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## Semiparametric additive marginal regression models for multiple type recurrent events

**Xiaolin Chen,**

Academy of Mathematics and Systems Science, Chinese Academy of Sciences Beijing 100190, P.R. China

**Qihua Wang,**

Academy of Mathematics and Systems Science, Chinese Academy of Sciences Beijing 100190, P.R. China

**Jianwen Cai,** and

Department of Biostatistics, University of North Carolina at Chapel Hill Chapel Hill, North Carolina 27599-7420, U.S.A.

**Viswanathan Shankar**

Department of Biostatistics, University of North Carolina at Chapel Hill Chapel Hill, North Carolina 27599-7420, U.S.A.

### Abstract

Recurrent event data are often encountered in biomedical research, for example, recurrent infections or recurrent hospitalizations for patients after renal transplant. In many studies, there are more than one type of events of interest. Cai and Schaubel (2004) advocated a proportional marginal rate model for multiple type recurrent event data. In this paper, we propose a general additive marginal rate regression model. Estimating equations approach is used to obtain the estimators of regression coefficients and baseline rate function. We prove the consistency and asymptotic normality of the proposed estimators. The finite sample properties of our estimators are demonstrated by simulations. The proposed methods are applied to the India renal transplant study to examine risk factors for bacterial, fungal and viral infections.

### Keywords

additive model; empirical process; multiple type recurrent events; recurrent events

## 1. Introduction

In biomedical research, the events of interest can occur multiple times on the same subject. This kind of events are termed as recurrent events in the literature. Examples of recurrent events include repeated opportunistic infections among HIV patients, recurrent seizures in epileptic patients, multiple hospitalizations among organ transplant recipients and so on.

Developing statistical methods for the analysis of recurrent events has received much attention during the last two decades. Methods for the regression analysis of recurrent events can be classified into two categories: the conditional methods and the marginal methods. The conditional methods are based on modeling the intensity or hazard functions (Prentice et al., 1981; Andersen and Gill, 1982), while the marginal methods model the mean or rate function (Pepe and Cai, 1993; Lawless and Nadeau, 1995; Lin et al., 2000; Schaubel et al., 2006). Compared with the conditional methods, the marginal methods have the advantage that the mean number of the recurrent events is easier to interpret than the event intensity.

For the recurrent event data, Lin et al. (2000) established the rigorous theory for both the parameter estimation and model checking for the multiplicative rate model. As noted by Schaubel et al. (2006), the popularity of multiplicative rate model derives not only from their utility and wide applicability, but also from convention and the availability of statistical software. The additive rate model is an useful alternative to the multiplicative rate model when absolute rate differences is of interest. Schaubel et al. (2006) proposed a semiparametric additive rate model to analyze the recurrent event data. Liu et al. (2010) generalized this model to allow for the additive effects and the multiplicative effects simultaneously. Zeng and Cai (2010) proposed an additive rate model for the recurrent events with an informative terminal event.

All the aforementioned methods are for the analysis of recurrent events of a single type. Frequently, in many studies, the recurrent events of interest are of multiple types. Our motivating problem concerns end-stage renal disease patients from India. End-stage renal disease patients receive different types of immunosuppressions and being so, they are more susceptible to opportunistic infections. In our study, infections are ascribed to one of the three types: bacterial, fungal and viral origin. It has been established that exposure to infective agents and net state of immunosuppression are important determinants of infection risk in transplantation. Though in the developing countries, the immunosuppressive protocols are similar to that of developed countries, pandemicity of infective agents and other environmental factors increase the risk of infections in these patients to many folds. Hence, the main objective of the study is to investigate the risk factors for recurrent infections and to examine the absolute rate of bacterial, fungal and viral infections. Of primary interest is to study the role of immunosuppression on different types of infections which is very useful information to nephrologist in care for the renal transplant patients.

Statistical methods for handling multiple type recurrent events are relatively limited. Prentice et al. (1981) firstly suggested extending their conditional intensity model for recurrent event data to model multiple type infections classified as bacterial, fungal and viral origin. Abu-Libdeh et al. (1990) studied the relation of the nutritional supplement of selenium and the recurrence of several kinds of skin cancers. A joint regression model for cumulative mean functions arising from bivariate point process was studied by Ng and Cook (1999). Lawless et al. (2001) studying failures of surgically implanted shunts in children with hydrocephalus under gap times models discussed the possibility of extension to multiple type recurrent events and the problem of terminal events. Cai and Schaubel (2004) modeled physician office visits and hospitalizations attributable to asthma using proportional marginal rate model. Chen et al. (2005) developed joint models for multiple types recurrent events under interval censored data setup and described Gibbs sampling algorithms for fitting mixed Poisson models with piecewise constant baselines and multivariate lognormal random effects. Schaubel and Cai (2006a; 2006b) considered the analysis of multiple types recurrent event data with missing event types using estimating equations and multiple imputation approaches. Chen et al. (2009) described a likelihood approach based on the joint models for the multiple type recurrent events with partially missing event types. In this article, we propose a general additive marginal rate model for the multiple type recurrent events. We consider the estimating equations approach (Liang and Zeger, 1986) for obtaining the estimators of regression coefficients and baseline rate function.

The remainder of this article is organized as follows. In Section 2, we set up the necessary notations and describe the proposed semiparametric additive marginal regression model for the multiple type recurrent events along with the inference procedure. The asymptotic properties of the proposed estimators are stated in Section 3, the proofs of which are provided in the Appendix. In Section 4, we give a goodness-of-fit test. We report the

simulation studies in Section 5 and illustrate the method by applying it to the India renal transplant infection data in Section 6. Finally, we provide some concluding remarks in Section 7.

## 2. Model and Inference method

Assume that there are  $K$  different types of events of interest, i.e., every subject in the population may experience  $K$  different types of events. Let  $N_{i,k}^*(t)$  denote the number of events of type  $k$  during the time  $[0, t]$  for subject  $i$ . Similarly, let  $C_{i,k}$  be the censoring time for the recurrent events of type  $k$  for subject  $i$ . Usually the censoring times for the  $K$  different recurrent events are equal, i.e.,  $C_{i,k} = C_i$ . Let  $Z_{i,k}(t)$  denote the  $p \times 1$  covariate vector for the recurrent events of type  $k$ . The covariate  $Z_{i,k}(t)$  is possibly time-dependent and external (Kalbfleisch and Prentice, 2002). Let the at risk process be  $Y_{i,k}(t) = I(C_{i,k} \geq t)$ . Subject to right censoring, the  $k$ th observed recurrent event process is

$$N_{i,k}(t) = \int_0^t I(C_{i,k} \geq s) dN_{i,k}^*(s).$$

The rate function for the  $k$ th recurrent event process is

$$d\mu_k(t|Z_{i,k}(t)) = E \left\{ dN_{i,k}^*(t) | Z_{i,k}(t) \right\}.$$

In this article, we consider the following semiparametric additive rate model:

$$d\mu_k(t|Z_{i,k}(t)) = d\mu_{0,k}(t) + g \left( \beta_0^T Z_{i,k}(t) \right) dt, \quad (1)$$

where  $\mu_{0,k}(t)$  is true baseline mean function,  $\beta_0$  is the true regression coefficient and  $g$  is a prespecified link function satisfying some regularity conditions given in Section 3. For the censoring mechanism, we assume that

$$E \left\{ dN_{i,k}^*(t) | Z_{i,k}(t), C_{i,k} \geq t \right\} = E \left\{ dN_{i,k}^*(t) | Z_{i,k}(t) \right\},$$

which is referred to as independent censoring in the literature.

Model (1) specifies a very large class of models. For example, it can accommodate event-type specific effects. different regression coefficients for different event types can be obtained by introducing event-type specific covariates in the covariate  $Z_{i,k}$ . Event-type

specific effects can be obtained by defining  $\beta = (\beta_1^T, \dots, \beta_K^T)^T$  and

$Z_{ik}(t) = [0_{i1}^T, 0_{i2}^T, \dots, 0_{i(k-1)}^T, [Z_{ik}(t)]^T, 0_{i(k+1)}^T, \dots, 0_{iK}^T]^T$ , where  $0$ s are zero vectors. This is illustrated in Section 5. Note that the baseline rate function is explicitly event specific.

