The Annals of Applied Statistics
2020, Vol. 14, No. 2, 956–976
https://doi.org/10.1214/20-AOAS1335

GENERALIZED ACCELERATED RECURRENCE TIME MODEL IN THE PRESENCE OF A DEPENDENT TERMINAL EVENT

BY BO WEI[1,*], ZHUMIN ZHANG[2,‡], HUICHUAN J. LAI[2,§] AND LIMIN PENG[1,†]

[1]*Department of Biostatistics and Bioinformatics, Emory University,* [*]*bo.wei@emory.edu;* [†]*lpeng@emory.edu*
[2]*Departments of Nutritional Sciences, University of Wisconsin–Madison,* [‡]*zhuminzhang@wisc.edu;* [§]*hlai@wisc.edu*

Recurrent events are commonly encountered in longitudinal studies. The observation of recurrent events is often stopped by a dependent terminal event in practice. For this data scenario, we propose two sensible adaptations of the generalized accelerated recurrence time (GART) model (*J. Amer. Statist. Assoc.* **111** (2016) 145–156) to provide useful alternative analyses that can offer physical interpretations while rendering extra flexibility beyond the existing work based on the accelerated failure time model. Our modeling strategies align with the rationale underlying the use of the survivors' rate function or the adjusted rate function to account for the presence of the dependent terminal event. For the proposed models, we identify and develop estimation and inference procedures which can be readily implemented based on existing software. We establish the asymptotic properties of the new estimator. Simulation studies demonstrate good finite-sample performance of the proposed methods. An application to a dataset from the Cystic Fibrosis Foundation Patient Registry (CFFPR) illustrates the practical utility of the new methods.

1. Introduction. Recurrent events are commonly encountered in longitudinal follow-up studies of chronic diseases. Examples of recurrent events include repeated infections, hospitalizations or cancer tumor recurrences. The analysis of recurrent events data has been extensively studied in literature. Well-known methods include assessing or modeling the intensity function of recurrent events (Andersen and Gill (1982), Pepe and Cai (1993), for example), the gap time between recurrent events (Huang and Liu (2007), Lin, Sun and Ying (1999), Prentice, Williams and Peterson (1981), e.g.) and the mean/rate function of recurrent events (Cook and Lawless (1997), Lin et al. (2000), for example).

More recently, Huang and Peng (2009) introduced a new concept, called time to expected frequency, as a new quantitative device to flexibly characterize the progression of the recurrent events. As further explained in Section 2, time to expected frequency can be roughly viewed as the inverse function of the mean function; consequently, it can be tackled without requiring assumptions on the dependency structure of recurrent events. Desirably, time to expected frequency also offers a natural physical interpretation that can deliver an alternative view regarding the timing of recurrent events. Regression modeling of time to expected frequency was studied by Huang and Peng (2009) and Sun et al. (2016). These efforts have led to a general regression model for recurrent events data, referred to as the generalized accelerated recurrence time (GART) model. The GART model encompasses the accelerated failure time (AFT) model for recurrent events data (Lin, Wei and Ying (1998)) as a special case and reduces to a quantile regression model in the nonrecurrent event setting.

In practice, the observation of recurrent events is often terminated by some disease-related event (e.g., death) before the end of follow-up. For example, recurrent nonmucoid pseudomonas aeruginosa (PA) infections are commonly seen in cystic fibrosis (CF) patients. This PA phenotype, however, is usually terminated upon the occurrence of a mucoid PA infection.

Received July 2019; revised January 2020.
Key words and phrases. Recurrent events, counting process, Inverse probability censoring weighting, terminal event.

The development of a mucoid PA infection is believed to be closely related to the recurrences of nonmucoid PA infections (Heltshe et al. (2018)). Thus, a mucoid PA infection constitutes a dependent terminal event for the recurrent process of nonmucoid infections.

The presence of a dependent terminal event can complicate the inference on the recurrent event process corresponding to the setting without the dependent terminal event. One reason is that such "net" quantities of interest, such as the marginal rate or mean function, are not nonparametrically identifiable (Ghosh and Lin (2003)). Tackling such quantities generally requires additional modeling of the terminal event and its association with the recurrent events. Various types of joint models of the recurrent events and the dependent terminal event have been studied in literature (Ghosh and Lin (2003), Huang and Wang (2004), Liu, Wolfe and Huang (2004), Ye, Kalbfleisch and Schaubel (2007), among others).

Alternatively, one may assess the progression of recurrent events in conjunction with the terminal event. That is, rather than targeting the recurrent event process for the hypothetical setting where the terminal event does not exist, the analysis may be oriented to "crude" quantities which account for both the recurrent events and the terminal event. Examples of such quantities include the adjusted rate function (Luo, Wang and Huang (2010)), which depicts the rate of recurrent events before the occurrence of the terminal event, and the survivors' rate function, which represents the rate of recurrent events conditioning on the terminal event hasn't occurred (Cook and Lawless (1997)). The interpretations of such "crude" quantities do not assume the existence of the latent recurrent event process after the occurrence of the terminal event (which may be controversial in some practical situations). In particular, the interpretations of the survivors' rate function and the adjusted rate function bear a similar flavor to those of cause-specific hazard function and cumulative incidence function which are popularly used for competing risks data analyses. In addition, these quantities can be estimated without imposing additional modeling of the terminal event.

Many authors (Ghosh and Lin (2002), Liu, Wolfe and Huang (2004), Schaubel and Cai (2005), Zeng and Cai (2010), among others) have investigated either nonparametric or semiparametric estimation of the "crude" quantities for recurrent event data. For example, for the adjusted rate function, Ghosh and Lin (2002) studied a multiplicative effect model and proposed counting-process based estimation procedures which handle random censoring by either inverse weighting the probability of censoring or inverse weighting the survival probabilities of the terminal event time. Miloslavsky et al. (2004) further derived a modified estimation equation which can provide better estimation efficiency. Focusing on the survivors' rate function, Liu, Wolfe and Huang (2004) investigated a multiplicative effect model jointly with a proportional hazards model for the terminal event time, where a shared frailty was incorporated to account for the dependency between the recurrent events and the terminal event. An additive effect model was also studied by Zeng and Cai (2010), along with a linear transformation model assumed for the terminal event time.

Despite the increasing attention to the presence of a dependent terminal event in the recurrent events setting, none of the existing work has dealt with this complication under the GART modeling framework, which is a generalization of the traditional AFT modeling and offers additional flexibility to explore potential heterogeneous effects of covariates. In this work we aim to fill in this gap by discussing how to extend the GART model to properly accommodate the dependent terminal event and how to develop estimation and inference procedures accordingly. More specifically, we study two extensions of the GART model, where we adapt the concept of time to expected frequency, respectively, aligning with the strategy of using the survivors' rate function or the adjusted rate function to account for the presence of the dependent terminal event. It is interesting to uncover that the extension of the GART model based on the survivors' rate function can be estimated by the method of Sun et al. (2016) with the dependent terminal event treated as a random censoring event. This phenomenon is analogous to the known result that for dependently censored univariate survival data, performing the standard Cox regression with dependent censoring treated as independent censoring is the same as conducting the cause-specific proportional hazards regression (Kalbfleisch and Prentice (2002)). This finding justifies the application of the method of Sun et al. (2016) in the presence of a dependent terminal event as long as the interpretation is appropriately adapted. For the GART extension based on the adjusted rate function, we propose an unbiased estimating equation by employing the technique of inverse weight of censoring probability (IPCW) (Robins and Rotnitzky (1992)). The estimation and inference procedures for both extensions of the GART model can be readily implemented based on existing software.

The two GART extensions proposed in this work represent different perspectives for probing the influence of covariates on the "crude" recurrent event process that accounts for the presence of the dependent terminal event. This pertains to the different implications of survivors' rate function and adjusted rate function as illustrated in Luo, Wang and Huang (2010). The survivors' rate function depicts the event occurrences in the subgroup not experiencing the terminal event (i.e., "survivors") which may hold a different pattern from the raw event pattern observed from the whole population that is captured by the adjusted rate function. This is observed in the Cystic Fibrosis example discussed in Section 4.2. As an analogy with "crude" competing risks quantities, the cumulative adjusted rate function is a natural extension of the cumulative incidence function to the recurrent event setting, while the survivors' rate function targets "survivors" and, thus, shares the same rationale as the cause-specific hazard function. In practice, it is important to bear in mind these distinctions when deciding which GART extension fits better to the scientific problem at hand or when explaining discrepancies in results from applying the two proposed GART extensions.

The rest of this article is organized as follows. In Section 2 we introduce the data and notation for the recurrent events setting with a dependent terminal event, and briefly review the GART model. In Section 3 we present the proposed extensions of the GART model and the corresponding estimation procedures. We also establish the asymptotic properties of the proposed estimators and develop sample-based inference procedures. Numerical studies are reported in Section 4, including simulation studies that evaluate the finite-sample performance of our methods and an application to a dataset from the Cystic Fibrosis Foundation Patient Registry (CFFPR). Several remarks are provided in Section 5.

2. Background.

2.1. *Notation and data scenario.* We first introduce notation and describe the data scenario of interest. Let $T^{(j)}$ denote the time to the jth recurrent event ($j = 1, 2, \ldots$), D denote the time to a dependent terminal event and $(L, R]$ denote a random observation window for the recurrent events. Define $\tilde{R} = R \wedge D$, $\delta = I(D \le R)$ and $\mathbf{Z} = (1, \tilde{\mathbf{Z}}^\top)^\top$, where $\tilde{\mathbf{Z}}$ denotes a $p \times 1$ vector of covariates, $\wedge$ is the minimum operator and $I(\cdot)$ is the indicator function. The observed counting process of recurrent events is defined as $N(t) = \sum_{j=1}^{\infty} I(L < T^{(j)} \le t \wedge \tilde{R})$. The underlying recurrent event counting process, without accounting for the presence of the terminal event, is given by $N_0^*(t) = \sum_{j=1}^{\infty} I(T^{(j)} \le t)$. The underlying recurrent event counting process that accounts for the presence of the dependent terminal event is given by $N^*(t) = \sum_{j=1}^{\infty} I(T^{(j)} \le t \wedge D)$. Clearly, $N^*(t)$ does not jump for $t > D$, meaning it does not involve the information on the recurrent events that occur after the time D. We define the at-risk process as $Y(t) = I(L < t \le \tilde{R})$, acknowledging that a subject who has experienced the terminal event would not be considered as at risk for the recurrent event. We define $S_C(t|\mathbf{Z}) = \Pr(L < t \le R|\mathbf{Z})$.

The observed data include n i.i.d. replicates of $(L, \tilde{R}, \delta, N, \mathbf{Z})$, namely, $\{(L_i, \tilde{R}_i, \delta_i, N_i, \mathbf{Z}_i)\}_{i=1}^n$. We assume that L and R are conditionally independent of $N_0^*(\cdot)$ and D given $\mathbf{Z}$.

2.2. *A review of the GART model.* Sun et al. (2016) proposed the generalized accelerated recurrence time (GART) model for recurrent events data in the absence of the terminal event (i.e., $D=\infty$). Define $\mu_{\mathbf{Z}}(t)=E\{N_0^*(t)|\mathbf{Z}\}$ and $\tau_{\mathbf{Z}}(u)=\inf\{t\ge 0:\mu_{\mathbf{Z}}(t)\ge u\}$. The quantity $\mu_{\mathbf{Z}}(t)$ represents the mean function of recurrent events, and the quantity $\tau_{\mathbf{Z}}(u)$ is the so-called time to expected frequency u (Huang and Peng (2009)). Suppose $\mu_{\mathbf{Z}}(t)$ is smooth and strictly increasing. By the definition of $\tau_{\mathbf{Z}}(u)$, the expected frequency (or mean function) of recurrent events given covariates in $\mathbf{Z}$ at time $\tau_{\mathbf{Z}}(u)$ would equal u. This suggests that $\tau_{\mathbf{Z}}(u)$ can be roughly viewed as the inverse function of the mean function. By its definition, $\tau_{\mathbf{Z}}(u)$ has a direct "physical" interpretation on the time-scale (Reid (1994)).

