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TESTING INDEPENDENT CENSORING FOR LONGITUDINAL DATA

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Abstract: A common problem associated with longitudinal studies is the dropouts of subjects or censoring before the end of follow-up. In most existing methods, it is assumed that censoring is noninformative about missed responses. This assumption is crucial to the validity of many statistical procedures. We develop some nonparametric hypothesis testing procedures to test for independent censoring in the absence/presence of covariates. The test statistics are constructed by contrasting two estimators of the conditional mean of cumulative responses for each stratum of covariate space from sample subsets with different patterns of censoring. Our method does not require the modelling of longitudinal response processes, therefore is robust to model misspecifications. A diagnostic plot procedure is also developed that can be used to identify dependent censoring to certain covariate strata. The finite sample performances of the tests are investigated through extensive simulation studies. The potential of our methods is demonstrated through the application of the tests to a chronic granulomatous disease study.

Key words and phrases: CGD data, Gaussian multiplier method, informative censoring, integrated square test, marginal and conditional independent censoring, nonparametric tests, recurrent events, supremum test, weak convergence.

1. Introduction

Longitudinal data are repeated measurements collected on subjects over a period of time. Some response processes are observed at discrete sampling times. Others are continuously observed counting processes of recurrent events. There is an extensive literature on the analysis of longitudinal data. Among many others, recent works on nonparametric and semiparametric modelling of longitudinal data collected on observed sampling times include Hoover et al. (1998), Martinussen and Scheike (1999, 2000, 2001), Lin and Ying (2001) Wu and Zhang (2002), Fan and Li (2004) and Sun and Wu (2005). Data collected on counting processes at a finite set of sampling times are also called panel count data. Many authors have studied statistical methods for analyzing panel count data; cf., Sun and Kalbfleisch (1995), Cheng and Wei (2000), Sun and Wei (2000), Wellner and Zhang (2000), Hu, Sun and Wei (2003), and Lu, Zhang, and Huang

(2007). The mean rate modelling for recurrent events based on continuously observed counting processes has been studied by Pepe and Cai (1993), Lawless and Nadeau (1995), Lin et al. (2000), Scheike (2002), and Schaubel, Zeng and Cai (2006) among others. Many statistical models and procedures for the intensity of continuously observed counting processes are discussed by Andersen et al. (1993).

A common problem associated with longitudinal studies is the dropouts of study subjects or censoring for various reasons. In some situations, censoring may alter intensities or mean occurrence rate for the events of interest. For instance in a clinical trial, as noted in Andersen et al. (1993), if those patients who are particularly ill (or particularly well) are removed from study, then the remaining patients are no longer "representative" for the sample of patients that we would have had, had there been no such censoring. In most existing methods in the analysis of longitudinal data, it is assumed that longitudinal responses and censoring times are independent conditional on certain relevant covariates. That is, censoring is not informative about missed responses conditional on covariates. This assumption is crucial to the validity of many statistical procedures and its violation can mislead the outcomes of analysis. The goal of this study is to develop some hypothesis testing procedures to test whether censoring times are independent of longitudinal responses. Cautions and perhaps alternative approaches should be taken when there is evidence of dependent censoring.

Let $N_i^*(t)$ be the counting process of recurrent events for the ith subject, Z_i a p-dimensional covariate, and C_i the possible censoring time. In the study of recurrent event data, a basic assumption for identifiability is that, given the full data $F_\tau = \{N_i^*(t), Z_i;\, 0 \le t \le \tau\}$, the censoring event defining the observed data depends only on the observed part of the data, where τ is the end of follow-up time. This assumption is called *coarsening at random* (CAR); see Robins and Rotnitzky (1992) and Robins (1993). For right censored data it means that, under CAR, $\lambda_C(t|F_\tau) = \lambda_C(t|F_t)$ for $t < \tau$, where $\lambda_C(t|F_\tau) = P(t < C < t + dt|C > t, F_\tau)/dt$ is the conditional hazard function of censoring variable C given the full data F_τ. The CAR assumption is essential for the full data parameter of interest to be identifiable from the distribution of the observed data (Miloslavsky et al. (2004)). In the modelling of mean rate for the recurrent events, it is often assumed that $E\left[dN_i^*(t)|Z_i, C_i \ge t\right] = E\left[dN_i^*(t)|Z_i\right]$, $0 \le t \le \tau$, which, together with CAR, implies that the censoring C_i is independent of the counting process $N_i^*(t), 0 \le t \le \tau$, given the covariate Z_i, as noted in Miloslavsky et al. (2004). We thus formulate the independent censoring assumption as

$$\text{NIC1}: \quad E\left[dN_i^*(s)|Z_i, C_i \ge t\right] = E\left[dN_i^*(s)|Z_i\right], \quad 0 \le s \le t \le \tau. \tag{1.1}$$

The marginal independent censoring refers to the case where the covariate Z_i is removed from the conditioning set in (1.1). The conditional independent censoring does not imply marginal independent censoring, and vice versa. Independent censoring has been assumed in the statistical methods developed for the proportional mean rate model (Lin et al. (2000)), the semiparametric transformation mean rate model (Lin, Wei and Ying (2001)) and the additive mean rate model (Scheike (2002) and Schaubel, Zeng and Cai (2006)).

Miloslavsky et al. (2004) proposed a class of inverse probability of censoring weighted estimators for the proportional rate model in the presence of dependent censoring. The method requires that the censoring mechanism can be estimated consistently based on $\{N_i^*(t), X_i, 0 \leq t \leq \tau\}$, where X_i includes Z_i as a subset. This method can be implemented by assuming that dependent censoring is induced by omitting certain relevant covariates, and that the censoring mechanism C_i is independent of the counting process $N_i^*(t)$, $0 \leq t \leq \tau$, given all relevant covariates X_i. Thus independent censoring is still an assumption that needs to be checked.

In the analysis of longitudinal data, let $Y_i(t)$ be the response process and $N_i^*(t)$ the counting process of sampling time points for the ith subject. The full data under the CAR now is $F_\tau = \{N_i^*(t), Y_i(t)\, dN_i^*(t), Z_i;\, 0 \leq t \leq \tau\}$. We refer to the following assumption as independent censoring in case of longitudinal observations:

$$\text{NIC2}: \quad E\left[Y_i(s)dN_i^*(s)|Z_i, C_i \geq t\right] = E\left[Y_i(s)dN_i^*(s)|Z_i\right], \quad 0 \leq s \leq t \leq \tau. \tag{1.2}$$

NIC2 becomes NIC1 when $Y_i(\cdot) = 1$. The validity of NIC1 and NIC2 imply the noninformative censoring assumed in Hoover et al. (1998), Lin and Ying (2001), Martinussen and Scheike (1999, 2000, 2001), and Sun and Wu (2005).

Diggle (1989) developed a method of testing the hypothesis of random dropouts within groups. The method applies to the designs with fixed observation time points. Ridout (1991) introduced logistic regression models to analyze patterns of occurrence of dropouts in repeated measurement data to increase flexibility. Under the parametric modelling of longitudinal data, Chen and Little (1999) developed a Wald-type test of missing completely at random in estimating equation settings. Qu and Song (2002) proposed a generalized score type test based on quadratic inference functions, and showed that their test is asymptotically equivalent to Chen and Little's Wald-type test with improved numerical properties. Both tests assume the validity of the underlying parametric models and are constructed based on generalized estimating equations. In case of significantly small p-values, it may be difficult to determine whether this is due to the lack of missing at random or because of the misspecification of the underlying parametric model.

