Published in final edited form as:

Stat Med. 2013 July 10; 32(15): 2629–2642. doi:10.1002/sim.5717.

Bayesian analysis of recurrent event with dependent termination: an application to a heart transplant study

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Abstract

For a heart transplant patient, the risk of graft rejection and risk of death are likely to be associated. Two fully specified Bayesian models for recurrent events with dependent termination are applied to investigate the potential relationships between these two types of risk as well as association with risk factors. We particularly focus on the choice of priors, selection of the appropriate prediction model, and prediction methods for these two types of risk for an individual patient. Our prediction tools can be easily implemented and helpful to physicians for setting heart transplant patients' biopsy schedule.

Keywords

heart transplant; recurrent events; dependent termination; Bayesian; prior selection

1. Introduction

Cardiac transplant recipients may experience recurrent episodes of graft rejection after transplantation. These rejections are usually nonfatal and are treated successfully by drug therapy. However, a high frequency of these rejections is considered an indicator of underlying morbidity and poor quality of life. Endomyocardial biopsy (EMB) is an important tool in the detection and management of rejection episodes following transplant [1], but unnecessary EMB may cause over treatment and increased risk of infection and malignancy [2]. Moreover, biopsies are accompanied by procedural risks, patient discomfort, and increased expense [2]. Frequent EMB beyond the first year after transplant and long-term surveillance EMB are controversial issues in the heart transplant literature. By modeling the intensity of recurrent rejection and evaluating the risk of death given a patient's history of past graft rejection as well as factors such as gender and race, we can identify

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patients at high risk of rejection and death. Our study can help clinicians to tailor patients' optimal biopsy schedule.

Various statistical models have been developed to analyze recurrent event data as seen in our heart transplant study. Let $N(t)$ denote the number of rejections experienced by a patient by time t , $\bar{N}(t)$ denote the history of the rejection process $\bar{N}(t) = \{N(s) : s \leq t\}$, $\bar{Z}(t)$ denote the history of the fixed and/or time-dependent external covariate process $\bar{Z}(t) = \{Z(s) : s \leq t\}$, and T be termination time due to death. Some marginal models [3, 4] model the recurrent rejection process $\{N(t)\}$ conditional on part of the process history $\bar{H}_p(t-) \subseteq \{\bar{N}(t-), T > t-; \bar{Z}(t)\}$, such as a model for $E[dN_{(k)}(t) | \bar{N}_{(k)}(t-); \bar{Z}(t)]$ where k is the index of k th rejection [5], a model for estimating $E[dN_{(k)}(t) | \bar{N}_{(k)}(t-), N(t-) = k-1; \bar{Z}(t)]$ [6], and a model for estimating $E[dN(t) | T > t, \bar{Z}(t)]$ [7]. These models are defined via conditioning on different parts of the history, so the interpretation and the estimates of the regression parameter may vary considerably. In the mixed Poisson process model [3, 8], defined on the entire history, the probability of a new rejection in $[t, t + dt)$ is given by

$P[dN(t)=1|w, \bar{N}(t-), T > t; \bar{Z}(t)] \simeq w e^{\beta_1^T Z(t)} d\mu_0(t)$, where w is a patient-specific random effect, β_1 is a vector of regression parameters, and $\mu_0(t)$ is the baseline cumulative intensity. All these models are based on the assumption of noninformative censoring where the censoring event such as loss to follow-up and end of study is independent of the recurrent event process. However, in some cases where the recurrent event process is terminated by death, which itself is also an important outcome, a noninformative termination assumption is not appropriate.

Miloslavsky *et al.* [9] have shown that regression parameter estimates in a recurrent event model are biased when dependent termination is ignored. They proposed a model based on the coarsening at random (CAR) assumption [10–12] to improve the naïve estimates. However, their methods were not based on either likelihood or Bayes approaches. As a consequence, their methods do not allow dynamic prediction of future patients and events. In our heart transplant context, continuing with T as the termination time due to death, the CAR assumption implies that the risk of termination has the following property:

$$h_T(t|\bar{H}(\tau))h_T(t|\bar{H}(t-)),$$

where $\bar{H}(t-) = \{\bar{N}(t-), \bar{Z}(t-)\}$ and $[0, \tau)$ is the study interval or period of interest. In the model of Miloslavsky *et al.*, the termination process itself is not of interest, and there is no consideration of further right censoring of the termination event. The generalized mixed Poisson process (GMPP) model proposed by Sinha and Maiti [13] and Liu *et al.* [14] is a fully specified model defined on the complete history of the recurrent event process describing the joint distribution of the recurrent events and termination event processes as they sequentially unfold. This model does not satisfy the CAR assumption. The work of Sinha *et al.* [15] provides an overview of the fully specified models for recurrent events with dependent termination.