Under the GART model, covariate effects are formulated on the time to expected frequency,

$$\tau_{\mathbf{Z}}\big(G(u)\big)=\exp\{\mathbf{Z}^T\boldsymbol{\beta}_0(u)\},\quad u\in(0,U], \tag{1}$$

where $G(u)=\int_0^u g(s)\,ds$, $g(\cdot)$ is a known positive and continuous function and U is a positive constant in the frequency scale. The nonintercept coefficients in $\boldsymbol{\beta}_0(u)$ represent the effects of the corresponding covariates on time to expected frequency $G(u)$. The specification of $G(\cdot)$ determines the scale in which covariate effects are formulated. In practice, we recommend using $G(u)=u$ for simple interpretation. Other specifications of $G(\cdot)$ may be explored when the interpretation on a transformed frequency scale is desired or as an effort to improve the overall fit of the assumed model to the observed data. When all the nonintercept coefficients in $\boldsymbol{\beta}_0(u)$ are constant over u and $G(u)=u$, it can be shown that model (1) reduces to the accelerated failure time (AFT) model for recurrent events data (Lin, Wei and Ying (1998)). If the event of interest is not recurrent (i.e., $T^{(j)}=\infty$ for $j\ge 2$), then $\tau_{\mathbf{Z}}(u)$ becomes the conditional quantile function of $T^{(1)}$ given $\mathbf{Z}$, and, consequently, model (1) reduces to a quantile regression model for $T^{(1)}$.

Sun et al. (2016) showed that the GART model has an equivalent formulation in terms of the counting process,

$$E\{N\big(e^{\mathbf{Z}^T\beta_0(u)}\big)|\mathbf{Z}\}=E\bigg\{\int_0^u Y\big(e^{\mathbf{Z}^T\beta_0(s)}\big)g(s)\,ds\bigg|\mathbf{Z}\bigg\},\quad u\in(0,U]. \tag{2}$$

This counting process formulation of the GART model greatly facilitates the estimation of $\boldsymbol{\beta}_0(u)$. Specifically, it suggests the following stochastic integral based estimating equation:

$$n^{-1/2}\sum_{i=1}^n\mathbf{Z}_i\bigg\{N_i\big(\exp\{\mathbf{Z}_i^\top\boldsymbol{\beta}(u)\}\big)-\int_0^u Y_i\big(\exp\{\mathbf{Z}_i^\top\boldsymbol{\beta}(s)\}\big)g(s)\,ds\bigg\}=0. \tag{3}$$

As elaborated in Sun et al. (2016), the estimating equation (3) can be stably and effectively solved by a sequence of L_1-minimization problems. Desirable asymptotic properties, such as uniform consistency and weak convergence to a mean-zero Gaussian process, were established for the estimator derived based on equation (3).

3. The proposed models and inference procedures.

3.1. *An extension of the GART model based on survivors' rate function.* The survivors' rate function, defined as $\lambda^S_{\mathbf{Z}}(t)\doteq E\{dN^*(t)|D\ge t,\mathbf{Z}\}/dt$, has been used as a variant of the classic rate function for accounting for the presence of the terminal event (Cook and Lawless (1997)). The interpretation of $\lambda^S_{\mathbf{Z}}(t)$ targets the subgroup with $D\ge t$, and this shares the same rationale as that adopted by cause-specific hazard which is confined to a specific failure type in a competing risks setting. Let $\Lambda^S_{\mathbf{Z}}(u)\doteq\int_0^u\lambda^S_{\mathbf{Z}}(t)\,dt$, and we shall refer it to as the cumulative survivors' rate function.

We propose an extension of the GART model in the presence of the terminal event by viewing $\Lambda_{\mathbf{Z}}^S(u)$, the integral of the survivors' rate function, as the counterpart of the mean function $\mu_{\mathbf{Z}}(u)$ which is the integral of the classic rate function. Specifically, the GART model (1) is transformed to

$$\tau_{\mathbf{Z}}^S(G(u)) = \exp\{\mathbf{Z}^T \boldsymbol{\beta}_0^S(u)\}, \quad u \in (0, U], \tag{4}$$

where $\tau_{\mathbf{Z}}^S(u) \doteq \inf\{t \geq 0 : \Lambda_{\mathbf{Z}}^S(t) \geq u\}$ stands for the time to expected cumulative survivors' rate u. Here, $G(u)$ is defined in the same way as in the GART model (1).

Interestingly, we can show that model (4) has the same counting process formulation as in (2); see Proposition A1 in Appendix A,

$$E\{N(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)})|\mathbf{Z}\} = E\left\{\int_0^u Y(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)})g(s)\,ds \middle| \mathbf{Z}\right\}, \quad u \in (0, U]. \tag{5}$$

An important implication from this finding is that we can directly apply the estimation of Sun et al. (2016) procedure, theory and inference procedures which were originally designed for the setting, without the dependent terminal event, to address the proposed model (4). The critical distinction caused by the presence of a dependent terminal event is about the coefficient interpretation. When D is not independent of $N_0^*(t)$ given $\mathbf{Z}$, a nonintercept coefficient in $\boldsymbol{\beta}_0^S(u)$ represents a covariate effect on time to expected cumulative survivor's rate $G(u)$, rather than a covariate effect on time to expected frequency $G(u)$, which is the coefficient interpretation under the GART model. When D is independent of $N_0^*(\cdot)$ given $\mathbf{Z}$, the cumulative survivor's rate $\Lambda_{\mathbf{Z}}^S(u)$ equals the mean function $\mu_{\mathbf{Z}}(u)$. In this special case, $\boldsymbol{\beta}_0^S(u)$ has the same interpretation as the coefficients under the GART model. The connection discussed here is analogous to the relationship between the proportional cause-specific hazard regression for dependently censored data and the standard proportional hazards regression for randomly censored data which share the same estimation procedure but render different coefficient interpretation (Kalbfleisch and Prentice (2002)).

Following Sun et al. (2016), we can obtain an estimator of $\boldsymbol{\beta}_0^S(\cdot)$, denoted by $\hat{\boldsymbol{\beta}}^S(\cdot)$, as a right continuous piecewise-constant function that jumps only at the grid points of $S_{L(n)} = \{0 = u_0 < u_1 < \cdots < u_{L(n)} = U\}$. We set $\exp\{\mathbf{Z}_i^\top \hat{\boldsymbol{\beta}}^S(0)\} = 0$ for all i and then obtain $\hat{\boldsymbol{\beta}}^S(u_k)$ sequentially for $k = 1, 2, \ldots, L(n)$ by solving the estimating equation,

$$n^{-1/2}\sum_{i=1}^n \mathbf{Z}_i \left\{N_i(e^{\mathbf{Z}_i^\top \boldsymbol{\beta}(u_k)}) - \sum_{m=0}^{k-1} Y_i(e^{\mathbf{Z}_i^\top \hat{\boldsymbol{\beta}}^S(u_m)}) \times \int_{u_m}^{u_{m+1}} g(s)\,ds\right\} = 0 \tag{6}$$

for $\boldsymbol{\beta}(u_k)$. Since estimating equation (6) is not continuous and an exact solution may not exist, $\hat{\boldsymbol{\beta}}(u_k)$ is defined as a generalized solution to this estimating equation. Because estimating equation (6) is monotone, the set of its generalized solutions is a convex set of diameter $O(n^{-1})$ (Fygenson and Ritov (1994)). As discussed in Sun et al. (2016), the estimating function in (6) equals 0.5 times the gradient of the following L_1-type convex function:

$$\begin{aligned} l_k(\mathbf{h}) = {} & \sum_{i=1}^n \sum_{j=1}^\infty I(L_i \leq T_i^{(j)} \leq \tilde{R}_i)\left|\log T_i^{(j)} - \mathbf{Z}_i^\top \mathbf{h}\right| \\ & + \left|R^* - \left\{\sum_{i=1}^n \sum_{j=1}^\infty I(L_i \leq T_i^{(j)} \leq \tilde{R}_i)(-\mathbf{Z}_i)^\top \mathbf{h}\right\}\right| \\ & + \left|R^* - \left\{\sum_{i=1}^n 2\mathbf{Z}_i^\top \mathbf{h} \sum_{m=0}^{k-1} Y_i(\exp\{\mathbf{Z}_i^\top \hat{\boldsymbol{\beta}}^S(u_m)\}) \int_{u_m}^{u_{m+1}} g(s)\,ds\right\}\right|, \end{aligned}$$

where R^* is a very large number and $k = 1, \dots, L(n)$. Finding a generalized solution to equation (6) is then equivalent to locating the minimizer of the L_1-type convex objective function, $l_k(\mathbf{h})$. Therefore, we can obtain $\hat{\boldsymbol{\beta}}^S(u_k)$ as the minimizer of $l_k(\mathbf{h})$.

We would like to point out that the core foundation of the proof's of Sun et al. (2016) for the asymptotic properties of their estimator is the counting process model formulation of the GART model and the empirical process approximations thereof which are irrelevant to whether or not R is independent of the underlying recurrent event process. With $\tilde{R} \doteq R \wedge D$ serving as the counterpart of R, the counting process formulation of the proposed extension of the GART model based on survivors' rate function is the same as that of the GART model, as shown in equation (5). This fact thus allows us to directly apply the asymptotic arguments in Sun et al. (2016) to show that $\hat{\boldsymbol{\beta}}^S(u)$ is uniform consistent in u and weakly converges to a mean-zero Gaussian process at the root-n rate under some regularity conditions. Similarly, the inferences about $\boldsymbol{\beta}_0^S(\cdot)$ can be carried out in the same manner as those presented in Sun et al. (2016).

3.2. *Extension of the GART model based on the adjusted rate function.* The counting process $N^*(t) \doteq \sum_{j=1}^{\infty} I(T^{(j)} \le t \wedge D)$ naturally accounts for the presence of the terminal event and provides the base for defining the adjusted rate function. That is, the adjusted rate function can be defined as $\lambda_{\mathbf{Z}}^A(t) \doteq E\{dN^*(t)|\mathbf{Z}\}/dt$. We call $\Lambda_{\mathbf{Z}}^A(t) \doteq \int_0^t \lambda_{\mathbf{Z}}^A(s)\,ds$ the cumulative adjusted rate function. It is easy to see that $\Lambda_{\mathbf{Z}}^A(t) = E\{N^*(t)|\mathbf{Z}\}$; thus, $\Lambda_{\mathbf{Z}}^A(t)$ can be interpreted as the expected frequency of recurrent events before the occurrence of the terminal event. In the nonrecurrent event setting, $\Lambda_{\mathbf{Z}}^A(t)$ reduces to the so-called cumulative incidence function (Kalbfleisch and Prentice (2002)). The cumulative incidence function and $\Lambda_{\mathbf{Z}}^A(t)$ share the same spirit in terms of how to account for the presence of a dependent censoring event in the nonrecurrent event setting or of a terminal event in the recurrent event setting. The interpretation of $\Lambda_{\mathbf{Z}}^A(t)$ is generally applicable in recurrent events settings in the presence of a dependent or independent terminal event.

Following the strategy of using the adjusted rate function to account for the presence of the terminal event, we propose an extension of the GART model that takes the form

$$\tau_{\mathbf{Z}}^A\big(G(u)\big) = \exp\{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)\}, \quad u \in [\nu, U], \tag{7}$$

where $\tau_{\mathbf{Z}}^A(u) = \inf\{t \ge 0 : \Lambda_{\mathbf{Z}}^A(t) \ge u\}$, $G(u)$ is defined in the same way as in the GART model (1) and $0 < \nu < U$. The nonintercept coefficients in $\boldsymbol{\beta}_0^A(t)$ can be interpreted as covariate effects on time to cumulative adjusted rate $G(u)$.