We propose some robust inference procedures to test whether a censoring random variable C_i is marginally or conditionally independent of the recurrent process $N_i^*(t)$ when covariates may or may not be presented. For longitudinal data, we test whether C_i is marginally or conditionally independent of

$(N_i^*(t), Y_i(t)\, dN_i^*(t))$. In terms of Robin's (1976) classification of missing data and in case of right censoring, marginal independence corresponds to missing completely at random and conditional independence corresponds to missing at random. Our test statistics are not constructed based on any particular models for $N_i^*(t)$ and $Y_i(t)$, and thus are robust to model misspecifications; they can avoid the difficulty of existing approaches. The rest of the paper is arranged in the following way. In Section 2, tests of independence are developed in the absence of covariates. The tests of conditional independence are developed in Section 3. A simulation study is conducted in Section 4 to examine finite sample properties of the proposed test procedures. The proposed tests are illustrated in Section 5 with an application to a chronic granulomatous disease study. All proofs are allocated to the Appendix.

2. Testing of Independent Censoring in the Absence of Covariates

Assume that the processes $(N_i^*(t), Y_i(t), C_i)$, $1 \le i \le n$, are independent and identically distributed (iid). Let $N_i(t) = N_i^*(t \wedge C_i)$ and $\bar{N}^{(Y)}(t) = \int_0^t \sum_{i=1}^n Y_i(s) N_i(ds)$. For $0 \le s \le t$, let $N_i(s,t) = N_i^*(s) I(C_i \ge t)$ and $\bar{N}^{(Y)}(s,t) = \sum_{i=1}^n \int_0^s Y_i(u) N_i(du,t)$. $\bar{N}^{(Y)}(s,t)$ is the cumulative response over the time interval $[0,s]$ for those not censored by time t. For $Y_i(\cdot) = 1$, $\bar{N}^{(1)}(s,t)$ is the total number of observed recurrent events by time s for those not censored by time t.

Let $\alpha(t)dt = E(Y_i(t) dN_i^*(t))$ and $\mu(t) = \int_0^t \alpha(s)\, ds$. Then $\mu(t)$ is the expected cumulative response over the time interval $[0,t]$. When $Y_i(\cdot) = 1$, $\mu(t)$ is the mean function of the number of recurrent events by time t, and $\alpha(t)$ is the mean rate function of recurrent events. We construct two estimators of $\mu(s)$ from sample subsets based on two different patterns of uncensored longitudinal responses. If censoring is independent, both estimators are consistent estimators of $\mu(s)$. The two estimators would both be biased, however, in different ways under dependent censoring. Let

$$\bar{\mu}^{(Y)}(s) = \int_0^s (\bar{\xi}(u))^{-1} \bar{N}^{(Y)}(du),$$
$$\hat{\mu}^{(Y)}(s,t) = \int_0^s (\bar{\xi}(t))^{-1} \bar{N}^{(Y)}(du,t),$$

where $\bar{\xi}(t) = \sum_{i=1}^n \xi_i(t)$ and $\xi_i(t) = I(C_i \ge t)$ is the at risk process for the ith subject. The first estimator $\bar{\mu}^{(Y)}(s)$ uses observed data available up to time s, and the second estimator $\hat{\mu}^{(Y)}(s,t)$ is calculated based on the sample subset of subjects not censored by time t. Under independent censoring, both $\bar{\mu}^{(Y)}(s)$ and $\hat{\mu}^{(Y)}(s,s)$ are consistent estimator of $\mu(s)$ for $0 \le s \le \tau$. We consider the following test process based the weighted difference of these two estimators:

$$R^{(Y)}(t) = \sqrt{n} \int_0^t H(u) \left(\bar{\mu}^{(Y)}(du) - \hat{\mu}^{(Y)}(du,t) \right), \tag{2.1}$$

where $H(\cdot)$ is a weight process converging in probability to a bounded deterministic function $h(\cdot)$, i.e., $\sup_{0\le u\le\tau}|H(u)-h(u)|\xrightarrow{P}0$.

Let $\alpha_1^c(s)ds = E(Y_i(s)dN_i^*(s)|C_i \ge s)$, $\alpha_2^c(s,t)ds = E(Y_i(s)dN_i^*(s)|C_i \ge t)$, $\mu_1^c(s) = \int_0^s \alpha_1^c(u)\,du$, $\mu_2^c(s,t) = \int_0^s \alpha_2^c(u,t)\,du$. Under independent censoring NIC2, $\alpha_1^c(s) = \alpha_2^c(s,t) = \alpha(s)$ for $0 \le s \le t$. Let $G(t) = P(C_i \ge t)$ for the survival function of censoring variable C_i. The asymptotic results given in the following theorem establish that $R^{(Y)}(t)$ converges weakly to a mean zero Gaussian process under NIC2 and that $\bar{\mu}^{(Y)}(s)$ and $\hat{\mu}^{(Y)}(s,t)$ converge to different limits under dependent censoring.

Theorem 1. *Assume that $P(C_i \ge \tau) > 0$, $E(N_i^*(\tau)) < \infty$, and $E(Y_i(t)) < \infty$ for $0 \le t \le \tau$. Also assume that the weight process $H(t)$ can be written as the difference of two monotone processes, each of which converges in probability to a bounded deterministic function, such that $\sup_{0\le u\le\tau}|H(u)-h(u)|\xrightarrow{P}0$. Then the following decomposition holds uniformly in $0 \le t \le \tau$:*

$$\begin{aligned}R^{(Y)}(t) &= n^{-1/2}\sum_{i=1}^{n}\int_0^t \frac{h(u)[Y_i(u)dN_i(u) - I(C_i \ge u)d\mu_1^c(u)]}{G(u)}\\ &\quad -n^{-1/2}\sum_{i=1}^{n}\int_0^t h(u)(Y_i(u)dN_i(u) - \mu_2^c(du,t))\frac{I(C_i \ge t)}{G(t)}\\ &\quad +n^{1/2}\int_0^t H(u)(d\mu_1^c(u) - \mu_2^c(du,t)) + o_p(1). \qquad (2.2)\end{aligned}$$

Under independent censoring NIC2, *$R^{(Y)}(t)$, $0 \le t \le \tau$, converges weakly to a mean zero Gaussian process.*

Under NIC2, $\mu_1^c(u) = \mu_2^c(u,t) = \mu(u)$ for $0 \le u \le t$. The distribution of $R^{(Y)}(t)$ can be simulated using the Gaussian multiplier method described below. We estimate $G(t)$ by $\bar{\xi}(t)/n$, $\mu_1^c(u)$ by $\bar{\mu}^{(Y)}(u)$, and $\mu_2^c(u,t)$ by $\hat{\mu}^{(Y)}(u,t)$. Let ϕ_i, $i = 1,\ldots,n$, be iid standard normal random variables, and let

$$\begin{aligned}R^{*(Y)}(t) &= n^{1/2}\sum_{i=1}^{n}\phi_i\int_0^t \frac{H(u)}{\bar{\xi}(u)}\Big[Y_i(u)dN_i(u) - I(C_i \ge u)d\bar{\mu}^{(Y)}(u)\Big]\\ &\quad -n^{1/2}\sum_{i=1}^{n}\phi_i\int_0^t H(u)(Y_i(u)dN_i(u) - \hat{\mu}^{(Y)}(du,t))\frac{I(C_i \ge t)}{\bar{\xi}(t)}. \qquad (2.3)\end{aligned}$$

By Sun and Wu (2005), the distribution of $R^{(Y)}(\cdot)$ under NIC2 can be approximated by the distribution $R^{*(Y)}(\cdot)$ given the observed recurrent event data, which can be estimated by repeatedly generating independent sets of iid normal deviates. This approach is often called the Gaussian multiplier method and has been widely use to approximate the distribution of a Gaussian process that is the limit of some empirical processes, cf., Lin, Wei and Ying (1993) and Martinussen and Scheike (2006).

