Article

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

Statistical Methods in Medical Research
0(0) 1–18

DOI: 10.1177/0962280219859377
journals.sagepub.com/home/smm
SAGE

Mixture cure models with time-varying and multilevel frailties for recurrent event data

Richard Tawiah,[1] Geoffrey J McLachlan[2] and Shu Kay Ng[1]

Abstract

Many medical studies yield data on recurrent clinical events from populations which consist of a proportion of cured patients in the presence of those who experience the event at several times (uncured). A frailty mixture cure model has recently been postulated for such data, with an assumption that the random subject effect (frailty) of each uncured patient is constant across successive gap times between recurrent events. We propose two new models in a more general setting, assuming a multivariate time-varying frailty with an AR(1) correlation structure for each uncured patient and addressing multilevel recurrent event data originated from multi-institutional (multi-centre) clinical trials, using extra random effect terms to adjust for institution effect and treatment-by-institution interaction. To solve the difficulties in parameter estimation due to these highly complex correlation structures, we develop an efficient estimation procedure via an EM-type algorithm based on residual maximum likelihood (REML) through the generalised linear mixed model (GLMM) methodology. Simulation studies are presented to assess the performances of the models. Data sets from a colorectal cancer study and rhDNase multi-institutional clinical trial were analyzed to exemplify the proposed models. The results demonstrate a large positive AR(1) correlation among frailties across successive gap times, indicating a constant frailty may not be realistic in some situations. Comparisons of findings with existing frailty models are discussed.

Keywords

AR(1) cure frailty model, correlated survival data, hierarchical survival data, multilevel cure model, random effect

1 Introduction

Recurrent event data provide a typical example of multivariate survival data which commonly arise in longitudinal follow-up studies when an individual subject can encounter multiple failure times (e.g. gap time[1,2]) related to repeated occurrences of the event of interest. In practice, these kind of data are frequently observed in medical research, examples of which are repeated tumor occurrences in bladder cancer patients,[3] multiple hospital readmissions following surgery for colorectal cancer,[4] sequence of infection episodes in kidney disease patients[5] and successive exacerbations of respiratory disorders among patients with cystic fibrosis.[6,7] An intrinsic feature of such data is the presence of correlation which characterises the multiple failure times encountered by each patient. In modelling, it is crucial to account for this correlation structure in order to allow for valid inference and also yield insights into the latent etiological mechanisms underlying the recurring process of the disease. Box-Steffensmeier and De Boef[8] have discussed that such correlation may originate from heterogeneity across patients and/or event dependence (also known as serial dependence). Heterogeneity arises when some individuals are more susceptible to recurrence than others due to the existence of patient-specific unknown, unmeasured, or unmeasurable risk factors, e.g. varied lifestyle, genetic trait, etc. Serial dependence refers to the situation where the occurrence of an event induces an excess risk, mostly biological in nature (e.g. progressive deterioration of the heart muscle due to episodes of myocardial infarction) which makes recurrence more likely. Although several modelling techniques (e.g. see literature[1,9,10] for details) have been proposed for recurrent event

[1]School of Medicine and Menzies Health Institute Queensland, Griffith University, Queensland, Australia
[2]Department of Mathematics, University of Queensland, Queensland, Australia

Corresponding author:
Shu K Ng, School of Medicine and Menzies Health Institute Queensland, Griffith University, Nathan QLD 4111, Australia.
Email: s.ng@griffith.edu.au

data, frailty models[2,8,11,12] have become a widely used approach for handling the correlation structure when modelling the effect of covariates in a parametric or semi-parametric regression framework. These models are recognised as random effect generalisation of standard survival models, in which the random effect term called frailty denotes the unknown, unmeasurable or latent covariates that yield the correlation structure.

Frailty models are useful in practice. However, sometimes cure proportion (or long-term survivors) arises in the data and thus renders these models impractical and inappropriate for statistical analysis because they fail to account for the insusceptibility of cured patients. Cure proportion refers to the fraction of study subjects who respond favourably to treatment and are therefore insusceptible to the endpoint in perspective (e.g. tumor recurrence or death from breast cancer). Such patients are commonly seen in clinical studies of chronic diseases, for example cancer. Although certain cancers such as multiple myeloma are generally considered as incurable,[13] for some types (e.g. colorectal cancer,[14] head and neck carcinoma[15]) cure is possible, particularly when localised. Curative rate is often high for early staged cancers.[15] The presence of cure proportion in survival data induces heavy long-term censored times with a marginal survival distribution which levels off to non-zero probability in the long run. Recognising the need to analyze survival data with a possible fraction of cured patients led to the development of the mixture cure model. This model is a two component mixture regression framework that assumes that the study population consists of two distinct groups: those who are cured and not susceptible to the endpoint of interest and the uncured group who are at risk and will eventually develop the endpoint. As originally suggested by Farewell,[16] the vast number of studies on cure models generally considered the logistic model for the cure probability (or fraction). Nonetheless, different survival methods (e.g. Weibull model,[16,17] proportional hazards (PH) model,[18–22] Kaplan–Meier type estimator,[23] accelerated failure time (AFT) model,[24,25] power family of transformations model[26]) have been employed to model the latency distribution of failure times in the uncured patients. Yau and Ng,[17] Lai and Yau[21,26] and Peng and Taylor[27] extended the cure model by introducing random effect terms into the logistic and the survival components to account for institutional effects in the analysis of survival data from multi-institutional (multi-centre) clinical trials.

Cure model has been considered specifically for recurrent event data by some few authors, like Yu[14] and Rondeau et al.,[28] by using random effect in the survival part to accommodate the patient-specific frailties that affect the latency distribution of gap times in the uncured patients. In their models, it is assumed that the frailty for each uncured patient is constant across successive gap times between recurrent events. However, using constant frailty assumption may not be plausible in all situations, in that, sometimes frailty of each uncured patient varies stochastically over time,[12,29] analogous to the behaviour of a time-dependent continuous covariate. This motivates our study to consider a more general frailty mixture cure model, with a time-dependent random patient effect in the survival component and a random patient effect that is constant over time in the logistic part. The model considers all observations in the logistic and the survival components and it allows patients with one or more events to have a chance of being cured after each event. In the broad sense, our model is a generalisation of the AR(1) frailty model given by Yau and McGilchrist,[12] by allowing the possibility of a cure proportion in the study population. Moreover, we provide a multilevel extension of the proposed frailty mixture cure model which is applicable to hierarchical recurrent event data, which arise as a result of the occurrences of repeated failures in clustered populations, e.g. patients who are nested within health institutions in a multi-institutional clinical trial. In the multilevel model, we introduce additional random effect terms to examine institutional effect as well as treatment-by-institution interaction (i.e. random covariate) in the cured and the uncured patients.

We use the EM algorithm[19,20] to implement the generalised linear mixed model (GLMM) methodology[30,31] for estimation of model parameters. Within the GLMM framework, estimation of fixed and random effects can be achieved by maximising a log-likelihood, analogous to the likelihood associated with the best linear unbiased prediction (BLUP) in normal theory mixed models and variance components can be estimated through a set of residual maximum likelihood (REML) estimating equations which often leads to less biased estimates,[11,12,32] compared to other candidate methods like the maximum likelihood (ML) procedure. The advantage of the GLMM method is that it circumvents mathematical intractability issues related to complicated integrals that commonly arise when using other comparable methods, such as the marginal likelihood. The novelties in our proposed modelling methodologies pertain to the adoption of a multivariate time varying frailty with patient-specific AR(1) correlation structure within the context of cure models, and multilevel extension of mixture cure model, combining unobservable random effects, random covariates and AR(1) random effect structure in a unified modelling framework within the GLMM methodology.

The remaining sections of this paper are organised as follows. Section 2 describes the frailty mixture cure model and the multilevel frailty mixture cure model as well as their estimation methodology. In Section 3, the

performance of these models is examined by simulation studies in a small sample setting. For practical purposes, we provide an illustration of the models in Section 4 by analysing data on recurrent events in a colorectal cancer study and a rhDNase multi-institutional clinical trial. Finally, some discussions and concluding remarks are given in Section 5 to end the paper.

2 Models and estimation

2.1 The mixture cure model with AR(1) frailty

As previously noted, we consider a follow-up study in which patients encounter multiple failure times related to a recurrent event. Denote the observed data on the jth patient as $O_j = \{(t_{jk}, \delta_{jk}, x_j),\ j = 1, \ldots, M; k = 1, \ldots, n_j\}$, where M is the number of patients enrolled into the study and n_j is the number of recurrent events experienced by the jth patient. Overall, there are $\sum_{j=1}^{M} n_j = N$ observations in total. Let t_{jk} denote the gap time between any k successive events on the jth patient. Here, $\delta_{jk} = 1$ and $\delta_{jk} = 0$ denote a failure and censored observation at t_{jk}, respectively. Notice that x_j is a p-dimensional covariate vector on the jth patient, which may constitute, for example, some experimental (e.g. treatment) or prognostic factors.

Let Y_{jk} denote a binary indicator, such that $Y_{jk} = 1$ means patient j will eventually experience the kth recurrent episode of the disease, that is, an uncured patient, and $Y_{jk} = 0$ implies patient j will never experience the kth recurrent failure, that is, a cured patient, where y_{jk} denotes the realisation of Y_{jk}. Notice that y_{jk} is partially observable in the sense that we only know y_{jk} to be 1 when $\delta_{jk} = 1$ but y_{jk} is unknown when $\delta_{jk} = 0$. We define $P(Y_{jk} = 1) = \pi_k(x_j)$ as the probability of experiencing the kth event after the $(k-1)th$ event. Also, $P(Y_{jk} = 0) = 1 - \pi_k(x_j)$ can be defined as the probability of being cured after each event. The probabilities can be restricted to merely take into account the first recurrence per each individual. In this case, a patient who has an event has no chance of being cured. By doing so, we do not require random patient effects to enter into the logistic model which describes the effects of covariates on the cured probability.[14,28,33] However, statistical power is increased when all available recurrences are considered together in the logistic model instead of utilising only the first recurrence.[28] Therefore, considering all recurrences there is the need to summarise the dependence among the uncured statuses, induced by missing covariates or frailty. Thus, a patient-specific random effect v_{jk} can be attached to the linear predictor of the logistic regression model, expressed as

$$\begin{aligned} \pi_k(x_j) &= \frac{exp(\xi_{jk})}{1 + exp(\xi_{jk})} \\ \xi_{jk} &= w_j^T \alpha + v_{jk}; \quad (v_{jk} = v_j)\ \forall\ k \end{aligned} \tag{1}$$

where ξ_{jk} is the linear predictor, α is the fixed effect vector which measures the effects of covariates x_j on the uncured probability, $w_j = (1\ x_j^T)^T$, and v_j is the frailty for the jth cured patient, assumed to be constant over time. Notice that ξ_{jk}, and hence the conditional probability of failure given the $(k-1)$th event, $\pi_k(x_j)$, is also constant over time for each patient.[28] The superscript T denotes a vector transpose. A negative value of α means the corresponding covariate induces a lower probability of experiencing a recurrence (i.e. a higher cure probability) and a higher v_j means subject j is highly frail and would have a higher probability of developing recurrence, or a lower cure probability. Notice that the presence of 1 in w_j allows model (1) to incorporate an intercept term. The intercept is the baseline effect on the uncured probability which reflects the effect of those individuals with $x_j = 0$.