The goal of this manuscript is to implement and compare the GMPP and CAR models for Bayesian analysis of our heart transplant data and develop effective and logical tools for dynamic prediction of the risk of a new rejection and death for a heart transplant patient. To demonstrate the implementation of Bayesian analysis for recurrent events with termination, we include a careful development of priors, model comparison tools, and WinBUGS code for future users. For a comprehensible comparison between two models, we adopt a particular formulation of CAR model (within many available variations of CAR models) where the regression parameter has an interpretation similar to the corresponding parameter in the GMPP model. Unlike existing literature, we also for the first time demonstrate full Bayesian analysis using these two competing models followed by prediction of future patient events. For our transplant study, in particular, and for many other recurrent events in medicine, a major goal for aiding better clinical monitoring of a patient is a statistically sound tool for dynamic prediction of death and recurrence. The rest of this paper is organized as follows. In Section 2, we introduce the data set and notations. In Section 3, we briefly discuss the GMPP and CAR models. In Section 4, we discuss Bayesian methods including likelihood, priors, posteriors, and model comparison. We particularly focus on the choice of priors for some important model parameters. In Section 5, we present prediction methods. Concluding discussion is in Section 6.

2. The heart transplant data

Our heart transplant data contain 267 patients from the Medical University of South Carolina who received heart transplant between January 1992 and May 2007. In this analysis, we evaluate the effects of four important fixed covariates that are considered to be relevant to both rejections and death: gender ($Z_1 = 0$ male, $= 1$ female), race ($Z_2 = 0$ Caucasian, $= 1$ African American), age at transplant (Z_3), and body mass index (BMI) at transplant (Z_4). The median follow-up time is 5.66 years. The numbers of recurrent rejections in these patients over their follow-up times vary between 0 and 7. The terminating event is either death or acute rejection, which is soon followed by death. The termination (called ‘death’ for brevity) was subject to noninformative censoring such as dropout. About 30% of these patients died during the follow-up time. Table I provides the patients’ baseline characteristics.

We denote $T_{i1} < \dots < T_{im_i} < Y_i = \min(T_i, C_i)$ as m_i unequally spaced rejection times for patient i , $i = 1, \dots, n$, where T_i is the death time, subject to noninformative censoring at C_i . The observed data for patient i are therefore $\mathbf{T}_{io} = T_{i1}, \dots, T_{im_i}$; $\mathbf{Z}_i = (Z_{i1}, Z_{i2}, Z_{i3}, Z_{i4})$; $\mathbf{Y}_i, \delta_i$, where δ_i is the indicator for $T_i < C_i$. Although Stehlik *et al.* [2] discussed covariate effects on the risk of rejections, the complex relationships among covariates, rejection intensity, and risk of death have not been explored in depth.

3. Models

In this section, we describe the specific GMPP and CAR models that will be used for modeling our heart transplant data. We further develop these models within the Bayesian paradigm in Section 4. The GMPP [13–15] and CAR [9] model frameworks have distinct

key-modeling assumptions and properties. Interested readers can find more detailed discussion about theoretical consequences of these models in Sinha *et al.* [15].

3.1. GMPP model

The risk of death and risk of rejections for heart transplant patients are thought to be related through an underlying unobserved effect, for example, the patient's unobserved health state, which is represented in the GMPP model as a frailty, that is, as a latent patient-specific random effect. The GMPP model assumes that the risk of death at time t depends on the history of recurrent rejections $\bar{N}_i(t)$ only through the frailty. The GMPP model expresses the conditional intensity of rejection at time t as

$$\lambda_{N_i}(t|\bar{N}_i(t-), T_i \geq t, w_i; \mathbf{Z}_i) = w_i e^{\beta_1^T \mathbf{Z}_i} \lambda_0(t) \quad (1)$$

and the conditional risk of death as

$$h_{T_i}(t|\bar{N}_i(t-), w_i; \mathbf{Z}_i) = w_i^\alpha e^{\beta_2^T \mathbf{Z}_i} h_0(t), \quad (2)$$

where w_i is the frailty, $\beta_1^T = (\beta_{11}, \beta_{12}, \beta_{13}, \beta_{14})$ and $\beta_2^T = (\beta_{21}, \beta_{22}, \beta_{23}, \beta_{24})$ are vectors of regression parameters, and $\lambda_0(t)$ and $h_0(t)$ are unspecified baseline intensity and hazard rate functions. The GMPP model implies that both the risk of death and the risk of rejection depend on the rejection history only through the current count of rejections [15]. The parameter α in (2) quantifies the nature of dependence between the rejection history and risk of death, when $\alpha = 0$, $h_{T_i}(t|\bar{N}_i(t-), w_i; \mathbf{Z}_i)$ is free of $\bar{N}_i(t)$, representing independent termination, when $\alpha > 0$, $h_{T_i}(t|\bar{N}_i(t-), w_i; \mathbf{Z}_i)$ is an increasing function of $N_i(t-)$, and when $\alpha < 0$, $h_{T_i}(t|\bar{N}_i(t-), w_i; \mathbf{Z}_i)$ is a decreasing function of $N_i(t-)$ [15]. For mathematical convenience, we assume that the frailty $w_i \sim \text{i.i.d. Gamma}(\eta, \eta)$ with unit mean and variance η^{-1} .

