Statistics and Its Interface Volume 12 (2019) 1–9

Semiparametric estimation of differences in treatment-specific recurrent event means with a terminal event

Xiaowei Sun and Liuquan Sun*

Recurrent event data often arise from biomedical studies and a terminal event may preclude further occurrence of recurrent events. In comparing treatments, the marginal mean is frequently of interest, and treatment-specific differences in the mean number of events are often not constant over time. In this article, we propose a semiparametric method to compare treatment-specific recurrent event means by combining an additive hazards model for the terminal event and an additive rates model for the conditional recurrent event rate. The treatment effect is measured by the difference between treatment-specific recurrent event means. Estimation procedures are developed for the measure and the asymptotic properties of the proposed estimators are established. The finite sample performance of the proposed estimators is examined through simulation studies, and an application to a bladder cancer study demonstrates the usefulness of our method.

AMS 2000 subject classifications: Primary 62N01, 62N02; secondary 62G05.
Keywords and phrases: Additive models, Marginal mean, Recurrent events, Semiparametric method, Terminal event, Treatment effect.

1. INTRODUCTION

In many clinical and observational studies, recurrent event data are frequently encountered when each subject may experience a particular event repeatedly over time. Examples include tumor recurrences in cancer patients (Byar, 1980), recurrent seizures in epileptic patients (Albert, 1991), transient ischemic attacks in patients with cerebrovascular disease (Hobson et al., 1993) and repeated opportunistic infections in HIV-infected subjects (Li and Lagakos, 1997). Various methods have been proposed for the analysis of recurrent events, including the intensity and rate approaches (Anderson and Gill, 1982; Pepe and Cai, 1993; Lawless and Nadeau, 1995; Lin et al., 2000). A comprehensive review of the existing statistical methods for recurrent events data can be found in Cook and Lawless (2007).

*Corresponding author.

In many applications, however, there may exist a terminal event such as death, which precludes further recurrent events and is likely to be strongly correlated with recurrent events of interest. For example, patients may experience recurrent hospitalizations that are terminated by death. Various methods have been proposed for the analysis of recurrent events with a terminal event, and the existing methods generally fall into three approaches: marginal mean models, conditional rate models and intensity models. Marginal mean models focus on the marginal mean number of events, and the mean averages over surviving and deceased subjects (Ghosh and Lin, 2000, 2002). Conditional rate models consider the conditional recurrent event rate given survival, and a variation of this approach uses a frailty to account for the dependence between the recurrent and terminal events (Cook and Lawless, 1997; Schaubel and Cai, 2005; Ye et al., 2007; Kalbfleisch et al., 2013). The marginal and conditional methods explicitly acknowledge that the terminal event precludes further recurrences. Intensity models focus on the intensity functions of the recurrent events, and use frailties to account for the dependence between the recurrent and terminal events. In this case, the recurrent events are essentially taken as a latent process unobservable after the terminal event (Huang and Wang, 2004; Zeng and Lin, 2009).

This study is motivated by a bladder cancer study conducted by the Veterans Administration Cooperative Urological Research Group (Byar, 1980). All patients had superficial bladder tumors when they entered the trial, and were randomly assigned to placebo and thiotepa treatment groups. Note that the thiotepa treatment has a significant effect in reducing the recurrence of bladder tumor, and the treatment effect seems to change with time (Zhao et al., 2011; Dong and Sun, 2015). Therefore, our objective is to compare treatment-specific differences in tumor recurrence rates between placebo and thiotepa treatment groups, adjusting for baseline covariates.

In comparing treatments, the marginal mean is usually of direct interest, and investigators are often interested in differences between treatment-specific means. For example, a hospital administrator may want to compare the mean number of hospitalizations among kidney transplant recipients by donor type (Schaubel and Zhang, 2010). Ghosh and Lin (2000) proposed nonparametric tests for the difference between treatment-specific recurrent event means in the pres-

ence of a terminal event. However, treatment-specific differences in mean number of events are often not constant over time, particularly when the treatment-specific survival functions differ. In such cases, Schaubel and Zhang (2010) developed two semiparametric methods for estimating the difference or ratio of treatment-specific marginal mean numbers of events, and the inverse probability of treatment weighting was used to balance the treatment-specific adjustment covariate distributions. Pan and Schaubel (2009) proposed a semiparametric method for comparing treatment-specific recurrent event means, which combined a proportional hazards model for the terminal event and an additive rates model for the conditional recurrent event rate given survival. To our knowledge, there is no existing work that simultaneously uses the additive models for the hazard of the terminal event and the conditional recurrent event rate.

In this article, we propose a semiparametric method to compare treatment-specific recurrent event means. Without forcing the treatment effect to be a constant difference, the method combines an additive hazards model for the terminal event and an additive rates model for the conditional recurrent event rate. Under the proposed method, the treatment effect is measured by the difference between treatment-specific recurrent event means, which is estimated as a process over time. Estimation procedures are developed for the measure and the asymptotic properties of the proposed estimators are established.

The remainder of the article is organized as follows. In Section 2, we describe the proposed model, and present the estimating procedure. The asymptotic properties of the proposed estimators are established in Section 3. Section 4 reports some results from simulation studies conducted for evaluating the proposed method. An application to a bladder tumor study is provided in Section 5, and some concluding remarks are given in Section 6.

2. MODELS AND INFERENCE PROCEDURES

For subject i $(i = 1, ..., n)$, let $\tilde{N}_i^R(t)$ denote the number of recurrent events over the time interval $(0, t]$, and D_i be the terminal event time (e.g., death), where the terminal event stops further recurrent events in that $\tilde{N}_i^R(t)$ is constant after D_i. Let C_i be the censoring time or follow-up time. Write $T_i = C_i \wedge D_i$ and $Y_i(t) = I(T_i \geq t)$, where $a \wedge b = \min(a, b)$, and $I(\cdot)$ is the indicator function. Due to censoring, $\tilde{N}_i^R(t)$ is not fully observed, and the observed number of recurrent events is denoted by $N_i^R(t) = \tilde{N}_i^R(t \wedge T_i)$. Also, let $N_i^D(t)$ denote the observed number of the terminal event, where $N_i^D(t) = I(D_i \leq t \wedge T_i)$. Let Z_i and X_i denote the vectors of covariates associated with the recurrent and terminal events, respectively, which can overlap and will often be identical. Set $Z_i = (Z_{i1}, Z_{i2}')'$ and $X_i = (X_{i1}, X_{i2}')'$, where Z_{i1} and X_{i1} are (1/0) indicators for the treatment/placebo, and Z_{i2} and X_{i2} are adjustment covariates. For notational convenience, write $Z_i^{(1)} = (1, Z_{i2}')'$ and $X_i^{(1)} = (1, X_{i2}')'$ for a treated subject, and $Z_i^{(0)} = (0, Z_{i2}')'$ and $X_i^{(0)} = (0, X_{i2}')'$ for a placebo subject. In addition, let $\theta_0 = (\theta_{01}, \theta_{02}')'$ and $\beta_0 = (\beta_{01}, \beta_{02}')'$ denote the regression parameters for Z_i and X_i. Our objective is to compare the treatment and placebo with respect to marginal mean of the number of recurrent events in the presence of a terminal event.