For any uncured patient, the event of interest eventually occurs, so let T denote a random variable for the realisations t_{jk} such that $t_{jk} < \infty$ for all k in the jth uncured patient. Let $S_u(t_{jk})$ denote the conditional survival function of the uncured patients (i.e. latency distribution), which may similarly depend on the covariate vector x_j, thus written as $S_u(t_{jk}; x_j)$. Notice that the covariates entering the conditional survival function of the uncured and the incidence probability do not necessarily overlap. For the patients who are cured, $t_{jk} = \infty$. As these individuals will never experience the event, their conditional survival function degenerates to 1. The mixture cure model is the marginal survival function of the cured and uncured patients, given as

$$S(t_{jk}) = 1 - \pi_k(x_j) + \pi_k(x_j) S_u(t_{jk}; x_j) \tag{2}$$

For recurrent event data, some existing studies utilised the PH frailty model[14,28] and the conditional frailty model[34] to accommodate frailty and covariate effect on the latency distribution. In these studies,[14,28] it is assumed that the frailty for each uncured patient is constant across successive gap times. In contrast, the present work uses

the PH frailty model, with frailty effect V_{jk} assumed to vary over consecutive gap times within uncured patients. The model describing the hazard of recurrence for the jth uncured patient is therefore given by

$$\begin{aligned} h_u(t_{jk}; x_j) &= h_{u0}(t_{jk}) exp(\eta_{jk}) \\ \eta_{jk} &= x_j^T \beta + V_{jk} \end{aligned} \tag{3}$$

where η_{jk} is the linear predictor corresponding to the latency part, $h_{u0}(t_{jk})$ is an unspecified baseline hazard function for the uncured patients, β is the fixed effect parameter vector that quantifies the effect of covariates on the hazard rate of recurrence in the uncured patient and V_{jk} is the frailty of the kth recurrent event on the jth uncured patient. A negative value of β indicates that the corresponding covariate reduces the hazard rate of recurrence (i.e. a longer time between recurrence) in uncured patients and a higher value of V_{jk} corresponds to a substantial frailty in an uncured patient, that is, such patient is highly susceptible to the kth recurrent episode of the disease due to his/her own frailty. Combining equations (1) to (3), we obtain the mixture cure model with constant and time-dependent frailties. It includes Yau and McGilchrist's AR(1) frailty model[12] as a special case when $\pi_k = 1$.

Suppose we choose v and V to denote the random vectors corresponding to the frailty terms v_j and V_{jk}, respectively. These vectors can be regarded as a quantification of unknown or missing covariates associated with π_k and t_{jk}, respectively. Without loss of generality, we assume that frailties on different patients are independent and that both v and V are also independent. Due to the constant frailty assumption imposed on the random effect term in the logistic model, we consider $N(0, \theta_1^2 I_M)$ as the distribution for v, where I_M is an identity matrix with dimension M. To further account for the time varying frailties in the uncured patients, an AR(1) correlation structure is adopted for the gap times, so that V follows a multivariate normal distribution $MVN(0, \theta_2^2 G(\rho))$, where $G(\rho)$ is a $N \times N$ block diagonal matrix given by

$$G(\rho) = \begin{bmatrix} G_1(\rho) & 0 & \dots & 0 \\ & G_2(\rho) & \dots & 0 \\ & \text{Sym.} & \ddots & \vdots \\ & & & G_M(\rho) \end{bmatrix} \quad \text{and} \quad G_j(\rho) = \frac{1}{1-\rho^2} \begin{bmatrix} 1 & \rho & \dots & \rho^{n_j-1} \\ & 1 & \dots & \rho^{n_j-2} \\ & \text{Sym.} & \ddots & \vdots \\ & & & 1 \end{bmatrix}$$

where Sym. denotes that the matrix is symmetric. In the above, $G_j(\rho)$ denotes an AR(1) covariance structure for all recurrent events experienced by the jth uncured patient and ρ is the autoregressive correlation parameter that measures serial dependence between gap times. By this covariance structure, the gap times which occur closely in times within a patient are strongly correlated, while those which are far apart are weakly correlated. A larger value of ρ would imply that the hazard rate of recurrence increases in the uncured patients once an event has occurred. Also, a larger value of θ_1^2 and θ_2^2 depicts substantial heterogeneity due to frailty in the proportion of cured patients and in the failure time distribution of the uncured patients, respectively.

Let W, X, R_1, and R_2 denote the respective design matrices corresponding to the regression parameter vectors α, β, v, and V. It is worth noting that the linear predictors of the logistic and the hazard components can be rewritten in the form

$$\xi = W\alpha + R_1 v \ \text{ and } \ \eta = X\beta + R_2 V$$

Let l_A denote the complete-data conditional log-likelihood of the frailty cure model, defined by

$$l_A = log\left[\prod_{j=1}^{M} \prod_{k=1}^{n_j} \pi_{jk}^{y_{jk}} (1-\pi_{jk})^{1-y_{jk}} \prod_{j=1}^{M} \prod_{k=1}^{n_j} \{h_{u0}(t_{jk}) exp(\eta_{jk})\}^{\delta_{jk} y_{jk}} S_{u0}(t_{jk})^{y_{jk} exp(\eta_{jk})} \right] \tag{4}$$

where $\pi_{jk} = \pi_k(x_j)$, $h_{u0}(t_{jk}) = f(t_{jk})/S(t_{jk})$ and $S_{u0}(t_{jk}) = e^{-\Lambda_{u0}(t_{jk})}$. Notice that $\Lambda_{u0}(t_{jk})$ is the cumulative baseline hazard function for the uncured patients, given by $\Lambda_0(t_{jk}) = \int_0^{t_{jk}} h_{u0}(s) \mathrm{d}s$. Moreover, let

$$l_B = -\frac{1}{2}\left[Mlog(2\pi\theta_1^2) + \frac{1}{\theta_1^2} v^T v \right] - \frac{1}{2}\left[Nlog(2\pi\theta_2^2) + log|G| + \frac{1}{\theta_2^2} V^T G^{-1} V \right] \tag{5}$$

denote the logarithm of the joint density function on the basis of v and V, with v and V taken to be independent. In principle with the GLMM framework,[30,31] the sum $l = l_A + l_B$ can be viewed as a complete-data BLUP-type

log-likelihood or a penalised quasi-likelihood. Notice that maximisation of this likelihood is not straightforward because it involves the unknown functional form of $h_{u0}(t_{jk})$ and also partially missing observations of y_{jk}. Conforming with previous work,[19,20] the log-likelihood can be rewritten in terms of the likelihood contribution of the parameters of the random effect logistic regression model (1) and the PH frailty model (3), respectively, as

$$l_{\Phi} = \sum_{r=1}^{N} \{y_r \xi_r - log[1 + exp(\xi_r)]\} - \frac{1}{2}\left[Mlog\left(2\pi\theta_1^2\right) + \frac{1}{\theta_1^2} v^T v \right] \tag{6}$$

and

$$l_{\Omega} = \sum_{r=1}^{q} \left\{ \eta_r - log \sum_{l \in R(r)}^{N} y_l exp(\eta_l) \right\} - \frac{1}{2}\left\{ Nlog\left(2\pi\theta_2^2\right) + log|G| + \frac{1}{\theta_2^2} V^T G^{-1} V \right\} \tag{7}$$

where $\Phi = (\alpha, v)$, $\Omega = (\beta, V)$, $R(r)$ is the risk set, η_l and y_l are the respective values of η and y corresponding to the risk set and $t_{(1)} < \ldots < t_{(q)}$ are the q distinct gap times. Notice that equation (7) does not depend on $h_{u0}(t_{jk})$.

2.2 The multilevel frailty mixture cure model

Here, we consider the case where recurrent event data arise from clustered populations such as individuals who are grouped by their respective families, communities or patients who are nested within health institutions in a multi-institutional clinical trial. The appearances of repeated failure time observations within patients and also patients within institutions yield a hierarchical (or multilevel) data structure. For such data, the observed disease outcomes (i.e. recurrent failures) and the cure probability may be affected by patient and institution-specific characteristics; nevertheless, these are often unexplained by covariates. There is, therefore, the need to investigate unobservable patient and institutional effects when analysing such data. When investigating institutional effects in multi-institutional clinical trials, it is sometimes of concern to estimate the extent of heterogeneity in treatment effect across institutions (i.e. treatment-by-institution interaction). However, this is seldom considered when presenting random effect cure models for multi-institutional survival data.