Define  $M_{i,k}(t, \beta) = N_{i,k}(t) - \int_0^t Y_{i,k}(s) \left\{ d\mu_{0,k}(s) + g \left( \beta^T Z_{i,k}(s) \right) ds \right\}$ . It is easy to see that  $M_{i,k}(t, \beta)$  is a zero-mean stochastic process under the proposed model and the assumption of independent censoring. Throughout the paper, we use  $M_{i,k}(t)$  to denote  $M_{i,k}(t, \beta)$ . Following the idea of generalized estimating equations (Liang and Zeger, 1986), we specify the following estimating equations:

$$\sum_{i=1}^n \left[ dN_{i,k}(t) - Y_{i,k}(t) \left\{ d\mu_k(t) + g\left(\beta^T Z_{i,k}(t)\right) dt \right\} \right] = 0, \quad 0 \leq t \leq \tau, 1 \leq k \leq K, \quad (2)$$

$$\sum_{i=1}^n \sum_{k=1}^K \int_0^\tau Z_{i,k}(t) g^{(1)}\left(\beta^T Z_{i,k}(t)\right) \left[ dN_{i,k}(t) - Y_{i,k}(t) \left\{ d\mu_k(t) + g\left(\beta^T Z_{i,k}(t)\right) dt \right\} \right] = 0, \quad (3)$$

where  $g^{(1)}(\cdot)$  is the first order derivative of  $g(\cdot)$  and  $\tau$  is a prespecified study ending time satisfying  $P(Y_{i,k}(\tau) = 1) > 0$  for  $k = 1, \dots, K$  and  $i = 1, \dots, n$ . For fixed  $\tau$ , based on (2), after some algebraic manipulations, we can obtain that

$$\hat{\mu}_{0,k}(t, \beta) = \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) \left\{ dN_{i,k}^*(s) - g\left(\beta^T Z_{i,k}(s)\right) ds \right\}}{\sum_{j=1}^n Y_{j,k}(s)} \quad (4)$$

for  $k = 1, \dots, K$ . Substituting (4) into (3), again followed by some algebraic manipulations, leads to the following estimating equation:

$$\begin{aligned} U_n(\tau, \beta) &= \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)}\left(\beta^T Z_{i,k}(t)\right) \right. \\ &\quad \left. - \frac{\sum_{j=1}^n Y_{j,k}(t) Z_{j,k}(t) g^{(1)}\left(\beta^T Z_{j,k}(t)\right)}{\sum_{l=1}^n Y_{l,k}(t)} \right\} \left\{ dN_{i,k}(t) - Y_{i,k}(t) g\left(\beta^T Z_{i,k}(t)\right) dt \right\} \\ &= 0. \end{aligned}$$

For the simplicity of expression, we introduce some notations. Let

$S_k^{(d)}(t, \beta) = \frac{1}{n} \sum_{i=1}^n Y_{i,k}(t) Z_{i,k}(t)^{\otimes d} g^{(d)}\left(\beta^T Z_{i,k}(t)\right)$  for  $d = 0, 1, 2$ , where  $g^{(0)}(x) = 1$ ,  $g^{(d)}(x)$  is the  $d$ th-order derivative of  $g(x)$  for  $d = 1, 2$ , and for a vector  $a$ ,  $a^0 = 1$ ,  $a^1 = a$ ,  $a^2 = aa^T$ . Define  $E_k(t, \beta) = S_k^{(1)}(t, \beta) / S_k^{(0)}(t, \beta)$ . The limits of  $S_k^{(d)}(t, \beta)$  and  $E_k(t, \beta)$  are  $s_k^{(d)}(t, \beta)$  and  $e_k(t, \beta)$  respectively for  $k = 1, \dots, K$  and  $d = 0, 1, 2$ .

Using the above notations, we get the following estimating equation:

$$\begin{aligned} U_n(\tau, \beta) &= \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)}\left(\beta^T Z_{i,k}(t)\right) - E_k(t, \beta) \right\} \\ &\quad \times \left\{ dN_{i,k}(t) - Y_{i,k}(t) g\left(\beta^T Z_{i,k}(t)\right) dt \right\} \\ &= 0, \end{aligned} \quad (5)$$

which can also be expressed as

$$U_n(\tau, \beta) = \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)}\left(\beta^T Z_{i,k}(t)\right) - E_k(t, \beta) \right\} dM_{i,k}(t, \beta) = 0. \quad (6)$$

Different methods, such as Newton-Raphson algorithm, can be used to solve the above estimating equation when the equation does not have an explicit solution. As a specifical case, for function  $g(x) = x$ , we can obtain an explicit expression of the solution for (5),

$$\hat{\beta} = \left[ \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau Y_{i,k}(t) \left\{ Z_{i,k}(t) - \frac{\sum_{j=1}^n Y_{j,k}(t) Z_{j,k}(t)}{\sum_{l=1}^n Y_{l,k}(t)} \right\}^{\otimes 2} dt \right]^{-1} \times \left[ \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) - \frac{\sum_{j=1}^n Y_{j,k}(t) Z_{j,k}(t)}{\sum_{l=1}^n Y_{l,k}(t)} \right\} dN_{i,k}(t) \right].$$

Once we get a solution of the above estimating equation, denoted by  $\hat{\beta}$ , we can estimate the baseline mean function of the  $k$ th recurrent event by the Breslow-Aalen type estimator

$$\hat{\mu}_{0,k}(t) = \hat{\mu}_{0,k}(t, \hat{\beta}) = \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) \left\{ dN_{i,k}^*(s) - g(\hat{\beta}^T Z_{i,k}(s)) ds \right\}}{n S_k^{(0)}(s, \hat{\beta})} \quad (7)$$

for  $1 \leq k \leq K$ .

### 3. Asymptotic results

In this section, we present the asymptotic results for the proposed estimators. Similar to Cai and Schaubel (2004) and Liu et al. (2010), we assume the following regularity conditions:

- (a)  $\{N_{i,k}^*(\cdot), C_{i,k}, Z_{i,k}(\cdot)\}_{k=1}^K, i=1, \dots, n$ , are independent and identically distributed.
- (b)  $P(C_{i,k} > 0) > 0$ , for  $k = 1, \dots, K, i = 1, \dots, n$ .
- (c)  $N_{i,k}(\cdot)$  are bounded by a constant for  $k = 1, \dots, K, i = 1, \dots, n$ .
- (d)  $Z_{i,k}(\cdot), i = 1, \dots, n$ , have bounded total variations, i.e.,  $|Z_{i,j,k}(0)| + \int_0^\tau |dZ_{j,i,k}(t)| \leq H$  for all  $j = 1, \dots, p, k = 1, \dots, K, i = 1, \dots, n$ , where  $Z_{j,i,k}(t)$  is the  $j$ th component of  $Z_{i,k}(t)$  and  $0 < H < \infty$ .  $g^{(1)}(\beta_0^T Z_{i,k}(t)) Z_{i,k}(t)$  has bounded total variation, uniformly in  $i, k$ .
- (e) The matrix  $A$  is nonsingular, where

$$A = E \left[ \sum_{k=1}^K \int_0^\tau Y_{1,k}(t) \left\{ Z_{1,k}(t) g^{(1)}(\beta_0^T Z_{1,k}(t)) - e_k(t, \beta_0) \right\} g^{(1)}(\beta_0^T Z_{1,k}(t)) Z_{1,k}(t)^T dt \right].$$

- (f)  $g$  is twice continuous differentiable;  $\{g(\cdot), g^{(1)}(\cdot), g^{(2)}(\cdot)\}$  are uniformly continuous and bounded.

In the Appendix, we have derive the asymptotic properties of the estimated regression coefficients. Special results are listed in the following theorem.