Various test statistics can be constructed to test NIC1 and/or NIC2 based on the test process $R^{(Y)}(t)$, $0 \le t \le \tau$. Setting $Y_i(\cdot) \equiv 1$, we propose to use the test statistics $S^{(1)} = \sup_{0\le t\le\tau} |R^{(1)}(t)|$ and $L^{(1)} = \int_0^\tau (R^{(1)}(t))^2\, dt$ to test independent censoring NIC1, and the test statistics $S^{(Y)} = \sup_{0\le t\le\tau} |R^{(Y)}(t)|$ and $L^{(Y)} = \int_0^\tau (R^{(Y)}(t))^2\, dt$ to test NIC2. The test statistics for testing NIC1 and NIC2 can be obtained by taking $S = S^{(1)} + S^{(Y)}$ and $L = L^{(1)} + L^{(Y)}$. The critical values of these test statistics can be estimated by repeatedly generating $R^{*(1)}(t)$ and $R^{*(Y)}(t)$ while holding the observed data sequence fixed. We reject the null hypothesis NIC1 and/or NIC2 for large values of the test statistics. In testing independent censoring for recurrent event data, for example, we replace $R^{(1)}(t)$ in $S^{(1)}$ and $L^{(1)}$ by $R^{*(1)}(t)$ to obtain $S^{*(1)}$ and $L^{*(1)}$, respectively. The critical values of the test statistics $S^{(1)}$ and $L^{(1)}$ at the significance level α can be estimated by the upper α percentiles of $S^{*(1)}$ and $L^{*(1)}$, respectively, given the observed data sequence.

It follows from (2.2) that the presence of dependent censoring can be captured through the term $n^{1/2}\int_0^t H(u)(\mu_1^c(du) - \mu_2^c(du,t))$ which equals $n^{1/2}(\mu_1^c(t) - \mu_2^c(t))$ for $H(\cdot) = 1$, where $\mu_2^c(t) = \mu_2^c(t,t)$. This is further demonstrated in the following for testing dependent censoring for recurrent event processes. It has been argued by many authors that dependence between recurrent event process and censoring time can be fully explained by all the collected covariates, cf., Miloslavsky et al. (2004) and Zeng (2005). Suppose that X_i is the collection of covariates such that $N_i^*(\cdot)$ is independent of C_i given X_i. Setting $Y_i(\cdot) \equiv 1$,

$$\mu_1^c(t) = \int_0^t E(dN_i^*(s)|C_i \ge s) = \int_0^t E[E(dN_i^*(s)|X_i)|C_i \ge s],$$

$$\mu_2^c(t) = \int_0^t E(dN_i^*(s)|C_i \ge t) = \int_0^t E[E(dN_i^*(s)|X_i)|C_i \ge t].$$

Suppose $E(dN_i^*(t)|X_i) = \alpha_0(t)\exp(\gamma^T X_i)dt$, where $\alpha_0(t)$ is an unspecified baseline function and γ is an unknown vector of parameters. Then $\mu_1^c(t) = \int_0^t \alpha_0(s) E(\exp(\gamma^T X_i)|C_i \ge s)\, ds$ and $\mu_2^c(t) = A_0(t)E(\exp(\gamma^T X_i)|C_i \ge t)$ with $A_0(t) = \int_0^t \alpha_0(s)\, ds$. Let $q(t) = E(\exp(\gamma^T X_i)|C_i \ge t)$. If $\mu_1^c(t) = \mu_2^c(t)$ for all t, then $A_0(t)q(t) = \int_0^t \alpha_0(s)q(s)\, ds$, which implies that $q(t)$ does not depend on t. Thus, $E(dN_i^*(t)|C_i \ge t) = \alpha_0(t)E(\exp(\gamma^T X_i)|C_i \ge t) = E(dN_i^*(t))$. This shows that independent censoring is equivalent to $\mu_2^c(t) = \mu_1^c(t)$ for all t. By Theorem 1, the supremum test statistic $S^{(1)}$ and the integrated square test statistics $L^{(1)}$ yield consistent tests against any type of dependent censoring.

3. Testing of Conditional Independent Censoring Given Covariates

In the presence of a p-dimensional covariate Z_i, let $\alpha_1^c(s, Z_i)ds = E(Y_i(s) dN_i^*(s)|Z_i, C_i \geq s)$ and $\alpha_2^c(s,t,Z_i)ds = E(Y_i(s)dN_i^*(s)|Z_i, C_i \geq t)$. Let $\alpha(s, Z_i)ds = E(Y_i(s)dN_i^*(s)|Z_i)$ be the true regression function. Under NIC2, we have $\alpha_1^c(s, Z_i) = \alpha_2^c(s,t,Z_i) = \alpha(s, Z_i)$.

Assume that the processes $(N_i^*(t), Y_i(t), Z_i, C_i)$, $1 \leq i \leq n$, are independent identically distributed. Let $G_i(t) = G(t|Z_i) = P(C_i \geq t|Z_i)$ and $\hat{G}_i(t) = \hat{G}(t|Z_i)$ be its nonparametric or semiparametric estimator. Partition the covariate space into K strata, Δ_k, $k = 1, \ldots, K$. For each stratum, define $\mu_{1k}^c(s) = \int_0^s E[I(Z_i \in \Delta_k)\alpha_1^c(u, Z_i)]\,du$, $\mu_{2k}^c(s,t) = \int_0^s E[I(Z_i \in \Delta_k)\alpha_2^c(u,t,Z_i)]\,du$, and $\mu_k(s) = \int_0^s E[I(Z_i \in \Delta_k)\alpha(u, Z_i)]\,du$. Here $\mu_k(s)$ is the expected value in the kth stratum of the conditional mean of cumulative response given Z_i over time interval $[0, s]$. The other two terms $\mu_{1k}^c(s)$ and $\mu_{2k}^c(s,t)$ have similar interpretations except that they are obtained by conditioning on different subsets of censoring variable. Let

$$\bar{\mu}_k^{(Y)}(s) = \int_0^s n^{-1} \sum_{i=1}^n I(Z_i \in \Delta_k)(\hat{G}_i(u))^{-1} Y_i(u) N_i(du),$$
$$\hat{\mu}_k^{(Y)}(s,t) = \int_0^s n^{-1} \sum_{i=1}^n I(Z_i \in \Delta_k)(\hat{G}_i(t))^{-1} Y_i(u) N_i(du,t)$$

for $0 \leq s \leq t \leq \tau$. Then $\bar{\mu}_k^{(Y)}(s)$ and $\hat{\mu}_k^{(Y)}(s,t)$ are consistent estimators of $\mu_{1k}^c(s)$ and $\mu_{2k}^c(s,t)$, respectively. The two estimators $\bar{\mu}_k^{(Y)}(s)$ and $\hat{\mu}_k^{(Y)}(s,t)$ are calculated from sample subsets within stratum k based on two different patterns of uncensored longitudinal responses. Under NIC2, $\mu_{1k}^c(s) = \mu_{2k}^c(s,t) = \mu_k(s)$, and thus $\bar{\mu}_k^{(Y)}(s)$ and $\hat{\mu}_k^{(Y)}(s,t)$ are consistent estimators of $\mu_k(s)$. They are, however, biased in different ways under dependent censoring.