3.2. CAR model

As described in Section 1, the CAR assumption [10–12] requires that, given the entire history of covariates and recurrent rejection times in $[0, \tau]$, the risk of death at time t depends only on the observed history in $[0, \tau]$. We emphasize that the GMPP model does not satisfy the CAR assumption when $\alpha \neq 0$ because the dependence of both recurrent process and death on the frailty induces dependence of the risk of death on the recurrent process even beyond the observed history at the current time. CAR models can take different functional forms for the intensities. To facilitate a similar interpretation of covariate effects with the proportional intensity of the GMPP model, we consider the following CAR model:

$$\lambda_{N_i}(t|\bar{N}_i(t-), T_i \geq t; \mathbf{Z}_i) = \lambda_0(t)(1 + \eta^{-1} N_i(t-)) e^{\beta_1^T \mathbf{Z}_i}, \quad (3)$$

and

$$h_{T_i}(t|\overline{N}_i(t-); \mathbf{Z}_i) = h_0(t)(1 + \eta^{-1} N_i(t-))^\alpha e^{\beta_2^T \mathbf{Z}_i}, \quad (4)$$

where η^{-1} reflects the heterogeneity of this patient population and can take values greater than zero.

4. Bayesian inference

4.1. Likelihood and posterior

Let $\mathbf{T}_{io} = \{t_{i1} < \dots < t_{im_i}\}$ be the ordered rejection times for patient i , $i = 1, \dots, n$, where $m_i = N_i(y_i)$, and let $D_1 = \{\mathbf{T}_{io} : i = 1, \dots, n\}$ be the collection of rejection times for the n patients. Also, let $D_2 = \{y_i, \delta_i : i = 1, \dots, n\}$ be the collection of death times. Under GMPP model (1) and (2), the likelihood contribution from the sampling distribution of the data containing rejection times, D_1 , is

$$L_1(\beta_1^T, \lambda_0, \mathbf{w} | D_1, \mathbf{Z}) \propto \prod_{i=1}^n \left[\left(w_i e^{\beta_1^T \mathbf{Z}_i} \right)^{N_i(y_i)} \exp\{-\Lambda_i(y_i)\} \prod_{t \in \mathbf{T}_{io}} \lambda_0(t) \right],$$

where $\Lambda_i(t) = e^{\beta_1^T \mathbf{Z}_i} w_i \int_0^t \lambda_0(u) du$. Similarly, the likelihood contribution from the sampling distribution of the data containing death times, D_2 , is

$$L_2(\beta_2^T, h_0, \alpha, \mathbf{w} | D_2, \mathbf{Z}) \propto \prod_{i=1}^n \left[\left\{ w_i^\alpha e^{\beta_2^T \mathbf{Z}_i} h_0(y_i) \right\}^{\delta_i} \exp\{-H_i(y_i)\} \right],$$

where $H_i(t) = w_i^\alpha e^{\beta_2^T \mathbf{Z}_i} \int_0^t h_0(u) du$. Thus, the observed data likelihood is

$$L_o(\theta, \mathbf{w} | D_1, D_2, \mathbf{Z}) \propto \int L_1(\beta_1^T, \lambda_0, \mathbf{w} | D_1, \mathbf{Z}) \times L_2(\beta_2^T, h_0, \alpha, \mathbf{w} | D_2, \mathbf{Z}) \times g(\mathbf{w} | \eta) \prod_{i=1}^n dw_i,$$

where θ is the vector of all model parameters, that is, $\theta = (\beta_1^T, \beta_2^T, h_0, \lambda_0, \alpha)$, and

$g(\mathbf{w} | \eta) = \prod_i [\eta^\eta w_i^{\eta-1} e^{-w_i \eta} / \Gamma(\eta)]$. As we will discuss in Section 4.2, the baseline intensity $\lambda_0(t)$ and hazard $h_0(t)$ may be parametric, such as derived from the Weibull and exponential distributions, or more flexible forms may be used, such as a piecewise constant hazard [16] or a gamma process on the cumulative baseline hazards [16]. Adopting a common practice, we further assume that priors for all parameters are independent, so the joint prior $\pi(\theta)$ is the product of the marginal prior distributions for each parameter. The posterior distribution under the GMPP model is then given as

$$p(\theta, \mathbf{w} | D_1, D_2, \mathbf{Z}) \propto L_1(\beta_1^T, \lambda_0, \mathbf{w} | D_1, \mathbf{Z}) \times L_2(\beta_2^T, h_0, \alpha, \mathbf{w} | D_2, \mathbf{Z}) \times g(\mathbf{w} | \eta) \times \pi(\theta).$$

The posterior distributions for the CAR model are derived similarly; these are given in Appendix A.

4.2. Priors for model parameters

4.2.1. Priors for covariates: race, gender, age, and BMI—Selection of prior distributions is very important for Bayesian inference. Priors on β_1^T and β_2^T reflect the prior opinion/information about the effects of race, gender, age, and BMI on the risk of rejection and the risk of death. Because little is known about these covariate effects, we adopt normal priors with mean 0 and relatively large variances, which represent our skeptical prior belief that the covariates have small effects on the intensity.

4.2.2. Priors for α —For the important model parameter α , we investigate both normal and double exponential priors with mean 0 and large variances, as we have no prior information; however, a double exponential prior shrinks the prior opinion and in turn posterior more towards zero than a normal prior. This implies that the double exponential has a more skeptical prior view about the dependence between rejection and death.