#### Theorem 1

Under the regularity conditions (a) to (f),  $\hat{\beta}$  converges almost surely to  $\beta_0$ . Furthermore,  $n^{\frac{1}{2}}(\hat{\beta} - \beta_0)$  converges to a normal distribution with mean zero and covariance matrix  $\Sigma_0 =$

$A^{-1} {}_1(A^{-1})^T$ , where  $A$  is defined in Condition (e) and

$$\Sigma_1 = E \left[ \left[ \sum_{k=1}^K \int_0^\tau \left\{ Z_{1,k}(t) g^{(1)} \left( \beta_0^T Z_{1,k}(t) \right) - e_k(t, \beta_0) \right\} dM_{1,k}(t) \right]^{\otimes 2} \right]$$

The covariance matrix can be consistently estimated by  $\hat{\Sigma}_0 = \hat{A}^{-1} \hat{\Sigma}_1 (\hat{A}^{-1})^T$ , where

$$\hat{A} = \frac{1}{n} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau Y_{i,k}(t) \left\{ Z_{i,k}(t) g^{(1)} \left( \hat{\beta}^T Z_{i,k}(t) \right) - E_k(t, \hat{\beta}) \right\} g^{(1)} \left( \hat{\beta}^T Z_{i,k}(t) \right) Z_{i,k}(t)^T dt \quad (8)$$

and

$$\hat{\Sigma}_1 = \frac{1}{n} \sum_{i=1}^n \left[ \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)} \left( \hat{\beta}^T Z_{i,k}(t) \right) - E_k(t, \hat{\beta}) \right\} d\hat{M}_{i,k}(t, \hat{\beta}) \right]^{\otimes 2}$$

with

$$d\hat{M}_{i,k}(t, \hat{\beta}) = dN_{i,k}(t) - Y_{i,k}(t) \left\{ d\hat{\mu}_{0,k}(t, \hat{\beta}) + g \left( \hat{\beta}^T Z_{i,k}(t) \right) dt \right\}. \quad (9)$$

To study the asymptotic properties of estimators for the  $K$  different baseline mean functions, we have to define a new metric space (Spiekerman and Lin, 1998; Cai et al., 2004). Let  $D[0, \tau]$  be the space of cadlag functions on  $[0, \tau]$ . Set  $f(t) = [f_1(t), \dots, f_K(t)]^T$ ,  $f_k(t) \in D[0, \tau]$  for  $k = 1, \dots, K$ . Define  $D[0, \tau]^K$  to be the space consisting of such functions with the metric  $\|f, g\| = \max_k \{ \sup_{t \in [0, \tau]} |f_k(t) - g_k(t)| \}$  for any  $f, g \in D[0, \tau]^K$ . Define  $W_n(t) = [W_{1,n}(t), \dots, W_{K,n}(t)]^T$  where  $W_{k,n}(t) = n^{\frac{1}{2}} (\hat{\mu}_{0,k}(t) - \mu_{0,k}(t))$  for  $k = 1, \dots, K$ . The asymptotic results for the estimated baseline mean functions are given in the following theorem.

## Theorem 2

Under the regularity conditions (a) to (f),  $\hat{\mu}_{0,k}(t)$  converges almost surely to  $\mu_{0,k}(t)$ , uniformly in  $t \in [0, \tau]$ . Furthermore,  $W_n(t)$  converges to a zero-mean Gaussian field in  $D[0, \tau]^K$ , with covariance function  $\Sigma_{k,l}(s, t) = E[\varphi_{1,k}(s)\varphi_{1,l}(t)]$  where

$$\varphi_{1,k}(t) = \int_0^t \frac{dM_{1,k}(s)}{S_k^{(0)}(s)} - h_k(t)^T A^{-1} \sum_{k=1}^K \int_0^\tau \left\{ Z_{1,k}(t) g^{(1)} \left( \beta_0^T Z_{1,k}(t) \right) - e_k(t, \beta_0) \right\} dM_{1,k}(t)$$

with  $h_k(t) = \int_0^t e_k(s, \beta_0) ds$ .

The covariance function can be consistently estimated by

$$\hat{\psi}_{k,l}(s, t) = n^{-1} \sum_{i=1}^n \hat{\phi}_{i,k}(s) \hat{\phi}_{i,l}(t), \text{ where}$$

$$\hat{\phi}_{i,k}(t) = \int_0^t \frac{d\hat{M}_{i,k}(s, \hat{\beta})}{S_k^{(0)}(s)} - \int_0^t \frac{S_k^{(1)}(s, \hat{\beta})}{S_k^{(0)}(s, \hat{\beta})} ds \hat{A}^{-1} \hat{U}_i$$

with  $\hat{A}$  and  $d\hat{M}_{i,k}(t, \hat{\beta})$  as defined in (8), (9) and

$$\widehat{U}_i = \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)} \left( \widehat{\beta}^T Z_{i,k}(t) \right) - E_k(t, \widehat{\beta}) \right\} d\widehat{M}_{i,k}(t, \widehat{\beta}).$$

Pointwise confidence interval for  $\mu_{0,k}(t)$  can be constructed according to Theorem 2. To construct simultaneous confidence band for  $\mu_{0,k}(t)$  over a time interval, we need to obtain the distribution of the supremum of the process  $n^{\frac{1}{2}} (\widehat{\mu}_{0,k}(t) - \mu_{0,k}(t))$ , which is difficult analytically. Alternatively, we adapt the idea in Lin et al. (2000) to our situation and summarize the result in the following theorem.

### Theorem 3

Assume that  $G_1, \dots, G_n$  are independent standard normal variables which are independent of  $\{N_{i,k}^*(\cdot), C_{i,k}, Z_{i,k}(\cdot)\}, i = 1, \dots, n$ . Then under the conditions (a) to (f),

$$\widetilde{W}_{k,n}(t) = n^{-\frac{1}{2}} \sum_{i=1}^n \widehat{\phi}_{i,k}(t) G_i$$

has the same limit distribution as  $W_{k,n}(t)$ .

The proof of Theorem 3 is similar to that of Lin et al. (2000) and we will not repeat it here. Using the result in Theorem 3, to approximate the distribution of  $W_{k,n}(t)$ , we can obtain a large number of realizations from  $\widetilde{W}_{k,n}(t)$  by repeatedly generating the standard normal random sample  $G_1, \dots, G_n$  while fixing the data  $\{N_{i,k}^*(\cdot), C_{i,k}, Z_{i,k}(\cdot)\}, i = 1, \dots, n$ . We then can have the approximation of the distribution of the supremum of the process of  $W_{k,n}(t)$  over the interval of interest and construct the simultaneous confidence bands. It is noted that the confidence intervals or bands constructed by the above method can not guarantee the confidence intervals or bands to be positive. As Lin et al. (1994) and Lin et al. (1998), to avoid this issue, the log transformation can be used in the constructed of the confidence intervals or bands. Also this method can also improve the coverage probability in small samples. We omit the details about the special procedure. Interested readers can consult Lin et al. (1994) and Lin et al. (1998).

## 4. Goodness-of-fit test

In order to examine whether the fitted model is adequate, we consider a goodness-of-fit test statistics. We consider this problem under the situation when the covariates are time-independent. Define  $\widehat{M}_{i,k}(t) = \widehat{M}_{i,k}(t, \widehat{\beta})$ . Following the idea of Lin et al. (1993) and Lin et al. (2000), we define the following test statistics:

$$V(t, z) = n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K I(Z_{i,k} \leq z) \widehat{M}_{i,k}(t),$$

where  $(Z_{i,k} \leq z)$  denotes the situation that every component of  $Z_{i,k}$  is no larger than that of  $z$ . For the null distribution of  $V(t, z)$ , we have the following theorem.

