte Carlo Markov Chain method in estimating the parameters of the correlated frailty model [15].

Appendix A. Details of the SAS code used for fitting the new joint model

The SAS code assumes that the analyst has the data (called `temp` here) in the following format:

Id	Age	Sex	time	type_event	Age − event	MUA
1	51	1	0.46190	1	51	0.0063044553
1	51	1	1.23010	1	52	0.0067074528
1	51	1	1.80755	3	52	0.0067074528
2	63	1	1.92888	1	64	0.0177344073
2	63	1	2.26143	0	65	0.0187224403
3	58	0	2.76017	0	60	0.0047713446

Column `Id` stands for the patient's identification number, and `Age` and `Sex` stand for covariates age at diagnosis and sex. Column `time` shows the time to the event in years and column `type_event` the type of event (1 for recurrence, 3 for death and 0 for censoring). Column `Age − event` indicates the age at the occurrence of the event. Column `MUA` shows the population hazard; it corresponds to the population hazard for people with sex equal to covariate `Sex` and age equal to `Age − event`.

Three steps are necessary for parameter estimation:

- The first step consists in splitting the follow-up time for each patient; this will be used for the Cavalieri-Simpson approximation. In this example, the data are split into intervals of 0.2 years with a maximum follow-up of 5 years, which makes 25 distinct intervals.
- The second step consists in calculating the values of the B-splines for each patient's time to event; these values allow calculating the instantaneous baseline hazards and the cumulative baseline hazards using the Cavalieri-Simpson approximation. Calculating the values of B-splines requires version 9.2 of the SAS software with function `bspline` of procedure `proc IML`.
- The third step consists in estimating the parameters of the NJM using procedure `proc nlmixed`.

```
/* First Step: splitting of the data */
/* ################################# */

Data temp2;
Set temp;
Array split[25] split1-split25;
Array dur[25] dur1-dur25;
Array midp[25] midp1-midp25;
      Do j=1 to 25;
            split[j]=0.2*j;
            dur[j]=0; *split[i]-0.1;
            midp[j]=split[j]-0.1;
      end;
      Do j=1 to 25;
            if time<=split[j] then do;
                  if j=1 then do; dur[j]=time; midp[j]=time/2; split[j]=time;
end;
                  else do; dur[j]=time-split[j-1]; midp[j]=split[j-1]+(time-
split[j-1])/2;split[j]=time; end;
                  j=25;
            end;
            else
                  if j=1 then do; dur[j]=0.2; midp[j]=0.1; end;
                  else do; dur[j]=split[j]-split[j-1]; midp[j]=split[j-1]+0.1;
end;
      end;
run;
```

```
/* Second Step: Calculating the values of the B-splines for each patient's time
to event */
/* ########################################################################## */
/* In this example, we used cubic B-spline with one interior knot located at