Let $H_k(u)$ be some suitable weight processes such that $|H_k(u) - h_k(u)| \xrightarrow{P} 0$ for some bounded deterministic functions $h_k(u)$. We form the following test processes as weighted difference between the two estimators of $\mu_k(t)$:

$$R_k^{(Y)}(t) = \sqrt{n} \int_0^t H_k(u)\,(\bar{\mu}_k^{(Y)}(du) - \hat{\mu}_k^{(Y)}(du,t)), \quad k = 1, \ldots, K. \tag{3.1}$$

For longitudinal data, censoring time C_i is observed for each subject (taken as the last available observation time). The conditional distribution of censoring times can be estimated nonparametrically or through semiparametric models. Here we assume that censoring times C_i follow the proportional hazards model

$$\lambda_c(t|Z_i) = \lambda_0(t)\exp\{\beta^T Z_i\}, \tag{3.2}$$

where $\lambda_0(t)$ is an unspecified baseline function and β is a p-dimensional vector of parameters. Under (3.2), $G_i(t) = \exp\{-\Lambda_0(t)\exp\{\beta^T Z_i\}\}$ where $\Lambda_0(t) = \int_0^t \lambda_0(u)\,du$. The estimators for β and $\Lambda_0(t)$ can be obtained based on the standard partial likelihood method. Let $S^{(j)}(t,\beta) = n^{-1}\sum_{i=1}^n \xi_i(t)\exp\{\beta^T Z_i\}Z_i^{\otimes j}$, for $j = 0,1,2$, where $Z_i^{\otimes 0} = 1$, $Z_i^{\otimes 1} = Z_i$, and $Z_i^{\otimes 2} = Z_i Z_i^T$. Let $\bar{Z}(t;\beta) = S^{(1)}(t,\beta)/S^{(0)}(t,\beta)$ and $N_i^c(t) = I(C_i \leq t)$. The maximum partial likelihood estimator $\hat{\beta}$ of β solves the partial likelihood estimation equation

$$\sum_{i=1}^n \int_0^\tau \{Z_i - \bar{Z}(t;\beta)\}\,dN_i^c(t) = 0. \tag{3.3}$$

The Nelson-Aalen estimator for $\Lambda_0(t)$ is $\hat{\Lambda}_0(t) = \sum_{i=1}^n \int_0^t dN_i^c(s)/\sum_{j=1}^n \xi_j(s)\exp(\hat{\beta}^T Z_j)$. The survival function $G_i(t)$ can be estimated by $\hat{G}_i(t) = \exp\{-\hat{\Lambda}_0(t)\exp\{\hat{\beta}^T Z_i\}\}$.

Let $s^{(j)}(t) = ES^{(j)}(t,\beta)$ and $\bar{z}(t) = s^{(1)}(t)/s^{(0)}(t)$. Let $A = E\{\int_0^\tau (Z_i - \bar{z}(t))^{\otimes 2}\,dN_i^c(t)\}$. Assume that the matrix A is nonsingular. The asymptotic property for the test process $R_Z^{(Y)}(t) = (R_1^{(Y)}(t),\ldots,R_K^{(Y)}(t))$ is stated in the following theorem.

Theorem 2. *Assume that* $P(C_i \geq \tau) > 0$, $E(N_i^*(\tau)) < \infty$ *and* $E(Y_i(t)) < \infty$ *for* $0 \leq t \leq \tau$. *Assume that the weight processes* $H_k(t)$ *can be written as the difference of two monotone processes, each of which converges in probability to a bounded deterministic function, such that* $\sup_{0\leq u\leq\tau}|H_k(u) - h_k(u)| \xrightarrow{P} 0$ *for* $1 \leq k \leq K$. *Then, uniformly in* $0 \leq t \leq \tau$ *for* $1 \leq k \leq K$,

$$R_k^{(Y)}(t) = n^{-1/2}\sum_{i=1}^n r_{ki}(t) + n^{1/2}\int_0^t H_k(u)\,(\mu_{1k}^c(du) - \mu_{2k}^c(du,t)) + o_p(1), \tag{3.4}$$

where $r_{ki}(t)$*'s are defined in* (A.10). *Under conditional independent censoring NIC2,* $R_Z^{(Y)}(t)$ *converges weakly to a vector of K-dimensional mean zero Gaussian processes on* $[0,\tau]$.

Under NIC2, $\mu_{1k}^c(s) = \mu_{2k}^c(s,t)$ for $0 \leq s \leq t$. Let $\hat{r}_{ki}(t)$ be the empirical counterpart of $r_{ki}(t)$ by plugging in the consistent estimators $\hat{\beta}$, $\hat{\Lambda}_0(\cdot)$, $\hat{G}_i(\cdot)$, $S^{(i)}(\cdot,\hat{\beta})$, and $H_k(\cdot)$ for β, $\Lambda_0(\cdot)$, $G_i(\cdot)$, $s^{(i)}(\cdot,\hat{\beta})$, and $h_k(\cdot)$, respectively. Let $\phi_i, i = 1,\ldots,n$, be iid standard normal random variables, independent of the observed data. Define

$$R_k^{*(Y)}(t) = n^{-1/2}\sum_{i=1}^n \phi_i \hat{r}_{ki}(t), \tag{3.5}$$

and let $R_Z^{*(Y)}(t) = (R_1^{*(Y)}(t), \ldots, R_K^{*(Y)}(t))$. Then under NIC2, the processes $R_Z^{(Y)}(t)$ and $R_Z^{*(Y)}(t)$ converge weakly to the same mean zero Gaussian limit processes by Lemma 1 of Sun and Wu (2005). The null distribution of $R_Z^{(Y)}(\cdot)$ can be estimated using a number of realizations from $R_Z^{*(Y)}(\cdot)$ by repeatedly generating independent sets of iid standard normal random variables $\phi_i, i = 1, \ldots, n$.

The test statistics similar to those proposed in Section 2 can be constructed here. Let $S_Z^{(Y)} = \sum_{k=1}^K \sup_{0\le t\le\tau} |R_k^{(Y)}(t)|$ and $L_Z^{(Y)} = \sum_{k=1}^K \int_0^\tau (R_k^{(Y)}(t))^2\, dt$. We use the test statistics $S_Z^{(1)}$ and $L_Z^{(1)}$ to test NIC1 and $S_Z^{(Y)}$ and $L_Z^{(Y)}$ to test NIC2. The test statistics for testing NIC1 and NIC2 can be obtained by taking $S_Z = S_Z^{(1)} + S_Z^{(Y)}$ and $L_Z = L_Z^{(1)} + L_Z^{(Y)}$. Critical values can be estimated by repeatedly generating copies of $(R_Z^{*(1)}(\cdot), R_Z^{*(Y)}(\cdot))$ while holding the observed data fixed. The null hypotheses NIC1 and/or NIC2 are rejected for large values of the corresponding test statistics.