**Theorem 4**

Under the regularity conditions listed in Section 3, the null distribution of  $V(t, z)$  converges weakly to a zero-mean Gaussian process with covariance function  $E\{I(t_1, z_1)I(t_2, z_2)\}$  at  $(t_1, z_1)$  and  $(t_2, z_2)$ , where

$$\zeta_i(t, z) = \sum_{k=1}^K \int_0^t \left\{ I(Z_{i,k} \leq z) - \frac{f_k(s, z)}{s_k^{(0)}(s)} \right\} dM_{i,k}(s) \\ - \sum_{k=1}^K (h(t, z) + l(t, z)) A^{-1} \int_0^t \left\{ Z_{i,k} g^{(1)}(\beta_0^T Z_{i,k}) - e_k(t, \beta_0) \right\} dM_{i,k}(t)$$

with

$$f_k(t, z) = E\{I(Z_{i,k} \leq z) Y_{i,k}(t)\}, \\ h(t, z) = \sum_{k=1}^K \int_0^t f_k(s, z) dh_k(s)^T, \\ h_k(t) = \int_0^t e_k(s, \beta_0) ds$$

and

$$l(t, z) = \sum_{k=1}^K E \left\{ \int_0^t I(Z_{i,k} \leq z) Y_{i,k}(s) g^{(1)}(\beta_0^T Z_{i,k}) Z_{i,k}^T ds \right\}.$$

From the proof of Theorem 4, we can see that the null distribution of  $V(t, z)$  can be approximated by the zero-mean Gaussian process

$$\tilde{V}(t, z) = n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t \left\{ I(Z_{i,k} \leq z) - \frac{\hat{f}_k(s, z)}{\hat{s}_k^{(0)}(s)} \right\} d\hat{M}_{i,k}(s) \\ - n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \left\{ \hat{h}(t, z) + \hat{l}(t, z) \right\} \hat{A}^{-1} \\ \times \int_0^t \left\{ Z_{i,k} g^{(1)}(\beta_0^T Z_{i,k}) - E_k(t, \hat{\beta}) \right\} d\hat{M}_{i,k}(t), \quad (10)$$

where

$$\hat{f}_k(t, z) = \frac{1}{n} \sum_{i=1}^n I(Z_{i,k} \leq z) Y_{i,k}(t) \\ \hat{h}(t, z) = \sum_{k=1}^K \int_0^t \hat{f}_k(s, z) d\hat{h}_k(s)^T, \\ \hat{h}_k(t) = \int_0^t E_k(s, \hat{\beta}) ds$$

and

$$\hat{l}(t, z) = \sum_{k=1}^K \frac{1}{n} \sum_{i=1}^n \int_0^t I(Z_{i,k} \leq z) Y_{i,k}(s) g^{(1)}(\hat{\beta}^T Z_{i,k}) Z_{i,k}^T ds.$$

It is difficult to obtain the analytical expression of the covariance function. Thus we can utilize the method of resampling to get the asymptotic null distribution of  $V(t, z)$ . Specifically, define



$$\begin{aligned} \hat{V}(t, z) = & n^{-\frac{1}{2}} \sum_{i=1}^n \left[ \sum_{k=1}^K \int_0^t \left\{ I(Z_{i,k} \leq z) - \frac{\hat{f}_k(s, z)}{\hat{S}_k^{(0)}(s)} \right\} d\hat{M}_{i,k}(s) \right. \\ & \left. - \sum_{k=1}^K \left\{ \hat{h}(t, z) + \hat{l}(t, z) \right\} \hat{A}^{-1} \times \int_0^t \left\{ Z_{i,k} g^{(1)}(\beta_0^T Z_{i,k}) - E_k(t, \hat{\beta}) \right\} d\hat{M}_{i,k}(t) \right] G_i, \end{aligned} \quad (11)$$

where  $G_i, i = 1, \dots, n$  are i.i.d. standard normal distribution random variates, which are

independent of  $\{N_{i,k}^*(\cdot), C_{i,k}, Z_{i,k}\}_{k=1}^K, i = 1, \dots, n$ . It is easy to show that the null distribution of  $V(t, z)$  can be approximated by the conditional distribution of  $\hat{V}(t, z)$ . Hence to obtain the asymptotic null distribution of  $V(t, z)$ , we can get a large number of realizations of  $\hat{V}(t, z)$  by repeatedly generating random numbers  $G_i, i = 1, \dots, n$ , from standard normal distribution, while fixing the  $\{N_{i,k}^*(\cdot), C_{i,k}, Z_{i,k}\}_{k=1}^K, i = 1, \dots, n$ , at their observed values. To assess the goodness-of-fit of the proposed model, we could plot a few number of realizations of  $\hat{V}(t, z)$  and compare them with  $V(t, z)$  to see if there are some unusual patterns. But it is noted that plotting  $\hat{V}(t, z)$  versus  $t$  and  $z$  involves high-dimensional graphics. And this is difficult now. Alternatively, we can use the supremum test  $\sup_{t,z} |V(t, z)|$  to obtain the  $p$ -value of the test, which could be used to judge the adequacy of the model. The  $p$ -value can be obtained by comparing the observed value of  $\sup_{t,z} |V(t, z)|$  to a large number of realizations from  $\sup_{t,z} |\hat{V}(t, z)|$ .

## 5. Simulation Studies

We conducted extensive simulation studies to examine the finite sample properties of our proposed estimators in this section.

Specially, we simulated two different types of recurrent events with the sample size being  $n = 50, 100$  and  $200$ . Firstly, we considered the model with the same regression coefficients and covariates for the two types of recurrent events. The dimension of the covariates  $Z_i$  is 2. The first component of  $Z_i$  follows the uniform distribution on  $(0, 1)$ , while the second follows Bernoulli distribution with success probability 0.5. Let  $\beta_0 = (0, 0.5)^T$ . For the same subject, we introduced a frailty variable to induce positive correlation for the within-subject events. We assume that the frailty variable,  $Q_i$ , followed a Gamma distribution with expectation 0.25 and the variance 0.25 with  $\beta_0^T Z_i = 0, 0.25, 0.5$  and  $1$ . To avoid too large frailty variable, which will induce too many recurrent events for one subject, we took  $Q_i^* = \min(Q_i, 1.5)$ . For the two different baseline mean functions, we considered  $\mu_{0,1}(t) = 0.1 \cdot t = 0.25t$  and  $\mu_{0,2}(t) = 0.2 \cdot t = 0.5t$  respectively. Then the  $k$ th type recurrent events were generated from the Poisson process with intensity function

$$\lambda_{i,k}(t) = Q_i^* + \gamma_{0,k} + \beta_0^T Z_i.$$

Under the above setups, the marginal additive rate model was

$$E \left\{ dN_{i,k}^*(t) | Z_i \right\} = E(Q_i^*) dt + d\mu_{0,k}(t) + \beta_0^T Z_i dt = \left\{ E(Q_i^*) + \gamma_{0,k} + \beta_0^T Z_i \right\} dt,$$

for  $k = 1, 2$ . The censoring time was generated from  $U(0, \tau)$  with  $\tau = 5$ . Under the above settings, the average number of events for the first type of recurrent events is

approximately 1.8 per subject, while that of the second type of recurrent events is approximately 2.5 per subject.

As advised by one reviewer, secondly, we consider the model with different regression coefficients for different types of recurrent events. The covariate  $Z_{i,1}$  and  $Z_{i,2}$  are independent and identically distributed as the Bernoulli distribution with the success probability 0.5, where  $Z_{i,1}$  is the covariate for the first type of the recurrent events and  $Z_{i,2}$  is the covariate for the second type of the recurrent events. The regression coefficient for  $Z_{i,1}$  was set to be 0.5, while that for  $Z_{i,2}$  was 0.3. Following the descriptions in Section 2, we defined  $\mathbf{0} = (0.5, 0.3)^T$ ,  $Z_{i,1}^* = (Z_{i,1}, 0)^T$ , and  $Z_{i,2}^* = (0, Z_{i,2})^T$ . The other design elements were the same as the model with the same regression coefficients and the same covariates. Under these design elements, the  $k$ th type recurrent events were generated from the Poisson process with intensity function

$$\lambda_{i,k}(t) = Q_i^* + \gamma_{0,k} + \beta_0^T Z_{i,k}^*.$$

Then the marginal additive rate model was

$$E \left\{ dN_{i,k}^*(t) | Z_{i,k}^* \right\} = E(Q_i^*) dt + d\mu_{0,k}(t) + \beta_0^T Z_{i,k}^* dt = \left\{ E(Q_i^*) + \gamma_{0,k} + \beta_0^T Z_{i,k}^* \right\} dt,$$

for  $k = 1, 2$ . In this situation, the average number of events for the first type of recurrent events is about 1.8 per subject, while that of the second type of recurrent events is about 2 per subject.

The summaries of our simulation results are presented in Tables 1 and 2. All the results are based on 1000 replicates. It can be seen from the results in Tables 1 and 2 that our methods works well. The biases of the estimated regression coefficients are approximately 0s. The asymptotic standard errors (ASEs) are very close to the empirical standard errors (ESEs). The empirical coverage probabilities are very close to their nominal level, 0.95. As the sample size  $n$  increases, the biases, ASEs and ESEs decrease while the CPs are closer to the nominal level in general. For the fixed sample size, the estimated regression coefficients with  $\tau^2 = 0$  have smallest biases, ASEs and ESEs in general. But because of the truncation for the frailty variable, the ASEs and ESEs of the estimated regression coefficients become larger firstly and then smaller as the  $\tau^2$  increases.