t=1; so we need to define 3 additional boundary knots for the lower bound (at t=-
2, -1, 0) and 3 additional boundary knots for the upper bound (at t=6, 7, 8) */

proc iml;
      USE temp2;
      READ all var {id time};
      knots = {-2 -1 0 1 6 7 8};
      bsp = bspline(time, 3, knots);
      CREATE base_bspline FROM bsp; APPEND FROM bsp;
quit;

Data base_bspline;
SET base_bspline;
rename COL1=bsp1 COL2=bsp2 COL3=bsp3 COL4=bsp4 COL5=bsp5;
aa=1;
run;

Data temp2;
SET temp2;
aa=1;
run;

Data temp3;
merge temp2 base_bspline;
by aa;
run;

data tpsbsp;
set temp2;
keep id time split1-split25 midp1-midp25;
run;

%macro cbase;
      %do k=1 %to 25;
      proc iml;
      USE tpsbsp;
      READ all var {split&k};
      knots = {-2 -1 0 1 6 7 8};

                  bsp = bspline(split&k, 3, knots);
                  CREATE basesp_split&k FROM bsp; APPEND FROM bsp;
      quit;

      Data basesp_split&k; set basesp_split&k;
      Rename col1=bsp1_split&k col2=bsp2_split&k
      col3=bsp3_split&k col4=bsp4_split&k col5=bsp5_split&k;
      aa=1;
      Run;

      proc iml;
      USE tpsbsp;
      READ all var {midp&k};

      knots = {-2 -1 0 1 6 7 8};
                  bsp = bspline(midp&k, 3, knots);
                  CREATE basesp_midp&k FROM bsp; APPEND FROM bsp;
      quit;

      Data basesp_midp&k; set basesp_midp&k;
      Rename col1=bsp1_midp&k col2=bsp2_midp&k col3=bsp3_midp&k col4=bsp4_midp&k
      col5=bsp5_midp&k;
      aa=1;
      Run;
```

```
      Data temp3;
      merge temp3 basesp_split&k basesp_midp&k;
      by aa;
      run;

      %end;

%mend cbase;

%cbase;

/* Third step: estimating the parameters */

/* ######################################## */

proc nlmixed data=temp3 qpoints=10 ;
      /* Starting values */
      parms a0=0.5 a1=0 a2=0 a3=0 a4=0 b0=0.5 b1=0 b2=0 b3=0 b4=0
      betaAge_Recur=0 betaSex_Recur =0 theta=0.5 betaAge_Surv=0
      betaSex_Surv=0 gamma=0.5;
      bounds theta >=0;

      Array bsp1_split[25] bsp1_split1-bsp1_split25;
      Array bsp2_split[25] bsp2_split1-bsp2_split25;
      Array bsp3_split[25] bsp3_split1-bsp3_split25;
      Array bsp4_split[25] bsp4_split1-bsp4_split25;
      Array bsp5_split[25] bsp5_split1-bsp5_split25;

      Array bsp1_midp[25] bsp1_midp1-bsp1_midp25;
      Array bsp2_midp[25] bsp2_midp1-bsp2_midp25;
      Array bsp3_midp[25] bsp3_midp1-bsp3_midp25;
      Array bsp4_midp[25] bsp4_midp1-bsp4_midp25;
      Array bsp5_midp[25] bsp5_midp1-bsp5_midp25;

      Array bas_rec[25] bas_rec1-bas_rec25;
      Array bas_dea[25] bas_dea1-bas_dea25;
      Array split[25] split1-split25;
      Array midp[25] midp1-midp25;
      Array dur[25] dur1-dur25;

      Do m=1 to 25;
      if m=1 then bas_rec[m]=(exp(a0*bsp1_split[m] + a1*bsp2_split[m] +
      a2*bsp3_split[m] + a3*bsp4_split[m] + a4*bsp5_split[m])+