4.2.3. Priors for η^{-1} —In both the GMPP model given by (1) and (2) and the CAR model given by (3) and (4), η^{-1} reflects the heterogeneity of this patient population. We consider three types of priors for η^{-1} : noninformative (uniform), weakly informative half-Cauchy [17, 18], and informative exponential priors. To determine reasonable values for hyperparameters, we use simulation to examine the distributions of variables immediately dependent upon η^{-1} , that is, the frailties w and w^α in the GMPP model and $1 + \eta^{-1}N_f(t-)$ and $(1 + \eta^{-1}N_f(t-))^\alpha$ in the CAR model. The uniform (0, 5) and half-Cauchy priors with scale parameter 5 generate reasonable frailties: 95% of the frailties are within (0, 4). However, these two priors on η^{-1} and together with a normal or double exponential prior on α can produce unrealistically large w^α . The simulation study of both w and w^α under the exponential prior with rate 2 for η^{-1} suggests that 95% of the prior probability for both variables is within realistic ranges. Similarly, the exponential prior permits more realistic ranges for $1 + \eta^{-1}N_f(t-)$ and $(1 + \eta^{-1}N_f(t-))^\alpha$ than the uniform and half-Cauchy priors.

4.2.4. Priors for $\lambda_0(\cdot)$ and $h_0(\cdot)$ —We consider both parametric and semiparametric/nonparametric forms for the recurrent rejection baseline intensity $\lambda_0(t)$ and hazard of death $h_0(t)$. Specifically, we try Weibull and piecewise constant for $\lambda_0(t)$ and also the Gamma process for the cumulative baseline intensity $\Lambda_0(t)$. We use the Weibull and constant hazard for $h_0(t)$. Gamma priors (with known mean and variance) are used for the parameters in the Weibull $\lambda_0(t)$ and constant $h_0(t)$. In the piecewise constant model for $\lambda_0(t)$, based on the heart transplant literature [19, 20], we use a Gamma prior with known mean and variance for the baseline intensity (λ_{0j} , $j = 1, \dots, 5$) in each of the five time intervals (0–3 months, 4–6 months, 7–12 months, 13–36 months, and greater than 36 months). The Gamma prior process for $\Lambda_0(t)$ also has known mean and precision. We explored the priors for the

parameters in these baseline functions, and both GMPP and CAR models are not sensitive to the choice of means and precisions of these prior distributions.

4.3. Model fitting

MCMC tools are used to sample from the joint posterior distribution [21,22]. Details can be found in previous work including Sinha [3], Ibrahim, Chen and Sinha [16], and Sinha *et al.* [15]. We use WinBUGS [23] for Gibbs sampling and follow the recommendations of Gelman and Rubin [24] to monitor convergence. For each model, we use three chains and 50,000 iterations with 45,000 burn-ins in each chain. We checked the estimated scale reduction factor of the Gelman and Rubin statistic and several other convergence criteria by using CODA [25]; all of which suggested adequate performance. An outline of example WinBUGS code is included in Appendix B.

4.4. Results

With the different forms for the baseline intensity $\lambda_0(t)$ and hazard $h_0(t)$, we explore five GMPP and CAR models, respectively. Model 1 is parametric with Weibull $\lambda_0(t)$ and constant $h_0(t)$. Models 2–5 are semiparametric models: model 2 has piecewise constant $\lambda_0(t)$ and constant $h_0(t)$; model 3 has piece-wise constant $\lambda_0(t)$ and Weibull $h_0(t)$; model 4 uses the gamma process on $\Lambda_0(t)$ and constant $h_0(t)$; and model 5 is gamma process on $\Lambda_0(t)$ and Weibull $h_0(t)$. Within each model, results are not sensitive to the different priors on remaining model parameters discussed in Section 4.2, including the key model parameters α and η^{-1} .

Tables II and III provide posterior means with 95% credible intervals for the parameters in the GMPP and CAR models. Among GMPP models, results from models 1–3 are similar. In particular, age is the only factor that is identified as a risk factor for rejection—patients of younger age at transplant have higher risk of a new rejection. This result is consistent with other studies on heart transplant [2]. Models 4 and 5 identify age as a risk factor not only for rejection but also for death. In all five GMPP models, both η^{-1} and α are well above zero, which implies that the hazard of death does depend on the past history of rejections. We infer that patients who are more prone to rejections are also at a higher risk of death. Strong posterior evidence of a moderately high value of η^{-1} indicates that the CAR model may not be appropriate.

All CAR models also identify age as a significant risk factor for rejection. The magnitude of the age effect on the conditional risk of rejection from CAR models is very close to that from GMPP models. Besides age, BMI is also a significant factor for rejection from all CAR models. Interestingly, except for CAR model 1, all other models detect a negative relationship between BMI and risk of rejection.

4.5. Model comparison

We use conditional predictive ordinate (CPO) values to compare the GMPP and CAR models. Detailed discussion about CPO can be found in Gelfand *et al.* [26] and Sinha *et al.* [15]. For subject i , the cross-validated posterior predictive probability evaluated at the observed data point $(\mathbf{N}_{i,\text{obs}}, y_i, \delta_i)$ is given by

$$\text{CPO}_i = \Pr[\mathbf{N}_i = \mathbf{N}_{i,\text{obs}}, Y_i = y_i, \delta_i | \mathbf{O}_{(-i)}] = \int \Pr[\bar{N}_i(y_i) = \mathbf{N}_{i,\text{obs}}, Y_i = y_i, \delta_i | \theta] \times p(\theta | \mathbf{O}_{(-i)}) d\theta,$$

where $\mathbf{O}_{(-i)}$ is the observed data with subject i removed, θ is the vector of model parameters, and $\mathbf{N}_{i,\text{obs}}$ is the observed recurrent rejection history data for subject i . A larger CPO value indicates a better fit. Thus, the relative fit of two models for observation i can be evaluated by the log of the ratio of the CPO_i values. An overall relative comparison of the two models is the log pseudo-Bayes factor [27], given by the difference of the sum of the log CPO_i values for each model.