We consider an extension of the proposed frailty cure model in equations (1) to (3), by using random effects to model patient effect, institutional effect and treatment-by-institution interaction in both the logistic and hazard components. This leads to a three-level random effect (frailty) mixture cure model, with respective linear predictors of the logistic and hazard model specified as

$$\xi_{ijk}^{*} = w_{ij}^T \alpha + \left(1 \; x_{ij1}\right) u_i + v_{ij} \quad \text{and} \quad \eta_{ijk}^{*} = x_{ij}^T \beta + \left(1 \; x_{ij1}\right) U_i + V_{ijk}$$

where $u_i = (u_{i0}^T \; u_{i1}^T)^T$ and $U_i = (U_{i0}^T \; U_{i1}^T)^T$ are institution-specific random coefficients specific to the cured and uncured components of the model, respectively and $w_{ij} = (1 \; x_{ij}^T)^T$. Specifically, u_{i0} and U_{i0} are the random baseline risk of the ith institution (i.e. main institution effects) in the cured and uncured patients, and u_{i1} and U_{i1} are the random treatment-by-institution interaction of the ith institution in the cured and uncured patients and $x_{ij} = \left(x_{ij1}, \ldots, x_{ijp}\right)^T$ is a vector of covariates for the jth patient within the ith institution. We assume that x_{ij1} is the realisation for treatment covariate, which takes on 0/1 to indicate placebo/therapy group. The other realisations $x_{ij2}, \ldots, x_{ijp}$ could be any prognostic variables recorded in the study. In the fixed effect parameter vectors $\alpha = (\alpha_0, \alpha_1, , \ldots, \alpha_p)^T$ and $\beta = (\beta_1, \ldots, \beta_p)^T$, α_1 and β_1 are measures for overall treatment effects in the cured and uncured patients, respectively. The log-treatment hazard ratio of the ith institution in the cured and the uncured patients is given by $\alpha_1 + u_{i1}$ and $\beta_1 + U_{i1}$, respectively. Note that v_{ij} is the frailty of the jth cured patient nested in the ith institution (assumed to be constant over time) and V_{ijk} is the frailty of the kth possible failure on the jth uncured patient nested in the ith institution. The distributions of v_{ij} and V_{ijk} depend on the variance components θ_1^2, θ_2^2 and ρ and have the same normal assumption as those of the frailty mixture cure model in equations (1) to (3).

The quantities u_0, u_1, U_0 and U_1 are, respectively, taken as random vectors of u_{i0}, u_{i1}, U_{i0} and U_{i1}, which are assumed to arise independently from

$$\begin{pmatrix} u_0 \\ u_1 \end{pmatrix} \sim N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \gamma_0^2 I_D & 0 \\ 0 & \gamma_1^2 I_D \end{pmatrix} \right] \quad \text{and} \quad \begin{pmatrix} U_0 \\ U_1 \end{pmatrix} \sim N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_0^2 I_D & 0 \\ 0 & \sigma_1^2 I_D \end{pmatrix} \right]$$

where the variance components are measures for institutional heterogeneity in the baseline risk and in treatment effects in both the cured and uncured patients.

2.3 Estimation procedure

The estimation procedure for the proposed frailty mixture cure model in equations (1) to (3) is outlined in this section. Recall that realisations y_{jk} are not completely observed. Hence, we consider an EM-type estimation procedure. Within this procedure, the random effects can be regarded as missing variables. However, the conditional expectation of the random effects required in the E-step is mostly not available in closed form and thus leads to intractable E-step which is usually difficult to evaluate. Ng[35] presents a comprehensive and useful discussion on recent methodological developments for dealing with intractable E-steps and complicated M-steps in the EM algorithm. The Laplace formula approach used by Abrahantes and Burzykowski[36] and the Markov chain Monte Carlo (MCMC) method adopted in Vaida and Xu[37] are possible ways of overcoming intractable E-step issues in random effect models. However, difficulty of implementation still exists due to the complexity of the AR(1) random effect structure used in our model. With random effects conditionally fixed in the BLUP-type log-likelihood according to the GLMM methodology,[30,31] the estimation procedure considered here averts intractable issues in the E-step.

Let $\Psi = (\theta_1^2, \theta_2^2, \rho)$ denote the parameter vector of the variance components. The E-step computes the conditional expectation of y_{jk} using

$$g_{jk} = E\{y_{jk}|(\Phi, \Omega, \Psi, S_{u0}(.))\} = \delta_{jk} + \frac{(1-\delta_{jk})\pi_k(x_j)S_{u0}(t_{jk})^{exp(\eta_{jk})}}{1-\pi_k(x_j)+\pi_k(x_j)S_{u0}(t_{jk})^{exp(\eta_{jk})}} \tag{8}$$

where g_{jk} is the posterior probability of the jth patient being uncured, given the kth possible failure. Equation (8) uses g_{jk} to update the y_{jk}'s in equations (6) and (7). Various approaches for estimating $S_{u0}(t_{jk})$ appear in literature. Taylor[23] used a Kaplan–Meier type estimator. This approach did not incorporate a covariate on the latency part and thus it forms a special case of the estimation procedure in the PH cure model when $\beta = 0$. To incorporate β, $S_{u0}(t_{jk})$ may be estimated using the Breslow-type estimator, the product-limit estimator or the piecewise constant parametric procedure.[19,20,38] For simplicity, we adopt the Breslow-type estimator, given as

$$\hat{S}_{u0}(t_{jk}) = exp\left\{-\frac{\sum_{k:t_{(k)}\le t} d_k}{\sum_{l\in R(t_k)} g_l^{(m)} exp\eta_l}\right\} \tag{9}$$

where d_k is the number of uncensored failures at $t_{(k)}$. Denote t_h as the largest uncensored gap time. To obtain a proper estimate of $S_{u0}(t)$ and good estimates of α and β, the Breslow-type estimator (9) is applied when $t_{jk} \le t_h$ and when $t_{jk} > t_h$ we compute $S_{u0}(t)$ from the exponential-tail (ETAIL) completion method,[38] given by

$$\hat{S}_{u0}(t_{jk}) = exp\left(-\hat{\lambda}t_{jk}\right) \tag{10}$$

where $\lambda = -log\{S_{u0}(t_h)\}/t_h$. Maximum likelihood techniques are required in the M-step in order to estimate the parameters of Φ and Ω. Estimates of Φ is given by an iterative maximisation of (6) using the Newton–Raphson procedure

$$\begin{bmatrix}\tilde{\alpha}^{(m)}\\ \tilde{v}^{(m)}\end{bmatrix} = \begin{bmatrix}\tilde{\alpha}^{(m-1)}\\ \tilde{v}^{(m-1)}\end{bmatrix} + \zeta_\Phi^{-1}\begin{bmatrix}W^T\\ R_1^T\end{bmatrix}\Im_\xi - \zeta_\Phi^{-1}\begin{bmatrix}0\\ \hat{\theta}_1^{-2}v^{(m-1)}\end{bmatrix}, \tag{11}$$

where $\tilde{\alpha}^{(m)}$ and $\tilde{v}^{(m)}$ are the estimates of α and v in the mth iteration, ζ_Φ is the negative second derivative of l_Φ with respect to Φ and $\Im_\xi$ is the first derivative of l_Φ with respect to ξ. Let $\Theta_\xi = -\partial^2 l_\Phi/\partial\xi\partial\xi^T$, then ζ_Φ is given by

$$\zeta_\Phi = -\frac{\partial^2 l_\Phi}{\partial\Phi\partial\Phi^T} = \begin{bmatrix}W^T\Theta_\xi W & W^T\Theta_\xi R_1\\ R_1^T\Theta_\xi W & R_1^T\Theta_\xi R_1 + \hat{\theta}_1^{-2}I_M\end{bmatrix} \quad \text{and} \quad \zeta_\Phi^{-1} = \begin{bmatrix}H_\alpha & H_{\alpha,v}\\ H_{v,\alpha} & H_v\end{bmatrix}$$

Estimation of Ω is based on iterative maximisation of (7) through the Newton-Raphson procedure

$$\begin{bmatrix} \tilde{\beta}^{(m)} \\ \tilde{V}^{(m)} \end{bmatrix} = \begin{bmatrix} \tilde{\beta}^{(m-1)} \\ \tilde{V}^{(m-1)} \end{bmatrix} + \zeta_{\Omega}^{-1} \begin{bmatrix} X^T \\ R_2^T \end{bmatrix} \Im_{\eta} - \zeta_{\Omega}^{-1} \begin{bmatrix} 0 \\ \hat{\theta}_2^{-2} G^{-1} V^{(m-1)} \end{bmatrix} \tag{12}$$

where ζ_{Ω} is the negative second derivative of l_{Ω} with respect to Ω, and $\Im_{\eta}$ is the first derivative of l_{Ω} with respect to η. Also, letting $\Theta_{\eta} = -\partial^2 l_{\Omega}/\partial\eta\partial\eta^T$, then ζ_{Ω} is similarly given as

$$\zeta_{\Omega} = -\frac{\partial^2 l_{\Omega}}{\partial\Omega\partial\Omega^T} = \begin{bmatrix} X^T\Theta_{\eta}X & X^T\Theta_{\eta}R_2 \\ R_2^T\Theta_{\eta}X & R_2^T\Theta_{\eta}R_2 + \hat{\theta}_2^{-2}G^{-1} \end{bmatrix} \quad \text{and} \quad \zeta_{\Omega}^{-1} = \begin{bmatrix} H_{\beta} & H_{\beta,V} \\ H_{V,\beta} & H_V \end{bmatrix}$$

Details of the derivatives $\Im_{\xi} = dl_{\Phi}/d\xi$, $\Theta_{\xi} = -\partial^2 l_{\Phi}/\partial\xi\partial\xi^T$, $\Im_{\eta} = dl_{\Omega}/d\eta$ and $\Theta_{\eta} = -\partial^2 l_{\Omega}/\partial\eta\partial\eta^T$ are provided in Appendix A as supplementary material from the journal website. The REML estimating equations for θ_1^2 and θ_2^2 are

$$\theta_1^2 = M^{-1}\left[tr\left(H_v + v^T v\right)\right] \tag{13}$$

and

$$\theta_2^2 = N^{-1}\left[trG^{-1}H_V + V^T G^{-1} V\right] \tag{14}$$

where $G^{-1} = \left(1+\rho^2\right)I - \rho J - \rho^2 K$ and tr denotes trace of a matrix. Notice that I, J and K are block diagonal matrices with respective sub-entries I_j, J_j and K_j each with n_j rows and columns; see Appendix A, supplementary material for details. Substituting the expression of G^{-1} into equation (14), the estimating equation of θ_2^2 reduces to

$$\theta_2^2 = N^{-1}\left[\left(1+\rho^2\right)B_1 - 2\rho B_2 - \rho^2 B_3\right] \tag{15}$$

where $B_1 = tr\left[I\left(H_V + VV^T\right)\right], B_2 = (1/2)tr\left[J\left(H_V + VV^T\right)\right]$ and $B_3 = tr\left[K\left(H_V + VV^T\right)\right]$. The REML estimating equation for ρ is a solution to the equation

$$tr\left[\left(\frac{\partial G^{-1}}{\partial\rho}\right)G\right] = \frac{1}{\theta_2^2}\left[tr\left(G + VV^T\right)\frac{\partial G^{-1}}{\partial\rho}\right] \tag{16}$$

where $tr\left((\partial G^{-1}/\partial\rho)G\right) = -\left[2\rho/\left(1-\rho^2\right)\right]$ and $\partial G^{-1}/\partial\rho = 2\rho I - J - 2\rho K$. Substituting these expressions into equation (16) and replacing θ_2^2 by its REML equation (15), we obtain the cubic equation[39]

$$f(\rho) = A_1\rho^3 + A_2\rho^2 + A_3\rho + A_4 = 0$$

where $A_1 = (N-M)(B_1 - B_3), A_2 = (2M-N)B_2, A_3 = NB_3 - (N+M)B_1$, and $A_4 = NB_2$. Estimate of ρ is a Newton–Raphson solution of the above cubic equation given by

$$\hat{\rho} = \rho - \frac{f(\rho)}{f'(\rho)} \tag{17}$$

where $f'(\rho)$ is the first derivative of $f(\rho)$ with respect to ρ. Computational details of the estimation procedure are summarised in the following:

Step 1. Set the initial values of Φ and Ω to zero and set those of Ψ to relatively small values. Also set the initial values of g_{jk} to 1 if $\delta_{jk} = 1$ and to a sufficiently small value if otherwise.