                              exp(a0*0.1666667 + a1*0.7619048 + a2*0.07142857) +
                              4*exp(a0*bsp1_midp[m] + a1*bsp2_midp[m] +
      a2*bsp3_midp[m] + a3*bsp4_midp[m] + a4*bsp5_midp[m]))/6;
      else bas_rec[m]=(exp(a0*bsp1_split[m-1] + a1*bsp2_split[m-1] +
      a2*bsp3_split[m-1] + a3*bsp4_split[m-1] + a4*bsp5_split[m-1])+
                       exp(a0*bsp1_split[m] + a1*bsp2_split[m] +
      a2*bsp3_split[m] + a3*bsp4_split[m] + a4*bsp5_split[m]) +
                       4*exp(a0*bsp1_midp[m] + a1*bsp2_midp[m] + a2*bsp3_midp[m]
      + a3*bsp4_midp[m] + a4*bsp5_midp[m]))/6;

      if m=1 then bas_dea[m]=(exp(b0*bsp1_split[m] + b1*bsp2_split[m] +
      b2*bsp3_split[m] + b3*bsp4_split[m] + b4*bsp5_split[m])+
                              exp(b0*0.1666667 + b1*0.7619048 + b2*0.07142857) +
                              4*exp(b0*bsp1_midp[m] + b1*bsp2_midp[m] +
      b2*bsp3_midp[m] + b3*bsp4_midp[m] + b4*bsp5_midp[m]))/6;

      else bas_dea[m]=(exp(b0*bsp1_split[m-1] + b1*bsp2_split[m-1] +
      b2*bsp3_split[m-1] + b3*bsp4_split[m-1] + b4*bsp5_split[m-1])+
                       exp(b0*bsp1_split[m] + b1*bsp2_split[m] +
      b2*bsp3_split[m] + b3*bsp4_split[m] + b4*bsp5_split[m]) +
                       4*exp(b0*bsp1_midp[m] + b1*bsp2_midp[m] + b2*bsp3_midp[m]
      + b3*bsp4_midp[m] + b4*bsp5_midp[m]))/6;
      end;

      * base hazard and cumulative baseline hazard for recurrent events;
```

```
        base_haz_r=exp(a0*bsp1 + a1*bsp2 + a2*bsp3 + a3*bsp4 + a4*bsp5);

        cum_base_haz_r=0;
        Do m=1 to 25;
        cum_base_haz_r= cum_base_haz_r + bas_rec[m]*dur[m];
        end;

        * base hazard and cumulative baseline hazard for death events;
        base_haz_d=exp(b0*bsp1 + b1*bsp2 + b2*bsp3 + b3*bsp4 + b4*bsp5);

        cum_base_haz_d=0;
        Do m=1 to 25;
        cum_base_haz_d= cum_base_haz_d + bas_dea[m]*dur[m];
        end;

        /* COVARIATES */
        mu1= betaAge_Recur * Age + betaSex_Recur * Sex + w;                  /*
        for recurrent event */
        mu2= betaAge_Surv * Age + betaSex_Surv * Sex + gamma * w;    /* for
        death event */

        loglik1=-exp(mu1) * cum_base_haz_r;
        loglik2=-exp(mu2) * cum_base_haz_d;

        if type_event=1 then loglik= log(base_haz_r) + mu1;
                    /*log likelihood for recurrent event */
        if type_event=3 then loglik=loglik1 + log(base_haz_d*exp(mu2)+MUA) +
        loglik2;     /*log likelihood for excess death */
        if type_event=0 then loglik=loglik1 + loglik2;
                                    /*log likelihood for censoring */

        model time ~ general(loglik);
        random w ~ normal(0, theta) subject=id;
        ods output ParameterEstimates=estimation FitStatistics=fit1
        convergencestatus=convergence;
run;
```