The CPO criteria support all five GMPP models more than CAR models. Figures 1–5 are plots of the log CPO ratios from GMPP and CAR models with different baseline intensity $\lambda_0(t)$ and hazard $h_0(t)$ functions. A log CPO ratio greater than 0 indicates a relatively better fit of the GMPP model than the CAR model for that particular patient's data. Within each comparison, more than 90% of log CPO ratios are greater than 0, which implies that the GMPP models fit most data better than CAR models. These results are not surprising as our analyses have indicated evidence of a random effect that impacts a patient's risk of both a new rejection and death.

We further compare among five GMPP models by using pseudo-Bayes factor [27]. The log pseudo-Bayes factors for comparing model 2 with the other four models are much larger than 2 (results not shown). According to Jeffreys' scale [28], model 2 (with piecewise constant and constant $h_0(t)$) is decisively the best among all five GMPP models.

5. Model predictions

The fully specified stochastic Bayesian models for recurrent events with informative termination discussed in the previous sections can be used to predict future outcomes. For example, we can predict the probability that a patient survives and is free of rejection within a future time interval, say the next 6 months.

The following prediction tools are based on the GMPP model as it is found to be more suitable for our data than the CAR model. By using (1) and (2), the probability of death within a future time interval (t_1, t_2) for a new patient (not in the data set) with covariate vector $\mathbf{Z}_{\text{new}}$ and number of rejections k prior to t_1 , given that this patient is still alive at time t_1 , is

$$\Pr[T_{\text{new}} \in [t_1, t_2] | N_{\text{new}}(t_1-) = k, T_{\text{new}} > t_1; \mathbf{Z}_{\text{new}}] = 1 - \frac{E_w[w_{\text{new}}^k \exp\{-\Lambda_{\text{new}}(t_1)w_{\text{new}} - H_{\text{new}}(t_2)w_{\text{new}}^\alpha\}]}{E_w[w_{\text{new}}^k \exp\{-\Lambda_{\text{new}}(t_1)w_{\text{new}} - H_{\text{new}}(t_1)w_{\text{new}}^\alpha\}]}, \quad (5)$$

where E_w is the expectation with respect to the frailty distribution,

$\Lambda_{\text{new}}(t) = e^{\beta_1^T \mathbf{Z}_{\text{new}}} \int_0^t \lambda_0(u) du$, and $H_{\text{new}}(t) = e^{\beta_2^T \mathbf{Z}_{\text{new}}} \int_0^t h_0(u) du$. In the special case when $\alpha = 1$, (5) simplifies as

$$1 - \frac{\{\Lambda_{\text{new}}(t_1) + H_{\text{new}}(t_1) + \eta\}^{k+\eta}}{\{\Lambda_{\text{new}}(t_1) + H_{\text{new}}(t_2) + \eta\}^{k+\eta}}.$$

For this new patient, we may also be interested in the probability of living beyond a future time point t_f without having a new rejection between the current time (time at prediction) t and t_f that is,

$$\Pr[T_{\text{new}} > t_f, N_{\text{new}}(t_f -) = k | N_{\text{new}}(t -) = k, T_{\text{new}} > t; \mathbf{Z}_{\text{new}}] = \frac{E_w[w_{\text{new}}^k \exp\{-\Lambda_{\text{new}}(t_f)w_{\text{new}} - H_{\text{new}}(t_f)w_{\text{new}}^\alpha\}]}{E_w[w_{\text{new}}^k \exp\{-\Lambda_{\text{new}}(t)w_{\text{new}} - H_{\text{new}}(t)w_{\text{new}}^\alpha\}]}.$$

(6)

We can even predict the probability of a more general situation that the new patient lives beyond a future time point t_f with m rejections between t and t_f that is,

$$\begin{aligned} \Pr[T_{\text{new}} > t_f, N_{\text{new}}(t_f -) = k + m | N_{\text{new}}(t -) = k, T_{\text{new}} > t; \mathbf{Z}_{\text{new}}] \\ = \frac{E_w[w_{\text{new}}^k \exp\{-\Lambda_{\text{new}}(t_f)w_{\text{new}} - H_{\text{new}}(t_f)w_{\text{new}}^\alpha\}]}{E_w[w_{\text{new}}^k \exp\{-\Lambda_{\text{new}}(t)w_{\text{new}} - H_{\text{new}}(t)w_{\text{new}}^\alpha\}]} \\ \times \frac{(\Lambda_{\text{new}}(t_f) - \Lambda_{\text{new}}(t))^m}{m!}. \end{aligned}$$