Note that if NIC2 does not hold, i.e., the censoring is not independent conditional on Z_i, then $\alpha_1^c(u, , Z_i) \neq \alpha_2^c(u, t, Z_i)$ for some $0 \le u \le t$ and Z_i. Suppose that $h_k(u) > 0$, $0 \le u \le \tau$ for $k = 1, \cdots, K$. If a partition Δ_k is chosen such that $P(Z_i \in \Delta_k) \neq 0$ and $E[\alpha_1^c(u, Z_i)|Z_i \in \Delta_k] \neq E[\alpha_2^c(u, t, Z_i)|Z_i \in \Delta_k]$, then $\int_0^t h_k(u)(\mu_{1k}^c(du) - \mu_{2k}^c(du, t)) \neq 0$ and $n^{1/2} \int_0^t h_k(u)\,(\mu_{1k}^c(du) - \mu_{2k}^c(du, t)) \xrightarrow{P} \infty$ for some $t \in [0, \tau]$, in which case the test statistics $S_Z^{(Y)}$ and $L_Z^{(Y)}$ converge in probability to ∞ as $n \to \infty$.

The test statistics based on stratifications over the values of covariates are more sensitive in detecting dependent censoring conditional on the covariates. Without stratifications, the tests are able to detect marginal dependence between censoring time C_i and response processes $N_i^*(t)$ and/or $Y_i(t)dN_i^*(t)$, but not sensitive to conditional dependence. Since much literature on recurrent events and longitudinal data analysis assumes conditional independence given covariates, the tests developed here provide a tool to check the validity of these assumptions. The tests developed here do not assume any models for $(N_i^*(\cdot), Y_i(\cdot))$; they are robust and applicable to many situations regardless of the underlying models.

Let us look at a simple case to see how dependent censoring is captured by the proposed test statistics for NIC1. Set $Y_i(\cdot) \equiv 1$ and assume that $N_i^*(\cdot)$ and C_i are dependent conditional on Z_i and independent conditional on a larger set of covariates X_i. Assume that $E\{dN_i^*(t)|X_i\} = \alpha_0(t)\exp(\gamma^T X_i)\, dt$, where $\alpha_0(t)$ is an unspecified baseline function and γ is an unknown vector of parameters. It follows that $\alpha_1^c(s, Z_i)ds = E[E\{dN_i^*(s)|X_i\}|Z_i, C_i \ge s] = \alpha_0(s)\, E\{\exp(\gamma^T X_i)|Z_i, C_i \ge s\}ds$ and $\alpha_2^c(s, t, Z_i)ds = E[E\{dN_i^*(s)|X_i\}|Z_i, C_i \ge t] = \alpha_0(s)\, E\{\exp(\gamma^T X_i)|Z_i, C_i \ge t\}ds$. Let $q_k(t) = E[I(Z_i \in \Delta_k)\, E\{\exp(\gamma^T X_i)|Z_i, C_i \ge t\}]$. Then $E[I(Z_i \in \Delta_k)\, \alpha_1^c(s, Z_i)] = \alpha_0(s)\, q_k(s)$ and $E[I(Z_i \in \Delta_k)\, \alpha_2^c(s, t, Z_i)] = \alpha_0(s)\, q_k(t)$. If

$\mu^c_{1k}(t) = \mu^c_{2k}(t,t)$ for $0 \le t \le \tau$, $1 \le k \le K$, then $\int_0^t E[I(Z_i \in \Delta_k)\alpha^c_1(s, Z_i)]\, ds = \int_0^t E[I(Z_i \in \Delta_k)\alpha^c_2(s,t,Z_i)]\, ds$. Hence $\int_0^t \alpha_0(s)q_k(s)\, ds = \int_0^t \alpha_0(s)q_k(t)\, ds$. It follows that $q_k(t)$ does not depend on t, $0 \le t \le \tau$ for $1 \le k \le K$. In case Z_i is a discrete random variable taking K different values classified by $\Delta_1, \ldots, \Delta_K$, this implies that $E\{\exp(\gamma^T X_i)|Z_i \in \Delta_k, C_i \ge t\}$ does not depend on t for $0 \le t \le \tau$ and $1 \le k \le K$, hence not on C_i. We have $E[dN^*_i(t)|Z_i, C_i \ge t] = \alpha_0(t)\, E\{\exp(\gamma^T X_i)|Z_i\} = E[E\{dN^*_i(t)|X_i\}|Z_i] = E\{dN^*_i(t)|Z_i\}$. Thus $N^*_i(\cdot)$ and C_i are independent given Z_i. This shows that, for discrete Z_i, the conditional independence of $N^*_i(\cdot)$ and C_i given Z_i is equivalent to $\mu^c_{1k}(t) = \mu^c_{2k}(t,t)$ for $0 \le t \le \tau$, $1 \le k \le K$.

In general, given that $h_k(t) > 0$ for $0 \le t \le \tau$, the tests based on $L^{(1)}_Z$ and $S^{(1)}_Z$ for testing NIC1 can detect dependent censoring at the stratum level. Theoretically speaking, the tests are more sensitive to dependent censoring when there are more strata. However, a large number of strata may slow the rate of convergence of the test process $R^{(1)}_k(t)$ within each stratum and affect the performance of the tests in terms of size and power. Similar remarks apply to the tests for NIC2.

4. Simulation Studies

In this section, we report on a simulation study to investigate the finite sample performance of the proposed tests. Simulation experiments were conducted for the tests of independent censoring for recurrent events processes in the absence/presence of covariates and for tests of conditional independent censoring for longitudinal response processes given covariates. All test statistics were constructed using the identity weight process.

4.1. Tests of independent censoring for recurrent event processes in the absence of covariates

First, we describe the settings of simulation models under the null hypothesis NIC1 to examine the sizes of the tests $L^{(1)}$ and $S^{(1)}$ for independence between recurrent event processes $N^*_i(\cdot)$ and censoring times C_i without conditioning on covariates. We simulated the recurrent event process $N^*_i(t)$ from a Poisson process on $[0,5]$ with $E(N^*_i(t)) = \gamma_0 t$ and censoring C_i was taken to be uniformly distributed over $(0, \nu_0)$, independent of $N^*_i(\cdot)$. The parameters γ_0 and ν_0 were chosen to yield different levels of censorings and different numbers of observations per subject by $\tau = 5$. The following settings of the parameters (γ_0, ν_0) were selected to check the sizes of the tests $L^{(1)}$ and $S^{(1)}$:

$M1 : (\gamma_0, \nu_0) = (1.1, 15)$; $M2 : (\gamma_0, \nu_0) = (0.8, 15)$;
$M3 : (\gamma_0, \nu_0) = (1.0, 8)$; $M4 : (\gamma_0, \nu_0) = (0.8, 8)$.