Step 2. Given the current estimates of Φ, Ω, Ψ and $S_{u0}(t)$ from equations (9) and (10), use equation (8) to update g_{jk}.

Step 3. For fixed g_{jk}, use equations (11) and (12) to, respectively, update Φ and Ω iteratively until convergence in this step. This step converges and proceeds to Step 4 when $\max|(\Phi_{m+1} - \Phi_m), (\Omega_{m+1} - \Omega_m)| < \varepsilon$, where $\varepsilon = 0.001$.

Step 4. Given the current estimates of v and V obtained from Φ and Ω in Step 3, use equations (13), (15) and (17) to respectively update the values of θ_1^2, θ_2^2 and ρ in Ψ.
Step 5. Repeat steps 2 to 4 until convergence of the entire iterative scheme.
In general, the estimation converges when both $\max|(\Phi_{m+1} - \Phi_m), (\Omega_{m+1} - \Omega_m)| < \varepsilon$ and $\max|\Psi_{m+1} - \Psi_m| < \varepsilon$ criteria are satisfied.

The standard errors of the fixed effect parameters α and β are computed using an approximate Louis's formula.[40] Also, the standard errors of the variance components θ_1^2, θ_2^2 and ρ are obtained by inverting the REML information matrix. Details can be found in Appendix A, supplementary material. The estimation procedure described here can be extended to obtain estimates of the multilevel frailty cure model; details are given in Appendix B as supplementary material. The proposed methodology is computationally implemented as R program (Appendix C). Appendices A–C can be found in Supplementary Information file available with this paper from the journal website.

3 Simulation studies

Simulation studies are carried out to assess the performances of the proposed mixture cure model and its multilevel extension. The simulation procedure and their results are described respectively in sub-sections (3.1) and (3.2) for the frailty mixture cure model and the multilevel frailty mixture cure model.

3.1 Simulation for the frailty cure model

In this simulation, we assume patients are followed up to a maximum time of 2000 days, approximately 5.5 years from the onset of the study. To evaluate the performance of the model in larger and smaller samples, we considered two schemes of follow-up studies, one with 1000 patients and the other with 200 patients. For simplicity, we assume a single covariate, that is, x_{j1} regarded as a treatment variable which enters the linear predictor of the hazard and the logistic components of the mixture cure frailty model. Covariate x_{j1} is drawn from the Bernoulli distribution with a 0.5 probability. Furthermore, we set the true values of the fixed effect parameters as $\alpha_0 = 0.5$; $\alpha_1 = -0.8$ and $\beta_1 = -0.5$. The true values of the variance components are similarly chosen as $\theta_1^2 = 0.4, 0.5$; $\theta_2^2 = 0.5, 0.7$ and $\rho = 0.3, 0.8, 0.9$. The censoring time and the gap times are generated as follows: First, time lost to follow-up c_j is generated for each patient using a uniform distribution with maximum 2000 days. Next, v_j is generated from $N(0, \theta_1^2)$ and the binary indicator y_{jk} for each patient is generated from the Bernoulli distribution with the probability of being uncured given by the logistic regression model in equation (1). If a patient is cured, the failure time for that patient is taken to be infinitely large (i.e. $t_{jk} = \infty$) and subsequently censored at c_j. On the other hand, when a patient is uncured, V_{jk} is generated from $MVN(0, \theta_2^2 G(\rho))$. Then, the gap times (i.e. t_{jk}, for $k = 1, \ldots, n_j$) for the uncured patient are generated from the frailty model in equation (3). This is done repeatedly until the corresponding uncured patient gets cured or until $\sum_{k=1}^{n_j} t_{jk} \geq c_j$. In doing so, we assume that the baseline hazard of the frailty model follows the Weibull distribution with parameters $\lambda = 0.8$ and $\tau = 0.5$. We considered distinct scenarios of combinations of the true parameter values. In each scenario, 500 replicated data sets $(t_{jk}, \delta_{jk}, x_{j1})$ are generated and the EM REML procedure detailed in section 2.3 is applied for estimation.

We report for each scenario, the average bias (Ave. bias), the average of the standard error estimates (SEE), the standard error (SE) of the estimates over 500 replications and the coverage probability (CP) of 95% confidence interval (CI) based on the normal approximation for larger sample size (M=1000) and smaller sample size (M=200) as summarised in Tables 1 and 2, respectively. For larger sample size (Table 1), the degree of bias of the fixed effect parameters α_0, α_1 and β_1 and the variance components θ_1^2, θ_2^2 and ρ are quite small when there is a lower and also a higher-order dependence among frailties across successive gap times. In the case of smaller sample size (Table 2, simulation 1), these parameters have moderately small bias when the dependence structure goes to a low level. However, the magnitude of bias of the fixed effect parameters increases when the dependence structure is of higher order (Table 2, simulations 2 and 3). Comparing in terms of bias, it is clear that the model performs reasonably well in the larger sample than the smaller sample. Regarding the standard errors of the fixed effect parameters α_0, α_1 and β_1, SEE and SE are comparable in all scenarios in both samples, indicating that the standard errors of these parameters are well estimated. For the variance components, SEE and SE for ρ are quite comparable while those of θ_1^2 and θ_2^2 have moderate differences. It is seen that the standard error estimates of ρ increase marginally when its true value goes to a low level, in both samples. The CPs of α_0, α_1 and β_1 are close to

Table 1. Bias, standard error and coverage probability of the REML estimators for the frailty mixture cure model based on 500 replications of simulated data with M = 1000 patients.

Parameter	True value	Ave. bias	SEE	SE	CP	Parameter	True value	Ave. bias	SEE	SE	CP
Simulation 1						Simulation 2					
α_0	0.5	−0.048	0.066	0.068	0.933		0.5	0.045	0.066	0.061	0.937
α_1	−0.8	0.039	0.099	0.099	0.928		−0.8	0.035	0.100	0.092	0.956
β_1	−0.5	0.016	0.084	0.086	0.934		−0.5	0.028	0.120	0.114	0.931
θ_1^2	0.4	−0.021	0.094	0.046	1.000		0.4	−0.016	0.095	0.048	1.000
θ_2^2	0.5	−0.006	0.067	0.010	1.000		0.5	0.004	0.085	0.022	1.000
ρ	0.3	0.014	0.104	0.076	0.984		0.8	−0.028	0.041	0.036	0.982
Simulation 3						Simulation 4					
α_0	0.5	−0.044	0.066	0.070	0.920		0.5	0.043	0.067	0.070	0.939
α_1	−0.8	0.041	0.100	0.098	0.950		−0.8	0.038	0.101	0.101	0.944
β_1	−0.5	0.026	0.089	0.087	0.932		−0.5	0.031	0.131	0.119	0.939
θ_1^2	0.5	−0.075	0.096	0.053	1.000		0.5	−0.071	0.098	0.060	1.000
θ_2^2	0.7	−0.009	0.075	0.012	1.000		0.7	0.009	0.098	0.038	0.974
ρ	0.3	−0.008	0.085	0.068	0.956		0.8	−0.046	0.037	0.033	0.987
Simulation 5											
α_0	0.5	0.041	0.066	0.061	0.942						
α_1	−0.8	0.033	0.101	0.090	0.948						
β_1	−0.5	0.032	0.136	0.155	0.944						
θ_1^2	0.4	−0.013	0.096	0.038	1.000						
θ_2^2	0.5	0.004	0.081	0.019	1.000						
ρ	0.9	−0.033	0.029	0.018	0.964						

the nominal level, while those of θ_1^2, and θ_2^2 are above the nominal level in all instances. The use of the normal approximation for the CI of the variance component estimates, which are typically right-skewed, is possibly one of the reasons why θ_1^2 and θ_2^2 have poor CPs. For the case of ρ, the CPs are close to the nominal level in the simulations with larger sample size.

Moreover, in simulation sets 4 and 5 in Table 2, we examined the robustness of the estimation method to misspecification of the AR(1) covariance structure. In these simulations, we generated data from the proposed model by assigning ρ in the distribution of V_{jk} to zero and again, by taking it to be constant over time. It is important to realise that $\rho = 0$ reduces the AR(1) covariance structure to a diagonal covariance structure. We performed estimation by means of the proposed EM REML method presented in section 2.3. From these simulation results, it is evident that the estimation method is not sensitive to misspecification of the AR(1) covariance structure as the magnitude of bias observed are reasonably small for both the fixed effect and the variance component parameters. However, these simulations represent a sub-context of misspecification of the covariance structure, termed as under-specification; see, for example, Kwok et al.[41] In future research, it would be valuable to consider further simulation studies to examine the performance of the estimation method when there is over-specification and also general misspecification of the AR(1) covariance structure.