## 6. Analysis of the India Renal Transplant Data

We now apply the proposed methods to a cohort of renal transplant patients who had acquired opportunistic infections during the post transplantation follow-up. Patients who received primary renal transplantation at a tertiary care teaching hospital in Southern India between 1994 and 2007 were studied. We considered a subset of 991 transplant patients for this illustration. Patients were followed to the end of 2008. The median follow-up time was 75.2 months (range: 0 to 179.5 months).

Data were collected prospectively on the transplant patients, which included date of transplantation, information on the subsequent infections that are ascribed to one of the three organism types: bacterial, systemic mycoses (fungal) and viral. A total of 829 infection episodes were observed among these patients. The average number of infections per patient observed was 2 (sd=1.2). Nearly 43% had at least one infection and 22% ( $n=219$ ) had multiple infections of either the same type or of different types. Of those who had multiple infections, 40% acquired infections of the same type, while 52% had two out of three

infection types and 8% acquired all three infection types. Table 3 summarizes the distribution of infections across patients and types of infections. The primary clinical objective of the investigation is to find the risk factors associated with the multiple type infections especially the role of immunosuppression. Risk factors of interest include type of immunosuppression, role of pre-transplant (pre Tx DM) or post-transplant diabetes (post Tx DM) mellitus, acute rejection, age of patient and gender of patient. Patients received different combination of primary immunosuppression and we grouped them into three major regimens: (i) a combination of prednisolone (Pred), azathiaprine (AZA) and calcineurin inhibitor (CNI) (PAC), (ii) combination of prednisolone, CNI and mycophenolate mofetil (MMF) or mycophenolate sodium (MPA) (PCM), and (iii) a group consisting of drugs that are non-CNI based regimens. We centered the age of the patient to 34 years (Age-34).

We considered the following model:

$$E[dN_k^*(t) | Z_k(t)] = d\mu_{0,k}(t) + \beta_0^T Z_k(t) dt,$$

with event-specific effect for immunosuppression and common effect for other covariates with

$$\begin{aligned} \beta^T Z(t) = & \beta_{1,B} IMM_{PAC} * I(Type=1) + \beta_{2,B} IMM_{PCM} * I(Type=1) \\ & + \beta_{3,F} IMM_{PAC} * I(Type=2) + \beta_{4,F} IMM_{PCM} * I(Type=2) \\ & + \beta_{5,V} IMM_{PAC} * I(Type=3) + \beta_{6,V} IMM_{PCM} * I(Type=3) + \beta_7 Age \\ & + \beta_8 Sex + \beta_9 PreTxDM + \beta_{10} PostTxDM + \beta_{11} Rejection, \end{aligned}$$

where  $\beta_B$ ,  $\beta_F$  and  $\beta_V$  denote the bacterial, fungal and viral infection specific parameters, respectively.

Table 4 presents the parameter estimates, standard error of the estimates, and the associated Wald test and p values. The values presented in the table are  $10^3$  times the original values. Interestingly, the effect of immunosuppression is different for different type of infections. For bacterial infections, patients in the PCM group have 7.2 more infections per 1,000 patients per month compared to those in the non-CNI regimen. While, for fungal infection, patients in the PCM group have 1 less infection per 1,000 patients per month than those in the non-CNI immunosuppression group. Similarly decreased effect were observed for viral infection in the PAC group and the PCM group compared to the non-CNI group, however, it was not statistically significant.

Post transplant diabetes mellitus (Risk Difference (RD)=0.95) and post transplant episodes of acute rejections (RD=1.26) are associated with increased rate of infections. Though the presence of pre-transplant hyperglycemia showed an elevated rate of infection (RD=1.17) compared to those without diabetes mellitus, it was not statistically significant. Older patients tend to have more frequent infection while male patients tend to have a decreased infections rate compared to females, although none of these effects were statistically significant.

## 7. Discussion

In this paper, we proposed a semiparametric additive marginal rate model for the analysis of multiple type recurrent event data, which is an useful alternative model to the semiparametric multiplicative marginal rate model suggested by Cai and Schaubel (2004). The class of the link function  $g$  is very rich. Many conventional functions, such as  $g(x) = e^x$ ,

belong to this class. If we choose  $g(x) = x$ , we can obtain an explicit expression of estimators of the true regression parameters. In this article, we used the estimating equations approach to make inference. The consistency and asymptotic normality of the proposed estimator were established. Extensive simulation studies demonstrated the validity of the asymptotic approximation in finite samples.

Schaubel and Cai (2006a, 2006b) considered the analysis of multiple type recurrent event data with possibly missing event type under the semiparametric multiplicative rate model. For the additive rate model, our method can be similarly extended to incorporate such missing event type recurrent event data. Another complication arises when recurrent events are stopped by a terminal event such as death. Methods for a single type of recurrent events with a terminal event have been proposed in the literature, for example, Ghosh and Lin (2000), Ghosh and Lin (2002), Liu et al. (2004), Zeng and Cai (2010), among others. However, terminal event has not been dealt with for the multiple type recurrent events. This is a topic meriting further research.

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## Appendix: Sketch proofs of the main results

### Proof of Theorem 1

Firstly, we prove the strong consistency. Define  $\hat{A}_1(\beta) = -\frac{1}{n} \frac{\partial U_n(\tau, \beta)}{\partial \beta}$ . After some algebraic computations, we can obtain

$$\begin{aligned} \hat{A}_1(\beta) &= \frac{1}{n} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)}(\beta^T Z_{i,k}(t)) - E_k(t, \beta) \right\} Y_{i,k}(t) g^{(1)}(\beta^T Z_{i,k}(t)) Z_{i,k}(t)^T dt \\ &\quad - \frac{1}{n} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau Z_{i,k}(t) g^{(2)}(\beta^T Z_{i,k}(t)) Z_{i,k}(t)^T dM_{i,k}(t, \beta) \\ &\quad + \frac{1}{n} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \frac{\partial E_k(t, \beta)}{\partial \beta} dM_{i,k}(t, \beta) \\ &\equiv a(\beta) - b(\beta) + c(\beta). \end{aligned} \quad (\text{A.1})$$

Under Conditions (d) and (f), we can find a  $\delta > 0$  such that  $\hat{A}_1(\beta)$  is sufficiently close to  $\hat{A}_1(\beta_0)$  whenever  $\|\beta - \beta_0\| < \delta$ , uniformly in  $n$ . On the other hand, we can write

$$\begin{aligned} a(\beta_0) &= \frac{1}{n} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)}(\beta_0^T Z_{i,k}(t)) - e_k(t, \beta_0) \right\} Y_{i,k}(t) g^{(1)}(\beta_0^T Z_{i,k}(t)) Z_{i,k}(t)^T dt \\ &\quad + \frac{1}{n} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \{e_k(t, \beta_0) - E_k(t, \beta_0)\} Y_{i,k}(t) g^{(1)}(\beta_0^T Z_{i,k}(t)) Z_{i,k}(t)^T dt. \end{aligned} \quad (\text{A.2})$$

Through repeated applications of the Strong Law of Large Numbers (Sen and Singer, 1993), the second term of  $a(\beta_0)$  can be proven to converge almost surely to 0. By the Strong Law of Large Numbers (Sen and Singer, 1993), the first term of  $a(\beta_0)$  can be shown to converge almost surely to  $A$ , which is defined in Condition (e). Similarly, we can prove that  $b(\beta_0)$  and  $c(\beta_0)$  converges almost surely to 0. Therefore, we get that  $\hat{A}_1(\tilde{\beta})$  converges to  $A$  almost

surely if  $\tilde{\beta}$  converges to  $\beta_0$  almost surely. The consistency of  $\hat{\beta}$  can be proven using similar arguments as in Theorem 1 in Liu et al. (2010).