In Proposition A2 in the Appendix, we show that model (7) implies

$$\begin{aligned} &E\left\{\sum_{j=1}^{\infty} \frac{1}{S_C(T^{(j)}\big|\mathbf{Z})} I\big(L < T^{(j)} \le e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)} \wedge \tilde{R}\big)|\mathbf{Z}\right\} \\ &\quad = \int_0^u g(s)\,ds, \quad u \in [\nu, U]. \end{aligned} \tag{8}$$

By this result we propose to estimate $\boldsymbol{\beta}_0^A(u)$ based on the the estimating equation,

$$\mathbf{S}_n(\boldsymbol{\beta}, u) = 0, \tag{9}$$

where

$$\begin{aligned} &S_n(\boldsymbol{\beta}, u) \\ &\quad = n^{-1/2}\sum_{i=1}^{n} \mathbf{Z}_i \left\{\sum_{j=1}^{\infty} \frac{1}{\hat{S}_C(T_i^{(j)}|\mathbf{Z}_i)} I\big(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \boldsymbol{\beta}(u)} \wedge \tilde{R}_i\big) - \int_0^u g(s)\,ds\right\} \end{aligned} \tag{10}$$

and $\hat{S}_C(\cdot|\mathbf{Z})$ is a reasonable estimator of $S_C(\cdot|\mathbf{Z})$. For presentation simplicity, in the sequel we assume that L and R are independent of $\mathbf{Z}$. In this case $S_C(t|\mathbf{Z})$ is free of $\mathbf{Z}$ and equals $\Pr(R \geq t) - \Pr(L \geq t)$. Since R is only subject to the independent censoring by D and L is always observed, we shall estimate $\Pr(R \geq t)$ by the left-continuous version of the Kaplan–Meier estimator of $\Pr(R > t)$, denoted by $\hat{G}^R(t)$ and estimate $\Pr(L \geq t)$ by its empirical counterpart, denoted by $\hat{G}^L(t)$. A reasonable estimate for $S_C(t|\mathbf{Z})$ is then given by $\hat{S}_C(t) \doteq \hat{G}^R(t) - \hat{G}^L(t)$. When L and R are believed to be covariate-dependent, we can impose regression modeling of L and R given $\mathbf{Z}$ to provide a reasonable estimate for $S_C(\cdot|\mathbf{Z})$. For instance, we may assume Cox proportional hazards models for L and R. Since L is always observed and R is only subject to independent censoring by D, we can obtain the estimated baseline cumulative hazard functions, $\hat{\Lambda}_L(t)$ and $\hat{\Lambda}_R(t)$, and the estimated Cox regression coefficients, $\hat{\boldsymbol{\beta}}_L$ and $\hat{\boldsymbol{\beta}}_R$, using the standard partial likelihood estimation procedure. This then leads to a reasonable estimate for $S_C(t|\mathbf{Z})$, given by $\hat{S}_C(t|\mathbf{Z}) = \exp\{-\hat{\Lambda}_R(t)\exp(\mathbf{Z}^\mathsf{T}\hat{\boldsymbol{\beta}}_R)\} - \exp\{-\hat{\Lambda}_L(t)\exp(\mathbf{Z}^\mathsf{T}\hat{\boldsymbol{\beta}}_L)\}$. Similarly, we may estimate $S_C(t|\mathbf{Z})$ based on other available regression models for randomly censored data, such as the accelerate failure time model.

Note that equation (9) is monotone but not continuous. Thus, an exact solution may not exist. We then define an estimator of $\boldsymbol{\beta}_0^A(u)$, $\hat{\boldsymbol{\beta}}^A(u)$, as a generalized solution to equation (9) which belongs to a convex set of size $O(n^{-1})$ (Fygenson and Ritov (1994)). Following the arguments in Peng and Fine (2009), we only need to solve equation (9) on a fine grid $S_{L(n)}^A = \{\nu = u_0 < u_1 < \cdots < u_{L(n)} = U\}$ and then let $\hat{\boldsymbol{\beta}}^A(\cdot)$ be a right continuous piecewise-constant function that jumps only at the grid points of $S_{L(n)}^A$. We can show that locating $\hat{\boldsymbol{\beta}}^A(u_k)$ $(k = 1, \ldots, L(n))$ is equivalent to finding the minimizer of

$$\begin{aligned} U_n(\mathbf{h}, u) &= n^{-1/2} \sum_{i=1}^{n} \sum_{j=1}^{\infty} \frac{1}{\hat{S}_C(T_i^{(j)})} I\big(L_i < T_i^{(j)} \leq \tilde{R}_i\big) \big|\log T_i^{(j)} - \mathbf{Z}_i^\top \mathbf{h}\big| \\ &\quad + \left| R^* - \left\{ \sum_{i=1}^{n} \sum_{j=1}^{\infty} \frac{1}{\hat{S}_C(T_i^{(j)})} I\big(L_i < T_i^{(j)} \leq \tilde{R}_i\big)(-\mathbf{Z}_i)^\top \mathbf{h} \right\} \right| \\ &\quad + \left| R^* - \left\{ \sum_{i=1}^{n} 2\mathbf{Z}_i^\top \mathbf{h} \int_0^u g(s)\,ds \right\} \right|, \end{aligned} \tag{11}$$

where R^* is a sufficiently large number. This is because $\partial U_n(\mathbf{h}, u)/\partial \mathbf{h}$ equals two times $n^{1/2} S_n(\boldsymbol{\beta}, u)$ when R^* is chosen large enough to bound $|\sum_{i=1}^n 2\mathbf{Z}_i^\top \mathbf{h} \int_0^{u_k} g(s)\,ds|$ and $|\sum_{i=1}^n \sum_{j=1}^\infty \frac{1}{\hat{S}_C(T_i^{(j)}|\mathbf{Z})} I(L_i < T_i^{(j)} \leq \tilde{R}_i)(-\mathbf{Z}_i)^\top \mathbf{h}|$. The minimization of $U_n(\mathbf{h}, u)$ can be easily solved by using standard statistical software, such as the *l1fit*() function in S-PLUS or the *rq*() function in R package *quantreg*.

When the event of interest is not recurrent (i.e., $T^{(j)} = \infty$ for $j > 1$) and $L = 0$, the data considered in this work become the classic semicompeting risks data. In this special case, $\Lambda_{\mathbf{Z}}^A(t)$ boils down to the cumulative incidence function for $T^{(1)}$; hence, model (6) is the same as the cumulative incidence quantile regression model which has been studied for left truncated semi-competing risks data (Li and Peng (2011)) and competing risks data (Peng and Fine (2009)). Moreover, the proposed estimator $\hat{\boldsymbol{\beta}}^A(u)$ applied to such competing risks data coincides with the estimator's of Li and Peng (2011) applied to the same data and the estimator's of Peng and Fine (2009) applied to the competing risks portion of the data from ignoring the extra information on D.

3.2.1. *Asymptotic properties.* We establish the uniform consistency and weak convergence of the proposed estimator $\hat{\boldsymbol{\beta}}^A(\cdot)$. We first state the regularity conditions:

(C1) (i) There exists $v_R > 0$ such that $\Pr(R = v_R) > 0$ and $\Pr(R > v_R) = 0$; (ii) $\Pr(L < R) = 1$; (iii) $\inf_{t\in(0,v_R]} S_C(t) > 0$.

(C2) (i) $\|\mathbf{Z}\|$ is bounded; (ii) $N(\tilde{R})$ is bounded.

(C3) (i) $\boldsymbol{\beta}_0^A(u)$ is Lipschitz continuous in $u \in [\nu, U]$; (ii) $\lambda_{\mathbf{Z}}^A(t)$ is bounded above uniformly in t and $\mathbf{Z}$.

(C4) For some $\rho_0 > 0$ and $c_0 > 0$, $\inf_{\mathbf{b}\in\mathcal{B}(\rho_0)} \operatorname{eigmin} \mathbf{A}(\mathbf{b}) \ge c_0$, where $\mathcal{B}(\rho) = \{\mathbf{b} \in \mathbb{R}^{p+1} : \inf_{u\in[\nu,U]} \|\mathbf{b} - \boldsymbol{\beta}_0^A(u)\| \le \rho\}$ and $\mathbf{A}(\mathbf{b}) = E\{\mathbf{Z}^{\otimes 2} \exp(\mathbf{Z}^\top\mathbf{b})$
$\lambda_{\mathbf{Z}}^A(\exp(\mathbf{Z}^\top\mathbf{b}))\}$. Here, $\|\cdot\|$ denotes the Euclidean norm, "eigmin" denotes the minimal eigenvalue of a matrix and $\mathbf{u}^{\otimes 2} = \mathbf{u}\mathbf{u}^\top$.

Condition (C1) is assumed to ensure the inverse weights $\{S_C(T_i^{(j)})\}^{-1}$ can be consistently estimated. This condition is usually satisfied in follow-up studies with administrative censoring (or by imposing artificial truncation to the observed recurrent events) and a positive probability mass at $L = 0$. Conditions (C2) and (C3) are realistic assumptions; similar conditions are also adopted in Peng and Fine (2009) for the cumulative incidence quantile regression model in the competing risks setting. Condition (C4) implies that $S_n(\boldsymbol{\beta}, u)$ is strictly monotone in a neighborhood of $\boldsymbol{\beta}_0^A(u)$ for $u \in (0, U]$. This entails the identifiability of $\boldsymbol{\beta}_0^A(u)$ and the consistency of $\hat{\boldsymbol{\beta}}^A(u)$.

Under the regularity conditions (C1)–(C4), we have the following theorems:

THEOREM 1. *Suppose model* (7) *holds. Under conditions* C1–C4,

$$\lim_{n\to\infty} \sup_{u\in[\nu,U]} \|\hat{\boldsymbol{\beta}}^A(u) - \boldsymbol{\beta}_0^A(u)\| \to_p 0.$$

THEOREM 2. *Suppose model* (7) *holds. Under conditions* C1–C4, $n^{1/2}\{\hat{\boldsymbol{\beta}}^A(u) - \boldsymbol{\beta}_0^A(u)\}$ *converge weakly to a mean zero Gaussian process for* $u \in [\nu, U]$ *with the covariance function*

$$\boldsymbol{\Phi}(u', u) = \mathbf{A}\{\boldsymbol{\beta}_0^A(u')\}^{-1} E\{\boldsymbol{\xi}_1(u')\boldsymbol{\xi}_1(u)^\top\}\mathbf{A}\{\boldsymbol{\beta}_0^A(u)\}^{-1},$$

where $\boldsymbol{\xi}_1(u)$ *is defined in equation* (15) *in Appendix* B.

The proofs of Theorems 1–2 follow the similar arguments in Peng and Fine (2009). The detailed proofs are provided in Appendix B.

3.2.2. *Inference.* To make inference on $\boldsymbol{\beta}_0^A(u)$, we can apply a bootstrapping procedure such as the standard nonparametric bootstrapping with replacement or the resampling method proposed in Jin, Ying and Wei (2001).

Alternatively, we can also perform sample-based inference following the lines of Peng and Fine (2009). The sample-based inference does not involve resampling and repeating the proposed estimation procedure and, therefore, can save considerable computational time particularly when the sample size is large. More specifically, let $\hat{\boldsymbol{\Sigma}}(u, v)$ denote a consistent plug-in estimator of $\boldsymbol{\Sigma}(u, v) \doteq E\{\boldsymbol{\xi}_1(u)\boldsymbol{\xi}_1(v)\}$, which stands for the asymptotic covariance matrix of $\mathbf{S}_n(\boldsymbol{\beta}_0^A(u), u)$, where $\boldsymbol{\xi}_1(u)$ is defined in equation (15) in Appendix B. An example of $\hat{\boldsymbol{\Sigma}}(u, v)$ may be given by

$$\hat{\boldsymbol{\Sigma}}(u, u) = \frac{1}{n}\sum_{i=1}^{n}(\hat{\boldsymbol{\xi}}_{1,i}(u) - \hat{\boldsymbol{\xi}}_{2,i}(u))^{\otimes 2},$$