From the best GMPP model (GMPP model 2), age (β_{31}) is a significant factor for the risk of rejection. So, our prediction model is

$$\lambda_N(t | \bar{N}(t -), T > t, w; \mathbf{Z}) = \lambda_0(t) w e^{\beta_{31} Z_3} \quad \text{and} \quad h_T(t | \bar{N}(t -), w; \mathbf{Z}) = h_0(t) w^\alpha.$$

We can approximate the aforementioned probabilities, for example (6), using the prediction model as follows:

1. Draw $\varphi^{(p)} = \{\beta_{31}^{(p)}, \alpha^{(p)}, \lambda_0(\cdot)^{(p)}, h_0(\cdot)^{(p)}\}$; $p = 1, \dots, P$, from the posterior distribution $[\theta, \mathbf{w} | \text{Data}]$.
2. For each of the P draws $\varphi^{(p)}$, take Q draws $\{w_{\text{new}}^{(q)}; q = 1, \dots, Q\}$ from the posterior distribution $[w_{\text{new}} | \text{Data}; \theta^{(p)}]$. Now, approximate

$$\Pr^{(p)}[T_{\text{new}} > t_f, N_{\text{new}}(t_f-) = k | N_{\text{new}}(t-) = k, T_{\text{new}} > t; \mathbf{Z}_{\text{new}}] = \frac{E_w^{(p)}[w_{\text{new}}^k \exp\{-\Lambda_{\text{new}}(t_f)w_{\text{new}} - H_{\text{new}}(t_f)w_{\text{new}}^\alpha\}]}{E_w^{(p)}[w_{\text{new}}^k \exp\{-\Lambda_{\text{new}}(t)w_{\text{new}} - H_{\text{new}}(t)w_{\text{new}}^\alpha\}]}$$

by

$$\frac{\frac{1}{Q} \sum_{q=1}^Q \left[\left(w_{\text{new}}^{(q)} \right)^k \exp \left(-\Lambda_{\text{new}}^{(p)}(t_f) w_{\text{new}}^{(q)} - H_{\text{new}}^{(p)}(t_f) \left(w_{\text{new}}^{(q)} \right)^{\alpha^{(p)}} \right) \right]}{\frac{1}{Q} \sum_{q=1}^Q \left[\left(w_{\text{new}}^{(q)} \right)^k \exp \left(-\Lambda_{\text{new}}^{(p)}(t) w_{\text{new}}^{(q)} - H_{\text{new}}^{(p)}(t) \left(w_{\text{new}}^{(q)} \right)^{\alpha^{(p)}} \right) \right]}.$$

3. Approximate $\Pr[T_{\text{new}} > t_f, N_{\text{new}}(t_f-) = k | N_{\text{new}}(t-) = k, T_{\text{new}} > t; \mathbf{Z}_{\text{new}}]$ by

$$\frac{1}{P} \sum_{p=1}^P \Pr^{(p)}[T_{\text{new}} > t_f, N_{\text{new}}(t_f-) = k | N_{\text{new}}(t-) = k, T_{\text{new}} > t; \mathbf{Z}_{\text{new}}].$$

These prediction methods can be useful for clinicians to set a biopsy schedule specific for an individual patient. We illustrate our prediction methods for a new patient with characteristics matching a randomly selected patient from our data: a male Caucasian aged 41.7 years who experienced three rejection episodes during his first year after transplant and no rejections in the second and third years of follow-up. By using the first year experience, our prediction from GMPP model 2 (which uses only the age covariate) of the probability of rejection-free survival for the next 6 months is 0.65 (95% CI = [0.52, 0.79]); at the end of 2 years after transplant, we predicted this probability as 0.74 (95% CI = [0.66, 0.82]). These predictions agree well with the experience of the matching patient in our data.

6. Summary and discussion

This paper discusses the two fully specified stochastic models for analyzing recurrent event data with informative termination. If we believe that there is an underlying unobserved random effect that affects both the risk of recurrent event and the risk of termination, we should consider the GMPP model.

For our heart transplant data, all our GMPP and CAR models are not sensitive to the choice of priors. This finding may be due to the relatively large size of our data, and it may not be generalizable to other data. Comparing the two types of models, the GMPP model performs much better than the CAR model, and our analyses support the existence of an underlying patient-specific factor that affects the risk of recurrent rejection as well as death. Among the four covariates we examined, age is a significant factor for the risk of rejection. Patients of younger age at transplant are at higher risk for rejection. In the heart transplant literature, in addition to age, race is a risk factor for rejection. However, our models did not find this race effect, perhaps because of the small number of African American patients in our data. Another possible reason for not identifying race as a risk factor is that this patient population from South Carolina may be different from that in other studies. In particular, many African

Americans in South Carolina are Gullah, who have less non-African genetic admixture than other African American groups [29]. Among the four covariates, our best GMPP model did not identify any effect on the risk of death. This may be because, after adjustment for the random effect and the effect of covariates on the risk of rejection, no residual covariate effect remains.

We have also provided prediction methods that can be very useful tools when determining the frequency of biopsy and other monitoring of patients. We plan further assessment of these prediction methods in this transplant context.

Acknowledgments

We thank the editor and the reviewers for their comments and suggestions that have helped us improve this manuscript. This study was partially supported by the grants NIH/NINDS 5 U01 NS043127, NIH/NCRR P20RR017696, and NSF DMS0604666.