Appendix B. Additional results of the simulation study and of the sensitivity analysis regarding the different choices of knots for the baseline hazards

In the first part of this appendix, we report the results of the simulated scenarios not detailed in the article. In the second part, we describe the analysis we conducted to explore the sensitivity of the parameter estimates to the number and the location of knots for the baseline hazards of recurrence and the disease-specific mortality.

Additional results of the simulation study

Parameters (γ, θ) are generated as equal to (0,1) in scenario S1, equal to (0.5,1) in scenario S2, and equal to (1,2) in scenario S3. The other parameters are generated as described in the article. The results are reported in Table B.1.

Sensitivity analysis

In order to test the sensitivity of our results to the model specifications, we performed a supplementary analysis using B-splines and varying the number and positions of the knots for the baseline hazards of recurrence and the disease-specific mortality.

Method

Three supplementary models were used.

(1.) In the first supplementary model (NJMv1), we assumed one knot at the median time of the observed recurrence times (respectively, death times) for the baseline hazard of recurrence (respectively, the disease-specific mortality).

Table B.1. Mean of the estimates, coverage probability (CP), empirical standard errors (ESE), and mean of the standard errors (mean SE) in three scenarios using the new joint model and the classical joint model.

	New joint model				Classical joint model			
Parameter (True value)	Mean	CP (%)	ESE	Mean SE	Mean	CP (%)	ESE	Mean SE
Scenario S1								
$\beta_1(0)$	0.001	95.4	0.056	0.057	0.001	95.0	0.057	0.057
$\beta_2(1)$	0.999	94.6	0.134	0.132	0.999	94.6	0.134	0.132
$\alpha_1(0)$	−0.030	92.0	0.063	0.062	0.062	79.2	0.055	0.054
$\alpha_2(1)$	0.999	94.4	0.146	0.145	0.948	94.0	0.130	0.129
$\gamma(0)$	−0.002	94.8	0.108	0.102	−0.001	94.2	0.097	0.092
$\theta(1)$	0.999	92.6	0.136	0.129	0.999	92.6	0.136	0.129
Scenario S2								
$\beta_1(0)$	0.001	95.2	0.057	0.056	0.010	94.4	0.058	0.055
$\beta_2(1)$	1.014	96.6	0.127	0.133	1.009	96.0	0.126	0.133
$\alpha_1(0)$	−0.024	91.8	0.066	0.065	0.074	74.4	0.057	0.057
$\alpha_2(1)$	1.025	94.2	0.163	0.157	0.970	93.6	0.144	0.139
$\gamma(0.5)$	0.532	94.6	0.117	0.114	0.481	94.0	0.107	0.104
$\theta(1)$	0.991	93.4	0.137	0.131	0.982	92.8	0.135	0.129
Scenario S3								
$\beta_1(0)$	−0.010	94.8	0.072	0.073	0.016	93.4	0.070	0.071
$\beta_2(1)$	1.000	94.4	0.172	0.169	0.991	94.6	0.169	0.166
$\alpha_1(0)$	−0.033	94.8	0.091	0.09	0.082	84.0	0.079	0.080
$\alpha_2(1)$	1.016	93.8	0.227	0.220	0.958	92.8	0.199	0.194
$\gamma(1)$	1.047	95.4	0.134	0.124	0.958	90.6	0.119	0.111
$\theta(2)$	2.018	95.2	0.254	0.262	1.940	93.2	0.241	0.248

Table B.2. Results of the sensitivity analysis regarding the number and the locations of the B-spline knots with simulated data and scenario 1: mean of the estimates, coverage probability (CP), Empirical standard errors (ESE), and mean of the standard errors (mean SE) using supplementary models NJMv1, NJMv2, and NJMv3.

Parameter	NJMv1				NJMv2				NJMv3			
(True value)	Mean	CP (%)	ESE	Mean SE	Mean	CP (%)	ESE	Mean SE	Mean	CP (%)	ESE	Mean SE
$\beta_1(0)$	−0.010	93.2	0.059	0.057	−0.009	93.3	0.059	0.057	−0.009	93.4	0.059	0.057
$\beta_2(1)$	1.001	93.8	0.143	0.136	1.002	93.7	0.143	0.136	1.001	94.0	0.143	0.136
$\alpha_1(0)$	−0.030	92.6	0.082	0.078	−0.030	92.5	0.082	0.078	−0.030	92.4	0.082	0.078
$\alpha_2(1)$	1.019	95.6	0.188	0.193	1.020	95.5	0.188	0.193	1.02	95.6	0.188	0.193
$\gamma(1)$	1.058	97.0	0.166	0.174	1.058	96.7	0.167	0.174	1.058	97.2	0.167	0.175
$\theta(1)$	0.993	94.0	0.152	0.151	0.994	94.1	0.153	0.151	0.992	94.0	0.152	0.151

(2.) In the second supplementary model (NJMv2), we assumed two knots at 1 and 3 years for the baseline hazards of recurrence and the disease-specific mortality.
(3.) In the third supplementary model (NJMv3), we assumed two knots at the 33th and 66th percentiles of the observed recurrence times (respectively, death times) for the baseline hazard of recurrence (respectively, the disease-specific mortality).

Using these supplementary models, we re-analysed (i) the simulated data of scenario 1, that is, when parameters (γ, θ) are assumed equal to (1,1) and the age distribution of the population is between 50 and 90 years (see the main text of the article) and reported the results in Table B.2 and (ii) the real-data example and reported the results in Table B.3.

Results

(i) The performances obtained with these supplementary models were very close to the ones obtained using the NJM: there was a very small bias and a CP close to 95% with each parameter (Table B.2).