Let $dR(t|Z_i) = E\{d\tilde{N}_i^R(t)|D_i \geq t, Z_i\}$ be the conditional recurrent event rate given survival. We consider the following marginal additive rates model for $dR(t|Z_i)$:

$$dR(t|Z_i) = dR_0(t) + \theta_0' Z_i dt, \tag{1}$$

where $dR_0(t)$ is an unspecified baseline rate function and θ_0 is a vector of regression parameters. By following the estimation procedure of Schaubel et al. (2006), the regression parameter θ_0 can be estimated by $\hat{\theta} = \hat{A}^{-1}\hat{U}^R$ with

$$\begin{aligned} \hat{A} &= n^{-1}\sum_{i=1}^{n}\int_0^\tau Y_i(t)\{Z_i - \bar{Z}(t)\}^{\otimes 2}dt, \\ \hat{U}^R &= n^{-1}\sum_{i=1}^{n}\int_0^\tau \{Z_i - \bar{Z}(t)\}dN_i^R(t), \end{aligned}$$

and

$$\bar{Z}(t) = \frac{\sum_{i=1}^n Y_i(t)Z_i}{\sum_{i=1}^n Y_i(t)},$$

where τ is a prespecified constant such that $P(T_i \geq \tau) > 0$, and $a^{\otimes 2} = aa'$ for a vector a. The corresponding estimator of the baseline rate function $dR_0(t)$ is then estimated by $d\hat{R}_0(t) \equiv d\hat{R}_0(t; \hat{\theta})$, where

$$\hat{R}_0(t; \theta) = \int_0^t \frac{\sum_{i=1}^n Y_i(s)\{dN_i^R(s) - \theta' Z_i ds\}}{\sum_{i=1}^n Y_i(s)}.$$

Let $d\Lambda(t|X_i)$ be the hazard function for the terminal event time D_i given X_i. We specify the following additive hazards model for the terminal event:

$$d\Lambda(t|X_i) = d\Lambda_0(t) + \beta_0' X_i dt, \tag{2}$$

where $d\Lambda_0(t)$ is an unspecified baseline hazard function and β_0 is a vector of regression parameters. Using the approach of Lin and Ying (1994), the regression parameter β_0 can be estimated by $\hat{\beta} = \hat{B}^{-1}\hat{U}^D$ with

$$\begin{aligned} \hat{B} &= n^{-1}\sum_{i=1}^{n}\int_0^\tau Y_i(t)\{X_i - \bar{X}(t)\}^{\otimes 2}dt, \\ \hat{U}^D &= n^{-1}\sum_{i=1}^{n}\int_0^\tau \{X_i - \bar{X}(t)\}dN_i^D(t), \end{aligned}$$

and

$$\bar{X}(t) = \frac{\sum_{i=1}^n Y_i(t)X_i}{\sum_{i=1}^n Y_i(t)}.$$

Then the cumulative baseline hazard function $\Lambda_0(t) = \int_0^t d\Lambda_0(s)$ is estimated by $\hat{\Lambda}_0(t) \equiv \hat{\Lambda}_0(t; \beta)$, where

$$\hat{\Lambda}_0(t;\beta) = \int_0^t \frac{\sum_{i=1}^n \{dN_i^D(u) - Y_i(u)\beta' X_i du\}}{\sum_{i=1}^n Y_i(u)}.$$

Next, we consider a treatment effect measure, which is the difference in treatment-specific marginal recurrent event means. For $0 \le t \le \tau$, define

$$\mu_1(t) = E\{\tilde{N}_i^R(t)|Z_{i1} = 1\},$$

and

$$\mu_0(t) = E\{\tilde{N}_i^R(t)|Z_{i1} = 0\}.$$

The proposed treatment effect measure is given by

$$\phi(t) = \mu_1(t) - \mu_0(t). \tag{3}$$

It follows from the iterated expectations theorem that

$$\mu_1(t) = E\big[E\{\tilde{N}_i^R(t)|Z_{i1} = 1, Z_{i2}, X_{i2}\}\big],$$

where the outer marginal expectation is taken with respect to the marginal distribution of adjustment covariates $(Z_{i2}', X_{i2}')'$, and the inner one is the expectation of $\tilde{N}_i^R(t)$ conditional on $Z_{i1} = 1$ and (Z_{i2}, X_{i2}). Note that $Z_{i1} \equiv X_{i1}$, $Z_i^{(1)} = (1, Z_{i2}')'$ and $X_i^{(1)} = (1, X_{i2}')'$. Then

$$E\big[E\{\tilde{N}_i^R(t)|Z_{i1} = 1, Z_{i2}, X_{i2}\}\big] = E\big[E\{\tilde{N}_i^R(t)|Z_i^{(1)}, X_i^{(1)}\}\big].$$

Thus,

$$\begin{aligned}
\mu_1(t) &= E\big[E\{\tilde{N}_i^R(t)|Z_i^{(1)}, X_i^{(1)}\}\big] \\
&= E\Big[\int_0^t E\{d\tilde{N}_i^R(u)|Z_i^{(1)}, X_i^{(1)}\}\Big] \\
&= E\Big[\int_0^t E\{I(D_i \ge u)d\tilde{N}_i^R(u)|Z_i^{(1)}, X_i^{(1)}\}\Big] \\
&= E\Big[\int_0^t P(D_i \ge u|X_i^{(1)})E\{d\tilde{N}_i^R(u)|D_i \ge u, Z_i^{(1)}\}\Big] \\
&= E\Big[\int_0^t S(u|X_i^{(1)})dR(u|Z_i^{(1)})\Big],
\end{aligned}$$

where $S(t|X_i) = Pr(D_i \ge t|X_i)$. In a similar manner,

$$\begin{aligned}
\mu_0(t) &= E\big[E\{\tilde{N}_i^R(t)|Z_{i1} = 0, Z_{i2}, X_{i2}\}\big] \\
&= E[E\{\tilde{N}_i^R(t)|Z_i^{(0)}, X_i^{(0)}\}] \\
&= E\Big[\int_0^t S(u|X_i^{(0)})dR(u|Z_i^{(0)})\Big].
\end{aligned}$$