where $\hat{\boldsymbol{\xi}}_{1,i}(u) = \mathbf{Z}_i\{\sum_{j=1}^{\infty} \frac{1}{\hat{S}_C(T_i^{(j)})} I(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \hat{\boldsymbol{\beta}}^A(u)} \wedge \tilde{R}_i) - \int_0^u g(s)\,ds\}$, $\hat{\boldsymbol{\xi}}_{2,i}(u) = \frac{1}{n}\sum_{k=1}^n \mathbf{Z}_k\{\sum_{j=1}^{\infty} \frac{\hat{\boldsymbol{\xi}}_{\hat{S}_C,i}(T_k^{(j)})}{\hat{S}_C^2(T_k^{(j)})} \times I(L_k < T_k^{(j)} \le e^{\mathbf{Z}_k^\top \hat{\boldsymbol{\beta}}^A(u)} \wedge \tilde{R}_k)\}$ and $\hat{\boldsymbol{\xi}}_{\hat{S}_c,i}(T_k^{(j)}) = \hat{G}^R(T_k^{(j)}) \times I(T_k^{(j)} \ge \tilde{R}_i, \delta_i = 0)/\{\sum_{m=1}^n I(\tilde{R}_m \ge \tilde{R}_i)/n\} - \{I(L_i \ge t) - \frac{1}{n}\sum_{m=1}^n I(L_m \ge T_k^{(j)})\}$. First, find a symmetric and nonsigular $(p+1) \times (p+1)$ matrix $\mathbf{E}_n(u) = \{\mathbf{e}_{n,1}(u), \dots, \mathbf{e}_{n,p+1}(u)\}$ such that $\hat{\boldsymbol{\Sigma}}(u,u) = \{\mathbf{E}_n(u)\}^2$. Next, calculate $\mathbf{D}_n(u) = (\mathbf{S}_n^{-1}(\mathbf{e}_{n,1}(u), u) - \hat{\boldsymbol{\beta}}(u), \dots,$ $\mathbf{S}_n^{-1}(\mathbf{e}_{n,p+1}(u), u) - \hat{\boldsymbol{\beta}}(u))$, where $\mathbf{S}_n^{-1}(\mathbf{e}, u)$ is defined as the solution to $\mathbf{S}_n(\mathbf{b}, u) = \mathbf{e}$. Finally, we can estimate the asymptotic covariance matrix of $n^{1/2}\{\hat{\boldsymbol{\beta}}^A(u) - \boldsymbol{\beta}_0^A(u)\}$ and $n^{1/2}\{\hat{\boldsymbol{\beta}}^A(u') - \boldsymbol{\beta}_0^A(u')\}$ by $n\mathbf{D}_n(u')\mathbf{E}_n(u')^{-1}\hat{\boldsymbol{\Sigma}}(u', u)$ $\mathbf{E}_n(u)^{-1}\mathbf{D}_n(u)^T$. With $u = u'$, the asymptotic variance matrix of $n^{1/2}\{\hat{\boldsymbol{\beta}}^A(u) - \boldsymbol{\beta}_0^A(u)\}$ can then be estimated by $n\{\mathbf{D}_n(u)\}^{\otimes 2}$.

In addition, following the lines of Peng and Fine (2009), we can perform second-stage inference to test whether or not a coefficient function in $\boldsymbol{\beta}_0^A(u)$ is constant over u. Rejecting the constancy hypothesis for a nonintercept coefficient would indicate the lack-of-fit of a AFT-type model that imposes constant effects for all covariates.

4. Numerical studies.

4.1. *Monte-Carlo simulations.* We conduct Monte-Carlo simulations to evaluate the proposed method for the extended GART model (7) based on the adjusted rate function. We generate covariates Z_1 and Z_2, respectively, from Bernoulli(0.5) and Uniform($-5, 5$) distributions. Define $\eta_j = I(T^{(j)} \le D)$. We generate η_j $(j = 1, 2, \dots)$ as Bernoulli random variables that satisfy $\Pr(\eta_1 = 1) = p$ and $\Pr(\eta_{j+1} = 1|\eta_j = 1) = p$, $\Pr(\eta_{j+1} = 1|\eta_j = 0) = 0$. The value of p determines the number of recurrent events before the terminal event; setting a larger p tends to generate more recurrent events before the terminal event. Define $T_{j,D} = \exp\{\frac{T^{*(j)}}{3\gamma} Z_1 + \min(0.2, \frac{T^{*(j)}}{15\gamma})Z_2\}T^{*(j)}/\gamma$, where $\{T^{*(j)}, j = 1, 2, \dots\}$ are produced from a standard homogeneous Poisson process and γ follows the Gamma(2, 2) distribution. For $j \ge 1$ with $\eta_j = 1$, we let $T^{(j)} = T_{j,D}$; for j corresponding to the first $\eta_j = 0$, we let $D = T_{j,D}$. Under this set-up we can show that

$$
\begin{aligned}
\tau_{\mathbf{Z}}^A(u) = \exp\biggl\{&\log\biggl(\frac{1}{1-p}\biggl[\frac{2}{\{1-u(1-p)/p\}^{1/2}} - 2\biggr]\biggr) \\
&+ \frac{1}{3-3p}\biggl[\frac{2}{\{1-u(1-p)/p\}^{1/2}} - 2\biggr]Z_1 \\
&+ \min\biggl(0.2, \frac{1}{15-15p}\biggl[\frac{2}{\sqrt{1-u(1-p)/p}} - 2\biggr]\biggr)Z_2\biggr\}.
\end{aligned}
$$

This indicates that model (7) holds with $g(u) = u$. The effect of Z_1 on $\tau_{\mathbf{Z}}^A(u)$ is increasing with u, and the effect of Z_2 rises first and then becomes constant as u increases. Finally, we generate L as $w_1 \cdot \mathrm{Unif}(0, 1)$, where w_1 follows Bernoulli(0.8), and generate R as $w_2 \cdot \mathrm{Unif}(L, 30) + (1 - w_2) \cdot 30$, where w_2 follows Bernoulli(0.8).

In our simulations we consider $p = 0.8, 0.85, 0.9, 0.95$. In each setting we generate 1000 datasets with sample size 200. The estimator $\hat{\boldsymbol{\beta}}^A(u)$ is calculated on an equally spaced u-grid with 150 grid points. For $p = 0.8, 0.85, 0.9, 0.95$, the range of the u-grid is set as (0, 1.5], (0, 2.0], (0, 2.5] and (0, 3.0], respectively. When carrying out bootstrapping-based inference, we adopt standard nonparametric bootstrapping with replacement and set the size of resampling as 100. We further consider a more extreme case with $p = 0.5$. Simulation results pre-

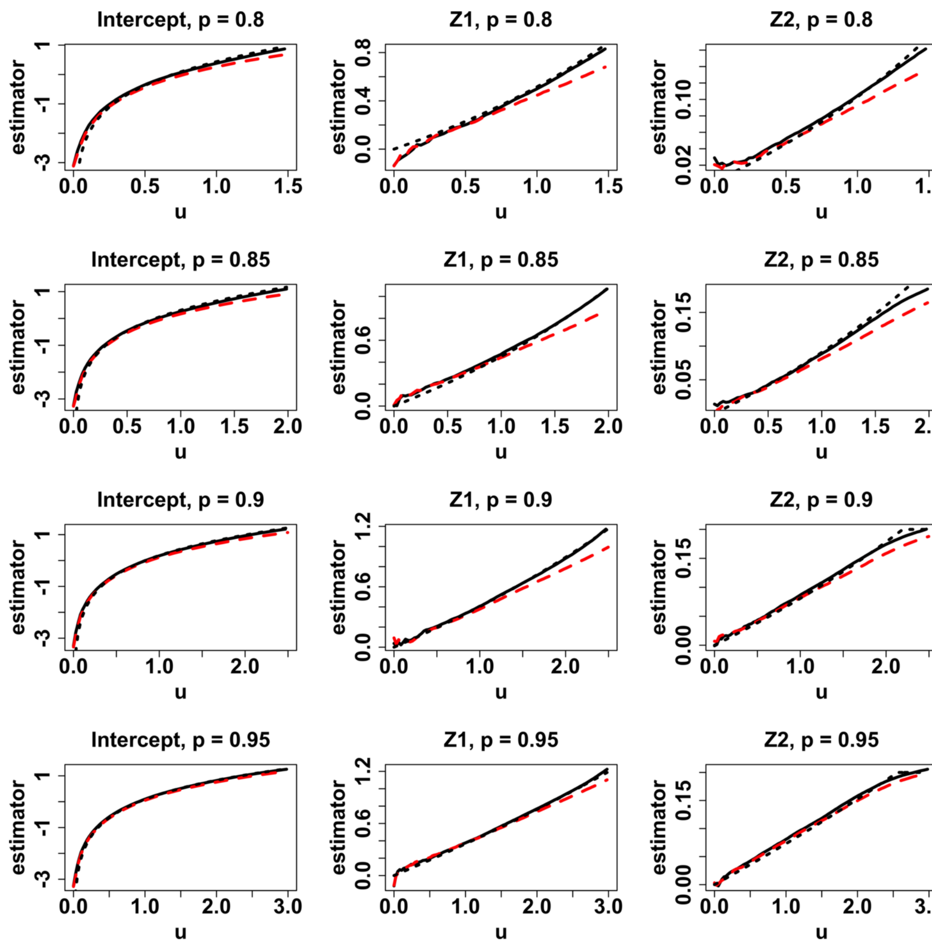

FIG. 1. *The proposed coefficient estimates for model* (7) (*solid lines*), *along with the true coefficients* $\boldsymbol{\beta}_0^A(u)$ (*dotted lines*) *and the coefficient estimates obtained from applying the method of Sun et al*. (2016) (*dashed lines*) *when sample size* $n = 200$.

sented in Section S1 of the Supplementary Material (Wei et al. (2020)) suggest reasonably good performance of the proposed method.

In Figure 1 we present the estimated coefficients for model (7) based on the method proposed in Section 3.2. We also plot the coefficient estimates obtained from naively applying the method of Sun et al. (2016). It is clearly shown that the proposed estimator $\hat{\boldsymbol{\beta}}^A(u)$ is virtually unbiased. Naively using the method of Sun et al. (2016) produces biased estimates for the covariate effects on $\tau_{\mathbf{Z}}^A(u)$, particularly when u is large. This is because the estimates of Sun et al. (2016) are consistent about the covariate effects on $\tau_{\mathbf{Z}}^S(u)$ which is generally different from $\tau_{\mathbf{Z}}^A(u)$. It is also noted as p increases, the departure of the empirical averages of the estimates of Sun et al. (2016) from the true $\boldsymbol{\beta}_0^A(u)$'s decrease. This is reasonable because, when p is closer to 1, the terminal event is more unlikely to occur before the end of the observation (i.e., R). Consequently, we expect $\tau_{\mathbf{Z}}^A(u)$ and $\tau_{\mathbf{Z}}^S(u)$ would be more similar; hence, the method targeting $\tau_{\mathbf{Z}}^A(u)$ and the method of Sun et al. (2016) which targets $\tau_{\mathbf{Z}}^S(u)$ would produce more agreeable results.

In Figure 2 we compare the estimated standard errors (SE) based on the sample-based inference procedure and those based on bootstrapping with the empirical standard deviations (SD) of the coefficient estimates. It is shown that both sample-based SEs and bootstrapping-based SEs are close to the empirical SDs in each setting, except for those at very small u's.

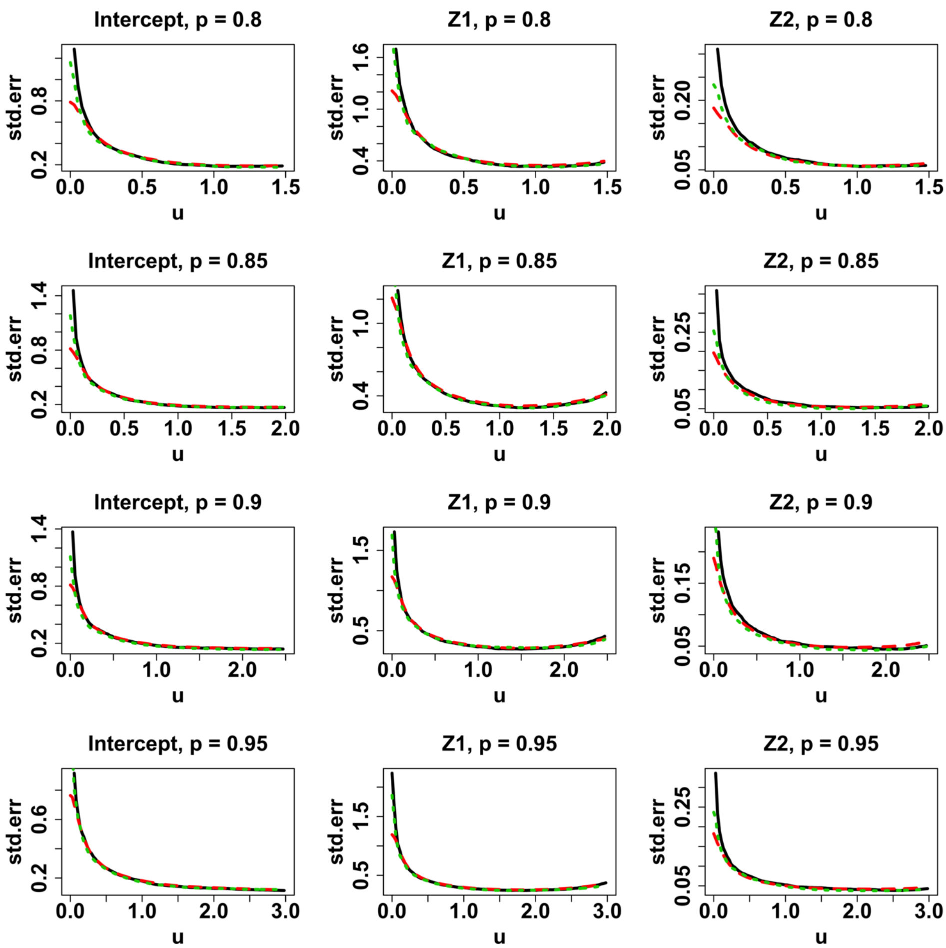

FIG. 2. *Estimated standard errors based on sample-based inference procedure (solid lines), estimated standard errors based on bootstrapping (dashed lines) and empirical standard deviations (dotted lines) with sample size* $n = 200$.