3.2 Simulation for the multilevel frailty cure model

In this simulation work, 500 replicated data sets are generated under a multi-institutional clinical trial setting using the multilevel frailty mixture cure model presented in section 2.2. We conceived a relatively large multi-institutional clinical trial consisting of 1000 patients, 25 each enrolled in 40 institutions. For comparison, we additionally considered a second scenario with 1500 patients (30 institutions, 50 patients from each institution). In both scenarios, approximately half of the patients within each institution are randomly assigned to treatment ($x_{ij1} = 1$), while the remaining patients are assigned to placebo ($x_{ij1} = 0$). The random effect terms u_0, u_1, U_0, U_1, v and V are generated independently from the normal distribution with zero mean and respective variance components $\gamma_0^2 = 0.4, 0.2$; $\gamma_1^2 = 0.2, 0.4$; $\sigma_0^2 = 0.5, 0.3$; $\sigma_1^2 = 0.3, 0.5$; $\theta_1^2 = 0.4$; $\theta_2^2 = 0.5$ and $\rho = 0.3, 0.7$. Under these random effect settings, the gap times are generated from the multilevel frailty cure model and the censoring time are obtained from the uniform distribution in the manner described in section 3.1, given that $\alpha_0 = 0.5; \alpha_1 = -0.8;$ and $\beta_1 = -0.5$.

Table 2. Bias, standard error and coverage probability of the REML estimators for the frailty mixture cure model based on 500 replications of simulated data with M = 200 patients.

Parameter	True value	Ave. bias	SEE	SE	CP	Parameter	True value	Ave. bias	SEE	SE	CP
Simulation 1						Simulation 2					
α_0	0.5	−0.064	0.147	0.148	0.926		0.5	−0.093	0.147	0.149	0.910
α_1	−0.8	0.057	0.223	0.218	0.950		−0.8	0.048	0.224	0.225	0.940
β_1	−0.5	0.030	0.190	0.189	0.948		−0.5	0.059	0.255	0.262	0.952
θ_1^2	0.4	−0.024	0.211	0.093	1.000		0.4	−0.023	0.214	0.087	1.000
θ_2^2	0.5	−0.010	0.152	0.020	1.000		0.5	−0.052	0.185	0.077	0.992
ρ	0.3	−0.018	0.237	0.184	0.974		0.8	−0.052	0.111	0.073	0.996
Simulation 3						Simulation 4					
α_0	0.5	−0.074	0.147	0.147	0.924		0.5	−0.062	0.147	0.148	0.920
α_1	−0.8	0.052	0.223	0.221	0.946		−0.8	0.055	0.223	0.221	0.946
β_1	−0.5	0.071	0.227	0.235	0.934		−0.5	0.024	0.178	0.182	0.940
θ_1^2	0.4	−0.035	0.211	0.090	1.000		0.4	−0.023	0.211	0.092	1.000
θ_2^2	0.5	−0.046	0.129	0.065	1.000		0.5	−0.014	0.137	0.020	1.000
ρ	0.9	−0.051	0.116	0.081	1.000		0.0	0.018	0.264	0.186	0.982
Simulation 5											
α_0	0.5	−0.058	0.146	0.149	0.922						
α_1	−0.8	0.054	0.222	0.221	0.942						
β_1	−0.5	0.027	0.202	0.209	0.946						
θ_1^2	0.4	−0.035	0.209	0.092	1.000						
θ_2^2	0.5	−0.028	0.130	0.037	1.000						
ρ (constant)	0.8	−0.031	0.177	0.103	1.000						

Summary results are given in Table 3. From the table the notations D and M_i denote the number of institutions and the number of patients within the ith institution, respectively. The estimated biases for the fixed effect parameters α_0, α_1 and β_1 are quite small. The standard errors of these parameters are well estimated, comparing SEE and SE. The CPs of α_0 and α_1 are close to the nominal level in both the relatively low ($\rho = 0.3$) and high ($\rho = 0.7$) correlation schemes. On the contrary, the CP of β_1 is closer to the nominal level when $\rho = 0.3$, but it falls below the nominal level when $\rho = 0.7$ in the simulations with 1000 patients. However, with an increase in sample size (M=1500), in simulation 6, we see that the bias of β_1 decreases in magnitude and its CP gets closer to the nominal level in the scenario with $\rho = 0.7$. The variance components have acceptable biases, but γ_1^2 is slightly biased towards zero in simulation sets 3 and 4. Nonetheless, as shown in the scenario with 30 institutions and 50 patients within each institution (simulations 5 and 6), the bias of γ_1^2 decreases with increasing sample size. The variance components have less biased estimates for smaller true values, but the extent of bias increases when the true values increase in magnitude. The standard error estimate of σ_1^2 increases when ρ tends to 0.3 relative to 0.7. Comparatively, the estimates of SEE and SE for the variance components have some slight differences. For instance, SEE of σ_0^2 and σ_1^2 are smaller than their corresponding SE estimates. This means that the proposed estimator may underestimate the standard errors of these variance component parameters. However, even in the circumstance where the standard errors of the variance components are accurately estimated, it is not advisable to employ them to test for statistical significance directly. This is because the null hypothesis of these parameters lies on the boundary of the parameter space, therefore, the normal approximation of the null test statistic is no longer appropriate.[32,37] On the other hand, the necessity of the random effects can be checked by displaying their prediction intervals over the institution or patient clusters, by means of the empirical Bayes (EB) method,[32,37] for example. We give a graphical illustration in Figure 3 in the next section.

4 Applications

4.1 Colorectal cancer hospital readmissions study

An application of the proposed frailty mixture cure model to a real data set on colorectal cancer hospital readmissions is demonstrated in this section. The data set is taken from a study consisting of 403 patients who received surgery to remove tumors after being diagnosed with colorectal cancer between January 1996 and December 1998. Follow-up started from the date of surgery up to June 2002. Some patients received

Table 3. Bias, standard error and coverage probability of the REML estimators for the multilevel frailty mixture cure model based on 500 replications of simulated data.

Parameter	True value	Ave. bias	SEE	SE	CP	Parameter	True value	Ave. bias	SEE	SE	CP
$D = 40, M_i = 25$											
Simulation 1											
α_0	0.5	−0.059	0.111	0.110	0.931	Simulation 2	0.5	−0.063	0.110	0.098	0.922
α_1	−0.8	0.034	0.120	0.121	0.937		−0.8	0.019	0.122	0.134	0.952
β_1	−0.5	0.055	0.120	0.120	0.930		−0.5	0.078	0.135	0.145	0.878
θ_1^2	0.4	−0.029	0.101	0.042	1.000		0.4	−0.019	0.099	0.037	1.000
θ_2^2	0.5	−0.007	0.121	0.014	1.000		0.5	0.017	0.129	0.025	1.000
ρ	0.3	0.006	0.119	0.072	0.997		0.7	−0.028	0.144	0.042	1.000
γ_0^2	0.4	−0.082	0.116	0.115	0.927		0.4	−0.089	0.120	0.121	0.928
γ_1^2	0.2	−0.039	0.100	0.081	1.000		0.2	−0.026	0.101	0.087	0.994
σ_0^2	0.5	−0.055	0.064	0.109	0.714		0.5	−0.066	0.077	0.109	0.604
σ_1^2	0.3	−0.046	0.100	0.109	0.934		0.3	−0.049	0.052	0.105	0.752
Simulation 3						Simulation 4					
α_0	0.5	−0.052	0.091	0.092	0.927		0.5	−0.053	0.090	0.094	0.925
α_1	−0.8	0.032	0.132	0.133	0.942		−0.8	−0.025	0.134	0.156	0.949
β_1	−0.5	0.068	0.137	0.138	0.920		−0.5	−0.072	0.149	0.149	0.893
θ_1^2	0.4	−0.031	0.066	0.041	1.000		0.4	−0.028	0.066	0.039	1.000
θ_2^2	0.5	−0.007	0.081	0.012	1.000		0.5	0.018	0.093	0.020	1.000
ρ	0.3	0.007	0.157	0.072	0.998		0.7	−0.020	0.178	0.044	0.994
γ_0^2	0.2	−0.039	0.138	0.070	1.000		0.2	−0.045	0.141	0.079	0.997
γ_1^2	0.4	−0.114	0.099	0.127	0.784		0.4	−0.099	0.100	0.112	0.801
σ_0^2	0.3	−0.029	0.065	0.079	0.878		0.3	−0.025	0.079	0.092	0.831
σ_1^2	0.5	−0.087	0.103	0.159	0.708		0.5	−0.089	0.052	0.131	0.617
$D = 30, M_i = 50$											
Simulation 5						Simulation 6					
α_0	0.5	−0.048	0.092	0.092	0.936		0.5	−0.050	0.094	0.094	0.931
α_1	−0.8	0.023	0.129	0.131	0.953		−0.8	0.023	0.133	0.138	0.957
β_1	−0.5	0.057	0.139	0.139	0.940		−0.5	0.056	0.144	0.141	0.944
θ_1^2	0.4	−0.028	0.064	0.035	1.000		0.4	−0.022	0.067	0.038	1.000
θ_2^2	0.5	−0.008	0.084	0.011	1.000		0.5	−0.019	0.092	0.017	1.000
ρ	0.3	−0.009	0.148	0.057	1.000		0.7	−0.025	0.154	0.034	0.991
γ_0^2	0.2	−0.029	0.125	0.065	1.000		0.2	−0.031	0.136	0.063	0.996
γ_1^2	0.4	−0.091	0.079	0.128	0.802		0.4	−0.087	0.080	0.155	0.811
σ_0^2	0.3	−0.025	0.052	0.081	0.880		0.3	−0.023	0.063	0.108	0.882
σ_1^2	0.5	−0.086	0.082	0.155	0.717		0.5	−0.086	0.048	0.140	0.703

chemotherapy whilst others did not. During the duration of follow-up, some patients experienced several readmissions due to recurrence of their colorectal cancer. In total, 861 readmissions were observed, ranging from 1 to 22, with mean 2.25 and median 1.0. The potential prognostic factors recorded in the study include gender, tumor stage measured by Dukes classification (i.e. A-B, C and D) and comorbidity quantified by Charlson index (i.e. 0, 1-2, $\geq$3). The data are available in the R library frailtypack. Details can be found in Gonzalez et al.[4] We consider times (in days) between successive hospitalisations as gap times related to recurrent events. Figure 1 displays Kaplan–Meier survival curves of the gap times corresponding to the first fives successive readmissions. It is seen that the curves decrease successively with the number of readmissions. The curves for the first and the fourth readmissions jump to zero after reaching a plateau, although those for the second, third and the fifth readmissions level off to non-zero survival probabilities. The curves drop to zero because the largest failure time for the first (i.e. 2175 from patient 79) and fourth (i.e. 1427 from patient 174) readmissions are uncensored. When these observations are removed from the data or taken to be censored, the readmission curves 1 and 4 level off to non-zero survival probabilities (figure not reported). In principle, it is reasonable to consider the possibility of a cure fraction in this data. Moreover, some patients may be highly frail due to unobserved heterogeneity and/or serial dependence, hence a frailty model accommodating cure fraction is more realistic for this data.