Secondly, we prove the asymptotic normality of  $\hat{\beta}$ . By Taylor expansion of  $U_n(\tau, \hat{\beta})$  at  $\beta_0$ , we obtain

$$\sqrt{n}(\hat{\beta} - \beta_0) = \hat{A}_1(\hat{\beta}^*)^{-1} \frac{1}{\sqrt{n}} U_n(\tau, \beta_0), \quad (\text{A.3})$$

where  $\hat{\beta}^*$  is between  $\hat{\beta}$  and  $\beta_0$ . Substituting the expression of  $U_n(\tau, \beta_0)$  into the above equation, we get

$$\begin{aligned} \sqrt{n}(\hat{\beta} - \beta_0) &= \hat{A}_1(\hat{\beta}^*)^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)}(\beta_0^T Z_{i,k}(t)) - E_k(t, \beta_0) \right\} dM_{i,k}(t) \\ &= \hat{A}_1(\hat{\beta}^*)^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)}(\beta_0^T Z_{i,k}(t)) - e_k(t, \beta_0) \right\} dM_{i,k}(t) \quad (\text{A.4}) \\ &\quad + \hat{A}_1(\hat{\beta}^*)^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ e_k(t, \beta_0) - E_k(t, \beta_0) \right\} dM_{i,k}(t). \end{aligned}$$

Using the empirical process techniques (Pollard, 1990; Biliias et al., 1997), it can be shown that

$$\frac{1}{\sqrt{n}} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ e_k(t, \beta_0) - E_k(t, \beta_0) \right\} dM_{i,k}(t) = o_p(1). \quad (\text{A.5})$$

Because  $\hat{\beta} \rightarrow_{a.s.} \beta$  and  $\hat{\beta}^*$  is between  $\hat{\beta}$  and  $\beta_0$ , we get  $\hat{\beta}^* \rightarrow_{a.s.} \beta$  and  $\hat{A}_1(\hat{\beta}^*) \rightarrow_{a.s.} A$ . Hence, we have

$$\begin{aligned} \sqrt{n}(\hat{\beta} - \beta_0) &= A^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)}(\beta_0^T Z_{i,k}(t)) - e_k(t, \beta_0) \right\} dM_{i,k}(t) \quad (\text{A.6}) \\ &\quad + o_p(1). \end{aligned}$$

Then the proof of asymptotic normality is completed by applying the Multivariate Central Limit Theorem (Sen and Singer 1993).

## Proof of Theorem 2

We firstly prove the uniform strong consistency. As usual, we make a simple decomposition

$$\hat{\mu}_{0,k}(t) - \mu_{0,k}(t) = \hat{\mu}_{0,k}(t) - \hat{\mu}_{0,k}(t, \beta_0) + \hat{\mu}_{0,k}(t, \beta_0) - \mu_{0,k}(t). \quad (\text{A.7})$$

For the first term of (A.7), using Taylor expansion, we can write

$$\begin{aligned}
\hat{\mu}_{0,k}(t) - \hat{\mu}_{0,k}(t, \beta_0) &= \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) \{dN_{i,k}^*(s) - g(\hat{\beta}^T Z_{i,k}(s)) ds\}}{\sum_{j=1}^n Y_{j,k}(s)} \\
&\quad - \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) \{dN_{i,k}^*(s) - g(\beta_0^T Z_{i,k}(s)) ds\}}{\sum_{j=1}^n Y_{j,k}(s)} \\
&= - \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) \{g(\hat{\beta}^T Z_{i,k}(s)) - g(\beta_0^T Z_{i,k}(s))\}}{\sum_{j=1}^n Y_{j,k}(s)} ds \quad (\text{A.8}) \\
&= \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) Z_{i,k}^T(s) g^{(1)}(\hat{\beta}^T Z_{i,k}(s)) ds}{\sum_{j=1}^n Y_{j,k}(s)} (\beta_0 - \hat{\beta}).
\end{aligned}$$

Under Conditions (d) and (f), using the strong consistency of  $\hat{\beta}$ , we can prove that the first term converges almost surely to 0 uniformly in  $t \in [0, \tau]$ .

For the second term of (A.7), we can write

$$\begin{aligned}
\hat{\mu}_{0,k}(t, \beta_0) - \mu_{0,k}(t) &= \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) \{dN_{i,k}^*(s) - g(\beta_0^T Z_{i,k}(s)) ds\}}{\sum_{j=1}^n Y_{j,k}(s)} - \mu_{0,k}(t) \\
&= \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) \{dN_{i,k}^*(s) - g(\beta_0^T Z_{i,k}(s)) ds\}}{\sum_{j=1}^n Y_{j,k}(s)} - \int_0^t d\mu_{0,k}(s) \\
&= \sum_{i=1}^n \int_0^t \frac{1}{\sum_{j=1}^n Y_{j,k}(s)} Y_{i,k}(s) \left\{ dN_{i,k}^*(s) - g(\beta_0^T Z_{i,k}(s)) ds - d\mu_{0,k}(s) \right\} \quad (\text{A.9}) \\
&= \sum_{i=1}^n \int_0^t \frac{1}{\sum_{j=1}^n Y_{j,k}(s)} dM_{i,k}(s).
\end{aligned}$$

Using the Uniform Strong Law of Large Number (Pollard, 1990) and Lemma 1 of Lin et al. (2000), the second term converges almost surely to 0 uniformly in  $t \in [0, \tau]$ .

Consequently,  $\hat{\mu}_{0,k}(t)$  converges almost surely to  $\mu_{0,k}(t)$  uniformly in  $t \in [0, \tau]$  for  $k = 1, \dots, K$ .

We now prove the weak convergence of  $W_{k,n}(t)$ . Using the above decomposition, we have

$$\begin{aligned}
W_{k,n}(t) &= \sqrt{n} (\hat{\mu}_{0,k}(t) - \mu_{0,k}(t)) \\
&= \sqrt{n} \{ \hat{\mu}_{0,k}(t) - \hat{\mu}_{0,k}(t, \beta_0) \} + \sqrt{n} \{ \hat{\mu}_{0,k}(t, \beta_0) - \mu_{0,k}(t) \}. \quad (\text{A.10})
\end{aligned}$$

For the first term of (A.10), using Taylor expansion, it is easy to obtain

$$\begin{aligned}
\sqrt{n} \{ \hat{\mu}_{0,k}(t) - \hat{\mu}_{0,k}(t, \beta_0) \} &= \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) Z_{i,k}^T(s) g^{(1)}(\hat{\beta}^{*T} Z_{i,k}(s)) ds}{\sum_{j=1}^n Y_{j,k}(s)} \sqrt{n} (\beta_0 - \hat{\beta}) \\
&= \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) Z_{i,k}^T(s) g^{(1)}(\beta_0^T Z_{i,k}(s)) ds}{\sum_{j=1}^n Y_{j,k}(s)} \sqrt{n} (\beta_0 - \hat{\beta}) \\
&\quad + \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) Z_{i,k}^T(s) \{ g^{(1)}(\hat{\beta}^{*T} Z_{i,k}(s)) - g^{(1)}(\beta_0^T Z_{i,k}(s)) \} ds}{\sum_{j=1}^n Y_{j,k}(s)} \\
&\quad \times \sqrt{n} (\beta_0 - \hat{\beta}) \\
&\equiv \eta_1(t) + \eta_2(t).
\end{aligned} \tag{A.11}$$

It is easy to see that

$$\begin{aligned}
\eta_1(t) &= \int_0^t E_k(s, \hat{\beta}^*) ds \sqrt{n} (\beta_0 - \hat{\beta}) \\
&= \int_0^t e_k(s, \beta_0) ds \sqrt{n} (\beta_0 - \hat{\beta}) + \int_0^t \{ E_k(s, \hat{\beta}^*) - e_k(s, \beta_0) \} ds \\
&\quad \times \sqrt{n} (\beta_0 - \hat{\beta}).
\end{aligned} \tag{A.12}$$

From Theorem 1, we have  $\sqrt{n}(\beta_0 - \hat{\beta}) = O_p(1)$ . It can be shown that

$$\sup_{t \in [0, \tau]} \left| \int_0^t \{ E_k(s, \hat{\beta}^*) - e_k(s, \beta_0) \} ds \right| = o_p(1). \tag{A.13}$$