Let $\hat{\theta} = (\hat{\theta}_1, \hat{\theta}_2')'$. In view of (1) and (2), by substituting in the survival and conditional rate function estimators, we can obtain the proposed treatment-specific mean estimators:

$$\hat{\mu}_1(t) = n^{-1}\sum_{i=1}^n \int_0^t \hat{S}(u|X_i^{(1)})\{d\hat{R}_0(u) + (\hat{\theta}_1 + Z_{i2}'\hat{\theta}_2)du\},$$

and

$$\hat{\mu}_0(t) = n^{-1}\sum_{i=1}^n \int_0^t \hat{S}(u|X_i^{(0)})\{d\hat{R}_0(u) + Z_{i2}'\hat{\theta}_2 du\},$$

where $\hat{S}(t|X_i) = \exp\{-\hat{\Lambda}_0(t) - \hat{\beta}' X_i t\}$ is the estimator of the survival function $S(t|X_i)$. Then for $0 \le t \le \tau$, the treatment effect on the recurrent event mean can be estimated by

$$\hat{\phi}(t) = \hat{\mu}_1(t) - \hat{\mu}_0(t). \tag{4}$$

It should be noted that apart from $\hat{\phi}(t)$, the hazard difference for the terminal event ($\hat{\beta}_1$) and the rate difference for recurrent events among survivors ($\hat{\theta}_1$) also provide useful additional information on treatment effects. Thus, the three estimators $\hat{\phi}(t)$, $\hat{\beta}_1$ and $\hat{\theta}_1$ describe treatment effects from different perspectives.

3. ASYMPTOTIC ANALYSIS

In order to study the asymptotic properties of the proposed estimators, we need the following regularity conditions:

(C1) $\{\tilde{N}_i^R(\cdot), D_i, C_i, Z_i, X_i\}$ are independent and identically distributed.

(C2) $P\{Y_i(\tau) = 1\} > 0$, $\Lambda_0(\tau) < \infty$, $R_0(\tau) < \infty$, and $E\{N_i^R(\tau)\} < \infty$.

(C3) X_{i2} and Z_{i2} are bounded almost surely.

(C4) A and B are nonsingular, where

$$A = E\Big[\int_0^\tau Y_i(t)\{Z_i - \bar{z}(t)\}^{\otimes 2}dt\Big],$$
$$B = E\Big[\int_0^\tau Y_i(t)\{X_i - \bar{x}(t)\}^{\otimes 2}dt\Big],$$

and $\bar{z}(t)$ and $\bar{x}(t)$ are the limits of $\bar{Z}(t)$ and $\bar{X}(t)$, respectively.

Define

$$\begin{aligned}
dM_i^D(t) &= dN_i^D(t) - Y_i(t)\{d\Lambda_0(t) + \beta_0' X_i dt\}, \\
dM_i^R(t) &= dN_i^R(t) - Y_i(t)\{dR_0(t) + \theta_0' Z_i dt\}, \\
U_i^D &= \int_0^\tau \{X_i - \bar{x}(t)\}dM_i^D(t), \\
U_i^R &= \int_0^\tau \{Z_i - \bar{z}(t)\}dM_i^R(t).
\end{aligned}$$

and let $\pi(t)$ be the limit of $n^{-1}\sum_{i=1}^n Y_i(t)$. The asymptotic properties of the estimators are established in the following theorems with the proof given in the Appendix.

Theorem 1. *Under the regularity conditions (C1)-(C4), $\hat{\phi}(t)$ converges almost surely to $\phi(t)$ uniformly in $t \in [0, \tau]$.*

Theorem 2. *Under the regularity conditions (C1)-(C4), $n^{1/2}\{\hat{\phi}(t) - \phi(t)\}$ converges weakly on $[0, \tau]$ to a zero-mean Gaussian process with covariance function $E[\{\Phi_{i1}(t) - \Phi_{i0}(t)\}\{\Phi_{i1}(s) - \Phi_{i0}(s)\}]$ at (t, s), where for $k = 0, 1$,*

$$\Phi_{ik}(t) = \xi_{ik1}(t) + \xi_{ik2}(t) + \xi_{ik3}(t) + \xi_{ik4}(t) + \xi_{ik5}(t),$$

$$\xi_{ik1}(t) = -E\Big[\int_0^t S(u|X_i^{(k)}) \int_0^u \{X_i^{(k)} - \bar{x}(r)\}' dr \times dR(u|Z_i^{(k)})\Big] B^{-1} U_i^D,$$

$$\xi_{ik2}(t) = E\Big[\int_0^t S(u|X_i^{(k)})\{Z_i^{(k)} - \bar{z}(u)\}' du\Big] A^{-1} U_i^R,$$

$$\xi_{ik3}(t) = \int_0^t E[S(u|X_i^{(k)})]\pi(u)^{-1} dM_i^R(u),$$

$$\xi_{ik4}(t) = -\int_0^t \{\mu_k(t) - \mu_k(u)\}\pi(u)^{-1} dM_i^D(u),$$

$$\xi_{ik5}(t) = \int_0^t S(u|X_i^{(k)}) dR(u|Z_i^{(k)}) - \mu_k(t).$$

The covariance function can be consistently estimated by the usual plug-in method: replacing all limiting quantities with their empirical counterparts in $\Phi_{ik}(t)$, and then averaging across $i = 1, ..., n$.

4. SIMULATION STUDIES

We conducted simulation studies to examine the finite sample properties of the estimators. In the study, the terminal event time D_i was generated from the following additive hazards model:

$$d\Lambda(t|X_i) = d\Lambda_0(t) + \beta_0 X_i dt,$$

where X_i follows a Bernoulli distribution with success probability 0.5, and $\Lambda_0(t) = 0.18t$. To examine the treatment effect on survival, we set $\beta_0 = 0$ or 0.5. The recurrent event times were generated from a Poisson process with the following rate function:

$$dR(t|Z_i, Q_i) = dR_0(t) + Q_i dt + \theta_0 Z_i dt,$$

where the frailty Q_i follows a gamma distribution with mean 0.25 and variance $\sigma^2 = 0.25$ or 0.5. The baseline rate $dR_0(t)$ is set to 0.125 or 0.25. The covariate Z_i is taken the same as X_i, both representing the treatment or exposure of interest. The regression parameter θ_0 is set to 1.5. The censoring time C_i was generated from a uniform distribution on $(0, 10)$. Under the preceding settings, the censoring rate is about 31.6% to 45.3%, and the average number of observed events per subject ranged from 3.2 to 4.8 for different model parameters. The results presented below are based on 1000 replications with sample sizes $n = 100$ and 200.