Table B.3. Results of the sensitivity analysis regarding the number and the locations of the B-spline knots for the parameter estimates relative to the recurrence hazard and the disease-specific mortality hazard for colon cancer patients using supplementary models NJMv1, NJMv2, and NJMv3 (AIC : Akaike information criterion).

	NJMv1		NJMv2		NJMv3	
Covariates and criteria	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Recurrence						
Men	0.04 (0.40)	0.92	0.04 (0.40)	0.92	0.04 (0.40)	0.92
Age	0.054 (0.018)	<0.01	0.053 (0.018)	<0.01	0.053 (0.018)	<0.01
Disease-specific mortality						
Men	−0.02 (1.11)	0.99	−0.01 (1.10)	0.99	−0.02 (1.10)	0.99
Age	0.245 (0.062)	<0.01	0.242 (0.061)	<0.01	0.241 (0.061)	<0.01
θ	7.06 (1.53)	<0.01	6.98 (1.51)	<0.01	6.99 (1.51)	<0.01
γ	2.87 (0.47)	<0.01	2.86 (0.47)	<0.01	2.85 (0.47)	<0.01
Model selection criteria						
−2*log likelihood	1316.7		1315.1		1315.1	
AIC	1348.7		1351.1		1351.1	

In each supplementary model, the mean of the SEs was also close to the empirical SE of each parameter.

(ii) The parameter estimates with these supplementary models were very close to the ones obtained using the NJM on real data.

Conclusion

Examining the results obtained with simulated data and real data, we conclude that the results are robust to different choices of the number and the locations of the B-spline knots.

Appendix C. Additional results obtained using the correlated frailty model on the real data after fixing the correlation parameter at different values

The following correlated frailty model was fitted on the real data example using SAS `proc nlmixed`:

$$\begin{aligned} r_i(t, \mathbf{x}_i, w_i) &= r_0(t)\exp(\boldsymbol{\beta}\mathbf{x}_i + w_{1i}) \\ \lambda_i(t, \mathbf{x}_i, w_i, a_i) &= \lambda_0(t)\exp(\boldsymbol{\alpha}\mathbf{x}_i + w_{2i}) + \lambda_P(a_i + t, \mathbf{z}_i) \end{aligned} \tag{1}$$

Table C.1. Parameter estimates relative to the recurrence hazard and the disease-specific mortality hazard for colon cancer patients using the correlated frailty model after fixing the correlation parameter at different values (AIC: Akaike information criterion).

	ρ fixed to 0		ρ fixed to 0.2		ρ fixed to 0.5		ρ fixed to 0.8	
Covariates and criteria	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Recurrence								
Men	0.097 (0.217)	0.66	0.086 (0.239)	0.72	0.071 (0.312)	0.82	0.053 (0.315)	0.87
Age	0.001 (0.009)	0.95	0.004 (0.01)	0.65	0.012 (0.012)	0.30	0.023 (0.013)	0.06
Disease-specific mortality								
Men	−0.09 (0.368)	0.80	−0.10 (0.428)	0.823	−0.060 (0.494)	0.90	−0.023 (0.567)	0.97
Age	0.068 (0.020)	<0.01	0.083 (0.022)	<0.01	0.097 (0.030)	<0.01	0.117 (0.030)	<0.01
σ_1^2	0.783 (0.353)	0.03	1.190 (0.403)	<0.01	1.758 (0.478)	<0.01	2.666 (0.600)	<0.01
σ_2^2	3.691 (1.967)	0.06	5.496 (2.181)	0.012	7.038 (5.010)	<0.01	9.814 (3.576)	<0.01
ρ	—	—	—	—	—	—	—	—
Model selection criteria								
−2*log likelihood	1507.9		1485.1		1446.3		1395.8	
AIC	1539.9		1517.1		1478.3		1427.8	

where parameters (w_1, w_2) are assumed to follow a bivariate normal distribution with mean (0,0) and variance-covariance matrix $\Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$. The other parameters are identical to those described in the article.

The parameter ρ was fixed at different values, $\rho \in \{0, 0.2, 0.5, 0.8\}$, and the parameter estimates are reported in Table C.1. These values were chosen so as to represent no correlation ($\rho = 0$), a low ($\rho = 0.2$), a moderate ($\rho = 0.5$), and a high ($\rho = 0.8$) correlation between the two processes.