Hence we have

$$\eta_1(t) = \int_0^t e_k(s, \beta_0) ds \sqrt{n} (\beta_0 - \hat{\beta}) + o_p(1). \tag{A.14}$$

Under Conditions (d) and (f), it can be shown that

$$\sup_{t \in [0, \tau]} \left| \sum_{i=1}^n \int_0^t \frac{Y_{i,k}(s) Z_{i,k}^T(s) \{ g^{(1)}(\hat{\beta}^{*T} Z_{i,k}(s)) - g^{(1)}(\beta_0^T Z_{i,k}(s)) \} ds}{\sum_{j=1}^n Y_{j,k}(s)} \right| = o_p(1). \tag{A.15}$$

Hence we have  $\eta_2(t) = o_p(1)$  uniformly in  $t \in [0, \tau]$ . Then

$$\begin{aligned}
\sqrt{n} \{ \hat{\mu}_{0,k}(t) - \hat{\mu}_{0,k}(t, \beta_0) \} &= \int_0^t e_k(s, \beta_0) ds \sqrt{n} (\beta_0 - \hat{\beta}) + o_p(1) \\
&= \frac{1}{\sqrt{n}} \sum_{i=1}^n \int_0^t e_k(s, \beta_0) ds \sum_{k=1}^K \int_0^\tau \{ Z_{i,k}(t) g^{(1)}(\beta_0^T Z_{i,k}(t)) - e_k(t, \beta_0) \} dM_{i,k}(t) + o_p(1).
\end{aligned} \tag{A.16}$$

For the second term of (A.10), we have

$$\begin{aligned}
\sqrt{n} \{ \hat{\mu}_{0,k}(t, \beta_0) - \hat{\mu}_{0,k}(t) \} &= \sqrt{n} \sum_{i=1}^n \int_0^t \frac{1}{\sum_{j=1}^n Y_{j,k}(s)} dM_{i,k}(s) \\
&= \frac{1}{\sqrt{n}} \sum_{i=1}^n \int_0^t \frac{1}{S_k^{(0)}(s)} dM_{i,k}(s) \\
&= \frac{1}{\sqrt{n}} \sum_{i=1}^n \int_0^t \frac{1}{s_k^{(0)}(s)} dM_{i,k}(s) \\
&\quad + \frac{1}{\sqrt{n}} \sum_{i=1}^n \int_0^t \left\{ \frac{1}{S_k^{(0)}(s)} - \frac{1}{s_k^{(0)}(s)} \right\} dM_{i,k}(s).
\end{aligned} \tag{A.17}$$

Using the Uniform Strong Law of Large Number (Pollard, 1990) and Lemma 1 of Lin et al. (2000), it can be shown that

$$\sup_{t \in [0, \tau]} \left| \frac{1}{\sqrt{n}} \sum_{i=1}^n \int_0^t \left\{ \frac{1}{S_k^{(0)}(s)} - \frac{1}{s_k^{(0)}(s)} \right\} dM_{i,k}(s) \right| = o_p(1). \tag{A.18}$$

Hence we have

$$\sqrt{n} \{ \hat{\mu}_{0,k}(t, \beta_0) - \mu_{0,k}(t) \} = \frac{1}{\sqrt{n}} \sum_{i=1}^n \int_0^t \frac{1}{s_k^{(0)}(s)} dM_{i,k}(s) + o_p(1). \tag{A.19}$$

Summarizing the above results, we arrive at

$$\begin{aligned}
\sqrt{n} (\hat{\mu}_{0,k}(t) - \mu_{0,k}(t)) &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \int_0^t \frac{1}{s_k^{(0)}(s)} dM_{i,k}(s) \\
&\quad + h_k(t) A^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k}(t) g^{(1)}(\beta_0^T Z_{i,k}(t)) - e_k(t, \beta_0) \right\} dM_{i,k}(t) \\
&\quad + o_p(1) \\
&= \frac{1}{\sqrt{n}} \sum_{i=1}^n \phi_{i,k}(t) + o_p(1),
\end{aligned} \tag{A.20}$$

where  $h_k(t) = \int_0^t e_k(s, \beta_0) ds$ .

From the above expression, the convergence in finite-dimensional distribution of  $W_n$  follows from the Multivariate Central Limit theorem.

To complete the proof, we also need the tightness of  $W_n$ . Because  $\phi_{i,k}(t)$  consists of

monotone functions,  $\frac{1}{\sqrt{n}} \sum_{i=1}^n \phi_{i,k}(t)$  is tight (Van der Vaart and Weller, 1996, p215). This completes the proof.

## Proof of theorem 4

It is easy to see that



$$\begin{aligned}
V(t, z) &= n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K I(Z_{i,k} \leq z) \widehat{M}_{i,k}(t) \\
&= n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t I(Z_{i,k} \leq z) d\widehat{M}_{i,k}(s) \\
&= n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t I(Z_{i,k} \leq z) dM_{i,k}(s) \\
&\quad - n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t I(Z_{i,k} \leq z) Y_{i,k}(s) d\{\widehat{\mu}_{0,k}(s) - \mu_{0,k}(s)\} \\
&\quad - n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t I(Z_{i,k} \leq z) Y_{i,k}(s) \left\{ g(\widehat{\beta}^T Z_{i,k}) - g(\beta_0^T Z_{i,k}) \right\} ds \\
&\equiv \omega_1(t, z) - \omega_2(t, z) - \omega_3(t, z).
\end{aligned} \tag{A.21}$$

Note that  $\omega_2(t, z)$  can be rewritten as

$$\omega_2(t, z) = \sum_{k=1}^K \int_0^t \frac{1}{n} \sum_{i=1}^n I(Z_{i,k} \leq z) Y_{i,k}(s) d\widehat{\mu}_{0,k}(s) - \mu_{0,k}(s). \tag{A.22}$$

From the proof of Theorem 2, we can see that

$$\begin{aligned}
\sqrt{n} \{\widehat{\mu}_{0,k}(t) - \mu_{0,k}(t)\} &= - \int_0^t \frac{\sum_{i=1}^n Y_{i,k}(s) Z_{i,k}^T g^{(1)}(\widehat{\beta}^{*T} Z_{i,k})}{\sum_{j=1}^n Y_{j,k}(s)} ds \sqrt{n} (\widehat{\beta} - \beta_0) \\
&\quad + n^{-\frac{1}{2}} \sum_{i=1}^n \int_0^t \frac{1}{\frac{1}{n} \sum_{j=1}^n Y_{j,k}(s)} dM_{i,k}(s).
\end{aligned} \tag{A.23}$$

So  $\omega_2(t, z)$  can be written as

$$\begin{aligned}
\omega_2(t, z) &= - \sum_{k=1}^K \int_0^t \left( \frac{1}{n} \sum_{i=1}^n I(Z_{i,k} \leq z) Y_{i,k}(s) \right) \frac{\sum_{j=1}^n Y_{j,k}(s) Z_{j,k}^T g^{(1)}(\widehat{\beta}^{*T} Z_{j,k})}{\sum_{l=1}^n Y_{l,k}(s)} ds \\
&\quad \times \sqrt{n} (\widehat{\beta} - \beta_0) + n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t \frac{\frac{1}{n} \sum_{j=1}^n I(Z_{j,k} \leq z) Y_{j,k}(s)}{\frac{1}{n} \sum_{l=1}^n Y_{l,k}(s)} dM_{i,k}(s).
\end{aligned} \tag{A.24}$$

By the Uniform SLLN (Pollard, 1990),  $\frac{\sum_{j=1}^n Y_{j,k}(t) Z_{j,k}^T g^{(1)}(\widehat{\beta}^{*T} Z_{j,k})}{\sum_{l=1}^n Y_{l,k}(t)}$  converges to  $e_k(t,$