On application of the proposed frailty mixture cure model, all covariates are included in both the logistic and the hazard component. Table 4 gives a summary of the results using the EM REML procedure for estimation.

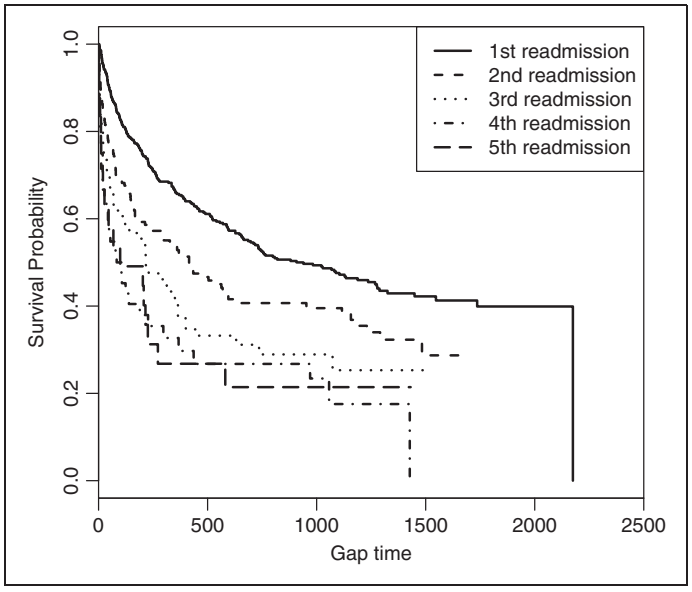

Figure 1. Kaplan–Meier curves of the gap times for the first five readmissions related to colorectal cancer.

Table 4. Parameter and standard error estimates of the frailty cure model for the hospital readmission data.

Logistic component				Hazard component			
Parameter	Estimate	OR	SE	Parameter	Estimate	HR	SE
Intercept	0.309	1.362	0.223				
Chemotherapy	−0.058	0.944	0.225	Chemotherapy	−0.307^	0.736	0.180
Gender(female)	−0.514*	0.598	0.208	Gender(female)	−0.413*	0.662	0.171
Dukes stage				Dukes stage			
C	0.478*	1.613	0.226	C	0.183	1.201	0.201
D	3.838*	46.433	1.021	D	0.221	1.247	0.193
Charlson index				Charlson index			
1–2	0.512	1.669	0.449	1–2	0.274	1.315	0.329
≥3	0.456	1.578	0.283	≥3	0.374*	1.454	0.153
Patient frailty				Patient frailty			
θ_1^2	0.187		0.170	θ_2^2	0.102		0.094
				ρ	0.907		0.086

CI: confidence interval; SE: standard error; Male: reference category for gender; A-B: reference category for Dukes' stage; 0: reference category for Charlson index.
*$p < 0.05$.
^$p < 0.10$.

The results of the parameter estimates, odds ratios (OR), hazard ratios (HR) and their corresponding standard errors (SE) are presented. In the model, the reference group consists of male patients who did not receive chemotherapy, had Dukes stage A-B and Charlson comorbidity index 0. From Table 4 it is seen that chemotherapy has negative coefficient estimates in both components, with a nonsignificant effect in the logistic part and a significant effect observed at 0.10 level in the hazard component. These suggest that chemotherapy minimises the hazard rate of readmission in the uncured patients but it leads to a negligible effect in curing the disease. Female gender has significant effect in both the logistic and the hazard component. In the logistic component, the results (OR: 0.598; 95% CI: 0.398–0.899) clearly depict that female patients are substantially more likely to be cured than males. Regarding the hazard part, the uncured female patients have significantly (HR: 0.662; 95% CI: 0.473–0.925) longer times to colorectal cancer-related hospital readmission compared to the males who are uncured. Dukes stage C has a significant increasing effect (OR: 1.613; 95% CI: 1.036–2.512) in the logistic

component but its effect in the hazard part is not significant. Dukes stage D is identified as the most important significant factor that reduces the probability of being cured (OR: 46.433; 95% CI: 6.277–343.491). However, it showed a nonsignificant effect on the hazard rate of readmission in the uncured patients. The effect of Charlson comorbidity index 1–2 is not significant in both the logistic (OR: 1.669; 95% CI: 0.692–4.023) and the hazard component (HR: 1.315; 95% CI: 0.690–2.506). Higher comorbidity (Charlson index ≥ 3) significantly increases the hazard rate of readmissions (HR: 1.454; 95% CI: 1.077–1.962) in the uncured patients. Nevertheless, its effect on the probability of readmission is not significant (OR: 1.578; 95% CI: 0.906–2.747), although it revealed a positive coefficient estimate. Regarding the random effect terms, θ_1^2 and θ_2^2 are quite small. This suggests that there is little unobserved heterogeneity in the cure probability of the proportion of cured patients and in the time between readmissions among the uncured patients. In contrast, ρ is large, suggesting the presence of within subject serial dependence among the uncured patients. In practical terms, this means that the occurrence of colorectal cancer hospital admission increases the risk of further readmission related to the disease. This underscores the importance of allowing AR(1) correlation parameter in the model.

Yu[14] and Rondeau et al.[28] analyzed these data using cure frailty models with constant random effects. In Yu's work, a random effect is only attached to the hazard part and it is assumed to follow the gamma distribution, unlike our model and that of Rondeau in which the random effects are assumed to be normally distributed. To some extent, the results from our work concerning the magnitudes of the estimated fixed effects in the logistic and the survival parts have moderate differences when compared to the results in these existing studies. For example, the Yu's model and the model by Rondeau et al. did not obtain a significant finding regarding gender difference in the cure probability. But the directions of the fixed effects are consistent with their work, except that higher comorbidity (Charlson index ≥ 3) revealed a decreasing effect on the cure probability within the framework of our model, but it is vice versa in Yu's model. In Rondeau et al.'s work, the Charlson index was only used in the survival part.

4.2 Pulmonary exacerbations in the study of rhDNase

We consider the rhDNase data for illustration of the multilevel frailty mixture cure model presented in section 2.2. The data consist of 647 cystic fibrosis patients who were enrolled in a multi-institutional clinical trial to receive rhDNase (i.e. a purified recombinant form of the human enzyme DNase I) or placebo. The patients were susceptible to an accumulation of mucus in the lungs, which leads to pulmonary exacerbations and progressive deterioration of lung function. The aim of the trial was to evaluate the efficiency of rhDNase relative to placebo in preventing recurrence of pulmonary exacerbations in patients with cystic fibrosis. During the study duration, treatment was administered daily to patients in 51 institutions and followed for approximately 170 days. The number of patients within institutions ranged from 4 to 24 with mean 12.7 and median 12.0. A baseline measurement of forced expiratory volume (denoted as baseline FEV_1) was taken for each patient at the start of the study; this is a measure of lung function and is expected to be related to the frequency of exacerbations. The occurrences of exacerbations over the study period were recorded for each patient. At the end of the study, the number of recurrent exacerbations recorded ranged from 1 to 5 with mean 1.5 and median 1.0. The data are publicly available in R through the survival library and details can be found in Therneau and Hamilton[6] and Cook and Lawless.[7]

In Figure 2 we show Kaplan–Meier survival curves of the gap times corresponding to the first three recurrent exacerbations of pulmonary disorders. We exclude the fourth and the fifth recurrences because only few events are available at these levels. As indicated in the tails of the Kaplan–Meier plots, all the curves level off above 0.5. This instigates the question as to whether rhDNase has allowed more than 50% of the patients to be insusceptible to recurrence of pulmonary exacerbations. Due to the hierarchical structure of the data, the multilevel frailty cure model appears to be practical for this data. To apply this model, both treatment (0 = placebo, 1 = rhDNase) and baseline FEV_1 are considered as covariates in the logistic and hazard components. The results are summarised in Table 5. Compared to the results in previous work regarding the application of hazard-based models without cure fraction, including the Andersen-Gill model ($\beta_1 = -0.303$),[6] the conditional gap time frailty model ($\beta_1 = -0.373$),[8] and the multilevel frailty model ($\beta_1 = -0.473$),[32] it is evident that incorporation of cure fraction has shrunk the effect of rhDNase in the hazard part ($\beta_1 = -0.131$) and markedly shifted its effect to the logistic part, estimated as -0.510 (OR: 0.600; 95% CI: 0.416-0.866) which is significant at 5% level, while it is insignificant in the hazard component. Although rhDNase is not significant in the hazard part, the negative sign in the coefficient indicates that it has demonstrated an effect in reducing the hazard rate of recurrent pulmonary exacerbations in the uncured patients. Likewise, baseline FEV_1 is significant in the logistic component (OR: 0.970; 95% CI: 0.963–0.978) but

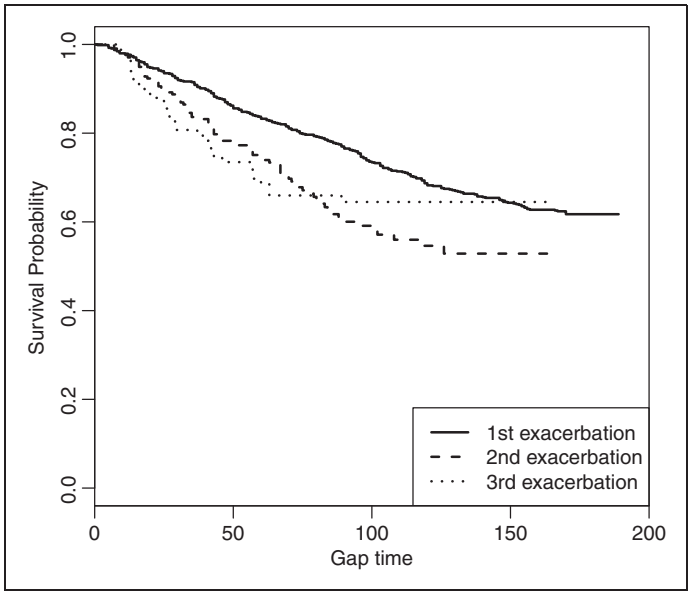

Figure 2. Kaplan–Meier curves of the gap times for the first three recurrences of pulmonary exacerbations.