We also report in Table C.1 the final log likelihood and the Akaike information criteria obtained after convergence of the optimization algorithm.

It is interesting to see that the log likelihood decreases when the correlation increases. This can be interpreted as a better fit of the correlated frailty model when the correlation is fixed at a high level. At the same time, the variances of the random effect and their corresponding SEs for the recurrence and the disease-specific mortality processes increase. As underlined in the paper, correlated frailty models are an important extension of shared frailty models but further research is needed to deal with computational issue and identifiability.

Acknowledgements

The authors thank FRANCIM and the following French cancer registries for their contribution to the high-resolution study on colorectal cancer: Bas-Rhin General Cancer Registry (M. Velten), Calvados Digestive Cancer Registry (G. Launoy), Côte d'Or Digestive Cancer Registry (AM. Bouvier), Doubs General Cancer Registry (AS. Woronoff), Hérault General Cancer Registry (B. Trétarre), Isère General Cancer Registry (M. Colonna), Manche General Cancer Registry (S. Bara), Somme General Cancer Registry (O. Ganry), and Tarn General Cancer Registry (P. Grosclaude).

The authors are also very grateful to Jean Iwaz, PhD, Hospices Civils de Lyon, for revising the manuscript.

The authors thank the ANR (Agence Nationale de la Recherche) for supporting the study. A part of this study was funded by grants from MESURE group (ANR grant number ANR-09-BLAN-0357) and CENSUR group (ANR grant number ANR-12-BSV1-0028).

References

1. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. Wiley: New York, 2002.
2. Collett D. *Modelling Survival Data in Medical Research*, Second Edition. Chapman & Hall/CRC Press: London, 2003.
3. Cook RJ, Lawless JF. *The Statistical Analysis of Recurrent Events*. Springer: New York, 2007.
4. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *Journal of the American Statistical Association* 1989; **84**(408):1065–1073.
5. Prentice RL, Williams B, Peterson A. On the regression analysis of multivariate failure time data. *Biometrika* 1981; **68**(2):373–379.
6. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *The Annals of Statistics* 1982; **10**(4):1100–1120.
7. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. Springer-Verlag: New York, 2000.
8. Wei LJ, Glidden DV. An overview of statistical methods for multiple failure time data in clinical trials. *Statistics in Medicine* 1997; **16**(8):833–839.
9. Kelly PJ, Lim LL. Survival analysis for recurrent event data: an application to childhood infectious diseases. *Statistics in Medicine* 2000; **19**(1):13–33.
10. Ghosh D. Methods for analysis of multiple events in the presence of death. *Controlled Clinical Trials* 2000; **21**(2):115–126.
11. Box-Steffensmeier JM, De Boef S. Repeated events survival models: the conditional frailty model. *Statistics in Medicine* 2006; **25**(20):3518–3533.
12. Oakes D. In *Frailty models for multiple event times*. Kluwer Academic Publisher: Netherlands, 1992; 371–379.
13. Hougaard P. *Analysis of Multivariate Survival Data*. Springer: New York, 2000.
14. Duchateau L, Janssen P. *The Frailty Model*. Springer: New York, 2008.
15. Wienke A. *Frailty Models in Survival Analysis*. Chapman & Hall/CRC Press: Boca Raton, 2010.
16. Liu Q, Pierce D. A note on Gauss–Hermite quadrature. *Biometrika* 1994; **81**(3):624–629.
17. Klein JP. Semiparametric estimation of random effects using the Cox model based on the EM algorithm. *Biometrics* 1992; **48**(3):795–806.
18. Rondeau V, Commenges D, Joly P. Maximum penalized likelihood estimation in a gamma-frailty model. *Lifetime Data Analysis* 2003; **9**(2):139–153.
19. Cook RJ, Lawless JF. Analysis of repeated events. *Statistical Methods in Medical Research* 2002; **11**(2):141–166.
20. Liu L, Wolfe RA, Huang X. Shared frailty models for recurrent events and a terminal event. *Biometrics* 2004; **60**(3):747–756.
21. Lancaster T, Intrator O. Panel data with survival: hospitalization of HIV-positive patients. *Journal of the American Statistical Association* 1998; **93**(441):46–53.