The bootstrapping-based SEs are slightly closer to the empirical SDs as compared to sample-based SEs.

We also evaluate the empirical coverage probabilities of the 95% confidence intervals (CI) constructed based on the sample-based and bootstrapping-based inference procedures. Figure 3 shows that the empirical coverage probabilities for the coefficients for Z_1 and Z_2 are fairly close to the nominal value 95%. The bootstrapping-based confidence intervals perform slightly better than the sample-based confidence intervals. For the intercept, the confidence intervals seem to be undercovered, particularly for small u's. In simulations with sample size 400, which are reported in Section S1 of the Supplementary Material (Wei et al. (2020)), we observe a clear improvement in the empirical coverage probabilities for the intercept.

In addition, additional simulation results reported in Section S1 of the Supplementary Material (Wei et al. (2020)) show that the proposed method is not sensitivity to the choice of $G(\cdot)$.

4.2. *An application to a dataset from the Cystic Fibrosis Foundation Patient Registry.* Cystic Fibrosis (CF) is one of the most common, life-shortening genetic disorders with an incidence of 1:3500 in newborns in the United States (Russell, Hertz and McMillan (2012)). The leading cause of the premature death is obstructive lung disease with recurrent respiratory infections, inflammations and structural airway damage. Pseudomonas aeruginosa (PA),

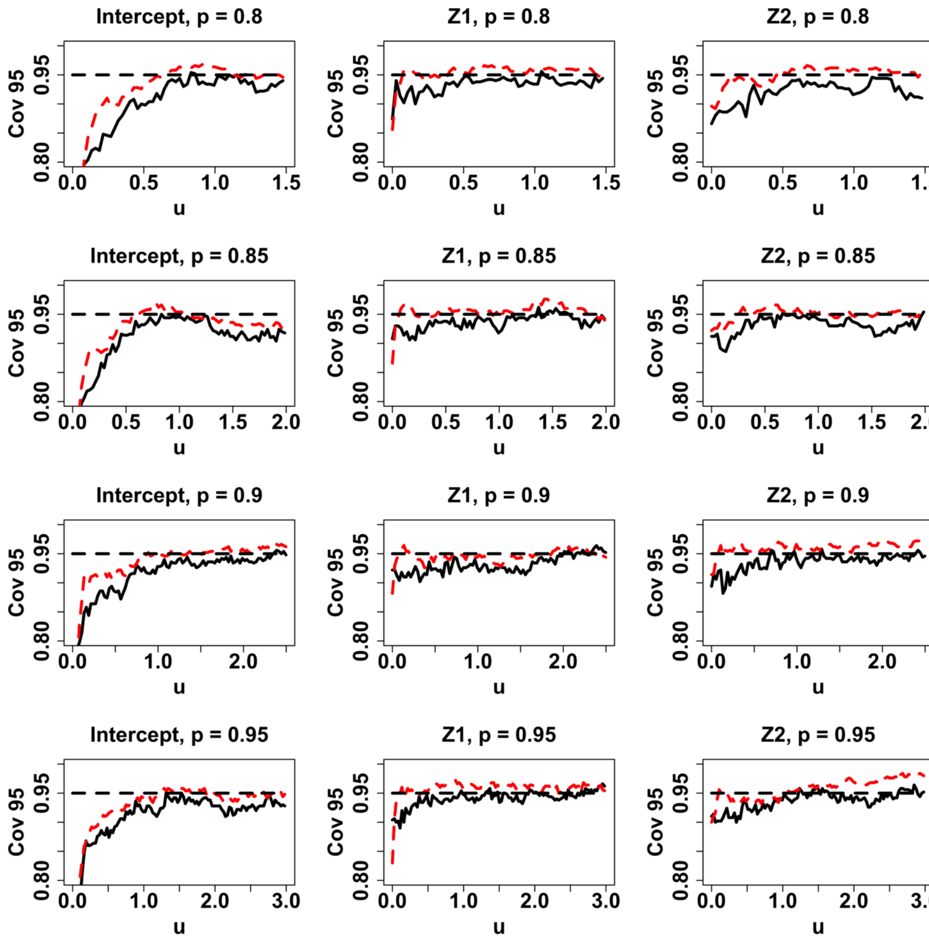

FIG. 3. *Empirical coverage probabilities of the* 95% *confidence intervals constructed based on the sample-based inference procedure* (*solid lines*) *and bootstrapping procedure* (*dashed lines*) *with sample size* $n = 200$.

a ubiquitous environmental bacterium, is one of the major pathogens in CF lungs which is associated with poor clinical outcomes and greater mortality (Davies (2002)). Respiratory tract cultures are routinely obtained for identifying PA and characterizing its phenotypes (mucoid or nonmucoid). The early PA infection is usually nonmucoid and antibiotic sensitive. But recurrent nonmucoid PA infections lead to chronic PA infections, then to mucoid PA phenotype (Mathee et al. (1999)). The development of mucoid PA yet can be more complicated than this widely held paradigm (Heltshe et al. (2018)). Mucoid PA is more resistant to antibiotics and more difficult to eradicate (Lyczak, Cannon and Pier (2002)). As a result, rarely patients can go back to the nonmucoid PA infection stage once acquiring a mucoid PA infection. Under these considerations a mucoid PA infection constitutes a dependent terminal event to the recurrent process of nonmucoid PA infections (in addition to death).

We apply the proposed method to a subdataset from the 2008 Cystic Fibrosis Foundation Patient Registry (CFFPR) data, which includes 1974 children who were born in or after 2000 with CF and had more than five years' follow-up. The objective of our analysis is to assess how several potential risk factors influence the recurrence of nonmucoid PA infections prior to the mucoid PA infection while alive. To this end, we set the time origin as birth. We define the recurrent event time $T^{(j)}$ as the age at the jth nonmucoid infection and time to the terminal event D as the age at the first mucoid PA infection or death, whichever occurred first. Age at the first CFFPR visit and age at the last follow-up visit correspond to the L and R, respectively.

TABLE 1
Summary statistics of the potential risk factors in the CFFPR dataset ($n = 1974$)

Potential risk factors		n (%)
Sex	Female	1024 (51.9%)
	Male	950 (48.1%)
F508del	Heterogeneous	1274 (64.5%)
	Homogeneous/other	700 (35.5%)
Meconium ileus	Yes	534 (72.9%)
	No	1440 (27.1%)
Pancreatic insufficiency status	Insufficient	1810 (91.7%)
	Sufficient	164 (8.3%)

In our dataset a total of 3459 nonmucoid PA infections before mucoid PA infections were documented, and 472 subjects experienced mucoid PA infections during the follow-up. There are 14 subjects who died before the first mucoid PA infection. Within each subject the number of nonmucoid PA infections before the first mucoid PA infection range from zero to 19, with mean and median equal to 1.75 and *one*, respectively. We consider risk factors including sex (coded as $Sex = 1$ if female and 0 otherwise), patient's CFTR genotype (coded as $F508/Other = 1$ if F508del heterogeneous and 0 otherwise), meconium ileus (MI) status (coded as $MI = 1$ if having the diagnosis of MI and 0 otherwise and pancreatic insufficiency status (coded as $Pancreat = 1$ if pancreatic insufficient and 0 otherwise). Table 1 provides a summary of these potential risk factors.

We first fit our dataset, the extended GART model based on the adjusted rate function, model (7), with $g(u) = 1$. In Figure 4 we plot the estimated regression coefficients with 95% pointwise confidence intervals (CI). The intercept coefficient estimates represent the estimated log time to cumulative adjusted rate (or, alternatively, expected frequency of nonmucoid PA infection before mucoid PA infection and death) for the reference group, which included CF boys with homozygous F508del mutations who had no MI and were pancreatic sufficient. For example, the estimated intercept coefficient plot suggests that the expected frequency of nonmucoid PA infection before mucoid PA infection while alive reaches 1, approximately, at the age of 4.4 years.

The nonintercept coefficient estimates represent the estimated effects of covariates on $\tau_{\mathbf{Z}}^{A}(u)$. Negative estimates indicate quicker progression to nonmucoid PA infection recurrence in the presence of mucoid PA infection and death. From Figure 4 it is observed that the coefficients for *Sex* and $F508$ are mostly small, with the 95% CIs fully covering zero. This suggests that gender and F508 genotype may have little effect on the acquisition and the recurrence of nonmucoid PA infections. The coefficients for *MI* and *Pancreat* are all negative, and, moreover, the upper bounds of the corresponding 95% CIs are mostly below zero. This indicates that CF children with MI or pancreatic insufficiency tend to have more rapid recurrence of nonmucoid PA infections compared to those without MI or pancreatic insufficiency. This finding is consistent with our expectation because MI and pancreatic insufficiency are generally known to be associated with worse prognosis of CF outcomes.

We also plot the coefficient estimates for the extended GART model (4) based on the survivors' rate function. As justified in Section 3, we obtain the coefficient estimates from implementing the method of Sun et al. (2016) while treating the mucoid PA infection as a part of the random observation window (i.e., setting R as the age at the first mucoid PA infection or death if either of these events occurred, otherwise the age at the last follow-up visit). The coefficient estimates for intercept *Sex*, $F508$ and *Pancreat*, based on model (4), are quite

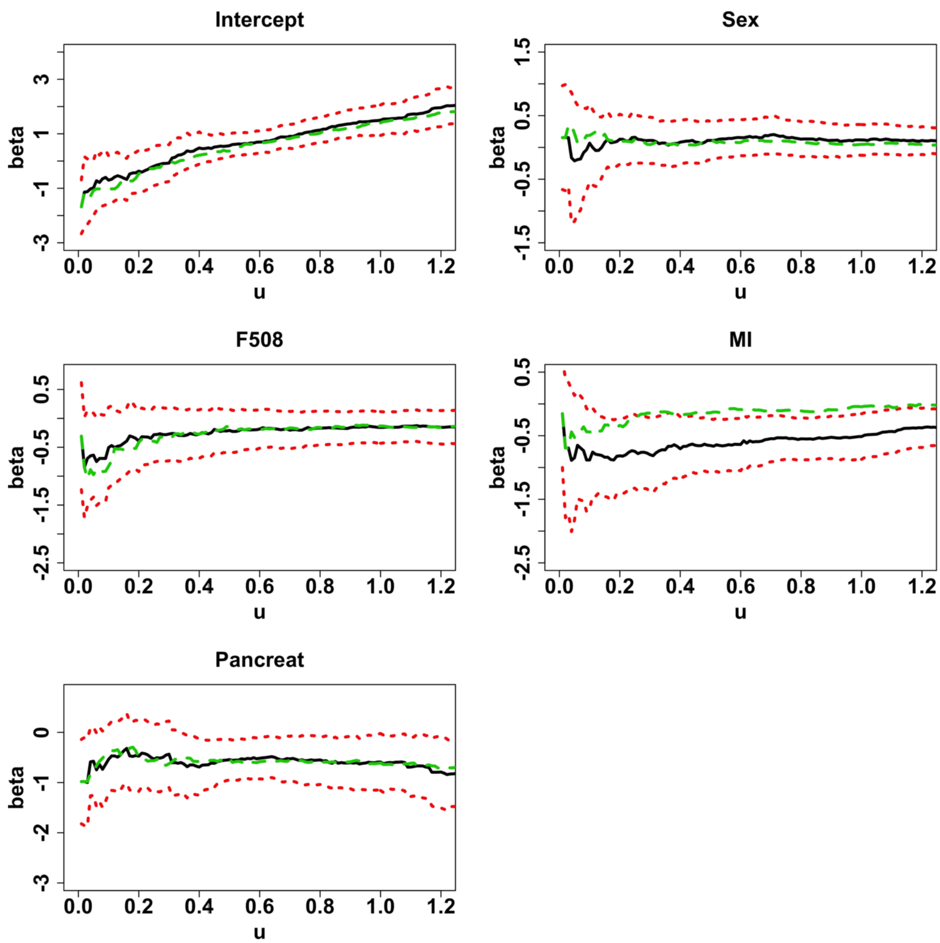

FIG. 4. *CFFPR data example: coefficient estimates (solid lines) and* 95% *pointwise CIs (dotted lines) for the extended GART model* (6) *based on the adjusted rate function, and the coefficient estimates for the extended GART model* (4) *based on the survivors' rate function (dashed lines).*

similar to those based on model (6), while they have different interpretations in terms of time to cumulative survivors' rate (rather than time to cumulative adjusted rate). For example, the intercept coefficient estimates based on model (4) represent the estimated log time to cumulative rate of nonmucoid PA infection given being mucoid PA infection-free and alive (i.e., "survivor") for the reference group. Figure 4 suggests that the cumulative survivors' rate of nonmucoid PA infection may reach one, approximately, at the age of 4.1 years, which is quite close to 4.4 years, the estimated time to expected frequency of 1 nonmucoid PA infection before mucoid PA infection (i.e., the cumulative adjusted rate for nonmucoid PA infection being one).