Tables 1 and 2 present the simulation results on estimation of $\phi(t)$ with $n = 100$ and 200 respectively. To examine the performance of the proposed estimators at early, middle and late follow-up times, we take time points $t = 3$, 5 and 7, respectively. In the tables, Bias is the sample mean of the estimate minus the true value, SE is the sampling standard error of the estimate, SEE is the sample mean of the

Table 1. Simulation results for the estimation of $\phi(t)$ with $n = 100$

β_0	σ^2	$dR_0(t)$	t	$\phi(t)$	Bias	SE	SEE	CP
0	0.25	0.125	3	3.4771	0.0311	0.4352	0.4420	0.955
			5	4.9452	0.0192	0.6239	0.6325	0.952
			7	5.9695	-0.0450	0.8581	0.8476	0.946
		0.25	3	3.4771	-0.0172	0.4673	0.4723	0.964
			5	4.9452	0.0251	0.6447	0.6512	0.948
			7	5.9695	0.0118	0.8637	0.8492	0.954
	0.5	0.125	3	3.4771	0.0253	0.5205	0.5331	0.948
			5	4.9452	-0.0151	0.6914	0.7102	0.959
			7	5.9695	-0.0883	0.9198	0.9514	0.952
		0.25	3	3.4771	0.0463	0.5826	0.5629	0.945
			5	4.9452	0.0361	0.7286	0.7530	0.952
			7	5.9695	-0.0154	0.9585	0.9507	0.950
0.5	0.25	0.125	3	1.5295	-0.0107	0.3961	0.4136	0.955
			5	1.4290	0.0512	0.6022	0.5952	0.952
			7	1.2413	-0.0373	0.8247	0.8270	0.948
		0.25	3	1.3997	0.0278	0.4240	0.4215	0.961
			5	1.1946	0.0167	0.6174	0.6252	0.954
			7	0.9261	0.0367	0.8328	0.8508	0.960
	0.5	0.125	3	1.5295	-0.0464	0.4945	0.4796	0.938
			5	1.4290	-0.0120	0.6638	0.6719	0.954
			7	1.2413	0.0494	0.9023	0.9528	0.956
		0.25	3	1.3997	0.0245	0.5552	0.5540	0.952
			5	1.1946	0.0304	0.7040	0.7262	0.956
			7	0.9261	0.0530	0.9381	0.9534	0.954

Table 2. Simulation results for the estimation of $\phi(t)$ with $n = 200$

β_0	σ^2	$dR_0(t)$	t	$\phi(t)$	Bias	SE	SEE	CP
0	0.25	0.125	3	3.4771	-0.0133	0.3304	0.3205	0.942
			5	4.9452	0.0629	0.5259	0.5125	0.951
			7	5.9695	-0.0432	0.7436	0.7543	0.952
		0.25	3	3.4771	0.0293	0.3605	0.3344	0.944
			5	4.9452	-0.0260	0.5345	0.5174	0.951
			7	5.9695	0.0225	0.7651	0.7558	0.957
	0.5	0.125	3	3.4771	-0.0390	0.4139	0.4624	0.968
			5	4.9452	-0.0416	0.6061	0.6101	0.946
			7	5.9695	0.0694	0.8205	0.8326	0.942
		0.25	3	3.4771	0.0517	0.4785	0.4955	0.955
			5	4.9452	0.0106	0.6331	0.6185	0.962
			7	5.9695	-0.0385	0.8466	0.8541	0.953
0.5	0.25	0.125	3	1.5295	-0.0518	0.3116	0.3050	0.942
			5	1.4290	0.0213	0.5059	0.5242	0.958
			7	1.2413	-0.0225	0.7313	0.7539	0.955
		0.25	3	1.3997	0.0180	0.3164	0.2979	0.952
			5	1.1946	-0.0118	0.5128	0.5306	0.962
			7	0.9261	0.0259	0.7426	0.7417	0.946
	0.5	0.125	3	1.5295	0.0231	0.3948	0.3766	0.949
			5	1.4290	-0.0305	0.5786	0.5903	0.943
			7	1.2413	-0.0578	0.8155	0.8528	0.955
		0.25	3	1.3997	-0.0522	0.4593	0.4636	0.951
			5	1.1946	-0.0273	0.6064	0.6125	0.957
			7	0.9261	0.0217	0.8268	0.8664	0.963

standard error estimate, and CP is the 95% empirical coverage probability based on the normal approximation. It can be seen from Tables 1 and 2 that the proposed estimators are nearly unbiased, there is a good agreement between the estimated and the empirical standard errors, and the 95% empirical coverage probabilities are reasonable.

5. AN APPLICATION

To demonstrate the usefulness of our method, we applied the proposed method to the bladder cancer data arising from cancer clinical trial conducted by the Veterans Administration Cooperative Urological Research Group (Byar, 1980). These data were analyzed by Ghosh and Lin (2000, 2002), Zhao et al. (2011) and Dong and Sun (2015), among others. In this study, the patients were randomly assigned to placebo and thiotepa treatment groups, and many patients had multiple recurrences of the bladder tumors. There were 85 bladder cancer patients with 47 in the placebo group and 38 in the thiotepa treatment group. For each patient, two covariates were measured: the number of initial tumors before entering the study and the size of the largest initial tumor. About 25.9% of patients died during the follow-up, and the total follow-up is 53 months. Note that the size of the largest initial tumor had been shown to have no effect on the recurrence rate (Ghosh and Lin, 2002). Here we focus on the effects of thiotepa treatment and number of initial tumors on the tumor recurrence process with a terminal event (death), and compare treatment-specific recurrent event means.

For the analysis, we defined $\tilde{N}_i^R(t)$ as the cumulative number of observed tumors at time t, and D_i as the death time (in month) of patient i ($i = 1, ..., 85$). Let X_{i1} be the treatment indicator (1, if the patient was in the thiotepa group; 0, if the patient was from the placebo group), and X_{i2} be the adjustment covariate which was defined as the logarithm of the number of the initial tumors plus 1. Set $X_i = (X_{i1}, X_{i2})'$ in model (2), and $Z_i = (Z_{i1}, Z_{i2})' = (X_{i1}, X_{i2})'$ in model (1). The estimates of the regression parameters $\beta_0 = (\beta_{01}, \beta_{02})'$ and $\theta_0 = (\theta_{01}, \theta_{02})'$ are given in Table 3. These results show that both the thiotepa treatment and the number of initial tumors have significant effects on the tumor recurrence process. Specifically, the thiotepa treatment significantly reduced the bladder tumor occurrence rate, and the patients with a higher number of initial tumors tended to have a higher tumor occurrence rate. In addition, both the thiotepa treatment and the number of initial tumors had significant effects on the hazard of death.