22. Huang CY, Wang MC. Joint modeling and estimation for recurrent event processes and failure time data. *Journal of the American Statistical Association* 2004; **99**(468):1153–1165.
23. Rondeau V, Mathoulin-Pelissier S, Jacqmin-Gadda H, Brouste V, Soubeyran P. Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. *Biostatistics* 2007; **8**(4):708–721.
24. Percy C, Stanek E, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *American Journal of Public Health* 1981; **71**(3):242–250.
25. Ashworth TG. Inadequacy of death certification: proposal for change. *Journal of Clinical Pathology* 1991; **44**(4):265–268.
26. Esteve J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. *Statistics in Medicine* 1990; **9**(5):529–538.
27. Remontet L, Bossard N, Belot A, Esteve J. An overall strategy based on regression models to estimate relative survival and model the effects of prognostic factors in cancer survival studies. *Statistics in Medicine* 2007; **26**(10):2214–2228.
28. Ghosh D, Lin DY. Semiparametric analysis of recurrent events data in the presence of dependent censoring. *Biometrics* 2003; **59**(4):877–885.
29. Hakulinen T, Tenkanen L. Regression analysis of relative survival rates. *Applied Statistics* 1987; **36**:309–317.
30. Liu L, Huang X. The use of Gaussian quadrature for estimation in frailty proportional hazards models. *Statistics in Medicine* 2008; **27**(14):2665–2683.
31. De Boor C. *A Practical Guide to Splines*. Springer: New York, 1978.
32. Belot A, Abrahamowicz M, Remontet L, Giorgi R. Flexible modeling of competing risks in survival analysis. *Statistics in Medicine* 2010; **29**:2453–2468.
33. Quarteroni A. *Méthodes Numériques Pour le Calcul Scientifique*. Springer-Verlag: Paris, 2000.
34. Ross SM. *Simulation*, Fourth Edition. Elsevier Academic Press: Amsterdam, 2006.
35. Belot A, Remontet L, Launoy G, Jooste V, Giorgi R. Competing risk models to estimate the excess mortality and the first recurrent-event hazards. *BMC Medical Research Methodology* 2011; **11**(1):78.
36. Molenberghs G, Verbeke G. Likelihood ratio, score, and wald tests in a constrained parameter space. *The American Statistician* 2007; **61**(1):22–27.
37. Liu L, Yu Z. A likelihood reformulation method in non-normal random effects models. *Statistics in Medicine* 2008; **27**(16):3105–3124.
38. Vaupel JW, Yashin AI. Heterogeneity's Ruses: some surprising effects of selection on population dynamics. *The American Statistician* 1985; **39**(3):176–185.
39. Aalen OO. Effects of frailty in survival analysis. *Statistical Methods in Medical Research* 1994; **3**(3):227–243.
40. Robert C, Casella G. *Monte Carlo Statistical Methods*. Springer: New York, 2004.
41. Therneau TM, Grambsch PM, Leming TR. Martingale-based residuals for survival models. *Biometrika* 1990; **77**(1):147–160.
42. Cortese G, Scheike TH. Dynamic regression hazards models for relative survival. *Statistics in Medicine* 2008; **27**(18):3563–3584.
43. Elashoff RM, Li G, Li N. A joint model for longitudinal measurements and survival data in the presence of multiple failure types. *Biometrics* 2008; **64**(3):762–771.
44. Williamson PR, Kolamunnage-Dona R, Philipson P, Marson AG. Joint modelling of longitudinal and competing risks data. *Statistics in Medicine* 2008; **27**(30):6426–6438.
45. Wienke A, Arbeev KG, Locatelli I, Yashin AI. A comparison of different bivariate correlated frailty models and estimation strategies. *Mathematical Biosciences* 2005; **198**(1):1–13.
46. Lesaffre E, Spiessens B. On the effect of the number of quadrature points in a logistic random effects model: an example. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 2001; **50**(3):325–335.
47. Sinha D, Maiti T, Ibrahim JG, Ouyang B. Current methods for recurrent events data with dependent termination. *Journal of the American Statistical Association* 2008; **103**(482):866–878.
48. Andersen PK, Borgan Ø, Gill RD, Keiding N. *Statistical Models Based on Counting Processes*. Springer-Verlag: New York, 1993.
49. Lawless JF. The analysis of recurrent events for multiple subjects. *Journal of the Royal Statistical Society.Series C (Applied Statistics)* 1995; **44**(4):487–498.
50. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 2000; **62**(4):711–730.
51. Cook RJ, Lawless JF. Marginal analysis of recurrent events and a terminating event. *Statistics in Medicine* 1997; **16**(8):911–924.
52. Luo X, Wang MC, Huang CY. A comparison of various rate functions of a recurrent event process in the presence of a terminal event. *Statistical Methods in Medical Research* 2010; **19**(2):167–182.
53. Conniffe D. Testing a model parameter when another is unidentified under the null. *The Economic and Social Review* 1998; **29**(4):357–367.
54. Conniffe D. Score tests when a nuisance parameter is unidentified under the null hypothesis. *Journal of Statistical Planning and Inference* 2001; **97**(1):67–83.
55. Hansen BE. Inference when a nuisance parameter is not identified under the null hypothesis. *Econometrica: Journal of the Econometric Society* 1996; **64**(2):413–430.
56. Davies RB. Hypothesis testing when a nuisance parameter is present only under the alternative. *Biometrika* 1977; **64**(2):247–254.
57. Davies RB. Hypothesis testing when a nuisance parameter is present only under the alternative. *Biometrika* 1987; **74**(1):33–43.
58. Wintrebert CMA, Putter H, Zwinderman AH, Van Houwelingen JC. Centre-effect on survival after bone marrow transplantation: application of time-dependent frailty models. *Biometrical Journal* 2004; **46**(5):512–525.