In Figure 4 the coefficient estimates for *MI* suggest that given mucoid PA and death haven't occurred, the timing of nonmucoid PA infection may be similar between CF children with MI and those without MI, while the MI phenotype seems to have a significant negative impact on time to cumulative adjusted rate of nonmucoid PA infections. Appropriately understanding the different implications of $\tau_{\mathbf{Z}}^{S}(u)$ and $\tau_{\mathbf{Z}}^{A}(u)$ can lead to a sensible explanation for the discrepant results on the effects of MI. One key is to note that, by the definitions of $\tau_{\mathbf{Z}}^{A}(u)$ and $\tau_{\mathbf{Z}}^{S}(u)$, a shorter time to the terminal event (D) is expected to reduce $\tau_{\mathbf{Z}}^{A}(u)$ but not necessarily results in a smaller $\tau_{\mathbf{Z}}^{S}(u)$. This is because $\tau_{\mathbf{Z}}^{S}(u)$ is oriented to depict the occurrences of nonmucoid PA infections among "survivors" with $D > t$ (i.e., subjects who haven't died or developed a mucoid PA infection by time t) which may hold a different event occurrence pattern from the whole population. As reported in literature (e.g. Oliveira et al. (2002), Sawyer et al. (1994)), the MI phenotype is generally associated with poorer clinical and survival outcomes in CF patients. This is confirmed by a simple log-rank test, which suggests worse mucoid PA infection free survival (i.e., $\Pr(D > t)$) for the MI group compared to the non-MI group ($p = 0.036$), as well as by fitting a censored quantile regression model for D over the covariate *MI*; please see Section S2 of the Supplementary Material (Wei et al. (2020)). Given this result, the estimated effects of MI on $\tau^A_{\mathbf{Z}}(u)$ likely amplify the *net* effects of MI on nonmucoid PA infections by taking into account the negative effect of MI on D. On the other hand, we may expect that the "survivors" in the MI group tend to be "stronger" or "less fragile" than the "survivors" in the non-MI group. Consequently, the comparison of survivors' timing of recurrent nonmucoid PA infections between the MI group and the non-MI group would be shifted in favor toward the MI group. These suggest that the effects of MI on D have opposite confounding impact on $\tau^A_{\mathbf{Z}}(u)$ and $\tau^S_{\mathbf{Z}}(u)$, thereby leading to different effects of MI on $\tau^S_{\mathbf{Z}}(u)$ and $\tau^A_{\mathbf{Z}}$ as shown in Figure 4

We also apply second-stage inference to test the constancy of covariate effects under the extended GART model based on the adjusted rate function. The results suggest that constant effects may be adequate for all covariates, except for *MI*. The constancy test for *MI*'s coefficient yields a p value of 0.027. This result is consistent with the gradually increasing trend observed for the coefficient of *MI* in Figure 4. This finding also suggests that the proposed GART modeling may provide a better fit to the CFFPR dataset than a AFT-type model that confines all covariate effects to be constant.

Overall, the presented analyses of the CFFPR dataset provide alternative views of risk factors for recurrent nonmucoid PA infections under the GART framework. The possible dependent termination by mucoid PA infection and death are appropriately handled and interpreted based on the proposed models and estimation methods.

5. Remarks. In this paper we investigate two extensions of the generalized accelerated recurrence time (GART) model for recurrent events data with a dependent terminal event. We adapt the GART modeling based on survivors' rate function and adjusted rate function which are established crude quantities for accommodating the presence of the terminal event in recurrent events settings.

It is worth pointing out that extending the concept of time to expected frequency to the concept of time to expected cumulative survivors' rate shares the same spirit as adopting cause-specific hazard in place of marginal hazard in the competing risks setting. In this work we have shown that the extended GART model, defined upon time to expected cumulative survivors' rate, can be estimated using the same procedure for the original GART model (Sun et al. (2016)). This finding is analogous to the important result for competing risks analysis (Prentice et al. (1978), Kalbfleisch and Prentice (2002)) that allows researchers to directly use the standard Cox regression procedure to analyze competing risks data as long as regression coefficients are properly interpreted as covariate effects on cause-specific hazards. Our results in Section 3.1 provide the key methodological justification and practical guidance for directly applying the GART method in the recurrent events setting with a dependent terminal event. In this case the interpretation of coefficient estimates should be tuned toward covariate effects on time to expected cumulative survivors' rate.

6. Acknowledgements. This work is partially supported by National Institutes of Health Grants R01HL113548, R01AG055634, and R01DK109692. The authors would like to thank the Cystic Fibrosis Foundation for the use of CF Foundation Patient Registry data to conduct this study. Additionally, we would like to thank the patients, care providers and clinic coordinators at CF Centers throughout the United States for their contributions to the CF Foundation Patient Registry.

APPENDIX A: JUSTIFICATION OF THE COUNTING PROCESS FORMULATIONS OF MODEL (4) AND MODEL (6)

The following are some regularity conditions:

(B0) (L, R) and $T^{(j)}$ are independent given $\mathbf{Z}$;
(B1) (L, R) and D are independent given $\mathbf{Z}$;
(B2) $\boldsymbol{\beta}_0^S(u)$ is continuously differentiable;
(B3) $S_C(e^{\mathbf{z}^\top \boldsymbol{\beta}_0^S(u)}|\mathbf{z}) > 0$ and $\Pr(e^{\mathbf{z}^\top \boldsymbol{\beta}_0^S(u)} < D|\mathbf{z}) > 0$ for $\mathbf{z} \in \mathcal{Z}$ and $u \in (0, U]$, where $\mathcal{Z}$ denotes the compact support of $\mathbf{Z}$;
(B3′) $S_C(t|\mathbf{z}) > 0$ for $0 < t < e^{\mathbf{z}^\top \boldsymbol{\beta}_0^A(U)} \wedge \nu_{\tilde{R}}$ for $\mathbf{z} \in \mathcal{Z}$, where $\nu_{\tilde{R}}$ denotes the upper bound of $\tilde{R}$'s support.

PROPOSITION A1. *Under conditions* (B0)–(B3), *model* (4) *and model* (5) *are equivalent*.

PROOF. Given the random observation window assumptions in (B0) and (B1), taking the derivative of $E\{N(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)})|\mathbf{Z}\}$ with respect to u, we get

$$
\begin{aligned}
&E\{dN(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)})|\mathbf{Z}\} \\
&\quad = E\left\{\sum_{j=1}^{\infty} I(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le T^{(j)} < e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u+du)}, e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le D,\right. \\
&\qquad \left. L < e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le R)\middle|\mathbf{Z}\right\} \cdot e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \mathbf{Z}^\top d\boldsymbol{\beta}_0^S(u) \\
&\quad = E\left\{\sum_{j=1}^{\infty} I(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le T^{(j)} < e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u+du)}, e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le D\middle|\mathbf{Z}\right\} \\
&\qquad \times \Pr\{L < e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le R)|\mathbf{Z}\} \cdot e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \mathbf{Z}^\top d\boldsymbol{\beta}_0^S(u) \\
&\quad = E\{dN^*(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)})|e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le D, \mathbf{Z}\} \Pr\{e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le D|\mathbf{Z}\} \\
&\qquad \times S_C(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}|\mathbf{Z}) \\
&\quad = S_C(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}|\mathbf{Z}) \Pr\{e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le D|\mathbf{Z}\} d\Lambda_{\mathbf{Z}}^S(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)})
\end{aligned} \tag{12}
$$

and

$$
\begin{aligned}
&E\{Y(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}) g(u)\, du\} \\
&\quad = E\{I(L < e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le R) I(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le D)|\mathbf{Z}\} g(u)\, du \\
&\quad = E\{I(L < e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} \le R)|\mathbf{Z}\} E\{I(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} < D)|\mathbf{Z}\} g(u)\, du \\
&\quad = S_C(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}|\mathbf{Z}) \Pr\{e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)} < D|\mathbf{Z}\} g(u)\, du.
\end{aligned} \tag{13}
$$

By the definition of $\tau_{\mathbf{Z}}^S(\cdot)$, model (4) implies $\Lambda_{\mathbf{Z}}^S(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}) = G(u)$, and, hence, $d\Lambda_{\mathbf{Z}}^S(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}) = g(u)\, du$. By equations (12) and (13), we then have $E\{dN(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}|\mathbf{Z}\} = E\{Y(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}) g(u)\, du\}$ which implies model (5).

Similarly, suppose model (5) holds. We then have $E\{dN(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}|\mathbf{Z}\} = E\{Y(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}) \times g(u)\, du\}$. It follows from equations (12) and (13) that $d\Lambda_{\mathbf{Z}}^S(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}) = g(u)\, du$. Thus, we get $\Lambda_{\mathbf{Z}}^S(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^S(u)}) = G(u)$ which is equivalent to (4) by the definition of $\tau_{\mathbf{Z}}^S(\cdot)$. This shows that model (5) implies model (4). $\square$

PROPOSITION A2. *Under conditions* (B0), (B1) and (B3′), *model* (7) *implies* (8).