To examine the powers of the tests $L^{(1)}$ and $S^{(1)}$, we considered simulation models under which C_i depends on $N_i^*(\cdot)$. Let Z_i be a binary covariate with probability $p = 0.5$. The process $N_i^*(t)$ was taken to be a Poisson process conditional on Z_i with $E(N_i^*(t)|Z_i) = \gamma_0 t \exp(0.5\theta_0 Z_i)$. The censoring times C_i were generated based on the hazard function $\lambda_c(t|Z_i) = \beta_0 \exp(0.5\theta_0 Z_i)$, independent of $N_i^*(\cdot)$ conditional on Z_i. However, C_i and $N_i^*(\cdot)$ were dependent without conditioning on Z_i; larger value of $|\theta_0|$ induces higher correlation between C_i and $N_i^*(\cdot)$ in the absence of covariate Z_i. We chose $\theta_0 = 1.5$ and 2.0. The combination of the parameters $(\gamma_0, \beta_0, \theta_0)$ yielded different levels of censorings by $\tau = 5$, different numbers of observations per subject on $[0, \tau]$, and different degrees of dependence between C_i and $N_i^*(\cdot)$. We denote the settings of the parameters (γ_0, β_0) under the alternative hypotheses by

$$M5 : (\gamma_0, \beta_0) = (0.8, 0.07); \quad M6 : (\gamma_0, \beta_0) = (0.5, 0.05);$$
$$M7 : (\gamma_0, \beta_0) = (0.8, 0.15); \quad M8 : (\gamma_0, \beta_0) = (0.5, 0.10).$$

Table 1 shows the observed size and power of the test statistics $L^{(1)}$ and $S^{(1)}$ for selected models at the nominal level 0.05. Listed in Table 1 are also the percentage of censoring by $\tau = 5$, and the average number of observed events per subject under each model. The reported censoring rates here and in other tables refer to the percentages of the subjects with censored events in the time period $[0, \tau]$. They are within 6% of the actual percentages of the censoring of the simulation settings. Each entry was obtained from 1,000 independent samples. For each sample, the critical values of the tests were estimated from 1,000 realizations from $R^{*(1)}(t)$, $0 \le t \le \tau$, conditional on the observed sample data. The observed sizes of the tests are reasonably close to the nominal level 0.05. The powers increase as θ_0 increases. The powers also increase as the number of observations increases.

4.2. Tests of conditional independent censoring for recurrent event processes given covariates

Now, we describe the simulation models under the null hypothesis NIC1 to evaluate the performance of tests $L_Z^{(1)}$ and $S_Z^{(1)}$ for testing conditional independence between recurrent event processes $N_i^*(\cdot)$ and censoring times C_i given the covariates. We considered two covariates Z_{1i} and Z_{2i}, where Z_{1i} is a binary random variable with probability $p = 0.5$ and Z_{2i} is uniformly distributed on $[0, 1]$. The recurrent events process $N_i^*(t)$ was taken to be a Poisson process on $[0, 5]$ conditional on $Z_i = (Z_{1i}, Z_{2i})$, with

$$E(N_i^*(t)|Z_{1i}, Z_{2i}) = \gamma_0 t \exp(\theta_1 \gamma_1 Z_{1i} + \gamma_2 Z_{2i}). \tag{4.1}$$

Table 1. Empirical size and power of the tests $L^{(1)}$ and $S^{(1)}$ for marginal independence between censoring and recurrent event process at the nominal level $\alpha = 0.05$.

Censoring	Setting	θ_0	Avg.# obs.	Test	Sample size n 200	300	400	500	800
				Sizes					
30%	M1		3.8	$L^{(1)}$	0.039	0.037	0.038	0.050	0.042
				$S^{(1)}$	0.040	0.036	0.048	0.041	0.042
	M2		5.0	$L^{(1)}$	0.054	0.046	0.051	0.041	0.060
				$S^{(1)}$	0.061	0.049	0.051	0.043	0.060
50%	M3		3.4	$L^{(1)}$	0.054	0.054	0.039	0.061	0.068
				$S^{(1)}$	0.056	0.058	0.047	0.057	0.059
	M4		4.3	$L^{(1)}$	0.072	0.052	0.043	0.054	0.049
				$S^{(1)}$	0.065	0.054	0.045	0.057	0.056
				Powers					
30%	M5	1.5	3.3	$L^{(1)}$	0.296	0.389	0.495	0.617	0.817
				$S^{(1)}$	0.303	0.422	0.517	0.633	0.834
		2.0		$L^{(1)}$	0.624	0.795	0.905	0.948	0.998
				$S^{(1)}$	0.634	0.809	0.895	0.954	0.999
	M6	1.5	5.7	$L^{(1)}$	0.334	0.476	0.561	0.647	0.860
				$S^{(1)}$	0.349	0.500	0.594	0.684	0.858
		2.0		$L^{(1)}$	0.657	0.837	0.915	0.967	0.996
				$S^{(1)}$	0.694	0.835	0.929	0.971	0.996
50%	M7	1.5	2.9	$L^{(1)}$	0.385	0.543	0.625	0.789	0.919
				$S^{(1)}$	0.389	0.535	0.618	0.781	0.909
		2.0		$L^{(1)}$	0.740	0.899	0.954	0.983	0.999
				$S^{(1)}$	0.703	0.876	0.938	0.973	0.997
	M8	1.5	4.9	$L^{(1)}$	0.531	0.670	0.810	0.885	0.977
				$S^{(1)}$	0.496	0.671	0.799	0.884	0.977
		2.0		$L^{(1)}$	0.807	0.947	0.985	0.997	1.000
				$S^{(1)}$	0.800	0.938	0.978	0.995	1.000

The right censoring C_i was independent of $N_i^*(\cdot)$ conditional on Z_{1i} and Z_{2i} and had the proportional hazards function

$$\lambda_c(t|Z_i) = \beta_0 \exp(\theta_1 \beta_1 Z_{1i} + \beta_2 Z_{2i}). \tag{4.2}$$

It is easy to check that the hazard function of censoring times conditional on Z_{2i} is still proportional. The value of θ_1 induces dependence between C_i and $N_i^*(\cdot)$ conditional on Z_{2i}. When $\theta_1 = 0$, $N_i^*(\cdot)$ and C_i are conditionally independent given Z_{2i}. They are, however, dependent by conditioning on Z_{2i} alone if $\theta_1 \neq 0$. There is an increased dependence between $N_i^*(\cdot)$ and C_i conditional on Z_{2i} when $|\theta_1|$ is increased.

We list the following settings of parameters for (4.1) and (4.2). We chose the settings M9–M12 and $\theta_1 = 0$ to represent the models under the null hypotheses that $N_i^*(\cdot)$ and C_i are conditionally independent given Z_{2i}. The settings M13–M16 with $\theta_1 = 1.5$ and 2 are selected to represent the models under the alternative hypotheses that $N_i^*(\cdot)$ and C_i are dependent conditional Z_{2i}.

M9 : $(\gamma_0, \gamma_1, \gamma_2) = (1, 0, 5.5)$, $(\beta_0, \beta_1, \beta_2) = (0.07, 0, 1)$;

M10: $(\gamma_0, \gamma_1, \gamma_2) = (1, 0, 3.5)$, $(\beta_0, \beta_1, \beta_2) = (0.13, 0, 1)$;

M11: $(\gamma_0, \gamma_1, \gamma_2) = (1, 0, 5.0)$, $(\beta_0, \beta_1, \beta_2) = (0.15, 0, 1)$;

M12: $(\gamma_0, \gamma_1, \gamma_2) = (1, 0, 3.0)$, $(\beta_0, \beta_1, \beta_2) = (0.13, 0, 1)$;

M13: $(\gamma_0, \gamma_1, \gamma_2) = (1, 2, 2.5)$, $(\beta_0, \beta_1, \beta_2) = (0.07, 0.7, 0.9)$;

M14: $(\gamma_0, \gamma_1, \gamma_2) = (1, 2, 1.5)$, $(\beta_0, \beta_1, \beta_2) = (0.05, 0.7, 0.9)$;

M15: $(\gamma_0, \gamma_1, \gamma_2) = (1, 3, 1.5)$, $(\beta_0, \beta_1, \beta_2) = (0.15, 0.7, 0.9)$;

M16: $(\gamma_0, \gamma_1, \gamma_2) = (1, 2, 1.5)$, $(\beta_0, \beta_1, \beta_2) = (0.10, 0.7, 0.9)$.