59. Yau KK, McGilchrist CA. ML and REML estimation in survival analysis with time dependent correlated frailty. *Statistics in Medicine* 1998; **17**(11):1201–1213.
60. Fong DY, Lam KF, Lawless JF, Lee YW. Dynamic random effects models for times between repeated events. *Lifetime Data Analysis* 2001; **7**(4):345–362.
61. Rondeau V, Gonzalez JR. Frailtypack: a computer program for the analysis of correlated failure time data using penalized likelihood estimation. *Computer Methods and Programs in Biomedicine* 2005; **80**(2):154–164.
62. Rondeau V, Mazroui Y, Gonzalez JR. FRAILTYPACK: an R package for the analysis of correlated survival data with frailty models using the penalized likelihood estimation or parametrical estimation. *Journal of Statistical Software* 2012; **47**(4):1–28.
63. Abrahamowicz M, MacKenzie T, Esdaile JM. Time-dependent hazard ratio: modeling and hypothesis testing with application in lupus nephritis. *Journal of the American Statistical Association* 1996; **91**(436):1432–1439.
64. Yashin AI, Vaupel JW, Iachine IA. Correlated individual frailty: an advantageous approach to survival analysis of bivariate data. *Mathematical Population Studies* 1995; **5**(2):145–59, 183.
65. Kiernan K, Tao J, Gibbs P. Tips and strategies for mixed modeling with SAS/STAT procedures. *SAS Global Forum*, 2012; (paper 332–2012).
66. Zahl PH. Frailty modelling for the excess hazard. *Statistics in Medicine* 1997; **16**(14):1573–1585.
67. Locatelli I, Rosina A, Lichtenstein P, Yashin AI. A correlated frailty model with long-term survivors for estimating the heritability of breast cancer. *Statistics in Medicine* 2007; **26**(20):3722–3734.
68. Xue X, Brookmeyer R. Bivariate frailty model for the analysis of multivariate survival time. *Lifetime Data Analysis* 1996; **2**(3):277–289.