Since the treatment effect may vary over time (Zhao et al., 2011; Dong and Sun, 2015), we used $\phi(t)$ to compare treatment-specific differences between placebo and thiotepa treatment groups. Taking time points $t = 2$, 3 and 4 years, respectively, the estimates of $\phi(t)$ are summarized in Table 4. It can be seen that the estimated treatment-specific differences in mean number of events are often not constant over time, and the differences (absolute values) increase with time. At each time point, the difference between treatment-specific recurrent event means is highly significant. In summary, receiving a thiotepa treatment significantly reduces the recurrence of bladder tumor. These results are consistent with Zhao et al. (2011) and Dong and Sun (2015). However, we can obtain the estimated treatment-specific differences at any time t, which is a new insight for the analysis of the bladder cancer data.

Table 3. Analysis of the bladder cancer data: the estimation of β_0 and θ_0

	β_{01}	β_{02}	θ_{01}	θ_{02}
Est	-0.0994	0.0396	-0.2117	0.0595
SE	0.0036	0.0002	0.0224	0.0005
p-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Note: Est is the estimate of the parameter, and SE is the standard error estimate.

Table 4. Analysis of the bladder cancer data: the estimation of $\phi(t)$

t	$\hat{\phi}(t)$	SE	p-value
2 year	-0.4921	0.1739	0.0046
3 year	-0.5618	0.2050	0.0061
4 year	-0.6184	0.2461	0.0121

6. DISCUSSION

In this article, we proposed a semiparametric method to compare treatment-specific recurrent event means in the presence of a terminal event. The proposed method involved modeling the terminal event hazard and the conditional recurrent event rate, and a measure of the combined effects was proposed. Estimation procedures were developed for the measure and the asymptotic properties of proposed measure were established. The simulation results suggested that the proposed estimators perform well. An application to a bladder cancer study was provided to illustrate our method.

Since the proposed measure $\phi(t)$ incorporates treatment-specific differences in survival, it is not clear if an estimated treatment effect is the result of treatment-specific differences in the conditional event rate given survival or treatment-specific differences in survival. Thus, for a complete interpretation of $\phi(t)$, it should be carefully considered all three estimators $\hat{\phi}(t)$, $\hat{\theta}_1$ and $\hat{\beta}_1$. Here, we have used the additive hazards model for the terminal event. Other competing models, such as the additive-multiplicative hazards model, the accelerated failure time model and the linear transformation model, may be used as well.

The proposed method can be extended to other recurrent event models such as proportional rates/means models for recurrent events. For this case, we could consider the following marginal proportional rates model for $dR(t|Z_i)$:

$$dR(t|Z_i) = \exp\{\gamma_0' Z_i\} dR_0^*(t),$$

where $dR_0^*(t)$ is an unspecified baseline rate function and γ_0 is a vector of regression parameters. Then by following the estimation procedure of Lin et al. (2000), we can obtain the estimators $\hat{\gamma}$ and $\hat{R}_0^*(t)$ of γ_0 and $R_0^*(t)$, respectively. In a similar manner, the treatment effect on the recurrent event mean can be estimated by

$$\hat{\phi}^*(t) = \hat{\mu}_1^*(t) - \hat{\mu}_0^*(t),$$

where

$$\hat{\mu}_1^*(t) = n^{-1}\sum_{i=1}^{n}\int_0^t \hat{S}(u|X_i^{(1)})\exp\{\hat{\gamma}_1 + Z_{i2}'\hat{\gamma}_2\}d\hat{R}_0^*(u),$$

and

$$\hat{\mu}_0^*(t) = n^{-1}\sum_{i=1}^{n}\int_0^t \hat{S}(u|X_i^{(0)})\exp\{Z_{i2}'\hat{\gamma}_2\}d\hat{R}_0^*(u).$$

The asymptotic properties of $\hat{\phi}^*(t)$ can be proven in the same manner.

We assumed that the adjustment covariates are time-independent. The proposed estimation procedure can be extended in a straightforward manner to deal with time-dependent covariates. Furthermore, in some applications, the effects of adjustment covariates may vary over time. However, the proposed estimation procedure cannot be extended in a straightforward manner to deal with the case of time-varying coefficients. This is a challenging problem and requires further research efforts. In addition, the treatment-effect can be described through the ratio of treatment-specific means (Schaubel and Zhang, 2010), and the mean ratio might also be worthy of investigation.

ACKNOWLEDGEMENTS

The authors would like to thank the Editor, Professor Heping Zhang, an Associate Editor and two referees for their constructive and insightful comments and suggestions that greatly improve the article. This research was partly supported by the National Natural Science Foundation of China (Grant Nos. 11771431 and 11690015) and Key Laboratory of RCSDS, CAS (No. 2008DP173182).

APPENDIX

Proof of Theorem 1. Define

$$\hat{\mu}_1(t;\beta,\theta) = n^{-1}\sum_{i=1}^{n}\int_0^t \hat{S}(u|X_i^{(1)};\beta)\{d\hat{R}_0(u;\theta) + (\theta_1 + \theta_2'Z_{i2})du\},$$

and

$$\hat{\mu}_0(t;\beta,\theta) = n^{-1}\sum_{i=1}^{n}\int_0^t \hat{S}(u|X_i^{(0)};\beta)\{d\hat{R}_0(u;\theta) + \theta_2'Z_{i2}du\},$$

where $\theta = (\theta_1, \theta_2')'$ and $\hat{S}(t|X_i;\beta) = \exp\{-\hat{\Lambda}_0(t;\beta) - \beta' X_i t\}$. Note that

$$\hat{\phi}(t) = \hat{\mu}_1(t;\hat{\beta},\hat{\theta}) - \hat{\mu}_0(t;\hat{\beta},\hat{\theta}).$$