Table 2 presents the observed size and power of the tests $L_Z^{(1)}$ and $S_Z^{(1)}$ at the nominal level 0.05 for the selected models. The tests were constructed with $K = 2$ partitions of $Z_2 \leq 0.5$ and $Z_2 > 0.5$. Table 2 also presents the percentage of censoring by $\tau = 5$ and the average number of observed events per subject under each model. Each entry was estimated from 1,000 independent samples. For each sample the critical values of the tests were obtained from 1,000 realizations of $R_Z^{*(1)}(\cdot)$. The observed size of both tests were reasonably close to the nominal level 0.05 with $L_Z^{(1)}$ performing slightly better than $S_Z^{(1)}$. As the sample size increased from 200 to 800, the accuracy further improved. The power of both tests increased as θ_1 increased. Power also increased as censoring got heavier and as sample size increased.

4.3. Tests of conditional independent censoring for longitudinal processes given covariates

Here we examine the performance of the tests $L_Z^{(Y)}$ and $S_Z^{(Y)}$ for NIC2, that the censoring times C_i and longitudinal responses $Y_i(t)dN_i^*(t)$, $0 \leq t \leq \tau$, are conditionally independent given covariates. Consider the recurrent event processes $N_i^*(\cdot)$ on $[0, 5]$ to be Poisson processes conditional on Z_{2i} with

$$E(N_i^*(t)|Z_{2i}) = \gamma_0 t \exp(\gamma_1 Z_{1i} + \gamma_2 Z_{2i}). \tag{4.3}$$

Let the censoring times C_i follow the proportional hazards model

$$\lambda_c(t|Z_{1i}, Z_{2i}) = \beta_0 \exp(\theta_2 \beta_1 Z_{1i} + \beta_2 Z_{2i}), \tag{4.4}$$

Table 2. Empirical size and power of the tests $L_Z^{(1)}$ and $S_Z^{(1)}$ with $K = 2$ partitions for conditional independence between censoring and recurrent event process given covariates at nominal level $\alpha = 0.05$.

Censoring	Setting	θ_1	Avg.# obs.	Test	Sample size n 200	300	400	500	800
				Sizes					
30%	M9	0	3.8	$L_Z^{(1)}$	0.051	0.043	0.052	0.049	0.050
				$S_Z^{(1)}$	0.070	0.064	0.064	0.073	0.065
	M10	0	4.6	$L_Z^{(1)}$	0.032	0.032	0.052	0.056	0.054
				$S_Z^{(1)}$	0.055	0.048	0.066	0.073	0.061
50%	M11	0	3.3	$L_Z^{(1)}$	0.029	0.031	0.051	0.046	0.045
				$S_Z^{(1)}$	0.046	0.057	0.067	0.054	0.056
	M12	0	5.2	$L_Z^{(1)}$	0.030	0.034	0.054	0.054	0.052
				$S_Z^{(1)}$	0.052	0.054	0.065	0.069	0.060
				Powers					
30%	M13	1.5	3.7	$L_Z^{(1)}$	0.349	0.464	0.592	0.695	0.898
				$S_Z^{(1)}$	0.402	0.548	0.666	0.771	0.929
		2.0		$L_Z^{(1)}$	0.509	0.667	0.808	0.902	0.985
				$S_Z^{(1)}$	0.577	0.731	0.861	0.930	0.993
	M14	1.5	5.6	$L_Z^{(1)}$	0.441	0.569	0.678	0.802	0.945
				$S_Z^{(1)}$	0.535	0.641	0.771	0.863	0.965
		2.0		$L_Z^{(1)}$	0.647	0.829	0.913	0.970	0.999
				$S_Z^{(1)}$	0.749	0.887	0.953	0.978	1.000
50%	M15	1.5	4.3	$L_Z^{(1)}$	0.383	0.577	0.729	0.870	0.978
				$S_Z^{(1)}$	0.357	0.542	0.687	0.818	0.963
		2.0		$L_Z^{(1)}$	0.441	0.665	0.829	0.927	0.997
				$S_Z^{(1)}$	0.357	0.569	0.715	0.841	0.976
	M16	1.5	5.0	$L_Z^{(1)}$	0.436	0.630	0.766	0.879	0.980
				$S_Z^{(1)}$	0.458	0.644	0.788	0.878	0.983
		2.0		$L_Z^{(1)}$	0.609	0.807	0.922	0.972	0.998
				$S_Z^{(1)}$	0.601	0.803	0.909	0.964	1.000

and the longitudinal responses follow the additive model

$$Y_i(t) = (\psi_0 + \psi_1 t) + \theta_2\psi_2 Z_{1i} + \psi_3 Z_{2i} + \varepsilon_i(t), \tag{4.5}$$

where $\varepsilon_i(t)$ has a normal distribution with mean η_i and variance $\sigma_\varepsilon^2 = 1$ conditional on the ith subject, and η_i is normal with mean zero and variance $\sigma_\eta^2 = 1$. The triple $(C_i, N_i^*(\cdot), Y_i(\cdot)dN_i^*(\cdot))$ are conditional independent given the covariates (Z_{1i}, Z_{2i}). The $Y_i(\cdot)dN_i^*(\cdot)$ and C_i conditionally independent given Z_{2i} if $\theta_2 = 0$, and they are dependent by conditioning on Z_{2i} alone if $\theta_2 \neq 0$. The θ_2

induces dependence between $Y_i(\cdot)dN_i^*(\cdot)$ and C_i conditional on Z_{2i}. This dependence increases as $|\theta_2|$ increases.

The following settings of the parameters under (4.3), (4.4), and (4.5), together with the choices of $\theta_2 = 0, 2.0$ and 2.5, were used in simulations to check the performance of the tests $L_Z^{(Y)}$ and $S_Z^{(Y)}$.

Settings	$(\gamma_0, \gamma_1, \gamma_2)$	$(\beta_0, \beta_1, \beta_2)$	$(\psi_0, \psi_1, \psi_2, \psi_3)$
M17:	$(1, 0, 5.5)$	$(0.07, 0, 1)$	$(1, 0.5, 0, 1)$
M18:	$(1, 0, 3.5)$	$(0.13, 0, 1)$	$(1, 0.5, 0, 1)$
M19:	$(1, 0, 5.0)$	$(0.15, 0, 1)$	$(1, 0.5, 0, 1)$
M20:	$(1, 0, 3.0)$	$(0.13, 0, 1)$	$(1, 0.5, 0, 1)$
M21:	$(1, 0, 5.5)$	$(0.04, 1, 0.01)$	$(1, 0.5, 2.5, 1)$
M22:	$(1, 0, 3.5)$	$(0.04, 1, 0.01)$	$(1, 0.5, 2.5, 1)$
M23:	$(1, 0, 3.3)$	$(0.07, 1, 0.01)$	$(1, 0.5, 2.5, 1)$
M24:	$(1, 0, 2.5)$	$(0.07, 1, 0.01)$	$(1, 0.5, 2.5, 1)$

Table 3 presents the empirical size and power of the test statistics $L_Z^{(Y)}$ and $S_Z^{(Y)}$, which were obtained based on the partition of covariate space for Z_2 into two stratum $Z_2 \leq 0.5$ and $Z_2 > 0.5$. The percentage of censoring by $\tau = 5$ and the average number of observed events per subject under each model are also listed in Table 3. The observed sizes and powers of the tests at the nominal level 0.05 were estimated from 1,000 independent samples. For each sample the critical values of the tests were obtained from 1,000 realizations of $R_Z^{*(Y)}(\cdot)$. The observed size of the test $L_Z^{(Y)}$ were reasonably close to the nominal level 0.05 while the test $S_Z^{(Y)}$ had slightly inflated observed sizes at the 30% censoring rate. Both tests had improved observed sizes close to 0.05 at the 50% censoring rate. Since the construction of the test statistics involved the estimation of the conditional survival function of the censoring time. A smaller censoring rate can result in larger variation in the values of the test statistics, and thus more variability in the observed sizes. The empirical size became stable around the nominal level 0.05 as the percentage of censoring increased and as the sample size increased. The observed power increased as sample size, censoring percentage, or θ_2 increased.