Appendix A. Posterior for CAR model (3) and (4)

The likelihood contribution from the sampling distribution of the data containing rejection times $D_1 = \{\mathbf{T}_{io} : i = 1, \dots, n\}$ is

$$L_1(\beta_1^T, \lambda_0, |D_1, \mathbf{Z}) \propto \prod_{i=1}^n \left[\left(e^{\beta_1^T \mathbf{Z}_i} \right)^{N_i(y_i)} \exp(-\Lambda_i(y_i)) \prod_{j=1}^{N_i(y_i)} \lambda_0(t_{ij})(1 + \eta^{-1} N_i(t_{ij} -)) \right],$$

where $\Lambda_i(y_i) = e^{\beta_2^T \mathbf{Z}_i} \int_0^{y_i} \lambda_0(u)(1 + \eta^{-1} N_i(u)) du$. Similarly, the likelihood contribution from the sampling distribution of the data containing death times $D_2 = \{y_i, \delta_i : i = 1, \dots, n\}$ is

$$L_2(\beta_2^T, h_0, \alpha | D_2, \mathbf{Z}) \propto \prod_{i=1}^n \left[\left(e^{\beta_2^T \mathbf{Z}_i} h_0(y_i)(1 + \eta^{-1} N_i(y_i))^\alpha \right)^{\delta_i} \exp(-H_i(y_i)) \right],$$

where $H_i(y_i) = e^{\beta_2^T \mathbf{Z}_i} \int_0^{y_i} h_0(u)(1 + \eta^{-1} N_i(u))^\alpha du$. Thus, the observed data likelihood is

$$L_o(\theta | D_1, D_2, \mathbf{Z}) \propto L_1(\beta_1^T, \lambda_0, |D_1, \mathbf{Z}) \times L_2(\beta_2^T, h_0, \alpha | D_2, \mathbf{Z}),$$

where θ is the vector of all model parameters, that is, $\theta = (\beta_1^T, \beta_2^T, h_0, \lambda_0, \alpha, \eta)$. The posterior distribution under the CAR model is then given as

$$p(\theta | D_1, D_2, \mathbf{Z}) \propto L_o(\theta | D_1, D_2, \mathbf{Z}) \times \pi(\theta),$$

where $\pi(\theta)$ is the joint prior same as in the posterior distribution under the GMPP model discussed in Section 4.1.

Appendix B. Outline of WinBUGS code for the parametric GMPP model

This outline uses the Weibull baseline intensity for the recurrent rejection process and the exponential baseline hazard for the death times.

```

Model

{

  Z1 = race

  Z2 = gender

  Z3 = baseline age

  Z4 = baseline BMI

  i = index of patient

  for (i in 1:N) {

    # j = index of rejection episode

    for (j in s[i]+1: s[i+1]) {

      #covariate linear form

      BetaZ<-beta11*Z1[i]+beta21*Z2[i]+beta31*Z3[i]+beta41*Z4[i]

      #likelihood from recurrent rejections

      #(Weibull baseline intensity with parameter v, r)

      cen[j] ~ dpois(A[j])

      A[j] <- -log(part1[j]*part2[j])+10000

      part1[j] <-pow(v*r*pow(Y2[j],v-1)*exp(BetaZ)*W[i],delta[j])

      part2[j] < -exp(-r*W[i]*exp(BetaZ)*(pow(Y2[j], v)-pow(Y1[j], v)))

      #likelihood from death

      #(exponential baseline hazard with parameter lambda0)

      D[i] ~ dpois(B[i])

      B[i] <- lambda0*pow(W[i], alpha)*exp(BetaZ)*death[i]
    }
  }
}

```

```

#Gamma frailty with mean 1 and variance 1/eta

W[i] ~ dgamma(eta, eta)

} # end loop over rejection episode j

} # end loop over subject i

#variance for gamma frailty

var.W<-1/eta

#example priors

beta11~dnorm(0, 1)

beta21~dnorm(0, 1)

beta31~dnorm(0, 1)

beta41~dnorm(0, 1)

beta12~dnorm(0, 1)

beta22~dnorm(0, 1)

beta32~dnorm(0, 1)

beta42~dnorm(0, 1)

alpha~ddexp(0, 1)

var.W~dexp(2)

v~dgamma (1, 1)

r~dgamma(1, 1)

} # end Model

```

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Figure 1.
Plot of log CPO ratios from GMPP model 1 versus CAR model 1.

Figure 2.
Plot of log CPO ratios from GMPP model 2 versus CAR model 2.

Figure 3.
Plot of log CPO ratios from GMPP model 3 versus CAR model 3.

Figure 4.
Plot of log CPO ratios from GMPP model 4 versus CAR model 4.

Figure 5.
Plot of log CPO ratios GMPP from model 5 versus CAR model 5.

Table I

Baseline characteristics of the heart transplant patients.

Variable	N	Age at transplant mean (SD)	Body mass BMI at transplant mean (SD)
Gender			
Male	221	52.2 (10.3)	27.0 (4.2)
Female	46	47.6 (13.0)	24.1 (4.2)
Race			
Caucasian	201	52.9 (10.2)	26.6 (4.0)
African American	66	47.0 (11.8)	26.0 (5.3)

BMI, body mass index; SD, standard deviation.