Thus, to prove the consistency of $\hat{\phi}(t)$, it suffices to prove the consistency of $\hat{\mu}_1(t;\hat{\beta},\hat{\theta})$ and $\hat{\mu}_0(t;\hat{\beta},\hat{\theta})$. For this purpose, it follows from Theorems 1 and 2 of Schaubel et al. (2006) that $\hat{\theta} \to \theta_0$ almost surely, and $\hat{R}_0(t) \to R_0(t)$ almost surely uniformly in $t \in [0,\tau]$. Also by Lin and Ying (1994), we have that $\hat{\beta} \to \beta_0$ almost surely, and $\hat{\Lambda}_0(t) \to \Lambda_0(t)$ almost surely uniformly in $t \in [0,\tau]$. Since $S(t|X_i) = \exp\{-\Lambda_0(t) - {\beta_0}' X_i t\}$, it follows from the continuous mapping theorem that almost surely uniformly in $t \in [0,\tau]$, $\hat{S}(t|X_i;\hat{\beta}) \to S(t|X_i)$ and $\hat{\mu}_1(t;\hat{\beta},\hat{\theta}) \to \tilde{\mu}_1(t;\beta_0,\theta_0)$, where

$$\tilde{\mu}_1(t;\beta_0,\theta_0) = n^{-1}\sum_{i=1}^{n}\int_0^t S(u|X_i^{(1)})\{dR_0(u) + (\theta_{01} + \theta_{02}'Z_{i2})du\}.$$

Applying the uniform strong law of large numbers (Pollard, 1990), we obtain that almost surely uniformly in $t \in [0,\tau]$, $\tilde{\mu}_1(t;\beta_0,\theta_0) \to E\big[\int_0^t S(u|X_i^{(1)})\{dR_0(u) + (\theta_{01} + \theta_{02}'Z_{i2})du\}\big] \equiv \mu_1(t)$. Hence $\hat{\mu}_1(t;\hat{\beta},\hat{\theta}) \to \mu_1(t)$ almost surely uniformly in $t \in [0,\tau]$. Similar arguments can be applied to $\hat{\mu}_0(t;\hat{\beta},\hat{\theta})$.

Proof of Theorem 2. First write

$$\hat{\phi}(t) - \phi(t) = \{\hat{\mu}_1(t;\hat{\beta},\hat{\theta}) - \mu_1(t)\} - \{\hat{\mu}_0(t;\hat{\beta},\hat{\theta}) - \mu_0(t)\}.$$

Here, we show the weak convergence of $n^{1/2}\{\hat{\mu}_1(t;\hat{\beta},\hat{\theta}) - \mu_1(t)\}$. A similar proof can be used for $n^{1/2}\{\hat{\mu}_0(t;\hat{\beta},\hat{\theta}) - \mu_0(t)\}$. Note that

$$\begin{aligned}
&n^{1/2}\{\hat{\mu}_1(t;\hat{\beta},\hat{\theta}) - \mu_1(t)\} \\
=\ & n^{1/2}\{\hat{\mu}_1(t;\hat{\beta},\hat{\theta}) - \hat{\mu}_1(t;\beta_0,\hat{\theta})\} \\
&+n^{1/2}\{\hat{\mu}_1(t;\beta_0,\hat{\theta}) - \hat{\mu}_1(t;\beta_0,\theta_0)\} \\
&+n^{1/2}\{\hat{\mu}_1(t;\beta_0,\theta_0) - \tilde{\mu}_1(t;\beta_0,\theta_0)\} \\
&+n^{1/2}\{\tilde{\mu}_1(t;\beta_0,\theta_0) - \mu_1(t)\}.
\end{aligned} \tag{A1}$$

For the first term on the right-hand side of (A1), using the Taylor expansion and the uniform strong law of large numbers, we get that uniformly in $t \in [0,\tau]$,

$$\begin{aligned}
&n^{1/2}\{\hat{\mu}_1(t;\hat{\beta},\hat{\theta}) - \hat{\mu}_1(t;\beta_0,\hat{\theta})\} \\
=\ & n^{-1}\sum_{i=1}^{n}\int_0^t \frac{\partial \hat{S}(u|X_i^{(1)};\beta)}{\partial\beta'}\Big|_{\beta=\beta^*} n^{1/2}(\hat{\beta} - \beta_0) \\
&\times\{d\hat{R}_0(u) + \hat{\theta}' Z_i^{(1)}du\} \\
=\ & -n^{-1}\sum_{i=1}^{n}\int_0^t \hat{S}(u|X_i^{(1)};\beta^*)\int_0^u \{X_i^{(1)} - \bar{X}(r)\}'dr \\
&\times\{d\hat{R}_0(u) + \hat{\theta}' Z_i^{(1)}du\}n^{1/2}(\hat{\beta} - \beta_0)
\end{aligned} \tag{A2}$$

$$= -E\Big[\int_0^t S(u|X_i^{(1)})\int_0^u \{X_i^{(1)} - \bar{X}(r)\}' dr dR(u|Z_i^{(1)})\Big] \times n^{1/2}(\hat{\beta} - \beta_0) + o_p(1),$$

where β^* lies between $\hat{\beta}$ and β_0. It can be shown that (Lin and Ying, 1994)

$$n^{1/2}(\hat{\beta} - \beta_0) = B^{-1} n^{-1/2} \sum_{i=1}^n U_i^D + o_p(1). \tag{A3}$$

Thus, it follows from (A2) and (A3) that uniformly in $t \in [0, \tau]$,

$$n^{1/2}\{\hat{\mu}_1(t; \hat{\beta}, \hat{\theta}) - \hat{\mu}_1(t; \beta_0, \hat{\theta})\} = n^{-1/2} \sum_{i=1}^n \xi_{i11}(t) + o_p(1), \tag{A4}$$

where

$$\xi_{i11}(t) = -E\Big[\int_0^t S(u|X_i^{(1)}) \times \int_0^u \{X_i^{(1)} - \bar{x}(r)\}' dr dR(u|Z_i^{(1)})\Big] B^{-1} U_i^D.$$

For the second term on the right-hand side of (A1), in a similar manner, we obtain that uniformly in $t \in [0, \tau]$,

$$\begin{aligned} & n^{1/2}\{\hat{\mu}_1(t; \beta_0, \hat{\theta}) - \hat{\mu}_1(t; \beta_0, \theta_0)\} \\ = \; & n^{-1} \sum_{i=1}^n \int_0^t \hat{S}(u|X_i^{(1)}; \beta_0) \Big\{ \frac{\partial d\hat{R}_0(u; \theta)}{\partial \theta'}\Big|_{\theta=\theta^*} + Z_i^{(1)'} du \Big\} n^{1/2}(\hat{\theta} - \theta_0) \\ = \; & n^{-1} \sum_{i=1}^n \int_0^t \hat{S}(u|X_i^{(1)}; \beta_0)\{Z_i^{(1)} - \bar{Z}(u)\}' du \times n^{1/2}(\hat{\theta} - \theta_0) \\ = \; & E\Big[\int_0^t S(u|X_i^{(1)})\{Z_i^{(1)} - \bar{z}(u)\}' du\Big] \times n^{1/2}(\hat{\theta} - \theta_0) + o_p(1), \end{aligned} \tag{A5}$$

where θ^* lies between $\hat{\theta}$ and θ_0. It follows from Schaubel et al. (2006) that

$$n^{1/2}(\hat{\theta} - \theta_0) = A^{-1} n^{-1/2} \sum_{i=1}^n U_i^R + o_p(1). \tag{A6}$$