Table 5. Parameter and standard error estimates of the multilevel frailty cure model for the rhDNase data.

Logistic component				Hazard component			
Parameter	Estimate	OR	SE	Parameter	Estimate	HR	SE
Intercept	1.750*	5.755	0.281				
rhDNase	−0.510*	0.600	0.187	rhDNase	−0.131	0.877	0.164
Baseline FEV_1	−0.030*	0.970	0.004	Baseline FEV_1	−0.004	0.996	0.004
Institution				Insitution			
γ_0^2	0.378		0.175	σ_0^2	0.254		0.124
γ_1^2	0.034		0.246	σ_1^2	0.039		0.191
Patient				Patient			
θ_1^2	0.996		0.307	θ_2^2	0.137		0.287
				ρ	0.897		0.225

*$p < 0.05$.

insignificant in the hazard component (HR: 0.996; 95% CI: 0.988–1.00). These results suggest that patients with high measurements of baseline FEV_1 are more likely to be cured. In addition, the allowance of cure fraction has switched the effect baseline FEV_1 from the hazard part to the logistic part, when compared with previous work.[32]

Considering the variance components, it is observed that the institutional effects in the proportion of cured patients ($\hat{\gamma}_0^2 = 0.378$) and that on the hazard rate of uncured patients ($\hat{\sigma}_0^2 = 0.254$) are relatively large. Nevertheless, there is little treatment-by-institution interaction in both the logistic and the hazard part. At subject-level, heterogeneity across patients is small in the hazard part, compared to the heterogeneity among the proportion of cured patients ($\hat{\theta}_1^2 = 0.996$). Serial correlation is substantially large ($\hat{\rho} = 0.897$) in the hazard part.

To perform further analysis to highlight the extent of institutional variation in the baseline risk and in treatment effect among the proportion of cured and uncured patients, inference on prediction interval for the random effects is carried out (Figure 3), using the EB[32,37] prediction variance for 95% confidence interval estimation, with point prediction values obtained from the Newton-Raphson procedure at convergence of the EM REML estimation. The EB prediction variances of the random effects in the logistic and the hazard parts are obtained from the information matrix of the underlying log-likelihood of these models. Results are presented for the random effects

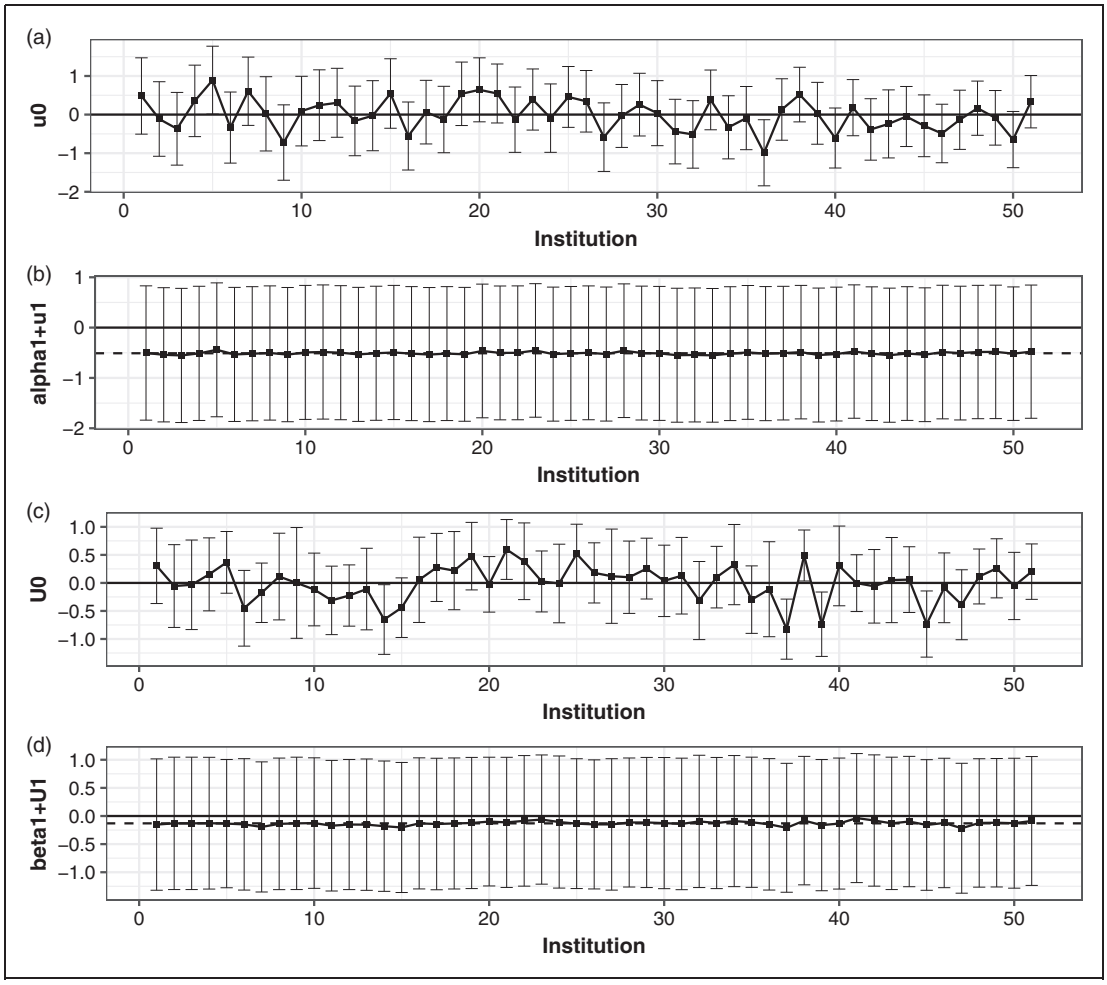

Figure 3. Institution-specific random effects and their 95% empirical Bayes prediction interval for (a) baseline risk u_{i0} and (b) treatment-by-institution interaction $\alpha_1 + u_{i1}$ in the proportion of cured patients and (c) baseline risk U_{i0} and (d) treatment-by-institution interaction $\beta_1 + U_{i1}$ in the proportion of uncured patients, in the rhDNase data under the multilevel frailty cure model. Horizontal line of 0 indicates zero baseline risk or zero treatment hazard rate, > 0 is high baseline risk or hazardous treatment effect and < 0 is low baseline risk or efficacious treatment effect. In (b) and (d) the dashed horizontal line indicates the estimated values α_1 and β_1, respectively. Institutions are sorted in increasing order of number of patients.

that characterise institutional baseline risks, u_{i0} and U_{i0} and the log-treatment hazard ratios $\alpha_1 + u_{i1}$ and $\beta_1 + U_{i1}$ over 51 institutions, with the institutions arranged in ascending order of their sizes; that is, number of patients enrolled. From Figure 3(a) and (c), we see quite substantial variation in institutional baseline risk but very little variation in treatment effects across institutions (Figure 3(b) and (d)), in both the proportion of cured and the uncured patients. In particular, the CI for Institution 36 in Figure 3(a) and Institutions 21, 37, 39 and 45 in Figure 3(c) do not include zero. Patients from Institution 36 would have a lower chance of developing recurrence of pulmonary exacerbation (i.e. an increased cure rate) and those from Institutions 37, 39 and 45 would have a reduced hazard rate for recurrence, whilst patients from Institution 21 have an increased hazard rate. The departure of their CI from zero can lead to significant heterogeneity in the baseline risk across institutions, in the proportion of cured and the uncured patients. It is observed that Institution 5 gives the highest baseline risk in the cure probability component, but Institution 21, on the other hand, gives the highest baseline risk in the hazard part. Again, in Figure 3(a) and (c), the interval lengths tend to vary across the institutions, while in the case of Figure 3(b) and (d) the intervals are almost of the same length due to small heterogeneity observed in treatment effect. Comparatively, the interval lengths are wider for $\alpha_1 + u_{i1}$ and $\beta_1 + U_{i1}$ than u_{i0} and U_{i0}. This is as a result of additional variance accounted by the fixed effect parameters. The predicted point values of $\alpha_1 + u_{i1}$ and $\beta_1 + U_{i1}$ depict that treatment has been effective in all the institutions, although greater efficiency is achieved in the

proportion of cured patients than in the uncured patients. This prediction inference can be presented in terms of the patient level random effects, in the same manner as described.

5 Discussion and conclusion

We have developed an extended modelling framework by allowing the possibility of a cure fraction in a PH frailty model for recurrent event data. Through the GLMM methodology, our models are developed semiparametrically with maximisation of the underlying log-likelihood carried out by an EM-type algorithm. Contrary to existing work, our proposed models introduce a random AR(1) patient effect, random covariate and a more general multilevel framework with different random effect structures in mixture cure models. An interesting feature of the models is that they allow patients to have a chance of being cured after each recurrence. The importance of these random effect cure models over the marginal cure models[42] is that they yield insight into the correlation structure underlying the data and they allow prediction inference concerning institution-specific and patient-specific random effects, which leads to a better understanding and interpretation of the variability in the data. Institution effects are sometimes modelled as fixed effects. However, the use of random effects is advantageous, in that, the fixed effect approach is subject to loss of efficiency and unstable regression coefficients when the underlying data consist of relatively many institutions and relatively few patients in each institution.[43] Another importance of our model is the inclusion of random covariate for treatment effect, because the standard approach which merely uses a summary measure (e.g. hazard ratio) based on fixed effect may not be sufficient to describe the trial results when treatment-by-institution interaction is large. Essentially, when such a finding is observed, it is often useful to explore reasons why such variation is seen in treatment effect. On the other hand, when the treatment effect is found to be homogeneous across institutions, then the conclusions concerning treatment can be generalised to the broader patient population.

Results of the simulation studies demonstrate a good performance of the models under different numerical scenarios. However, obtaining a good performance is not without assuring larger sample size, sufficient follow-up and the levelling off of the tail of the marginal survival curve of the successive recurrences with a substantial magnitude of long-term censored times. Application to the colorectal cancer hospital readmission data and the rhDNase data illustrate the feasibility of the proposed models in the practical setting. An interesting issue emerging from the usage of the readmission data is that the largest gap time (i.e. 2175) is not censored. In this circumstance, the estimation of the tail of $S_{u0}(t)$ is based on the Breslow method (9) instead of the ETAIL completion method (10). The Breslow method often fails to approximate the tail of $S_{u0}(t)$ to zero,[38] which usually necessitates the use of some tail completion methods to obtain valid estimates of regression coefficients. However, for this special case we observed that the Breslow method gradually decreases the tail of $S_{u0}(t)$ to zero, therefore avoiding a potential identifiability problem.