PROOF. Define $T^{*(j)} = I(T^{(j)} \le D) \times T^{(j)} + I(T^{(j)} > D) \times \infty$. By condition (B3′), $S_C(T^{(j)}|\mathbf{Z}) > 0$ when $L < T^{(j)} \le e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)}$. Given the random observation window assumptions, (B0) and (B1), and by the definition of $T^{*(j)}$, we get

$$
\begin{aligned}
&E\Biggl\{\sum_{j=1}^{\infty} \frac{1}{S_C(T^{(j)}|\mathbf{Z})} I\bigl(L < T^{(j)} \le e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)} \wedge \tilde{R}\bigr)\Big|\mathbf{Z}\Biggr\} \\
&\quad = E\Biggl\{\sum_{j=1}^{\infty} \frac{1}{S_C(T^{*(j)}|\mathbf{Z})} I\bigl(L < T^{*(j)} \le e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)} \wedge R\bigr)\Big|\mathbf{Z}\Biggr\} \\
&\quad = E\Biggl[\sum_{j=1}^{\infty} E\biggl\{\frac{1}{S_C(T^{*(j)}|\mathbf{Z})} I\bigl(L < T^{*(j)} \le R\bigr) I\bigl(T^{*(j)} \le e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)}\bigr)\Big|T^{*(j)}, \mathbf{Z}\biggr\}\Big|\mathbf{Z}\Biggr] \\
&\quad = E\Biggl[\sum_{j=1}^{\infty} \frac{1}{S_C(T^{*(j)}|\mathbf{Z})} S_C\bigl(T^{*(j)}|\mathbf{Z}\bigr) I\bigl(T^{*(j)} \le e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)}\bigr)\Big|\mathbf{Z}\Biggr] \\
&\quad = E\bigl(N^*\bigl(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)}\bigr)|\mathbf{Z}\bigr) \\
&\quad = \mu_{\mathbf{Z}}^A\bigl(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)}\bigr).
\end{aligned} \tag{14}
$$

By the definition of $\tau_{\mathbf{Z}}^A(\cdot)$, model (6) implies $\mu_{\mathbf{Z}}^A(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)}) = G(u)$. Then, (14) implies that (8) holds. □

APPENDIX B: PROOFS OF THEOREM 1 AND THEOREM 2

Define $G^R(t) = \Pr(R \ge t)$, $G^L(t) = \Pr(L \ge t)$, $N_i^R(t) = I(\tilde{R}_i \le t, \delta_i = 0)$, $Y_i^R(t) = I(\tilde{R}_i \ge t)$, $Y_i^{(j)}(t) = I(T_i^{(j)} \ge t)$, $y^R(t) = \Pr(\tilde{R} \ge t)$, $\lambda^R(t) = \lim_{\Delta \to 0} \Pr(\tilde{R} \in (t, t+\Delta), \delta = 0|\tilde{R} \ge t)/\Delta$, $\Lambda^R(t) = \int_0^t \lambda^R(s)\,ds$, $M_i^R(t) = N_i^R(t) - \int_0^t Y_i^R(s)\,d\Lambda^R(s)$ and $\boldsymbol{\xi}_{S_C,i}(t) = G^R(t)\int_0^t y^R(s)^{-1}\,dM_i^R(s) - \{I(L_i \ge t) - Pr(L \ge t)\}$, $i = 1, \dots, n$. Define

$$
\boldsymbol{\xi}_i(u) = \boldsymbol{\xi}_{1,i}(u) - \boldsymbol{\xi}_{2,i}(u), \tag{15}
$$

for $i = 1, \dots, n$, where $\boldsymbol{\xi}_{1,i}(u) = \mathbf{Z}_i\{\sum_{j=1}^{\infty} \frac{1}{S_C(T_i^{(j)}|\mathbf{Z})} I(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \boldsymbol{\beta}_0^A(u)} \wedge \tilde{R}_i) - \int_0^u g(s)\,ds\}$ and $\boldsymbol{\xi}_{2,i}(u) = E_{(L,R,D,\mathbf{Z},\bar{T})}\{\mathbf{Z}\sum_{j=1}^{\infty} \boldsymbol{\xi}_{S_C,i}(T^{(j)}) I(L < T^{(j)} \le e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)} \wedge \tilde{R})/S_C^2(T^{(j)})\}$. Here, $\bar{T} = (T^{(1)}, T^{(2)}, \dots)$, and $E_{(L,R,D,\mathbf{Z},\bar{T})}$ means expectation w.r.t. $(L, R, D, \mathbf{Z}, \bar{T})$.

PROOF OF THEOREM 1. Define $\mathbf{S}_n^G(\mathbf{b}, u) = n^{-1/2}\sum_{i=1}^n \mathbf{Z}_i[\sum_{j=1}^{\infty} \frac{1}{S_C(T_i^{(j)})} I(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \mathbf{b}} \wedge \tilde{R}) - \int_0^u g(s)\,ds]$ and $\boldsymbol{\mu}(\mathbf{b}, u) = E[\mathbf{Z}\{\mu_{\mathbf{Z}}^A(e^{\mathbf{Z}^\top \boldsymbol{\beta}_0^A(u)}) - G(u)\}]$. Hereafter, we use $\sup_{\mathbf{b}}$ or $\sup_u$ to denote supremum taken over $\mathbf{b} \in \mathbb{R}^{p+1}$ or $u \in [\nu, U]$, respectively.

First, under condition (C1), by the results on the Kaplan–Meier estimator (Pepe (1991)) and the results on empirical distributions (van der Vaart and Wellner (1997)), we have $\sup_{t<\upsilon^R} |\hat{G}^R(t) - G^R(t)| = o(n^{-1/2+r})$, a.s., and $\sup_{t<\upsilon^R} |\hat{G}^L(t) - G^L(t)| = o(n^{-1/2+r})$, a.s. for any $r > 0$. These imply that $\sup_{t<\upsilon^R} |\hat{S}_C(t) - S_C(t)| = o(n^{-1/2+r})$, a.s. for every

$r > 0$. Coupled with conditions (C2), it implies that

$$\begin{aligned}\sup_{\mathbf{b},u}\|n^{-1/2}S_n(\mathbf{b},u) - n^{-1/2}S_n^G(\mathbf{b},u)\| &= n^{-1}\sum_{i=1}^n \mathbf{Z}_i\left\{\frac{1}{\hat{S}_C(T_i^{(j)})} - \frac{1}{S_C(T_i^{(j)})}\right\} I\big(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \mathbf{b}} \wedge \tilde{R}\big)\\ &= o\big(n^{-1/2+r}\big), \quad \text{a.s.}\end{aligned}$$

Next, we show that the function class $\mathcal{F} = \{\mathbf{Z}_i\{\sum_{j=1}^\infty \frac{1}{S_C(T_i^{(j)})} I(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \mathbf{b}} \wedge \tilde{R}) - \int_0^u g(s)\,ds\}, \mathbf{b} \in \mathbb{R}^{p+1}, u \in [\nu, U]\}$ is Donsker and, thus, Glivenko–Cantelli (van der Vaart and Wellner (1997)). This is because the class of indicator functions is Donsker, both $\mathbf{Z}_i$ and $1/S_C(T_i^{(j)})$ are uniformly bounded, and $G(u)$ is monotone and uniformly bounded in $u \in [\nu, U]$. It then follows from the Clivenko–Cantelli theorem that $\sup_{\mathbf{b},u}\|n^{-1/2}S_n^G(\mathbf{b},u) - \boldsymbol{\mu}(\mathbf{b},u)\| = o(1)$, a.s. Therefore,

$$\sup_{\mathbf{b},u}\|n^{-1/2}S_n(\mathbf{b},u) - \boldsymbol{\mu}(\mathbf{b},u)\| = o(1), \quad \text{a.s.} \tag{16}$$

Mimicking the arguments in the proof of Theorem 1 in Peng and Fine (2009), we can show that $\inf_{\mathbf{b}\notin\mathcal{B}(\rho_0)}\|\boldsymbol{\mu}(\mathbf{b},u) - \boldsymbol{\mu}(\boldsymbol{\beta}_0^A(u),u)\| \ge c_0\rho_0$,

$$\boldsymbol{\mu}\big(\widehat{\boldsymbol{\beta}}^A(u),u\big) - \boldsymbol{\mu}\big(\boldsymbol{\beta}_0^A(u),u\big) = o(1), \quad \text{a.s.} \tag{17}$$

These imply that $\{\widehat{\boldsymbol{\beta}}^A(u) : u \in [0,U]\} \in \mathcal{B}(\rho_0)$ with probability 1 when n is large enough. By a Taylor expansion

$$\sup_u\|\widehat{\boldsymbol{\beta}}^A(u) - \boldsymbol{\beta}_0^A(u)\| = \sup_u\big\|\mathbf{A}\big(\check{\boldsymbol{\beta}}^A(u)\big)^{-1}\big[\boldsymbol{\mu}\big(\widehat{\boldsymbol{\beta}}^A(u),u\big) - \boldsymbol{\mu}\big(\boldsymbol{\beta}_0^A(u),u\big)\big]\big\|, \tag{18}$$

where $\check{\boldsymbol{\beta}}^A(u)$ is between $\widehat{\boldsymbol{\beta}}^A(u)$ and $\boldsymbol{\beta}_0^A(u)$. Since $\check{\boldsymbol{\beta}}^A(u) \in \mathcal{B}(\rho_0)$ for n large enough, it follows from (17), (18) and condition (C4) that

$$\sup_u\|\widehat{\boldsymbol{\beta}}^A(u) - \boldsymbol{\beta}_0^A(u)\| = o_p(1). \qquad \square$$

LEMMA 1. *For any positive sequence $\{d_n\}_{n=1}^\infty$ satisfying $d_n \to 0$,*

$$\begin{aligned}\lim_{n\to\infty}\sup_{\mathbf{b},\mathbf{b}'\in\mathcal{B}(\rho_0),\|\mathbf{b}-\mathbf{b}'\|\le d_n}\Bigg\|n^{-1/2}\sum_{i=1}^n \mathbf{Z}_i\Bigg\{\sum_{j=1}^\infty \frac{1}{S_C(T_i^{(j)})}\big\{I\big(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \mathbf{b}} \wedge \tilde{R}_i\big)\\ - I\big(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \mathbf{b}'} \wedge \tilde{R}_i\big)\big\}\Bigg\} - n^{1/2}\{\boldsymbol{\mu}(\mathbf{b},u) - \boldsymbol{\mu}(\mathbf{b}',u)\}\Bigg\| = 0, \quad \textit{a.s.}\end{aligned}$$

PROOF. Following the lines of Peng and Fine (2009) for their Lemma 1, we can similarly show

$$\begin{aligned}\mathrm{Var}\Bigg(\mathbf{Z}_i\Bigg\{\sum_{j=1}^\infty \frac{1}{S_C(T_i^{(j)})}\big\{I\big(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \mathbf{b}} \wedge \tilde{R}_i\big)\\ - I\big(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top \mathbf{b}'} \wedge \tilde{R}_i\big)\big\}\Bigg\}\Bigg) \le G_0\|\mathbf{b} - \mathbf{b}'\|\end{aligned}$$

holds given the uniform boundedness of $\lambda_{\mathbf{Z}}^A(t)$ and the boundedness of $1/S_C(\cdot)$, $\mathbf{Z}$ and $\mathcal{B}(\rho_0)$ implied by conditions (C1)–(C4). This then completes the proof of Lemma 1. $\square$

PROOF OF THEOREM 2. The proof follows the same idea as the proof of Theorem 2 in Peng and Fine (2009). Below we sketch the main steps.

First, we show that

$$\mathbf{S}_n\{\boldsymbol{\beta}_0^A(u), u\} \approx n^{-1/2}\sum_{i=1}^n\{\boldsymbol{\xi}_{1,i}(u) - \boldsymbol{\xi}_{2,i}(u)\} = n^{-1/2}\sum_{i=1}^n \boldsymbol{\xi}_i(u), \tag{19}$$

where $\approx$ denotes asymptotic equivalence uniformly in $u \in [\nu, U)$.

To prove (19), we derive, based on the result of Pepe (1991), that

$$\begin{aligned}
&\sup_{t\in[0,\upsilon^R)}\Bigg\| n^{1/2}\{\widehat{S}_C(t) - S_C(t)\} - n^{-1/2}\sum_{i=1}^n\bigg[G^R(t)\int_0^t y^R(s)^{-1}\,dM_i^R(s) \\
&\qquad - \{I(L_i \ge t) - \Pr(L \ge t)\}\bigg]\Bigg\| \\
&= \sup_{t\in[0,\upsilon^R)}\left\| n^{1/2}\{\widehat{S}_C(t) - S_C(t)\} - n^{-1/2}\sum_{i=1}^n \boldsymbol{\xi}_{S_C,i}(t)\right\| \to_{\text{a.s.}} 0.
\end{aligned}$$

In addition, we have $\sup_{t\in[0,\upsilon^R)}\|\widehat{S}_C(t) - S_C(t)\| \to_{a.s.} 0$. Based on these results, applying standard asymptotic arguments and the Glivenko–Cantelli Theorem, we then obtain that

$$\begin{aligned}
&\mathbf{S}_n\{\boldsymbol{\beta}_0^A(u), u\} \\
&\quad = \mathbf{S}_n^G\{\boldsymbol{\beta}_0^A(u), u\} + [\mathbf{S}_n\{\boldsymbol{\beta}_0^A(u), u\} - \mathbf{S}_n^G\{\boldsymbol{\beta}_0^A(u), u\}] \\
&\quad = n^{-1/2}\sum_{i=1}^n \boldsymbol{\xi}_{1,i}(u) - n^{-1/2}\sum_{i=1}^n \mathbf{Z}_i\left\{\sum_{j=1}^\infty \frac{\hat{S}_C(T_i^{(j)}) - S_C(T_i^{(j)})}{\hat{S}_C(T_i^{(j)})\cdot S_C(T_i^{(j)})}\right. \\
&\qquad \left.\times I\big(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top\boldsymbol{\beta}_0^A(u)} \wedge \tilde{R}_i\big)\right\} \\
&\quad \approx n^{-1/2}\sum_{i=1}^n \boldsymbol{\xi}_{1,i}(u) - n^{-1}\sum_{i=1}^n \mathbf{Z}_i\left\{\sum_{j=1}^\infty \frac{n^{-1/2}\sum_{k=1}^n \boldsymbol{\xi}_{S_C,k}(T_i^{(j)})}{S_C^2(T_i^{(j)})}\right. \\
&\qquad \left.\times I\big(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top\boldsymbol{\beta}_0^A(u)} \wedge \tilde{R}_i\big)\right\} \\
&\quad = n^{-1/2}\sum_{i=1}^n \boldsymbol{\xi}_{1,i}(u) - n^{-1/2}\sum_{k=1}^n \frac{1}{n}\sum_{i=1}^n \mathbf{Z}_i\left\{\sum_{j=1}^\infty \frac{\boldsymbol{\xi}_{S_C,k}(T_i^{(j)})}{S_C^2(T_i^{(j)})}\right. \\
&\qquad \left.\times I\big(L_i < T_i^{(j)} \le e^{\mathbf{Z}_i^\top\boldsymbol{\beta}_0^A(u)} \wedge \tilde{R}_i\big)\right\} \\
&\quad \approx n^{-1/2}\sum_{i=1}^n\{\boldsymbol{\xi}_{1,i}(u) - \boldsymbol{\xi}_{2,i}(u)\} = n^{-1/2}\sum_{i=1}^n \boldsymbol{\xi}_i(u).
\end{aligned}$$

This proves the result in (19).