Then by (A5) and (A6), we have that uniformly in $t \in [0, \tau]$,

$$n^{1/2}\{\hat{\mu}_1(t; \beta_0, \hat{\theta}) - \hat{\mu}_1(t; \beta_0, \theta_0)\} = n^{-1/2} \sum_{i=1}^n \xi_{i12}(t) + o_p(1), \tag{A7}$$

where

$$\xi_{i12}(t) = E\Big[\int_0^t S(u|X_i^{(1)})\{Z_i^{(1)} - \bar{z}(u)\}' du\Big] A^{-1} U_i^R.$$

For the third term on the right-hand side of (A1), note that

$$\begin{aligned} & n^{1/2}\{\hat{\mu}_1(t; \beta_0, \theta_0) - \tilde{\mu}_1(t; \beta_0, \theta_0)\} = \\ & n^{-1/2} \sum_{i=1}^n \int_0^t \hat{S}(u|X_i^{(1)}; \beta_0)\{d\hat{R}_0(u; \theta_0) - dR_0(u)\} \\ & + n^{-1/2} \sum_{i=1}^n \int_0^t \{\hat{S}(u|X_i^{(1)}; \beta_0) - S(u|X_i^{(1)})\} \\ & \times \{dR_0(u) + \theta_0' Z_i^{(1)} du\}. \end{aligned} \tag{A8}$$

By the continuous mapping theorem and the uniform strong law of large numbers, we obtain that almost surely uniformly in $t \in [0, \tau]$,

$$n^{-1} \sum_{i=1}^n \hat{S}(t|X_i^{(1)}; \beta_0) \longrightarrow E\big[S(t|X_i^{(1)})\big].$$

Thus, uniformly in $t \in [0, \tau]$,

$$\begin{aligned} & n^{-1/2} \sum_{i=1}^n \int_0^t \hat{S}(u|X_i^{(1)}; \beta_0)\{d\hat{R}_0(u; \theta_0) - dR_0(u)\} \\ = \; & \int_0^t E[S(u|X_i^{(1)})] n^{1/2}\{d\hat{R}_0(u; \theta_0) - dR_0(u)\} + o_p(1). \end{aligned} \tag{A9}$$

In addition, it can be checked that

$$\begin{aligned} & n^{1/2}\{d\hat{R}_0(t; \theta_0) - dR_0(t)\} \\ = \; & \{n^{-1} \sum_{i=1}^n Y_i(t)\}^{-1} n^{-1/2} \sum_{i=1}^n dM_i^R(t). \end{aligned} \tag{A10}$$

Plugging (A10) into (A9), we get that uniformly in $t \in [0, \tau]$,

$$\begin{aligned} & n^{-1/2} \sum_{i=1}^n \int_0^t \hat{S}(u; \beta_0|X_i^{(1)})\{d\hat{R}_0(u; \theta_0) - dR_0(u)\} \\ = \; & n^{-1/2} \sum_{i=1}^n \xi_{i13}(t) + o_p(1), \end{aligned} \tag{A11}$$

where

$$\xi_{i13}(t) = \int_0^t E[S(u|X_i^{(1)})]\pi(u)^{-1} dM_i^R(u).$$

Likewise, uniformly in $t \in [0, \tau]$,

$$n^{-1/2} \sum_{i=1}^n \int_0^t \{\hat{S}(u; \beta_0|X_i^{(1)}) - S(u|X_i^{(1)})\} \times \{dR_0(u) + \theta_0' Z_i^{(1)} du\} \tag{A12}$$

$$
\begin{aligned}
&= -n^{-1/2}\sum_{i=1}^{n}\int_0^t S(u|X_i^{(1)})\{\hat{\Lambda}_0(u;\beta_0)-\Lambda_0(u)\}\\
&\quad\times\{dR_0(u)+\theta_0' Z_i^{(1)}du\}+o_p(1)\\
&= -\int_0^t E[S(u|X_i^{(1)})dR(u|Z_i^{(1)})]n^{1/2}\{\hat{\Lambda}_0(u;\beta_0)\\
&\quad-\Lambda_0(u)\}+o_p(1).
\end{aligned}
$$

It can be shown that

$$
\begin{aligned}
&n^{1/2}\{\hat{\Lambda}_0(t;\beta_0)-\Lambda_0(t)\}\\
&= n^{-1/2}\sum_{i=1}^{n}\int_0^t\{n^{-1}\sum_{i=1}^{n}Y_i(u)\}^{-1}dM_i^D(u).
\end{aligned}
\tag{A13}
$$

In view of (A12) and (A13), by switching the order of integration, we have that uniformly in $t\in[0,\tau]$,

$$
\begin{aligned}
&n^{-1/2}\sum_{i=1}^{n}\int_0^t\{\hat{S}(u;\beta_0|X_i^{(1)})-S(u|X_i^{(1)})\}\\
&\quad\times\{dR_0(u)+\theta_0' Z_i^{(1)}du\}\\
&= n^{-1/2}\sum_{i=1}^{n}\xi_{i14}(t)+o_p(1),
\end{aligned}
\tag{A14}
$$

where

$$
\xi_{i14}(t)=-\int_0^t\{\mu_1(t)-\mu_1(u)\}\pi(u)^{-1}dM_i^D(u).
$$

It follows from (A8), (A11) and (A14) that uniformly in $t\in[0,\tau]$,

$$
\begin{aligned}
&n^{1/2}\{\hat{\mu}_1(t;\beta_0,\theta_0)-\tilde{\mu}_1(t;\beta_0,\theta_0)\}\\
&= n^{-1/2}\sum_{i=1}^{n}\big[\xi_{i13}(t)+\xi_{i14}(t)\big]+o_p(1).
\end{aligned}
\tag{A15}
$$