Table II

Results from the GMPP models.

Parameter	GMPP models				
	Model 1	Model 2	Model 3	Model 4	Model 5
Rejection					
Gender	0.47 (−0.05, 1.06)	0.21 (−0.27, 0.73)	0.19 (−0.30, 0.73)	0.37 (−0.25, 1.06)	0.27 (−0.36, 1.00)
Race	0.15 (−0.32, 0.58)	0.03 (−0.42, 0.46)	0.01 (−0.44, 0.45)	−0.22 (−0.74, 0.32)	−0.23 (−0.73, 0.36)
Age	−0.03 (−0.05, −0.02)	−0.04 (−0.06, −0.03)	−0.04 (−0.06, −0.03)	−0.07 (−0.09, −0.06)	−0.07 (−0.09, −0.06)
BMI	0.04 (−0.003, 0.08)	0.002 (−0.03, 0.04)	0.001 (−0.03, 0.03)	−0.03 (−0.06, 0.001)	−0.03 (−0.06, 0.005)
Death					
Gender	0.52 (−0.39, 1.44)	0.45 (−0.44, 1.33)	0.30 (−0.38, 0.98)	0.43 (−0.51, 1.32)	0.34 (−0.42, 1.29)
Race	−0.06 (−0.89, 0.72)	−0.11 (−0.92, 0.67)	−0.06 (−0.70, 0.53)	−0.18 (−0.95, 0.72)	−0.13 (−0.80, 0.69)
Age	−0.02 (−0.05, 0.01)	−0.02 (−0.06, 0.01)	−0.02 (−0.04, 0.01)	−0.04 (−0.07, −0.003)	−0.03 (−0.06, −0.01)
BMI	−0.01 (−0.09, 0.06)	−0.03 (−0.11, 0.03)	−0.01 (−0.06, 0.05)	−0.05 (−0.11, 0.02)	−0.02 (−0.12, 0.05)
α	1.92 (1.10, 2.97)	1.81 (0.91, 2.96)	1.08 (0.56, 1.72)	1.46 (1.02, 2.08)	1.13 (0.73, 1.72)
η^{-1}	1.10 (0.67, 1.65)	1.11 (0.67, 1.58)	1.15 (0.68, 1.72)	2.02 (1.43, 2.73)	2.00 (1.42, 2.64)

The baseline recurrent rejection intensity is $\lambda_0(t)$ and the baseline hazard for death is $h_0(t)$. Entries are the posterior mean computed from 5000 postburn-in iterations and the 95% credible interval. GMPP, generalized mixed Poisson process; BMI, body mass index.

Table III

Results from the CAR models.

Parameter	CAR models				
	Model 1	Model 2	Model 3	Model 4	Model 5
Rejection					
Gender	0.32 (−0.04, 0.66)	−0.03 (−0.38, 0.30)	−0.04 (−0.38, 0.30)	−0.20 (−0.54, 0.10)	−0.19 (−0.52, 0.12)
Race	0.28 (−0.04, 0.58)	0.15 (−0.13, 0.45)	0.15 (−0.16, 0.46)	0.16 (−0.15, 0.46)	0.15 (−0.16, 0.44)
Age	−0.03 (−0.04, −0.01)	−0.04 (−0.05, −0.03)	−0.04 (−0.05, −0.03)	−0.06 (−0.08, −0.05)	−0.06 (−0.07, −0.05)
BMI	0.03 (0.002, 0.06)	−0.02 (−0.05, −0.003)	−0.02 (−0.04, −0.002)	−0.08 (−0.10, −0.06)	−0.08 (−0.10, −0.06)
Death					
Gender	0.23 (−0.35, 0.79)	0.18 (−0.39, 0.77)	0.07 (−0.56, 0.65)	0.20 (−0.37, 0.74)	0.09 (−0.51, 0.69)
Race	0.15 (−0.38, 0.63)	0.14 (−0.37, 0.64)	0.07 (−0.43, 0.57)	0.11 (−0.38, 0.64)	0.02 (−0.51, 0.50)
Age	−0.005 (−0.03, 0.02)	−0.005 (−0.03, 0.03)	0.01 (−0.02, 0.03)	−0.001 (−0.03, 0.02)	0.003 (−0.01, 0.03)
BMI	−0.02 (−0.07, 0.04)	−0.03 (−0.09, 0.02)	−0.03 (−0.08, 0.03)	−0.02 (−0.06, 0.05)	−0.02 (−0.08, 0.05)
α	1.16 (0.57, 2.00)	0.94 (0.44, 1.55)	1.49 (0.91, 2.09)	3.12 (1.38, 5.95)	4.24 (2.33, 7.33)
η^{-1}	0.69 (0.34, 1.13)	1.00 (0.56, 1.55)	0.97 (0.60, 1.46)	0.17 (0.07, 0.32)	0.20 (0.09, 0.35)

The baseline recurrent rejection intensity is $\lambda_0(t)$, and the baseline hazard for death is $h_0(t)$. Entries are the posterior mean computed from 5000 postburn-in iterations and the 95% credible interval. CAR, coarsening at random; BMI, body mass index.