$z)$  uniformly in  $t$ . Similarly, it can be proven that  $\frac{1}{n} \sum_{j=1}^n I(Z_{j,k} \leq z) Y_{j,k}(t)$  converges to  $f_k(t, z)$  uniformly in  $t$  and  $z$ . Thus, the first term of (A.24) equals

$$- \sum_{k=1}^K \int_0^t f_k(s, z) e_k^T(s, \beta_0) ds \sqrt{n} (\widehat{\beta} - \beta_0) + o_p(1) \tag{A.25}$$

uniformly in  $t$  and  $z$ . By the Uniform SLLN and Lemma 1 of Lin et al. (2000), the second term of (A.24) is

$$n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t \frac{f_k(s, z)}{s_k^{(0)}(s)} dM_{i,k}(s) + o_p(1) \quad (\text{A.26})$$

uniformly in  $t$  and  $z$ . From the proof of Theorem 1, it has been shown that

$$\sqrt{n}(\hat{\beta} - \beta_0) = A^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ Z_{i,k} g^{(1)}(\beta_0^T Z_{i,k}) - e_k(t, \beta_0) \right\} dM_{i,k}(t) + o_p(1). \quad (\text{A.27})$$

Combing the (A.24), (A.25), (A.26) and (A.27), we arrive at

$$\begin{aligned} \omega_2(t, z) = & n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t \frac{f_k(s, z)}{s_k^{(0)}(s)} dM_{i,k}(s) \\ & + n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K h(t, z) A^{-1} \int_0^\tau \left\{ Z_{i,k} g^{(1)}(\beta_0^T Z_{i,k}) - e_k(t, \beta_0) \right\} dM_{i,k}(t) \\ & + o_p(1). \end{aligned} \quad (\text{A.28})$$

By Taylor expansion, we have

$$\begin{aligned} \omega_3(t, z) = & n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t I(Z_{i,k} \leq z) Y_{i,k}(s) \left\{ g(\hat{\beta}^T Z_{i,k}) - g(\beta_0^T Z_{i,k}) \right\} ds \\ = & n^{-1} \sum_{i=1}^n \sum_{k=1}^K \int_0^t I(Z_{i,k} \leq z) Y_{i,k}(s) g^{(1)}(\hat{\beta}^{*T} Z_{i,k}) Z_{i,k}^T ds \sqrt{n} \left\{ \hat{\beta} - \beta_0 \right\}, \end{aligned} \quad (\text{A.29})$$

where  $\hat{\beta}^*$  lies between  $\beta_0$  and  $\hat{\beta}$ . It can be shown that

$n^{-1} \sum_{i=1}^n \sum_{k=1}^K \int_0^t I(Z_{i,k} \leq z) Y_{i,k}(s) g^{(1)}(\hat{\beta}^{*T} Z_{i,k}) Z_{i,k}^T ds$  converges to  $l(t, z)$  almost surely uniformly in  $t$  and  $z$ . So we have

$$\omega_3(t, z) = l(t, z) \sqrt{n} \left\{ \hat{\beta} - \beta_0 \right\} + o_p(1). \quad (\text{A.30})$$

Using the results from the proof of Theorem 1, we get

$$\omega_3(t, z) = \frac{1}{\sqrt{n}} \sum_{i=1}^n \sum_{k=1}^K l(t, z) A^{-1} \int_0^\tau \left\{ Z_{i,k} g^{(1)}(\beta_0^T Z_{i,k}) - e_k(t, \beta_0) \right\} dM_{i,k}(t) + o_p(1). \quad (\text{A.31})$$

Based on the above results, we can arrive at

$$\begin{aligned} V(t, z) = & n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \int_0^t \left\{ I(Z_{i,k} \leq z) - \frac{f_k(s, z)}{s_k^{(0)}(s)} \right\} dM_{i,k}(s) \\ & - n^{-\frac{1}{2}} \sum_{i=1}^n \sum_{k=1}^K \{h(t, z) + l(t, z)\} A^{-1} \int_0^\tau \left\{ Z_{i,k} g^{(1)}(\beta_0^T Z_{i,k}) - e_k(t, \beta_0) \right\} dM_{i,k}(t) \\ & + o_p(1). \end{aligned} \quad (\text{A.32})$$

Since  $V(t, z)$  is represented asymptotically as a sum of independent identical distribution random vectors, the convergence of finite-dimensional distributions can be proven by the multivariate CLT. Using the results from modern empirical process, the tightness can also be obtained. Consequently the weak convergence is proven. This completes the proof.

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**Table 1**

Summaries of the simulation results for the estimated regression coefficients for the model with the same regression coefficient for different types of recurrent events.

<i>n</i>	<i>2</i>	<i>10 = 0</i>				<i>20 = 0.5</i>			
		Bias	ASE	ESE	CP	Bias	ASE	ESE	CP
50	0	0.009	0.202	0.216	0.925	0.003	0.117	0.125	0.931
	0.25	−0.004	0.276	0.305	0.921	−0.004	0.163	0.174	0.929
	0.5	0.005	0.278	0.315	0.924	0.001	0.164	0.176	0.936
	1	0.009	0.265	0.292	0.917	0.003	0.156	0.171	0.922
100	0	−0.004	0.143	0.147	0.942	−0.002	0.083	0.086	0.940
	0.25	0.007	0.200	0.203	0.955	−0.002	0.117	0.118	0.937
	0.5	0.007	0.202	0.215	0.942	0.001	0.119	0.122	0.935
	1	0.008	0.195	0.207	0.943	0.000	0.113	0.120	0.937
200	0	−0.003	0.101	0.100	0.942	−0.003	0.059	0.060	0.942
	0.25	−0.003	0.144	0.153	0.934	0.000	0.084	0.087	0.943
	0.5	−0.007	0.146	0.151	0.939	0.005	0.084	0.086	0.940
	1	−0.006	0.140	0.147	0.939	−0.002	0.081	0.083	0.948

**Table 2**

Summaries of the simulation results for the estimated regression coefficients for the model with the different regression coefficients for different types of recurrent events.

<i>n</i>	<i>2</i>	<i>10 = 0.5</i>				<i>20 = 0.3</i>			
		Bias	ASE	ESE	CP	Bias	ASE	ESE	CP
50	0	0.009	0.151	0.162	0.931	-0.017	0.161	0.167	0.936
	0.25	-0.006	0.188	0.204	0.924	-0.011	0.199	0.205	0.924
	0.5	0.005	0.188	0.197	0.945	-0.019	0.192	0.208	0.932
	1	-0.005	0.180	0.185	0.933	-0.008	0.184	0.196	0.936
100	0	0.004	0.108	0.109	0.948	-0.010	0.116	0.119	0.941
	0.25	-0.005	0.136	0.143	0.938	-0.005	0.142	0.143	0.942
	0.5	-0.009	0.135	0.135	0.950	0.008	0.141	0.140	0.947
	1	0.005	0.130	0.129	0.954	-0.002	0.136	0.139	0.946
200	0	0.001	0.078	0.077	0.944	-0.005	0.087	0.083	0.935
	0.25	-0.001	0.096	0.097	0.952	-0.006	0.105	0.102	0.949
	0.5	0.006	0.101	0.096	0.945	-0.005	0.105	0.101	0.940
	1	-0.002	0.096	0.093	0.940	-0.001	0.100	0.098	0.943

**Table 3**

Recurrent infections by type in the India renal transplant patients.

Infections type	Recurrent infections						
	0	1	2	3	4	5	6
Bacteria	708	165	67	38	8	3	2
Systemic mycoses	937	47	7	0	0	0	0
Virus	865	187	45	5	1	1	0

**Table 4**

Regression analysis of multiple type infections in the India renal transplant study

Covariates	Estimate ( $\times 10^3$ )	SE ( $\times 10^3$ )	Wald test ( $/SE$ ) <sup>2</sup>	p-value
Immunosuppression				
Bacteria				
PAC	0.096	0.074	1.686	0.194
PCM	7.173	2.591	7.661	0.006
Non CNI	ref			
Fungus				
PAC	-0.101	0.079	1.642	0.200
PCM	-1.168	0.392	8.896	0.003
Non CNI	ref			
Virus				
PAC	-0.116	0.112	1.063	0.303
PCM	-0.788	1.360	0.336	0.562
Non CNI	ref			
Age (centered 34 years)	0.001	0.016	0.005	0.942
Gender (male=1, female=0)	-0.684	0.501	1.867	0.172
Diabetes Mellitus (DM)				
Pre Tx DM	1.170	0.888	1.738	0.187
Post Tx DM	0.952	0.511	3.480	0.062
No DM	ref			
Acute Rejection (yes=1, no=0)	1.263	0.340	13.767	< 0.001