Next, by Lemma 1 and the uniform consistency of $\hat{\boldsymbol{\beta}}^A(u)$, we can show that

$$\mathbf{S}_n(\hat{\boldsymbol{\beta}}^A(u), u) - \mathbf{S}_n(\boldsymbol{\beta}_0^A(u), u) = \{\mathbf{A}(\boldsymbol{\beta}_0^A(u)) + \boldsymbol{\epsilon}_n(u)\}\cdot n^{1/2}\{\hat{\boldsymbol{\beta}}^A(u) - \boldsymbol{\beta}_0^A(u)\},$$

where $\sup_u \|\boldsymbol{\epsilon}_n(u)\| \to 0$, a.s. This, coupled with (19) and the definition of $\hat{\boldsymbol{\beta}}^A(u)$, implies

$$n^{1/2}\{\hat{\boldsymbol{\beta}}_0^A(u) - \boldsymbol{\beta}_0^A(u)\} \approx -n^{-1/2}\sum_{i=1}^n \mathbf{A}\{\boldsymbol{\beta}_0^A(u)\}^{-1}\boldsymbol{\xi}_i(u).$$

Following similar arguments for showing $\mathcal{F}$ is a Donsker class, we can show that $\{\boldsymbol{\xi}(u), u \in [\nu, U]\}$ is a Donsker class. By the Donsker theorem, $n^{1/2}\{\hat{\boldsymbol{\beta}}_0(u) - \boldsymbol{\beta}_0(u)\}$ converges weakly to a mean zero Gaussian process for $u \in [\nu, U]$ with the covariance function

$$\boldsymbol{\Phi}(u', u) = \mathbf{A}\{\boldsymbol{\beta}_0^A(u')\}^{-1} E\{\boldsymbol{\xi}(u')\boldsymbol{\xi}(u)^\top\}\mathbf{A}\{\boldsymbol{\beta}_0^A(u)\}^{-1}. \qquad \square$$

Acknowledgments. B. Wei and L. Peng supported in part by NIH R01 grant HL113548 and NIH R01 grant AG055634.

SUPPLEMENTARY MATERIAL

Supplementary materials (DOI: 10.1214/20-AOAS1335SUPP; .pdf). We provide additional results for our simulation studies and analysis of the CFFPR dataset.

REFERENCES

ANDERSEN, P. K. and GILL, R. D. (1982). Cox's regression model for counting processes: A large sample study. *Ann. Statist.* **10** 1100–1120. MR0673646

COOK, R. J. and LAWLESS, J. F. (1997). Marginal analysis of recurrent events and a terminating event. *Stat. Med.* **16** 911–924.

DAVIES, J. C. (2002). *Pseudomonas aeruginosa* in cystic fibrosis: Pathogenesis and persistence. *Paediatr. Respir. Rev.* **3** 128–134.

FYGENSON, M. and RITOV, Y. (1994). Monotone estimating equations for censored data. *Ann. Statist.* **22** 732–746. MR1292538 https://doi.org/10.1214/aos/1176325493

GHOSH, D. and LIN, D. Y. (2002). Marginal regression models for recurrent and terminal events. *Statist. Sinica* **12** 663–688. MR1929958

GHOSH, D. and LIN, D. Y. (2003). Semiparametric analysis of recurrent events data in the presence of dependent censoring. *Biometrics* **59** 877–885. MR2025111 https://doi.org/10.1111/j.0006-341X.2003.00102.x

HELTSHE, S. L., KHAN, U., BECKETT, V., BAINES, A., EMERSON, J., SANDERS, D. B., GIBSON, R. L., MORGAN, W. and ROSENFELD, M. (2018). Longitudinal development of initial, chronic and mucoid *Pseudomonas aeruginosa* infection in young children with cystic fibrosis. *J. Cyst. Fibros.* **17** 341–347. https://doi.org/10.1016/j.jcf.2017.10.008

HUANG, X. and LIU, L. (2007). A joint frailty model for survival and gap times between recurrent events. *Biometrics* **63** 389–397. MR2370797 https://doi.org/10.1111/j.1541-0420.2006.00719.x

HUANG, Y. and PENG, L. (2009). Accelerated recurrence time models. *Scand. J. Stat.* **36** 636–648. MR2573300 https://doi.org/10.1111/j.1467-9469.2009.00645.x

HUANG, C.-Y. and WANG, M.-C. (2004). Joint modeling and estimation for recurrent event processes and failure time data. *J. Amer. Statist. Assoc.* **99** 1153–1165. MR2109503 https://doi.org/10.1198/016214504000001033

JIN, Z., YING, Z. and WEI, L. J. (2001). A simple resampling method by perturbing the minimand. *Biometrika* **88** 381–390. MR1844838 https://doi.org/10.1093/biomet/88.2.381

KALBFLEISCH, J. D. and PRENTICE, R. L. (2002). *The Statistical Analysis of Failure Time Data*, 2nd ed. *Wiley Series in Probability and Statistics*. Wiley Interscience, Hoboken, NJ. MR1924807 https://doi.org/10.1002/9781118032985

LI, R. and PENG, L. (2011). Quantile regression for left-truncated semicompeting risks data. *Biometrics* **67** 701–710. MR2829124 https://doi.org/10.1111/j.1541-0420.2010.01521.x

LIN, D. Y., SUN, W. and YING, Z. (1999). Nonparametric estimation of the gap time distributions for serial events with censored data. *Biometrika* **86** 59–70. MR1688071 https://doi.org/10.1093/biomet/86.1.59

LIN, D. Y., WEI, L. J. and YING, Z. (1998). Accelerated failure time models for counting processes. *Biometrika* **85** 605–618. MR1665810 https://doi.org/10.1093/biomet/85.3.605

LIN, D. Y., WEI, L. J., YANG, I. and YING, Z. (2000). Semiparametric regression for the mean and rate functions of recurrent events. *J. R. Stat. Soc. Ser. B. Stat. Methodol.* **62** 711–730. MR1796287 https://doi.org/10.1111/1467-9868.00259

LIU, L., WOLFE, R. A. and HUANG, X. (2004). Shared frailty models for recurrent events and a terminal event. *Biometrics* **60** 747–756. MR2089451 https://doi.org/10.1111/j.0006-341X.2004.00225.x

LUO, X., WANG, M.-C. and HUANG, C.-Y. (2010). A comparison of various rate functions of a recurrent event process in the presence of a terminal event. *Stat. Methods Med. Res.* **19** 167–182. MR2649719 https://doi.org/10.1177/0962280208090220

LYCZAK, J. B., CANNON, C. L. and PIER, G. B. (2002). Lung infections associated with cystic fibrosis. *Clin. Microbiol. Rev.* **15** 194–222. https://doi.org/10.1128/cmr.15.2.194-222.2002

MATHEE, K., CIOFU, O., STERNBERG, C., LINDUM, P. W., CAMPBELL, J. I., JENSEN, P., JOHNSEN, A. H., GIVSKOV, M., OHMAN, D. E. et al. (1999). Mucoid conversion of *Pseudomonas aeruginos* by hydrogen peroxide: A mechanism for virulence activation in the cystic fibrosis lung. *Microbiology* **145** 1349–1357.

MILOSLAVSKY, M., KELEŞ, S., VAN DER LAAN, M. J. and BUTLER, S. (2004). Recurrent events analysis in the presence of time-dependent covariates and dependent censoring. *J. R. Stat. Soc. Ser. B. Stat. Methodol.* **66** 239–257. MR2035769 https://doi.org/10.1111/j.1467-9868.2004.00442.x

OLIVEIRA, M. C. L. A., REIS, F. J. C., MONTEIRO, A. P. A. F. and PENNA, F. J. (2002). Effect of meconium ileus on the clinical prognosis of patients with cystic fibrosis. *Braz. J. Med. Biol. Res.* **35** 31–38.

PENG, L. and FINE, J. P. (2009). Competing risks quantile regression. *J. Amer. Statist. Assoc.* **104** 1440–1453. MR2596999 https://doi.org/10.1198/jasa.2009.tm08228

PEPE, M. S. (1991). Inference for events with dependent risks in multiple endpoint studies. *J. Amer. Statist. Assoc.* **86** 770–778. MR1147104

PEPE, M. S. and CAI, J. (1993). Some graphical displays and marginal regression analyses for recurrent failure times and time dependent covariates. *J. Amer. Statist. Assoc.* **88** 811–820.

PRENTICE, R. L., WILLIAMS, B. J. and PETERSON, A. V. (1981). On the regression analysis of multivariate failure time data. *Biometrika* **68** 373–379. MR0626396 https://doi.org/10.1093/biomet/68.2.373

PRENTICE, R. L., KALBFLEISCH, J. D., PETERSON JR, A. V., FLOURNOY, N., FAREWELL, V. T. and BRESLOW, N. E. (1978). The analysis of failure times in the presence of competing risks. *Biometrics* 541–554.

REID, N. (1994). A conversation with Sir David Cox. *Statist. Sci.* **9** 439–455. MR1325436

ROBINS, J. M. and ROTNITZKY, A. (1992). Recovery of information and adjustment for dependent censoring using surrogate markers. In *AIDS Epidemiology* 297–331. Springer, Berlin.

RUSSELL, P. J., HERTZ, P. E. and MCMILLAN, B. (2012). *Biology*: *The Dynamic Science*. Cengage Learning, Boston, MA.

SAWYER, S. M., TAYLOR, R., MACMAHON, R. and ROBERTSON, C. F. (1994). Meconium ileus in cystic fibrosis. *Pediatr. Surg. Int.* **9** 180–184.

SCHAUBEL, D. E. and CAI, J. (2005). Analysis of clustered recurrent event data with application to hospitalization rates among renal failure patients. *Biostatistics* **6** 404–419.

SUN, X., PENG, L., HUANG, Y. and LAI, H. J. (2016). Generalizing quantile regression for counting processes with applications to recurrent events. *J. Amer. Statist. Assoc.* **111** 145–156. MR3494649 https://doi.org/10.1080/01621459.2014.995795

VAN DER VAART, A. W. and WELLNER, J. A. (1997). Weak convergence and empirical processes with applications to statistics. *J. Roy. Statist. Soc. Ser. A* **160** 596–608.

WEI, B., ZHANG, Z., LAI, H. and PENG, L. (2020). Supplement to "Generalized accelerated recurrence time model in the presence of a dependent terminal event." https://doi.org/10.1214/20-AOAS1335SUPP

YE, Y., KALBFLEISCH, J. D. and SCHAUBEL, D. E. (2007). Semiparametric analysis of correlated recurrent and terminal events. *Biometrics* **63** 78–87, 311. MR2345577 https://doi.org/10.1111/j.1541-0420.2006.00677.x

ZENG, D. and CAI, J. (2010). A semiparametric additive rate model for recurrent events with an informative terminal event. *Biometrika* **97** 699–712. MR2672492 https://doi.org/10.1093/biomet/asq039