It is easy to see that

$$
n^{1/2}\{\tilde{\mu}_1(t;\beta_0,\theta_0)-\mu_1(t)\}=n^{-1/2}\sum_{i=1}^{n}\xi_{i15}(t),
\tag{A16}
$$

where

$$
\xi_{i15}(t)=\int_0^t S(u|X_i^{(1)})dR(u|Z_i^{(1)})-\mu_1(t).
$$

Let

$$
\Phi_{i1}(t)=\xi_{i11}(t)+\xi_{i12}(t)+\xi_{i13}(t)+\xi_{i14}(t)+\xi_{i15}(t).
$$

Then it follows from (A1), (A4), (A7), (A15) and (A16) that uniformly in $t\in[0,\tau]$,

$$
n^{1/2}\{\hat{\mu}_1(t;\hat{\beta},\hat{\theta})-\mu_1(t)\}=n^{-1/2}\sum_{i=1}^{n}\Phi_{i1}(t)+o_p(1),
\tag{A17}
$$

which is asymptotically a sum of independent and identically distributed variables for each t. Since $\Phi_{i1}(t)$ $(i=1,...,n)$ can be written as sums or products of monotone functions of t and are thus tight (van der Vaart and Wellner, 1996). Similarly, we obtain that $n^{1/2}\{\hat{\mu}_0(t;\hat{\beta},\hat{\theta})-\mu_0(t)\}$ can be written asymptotically as a sum of independent and identically distributed variables for each t. After taking the difference between $n^{1/2}\{\hat{\mu}_1(t;\hat{\beta},\hat{\theta})-\mu_1(t)\}$ and $n^{1/2}\{\hat{\mu}_0(t;\hat{\beta},\hat{\theta})-\mu_0(t)\}$, we get that $\hat{\phi}(t)-\phi(t)$ is asymptotically a sum of independent and identically distributed terms and is tight. Thus, by the functional central limit theorem (Pollard, 1990), $n^{1/2}\{\hat{\phi}(t)-\phi(t)\}$ converges weakly to a zero-mean Gaussian process. The covariance function for $n^{1/2}\{\hat{\phi}(t)-\phi(t)\}$ at (t,s) is given by $E[\{\Phi_{i1}(t)-\Phi_{i0}(t)\}\{\Phi_{i1}(s)-\Phi_{i0}(s)\}]$, which can be consistently estimated by replacing all limiting quantities with their empirical counterparts, and then averaging over the sample.

Received 22 November 2017

REFERENCES

Albert, P. S. (1991). A two-state Markov mixture model for a time series of epileptic seizure counts. *Biometrics* **47** 1371–1381.

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

Byar, D. P. (1980). The Veterans Administration study of chemoprophylaxis for recurrent stage I bladder tumors: Comparisons of placebo, pyridoxine and topical thiotepa. In *Bladder Tumors and Other Topics in Urological Oncology* M. Pavone-Macaluso, P. H. Smith, and F. Edsmyr (eds), 363–370. Plenum, New York.

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

Cook, R. and Lawless, J. (2007). *The Statistical Analysis of Recurrent Events*. Springer, New York. MR2597020

Dong, L. and Sun, L. (2015). A flexible semiparametric transformation model for recurrent event data. *Lifetime Data Anal.* **21** 20–41. MR3299889

Ghosh, D. and Lin, D. (2000). Nonparametric analysis of recurrent events and death. *Biometrics* **56** 554–562. MR1795021

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

Hobson, R. W., Weiss, D. G., Fields, W. S., Goldstone, J., Moore, W. S., Towne, J. B., Wright, C. B. and the Veterans Affairs Cooperative Study Group (1993). Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *New Engl. J. Med.* **328** 221–227.

Huang, C. and Wang, M. (2004). Joint modeling and estimation for recurrent event processes and failure time data. *J. Amer. Statist. Assoc.* **99** 1153–1165. MR2109503

Kalbfleisch J., Schaubel, D., Ye, Y. and Gong, Q. (2013). An estimating function approach to the analysis of recurrent and terminal events. *Biometrics* **69** 366–374. MR3071055

Lawless, J. F. and Nadeau, C. (1995). Some simple robust methods for the analysis of recurrent events. *Technometrics* **37** 158–168. MR1333194

Li, Q. and Lagakos, S. (1997). Use of the Wei-Lin-Weissfeld method for the analysis of a recurring and a terminating event. *Stat. Med.* **16** 925–940.

Lin, D., Wei, L., Yang, I. and Ying, Z. (2000). Semiparametric regression for the mean and rate function of recurrent events. *J. Royal Stat. Soc. Ser. B* **62** 711–730. MR1796287

Lin D. and Ying, Z. (1994). Semiparametric analysis of the additive risk model. *Biometrika* **81** 61–71. MR1279656

Pan, Q. and Schaubel, D. (2009). Flexible estimation of differences in treatment-specific recurrent event means in the presence of a terminating event. *Biometrics* **65** 753–761. MR2649848

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.

Pollard, D. (1990). *Empirical Processes: Theory and Applications*, Institute of Mathematical Statistics, Hayward, CA. MR1089429

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

Schaubel, D., Zeng, D. and Cai, J. (2006). A semiparametric additive rates model for recurrent event data. *Lifetime Data Anal.* **12** 389–406. MR2338958

Schaubel, D. and Zhang, M. (2010). Estimating treatment effects on the marginal recurrent event mean in the presence of a terminating event. *Lifetime Data Anal.* **16** 451–477. MR2726219

van der Vaart, A. and Wellner, J. (1996). *Weak Convergence and Empirical Processes*. Springer, New York. MR1385671

Ye, Y., Kalbfleisch, J. and Schaubel, D. E. (2007). Semiparametric analysis of correlated recurrent and terminal events. *Biometrics* **63** 78–87. MR2345577

Zeng, D. and Lin, D. (2009). Semiparametric transformation models with random effects for joint analysis of recurrent and terminal events. *Biometrics* **65** 746–752. MR2649847

Zhao, X., Zhou, J. and Sun, L. (2011). Semiparametric transformation models with time-varying coefficients for recurrent and terminal events. *Biometrics* **67** 404–414. MR2829009

Xiaowei Sun
Institute of Applied Mathematics
Academy of Mathematics and Systems Science
Chinese Academy of Sciences
Beijing 100190
People's Republic of China
University of Chinese Academy of Sciences
Beijing 100049
People's Republic of China
E-mail address: sunxiaowei115@mails.ucas.ac.cn

Liuquan Sun
Institute of Applied Mathematics
Academy of Mathematics and Systems Science
Chinese Academy of Sciences
Beijing 100190
People's Republic of China
University of Chinese Academy of Sciences
Beijing 100049
People's Republic of China
E-mail address: slq@amt.ac.cn