The mixture models proposed herein have possible extensions in a number of ways. One approach is to extend the multilevel structure to more than three levels and to investigate the correlation structures of the random effect terms. For instance, correlated random effects may be used to specify the patient-specific frailty terms in the hazard and the logistic part. Similarly, in the multilevel model, such correlated random effect approach may be used to relax the independent assumption considered among the institution level random components. In addition, it would be valuable to consider some measure of model fit for the proposed modelling methodology. Extension to the two-component mixture of survival models[44–47] would be of interest in situations where the observed recurrent events are characterised by an acute phase followed by a stable phase after the index episode. An example arises in the study of urinary tract infections (UTI) in elderly women, where the duration between successive infection episodes can be described by two overlapping phases in time.[48] The AR(1) random effect structure could be used in this setting to allow for time-dependent frailties in both the acute and stable phases of recurrence. Alternative approach may focus on the use of bivariate random effects to induce correlation between stable and acute recurrences experienced by the same individual. Again, the proposed frailty cure model can be extended to incorporate a competing risks scenario, where recurrent events and a terminal event (e.g. death) are considered as two competing events. For example, in bone marrow transplantation studies, the endpoint of interest is time to leukemia relapse, but uncured patients can probably die during the follow-up period. In such a scenario, time to recurrent relapses and time to death observed on the same individual overlaps. However, in general competing risks scenarios that assume independent and mutually exclusive competing events, and the existence of overlapping times to different competing types makes it difficult to accommodate the cause-specific hazards and their corresponding log-likelihoods in the estimation inference of a frailty cure model.

Acknowledgements

We thank the editor and the reviewers for their helpful comments. Again, we would like to sincerely thank Professor Rondeau for providing the readmission data for this study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: RT gratefully acknowledges the financial support from Griffith University International Postgraduate Research Scholarship and Griffith University Postgraduate Research Scholarship (HTH). SKN and GJM acknowledge the support of a Discovery Grant from the Australian Research Council.

ORCID iD

Shu Kay Ng https://orcid.org/0000-0002-6865-9384

References

1. Kelly PJ and Lim LLY. Survival analysis for recurrent event data: an application to childhood infectious diseases. *Stat Med* 2000; **19**: 13–33.
2. Duchateau L, Janssen P, Kezic I, et al. Evolution of recurrent asthma event rate over time in frailty models. *J R Stat Soc Ser C Appl Stat* 2003; **52**: 355–363.
3. Byar DP. *The veterans administration study of chemoprophylaxis for recurrent stage I bladder tumors: comparisons of placebo, pyridoxine and topical thiotepa*. In: *Pavone-Maculuso M, Smith PH, Edsmyr F (eds). Bladder tumors and other topics in urological oncology*. Plenum: New York, 1980, pp.363-370.
4. Gonzalez JR, Fernandez E, Moreno V, et al. Sex differences in hospital readmission among colorectal cancer patients. *J Epidemiol Commun Health* 2005; **59**: 506–511.
5. McGilchrist CA and Aisbett CW. Regression with frailty in survival analysis. *Biometrics* 1991; **47**: 461–466.
6. Therneau TM and Hamilton SA. rhDNase as an example of recurrent event analysis. *Stat Med* 1997; **16**: 2029–2047.
7. Cook RJ and Lawless JF. *The statistical analysis of recurrent events*. New York, NY: Springer Science & Business Media, 2007.
8. Box-Steffensmeier JM and De Boef S. Repeated events survival models: the conditional frailty model. *Stat Med* 2006; **25**: 3518–3533.
9. Wei LJ and Glidden DV. An overview of statistical methods for multiple failure time data in clinical trials. *Stat Med* 1997; **16**: 833–839.
10. Metcalfe C and Thompson SG. Wei, Lin and Weissfeld's marginal analysis of multivariate failure time data: should it be applied to a recurrent events outcome? *Stat Meth Med Res* 2007; **16**: 103–122.
11. McGilchrist CA. REML estimation for survival models with frailty. *Biometrics* 1993; **49**: 221–225.
12. Yau KKW and McGilchrist CA. ML and REML estimation in survival analysis with time dependent correlated frailty. *Stat Med* 1998; **17**: 1201–1213.
13. Othus M, Barlogie B, LeBlanc ML, et al. Cure models as a useful statistical tool for analyzing survival. *Clin Cancer Res* 2012; **18**: 3731–3736.
14. Yu B. A frailty mixture cure model with application to hospital readmission data. *Biom J* 2008; **50**: 386–394.
15. Denaro N, Merlano MC and Russi EG. Follow-up in head and neck cancer: do more does it mean do better? a systematic review and our proposal based on our experience. *Clin Exp Otorhinolaryngol* 2016; **9**: 287–297.
16. Farewell VT. The use of mixture models for the analysis of survival data with long-term survivors. *Biometrics* 1982; **38**: 1041–1046.
17. Yau KKW and Ng ASK. Long-term survivor mixture model with random effects: application to a multi-centre clinical trial of carcinoma. *Stat Med* 2001; **20**: 1591–1607.
18. Kuk AYC and Chen CH. A mixture model combining logistic regression with proportional hazards regression. *Biometrika* 1992; **79**: 531–541.
19. Peng Y and Dear KBG. A nonparametric mixture model for cure rate estimation. *Biometrics* 2000; **56**: 237–243.
20. Sy JP and Taylor JMG. Estimation of Cox proportional hazards cure model. *Biometrics* 2000; **56**: 227–236.

21. Lai X and Yau KKW. Long-term survivor model with bivariate random effects: applications to bone marrow transplant and carcinoma study data. *Stat Med* 2008; **27**: 5692–5708.
22. Wu Y, Lin Y, Lu SE, et al. Extension of a Cox proportional hazards cure model when cure information is partially known. *Biostatistics* 2014; **15**: 540–554.
23. Taylor JMG. Semi-parametric estimation in failure time mixture models. *Biometrics* 1995; **51**: 899–907.
24. Li CS and Taylor JMG. A semi-parametric accelerated failure time cure model. *Stat Med* 2002; **21**: 3235–3247.
25. Xu L and Zhang J. An alternative estimation method for the semiparametric accelerated failure time mixture cure model. *Commun Stat Simul Comput* 2009; **38**: 1980–1990.
26. Lai X and Yau KKW. Extending the long-term survivor mixture model with random effects for clustered survival data. *Comput Stat Data Anal* 2010; **54**: 2103–2112.
27. Peng Y and Taylor JMG. Mixture cure model with random effects for the analysis of a multi-center tonsil cancer study. *Stat Med* 2011; **30**: 211–223.
28. Rondeau V, Schaffner E, Corbière F, et al. Cure frailty models for survival data: application to recurrences for breast cancer and to hospital readmissions for colorectal cancer. *Stat Meth Med Res* 2011; **22**: 243–260.
29. Fong DYT, Lam KF, Lawless JF, et al. Dynamic random effects models for times between repeated events. *Lifetime Data Anal* 2001; **7**: 345–362.
30. McGilchrist CA. Estimation in generalized mixed models. *J R Stat Soc Series B Stat Methodol* 1994; **56**: 61–69.
31. McGilchrist CA and Yau KKW. The derivation of BLUP, ML, REML estimation methods for generalised linear mixed models. *Commun Stat Theory Meth* 1995; **24**: 2963–2980.
32. Tawiah R, Yau KKW, McLachlan GJ, et al. Multilevel model with random effects for clustered survival data with multiple failure outcomes. *Stat Med* 2019; **38**: 1036–1055.
33. Lai X and Yau KKW. Multilevel mixture cure models with random effects. *Biom J* 2009; **51**: 456–466.
34. Xu Y, Cheung YB, Lam KF, et al. Estimation of summary protective efficacy using a frailty mixture model for recurrent event time data. *Stat Med* 2012; **31**: 4023–4039.
35. Ng SK. Recent developments in expectation-maximization methods for analyzing complex data. *Wiley Interdiscip Rev Comput Stat* 2013; **5**: 415–431.
36. Abrahantes JC and Burzykowski T. A version of the EM algorithm for proportional hazards model with random effects. *Biom J* 2005; **47**: 847–862.
37. Vaida F and Xu R. Proportional hazards model with random effects. *Stat Med* 2000; **19**: 3309–3324.
38. Peng Y. Estimating baseline distribution in proportional hazards cure models. *Comput Stat Data Anal* 2003; **42**: 187–201.
39. Wang K, Lee AH, Hamilton G, et al. Multilevel logistic regression modelling with correlated random effects: application to the smoking cessation for youth study. *Stat Med* 2006; **25**: 3864–3876.
40. Louis TA. Finding the observed information matrix when using the EM algorithm. *J R Stat Soc Series B Stat Methodol* 1982; **44**: 226–233.
41. Kwok OM, West SG and Green SB. The impact of misspecifying the within-subject covariance structure in multiwave longitudinal multilevel models: a Monte Carlo study. *Multivariate Behav Res* 2007; **42**: 557–592.
42. Peng Y, Taylor JMG and Yu B. A marginal regression model for multivariate failure time data with a surviving fraction. *Lifetime Data Anal* 2007; **13**: 351–369.
43. Yamaguchi T and Ohashi Y. Investigating centre effects in a multi-center clinical trial of superficial bladder cancer. *Stat Med* 1999; **18**: 1961–1971.
44. Ng SK, McLachlan GJ, Yau KKW, et al. Modelling the distribution of ischaemic stroke-specific survival time using an EM-based mixture approach with random effect adjustment. *Stat Med* 2004; **23**: 2729–2744.
45. Ng SK and McLachlan GJ. An EM-based semi-parametric mixture model approach to the regression analysis of competing-risks data. *Stat Med* 2003; **22**: 1097–1111.
46. McLachlan GJ and McGiffin DC. On the role of finite mixture models in survival analysis. *Stat Methods Med Res* 1994; **3**: 211–226.
47. Ng SK, Xiang L and Yau KKW. *Mixture Modelling for Medical and Health Sciences*. Boca Raton, FL: Chapman & Hall/CRC, 2019.
48. Lee AH, Zhao Y, Yau KKW, et al. A computer graphical user interface for survival mixture modelling of recurrent infections. *Comput Biol Med* 2009; **39**: 301–307.