5. Application to Chronic Granulotomous Disease Study

We applied the proposed tests to a placebo controlled randomized trial of gamma interferon in chronic granulotamous disease (CGD). Chronic granulotamous disease is a group of inherited rare disorders of the immune function characterized by recurrent pyogenic infections which usually present early in life and may lead to death in childhood. A description of this study can be found in

Table 3. Empirical size and power of the tests $L_Z^{(Y)}$ and $S_Z^{(Y)}$ with $K = 2$ partitions for conditional independence between censoring and longitudinal response process given covariates at nominal level $\alpha = 0.05$.

Censoring	Setting	θ_2	Avg.# obs.	Test	Sample size n 200	300	400	500	800
				Sizes					
30%	M17	0	3.0	$L_Z^{(Y)}$	0.043	0.049	0.062	0.076	0.054
				$S_Z^{(Y)}$	0.070	0.070	0.083	0.085	0.083
	M18	0	5.1	$L_Z^{(Y)}$	0.050	0.052	0.054	0.063	0.053
				$S_Z^{(Y)}$	0.077	0.069	0.073	0.088	0.068
50%	M19	0	3.0	$L_Z^{(Y)}$	0.027	0.034	0.047	0.035	0.036
				$S_Z^{(Y)}$	0.047	0.046	0.060	0.045	0.052
	M20	0	5.1	$L_Z^{(Y)}$	0.038	0.040	0.045	0.050	0.040
				$S_Z^{(Y)}$	0.048	0.046	0.057	0.068	0.045
				Powers					
30%	M21	2.0	3.5	$L_Z^{(Y)}$	0.063	0.136	0.226	0.321	0.629
				$S_Z^{(Y)}$	0.120	0.233	0.340	0.448	0.734
		2.5		$L_Z^{(Y)}$	0.194	0.387	0.622	0.748	0.958
				$S_Z^{(Y)}$	0.353	0.557	0.759	0.853	0.986
	M22	2.0	5.0	$L_Z^{(Y)}$	0.109	0.253	0.389	0.519	0.814
				$S_Z^{(Y)}$	0.184	0.368	0.493	0.641	0.883
		2.5		$L_Z^{(Y)}$	0.362	0.616	0.816	0.911	0.999
				$S_Z^{(Y)}$	0.525	0.728	0.885	0.959	0.999
50%	M23	2.0	4.3	$L_Z^{(Y)}$	0.312	0.547	0.751	0.860	0.976
				$S_Z^{(Y)}$	0.417	0.655	0.814	0.896	0.985
		2.5		$L_Z^{(Y)}$	0.540	0.779	0.941	0.981	1.000
				$S_Z^{(Y)}$	0.651	0.882	0.960	0.990	0.999
	M24	2.0	5.0	$L_Z^{(Y)}$	0.420	0.673	0.836	0.930	0.992
				$S_Z^{(Y)}$	0.535	0.748	0.885	0.950	0.997
		2.5		$L_Z^{(Y)}$	0.688	0.904	0.981	0.993	1.000
				$S_Z^{(Y)}$	0.779	0.947	0.986	0.999	1.000

Fleming and Harrington (1991). In order to study the ability of gamma interferon to reduce the rate of serious infections, a double-blinded clinical trial was conducted in which patients were randomized to placebo vs. gamma interferon.

Between October 1988 and March 1989, 128 eligible patients with CGD were accrued and followed for any recurrent serious infections. There were 63 patients on gamma interferon and 65 placebo. By the end of the trial, 30 of 65 placebo patients and 14 of 63 patients on gamma interferon had experienced at least one serious infection. Of the 30 placebo patients with at least one infection, eighteen had experienced one infection, five others had experienced two, four others had experienced three, three others had four or more. Of the 14 patients on gamma interferon with at least one infection, nine had experienced one infection, four others had experienced two, and one had a third infection. Overall, a total of 56 serious infections were observed on placebo compared to only 20 among patients on gamma interferon. The average number of observed events was 0.59 (76 of observed recurrent events for 128 individuals).

Let $N_i^*(t)$ be the number of observed serious infections by time t for ith subject. Lin et al. (2000) analyzed CGD data using the proportional mean rate model for $N_i^*(\cdot)$ and found that treatment and age are significant, indicating that gamma interferon is effective in reducing the rate of recurrent serious infections, and that older children have less frequent serious infection than younger ones. The analysis assumed that $N_i^*(\cdot)$ and the censoring time C_i are conditional independent given the treatment indicator and age. To check the validity of this assumption, the proposed tests were applied to test if censoring or drop-out of a patient is independent of recurrent serious infections.

First, we tested that censoring times and the recurrent event processes are independent in the absence of covariate. The longest follow-up time in CGD data was 1.2 years. We took τ=1 year. The values of the test statistics are $L^{(1)} = 1.72$ (p-value=0.121) and $S^{(1)} = 4.61$ (p-value=0.305), which are not significant at 5% significance level. The diagnosis plot of $R^{(1)}(t)$ against 50 realizations from $R^{*(1)}(t)$ shown in Figure 1 does not show visible patterns of departure of $R^{(1)}(t)$ from the realizations of $R^{*(1)}(t)$. We conclude that there is no significant evidence of dependence between censoring times and the recurrent event processes without conditioning on covariates.

Next, the test of independent censoring was conducted by conditioning on treatment indicator Z_1 and age Z_2. We considered a partition of covariate space into $K = 4$ partitions based on treatment groups and whether age ≤ 14.64 or > 14.64 years, where 14.64 is the mean age of the patients. The values of the test statistics are $L_Z^{(1)} = 8.70$ (p-value=0.004) and $S_Z^{(1)} = 21.39$ (p-value=0.017), significant at the 5% level. This suggested that censoring times in CGD data are not independent of the recurrent event processes for serious infections conditional on treatment indicator and age. The diagnosis plot, shown in Figure 2, of $R_Z^{(1)}(t)$ against 50 realizations from $R_Z^{*(1)}(t)$ also show the evidence of possible dependence between censoring times and the recurrent event process. Figure 2(b) indicates that censored patients on gamma interferon and over the average age of 14.64 years old tend to have more frequent serious infections compared to the uncensored patients in the same group. This casts reasonable doubt on the independent censoring assumption made in the analysis of CGD data by Lin et al. (2000). The effect of gamma interferon in reducing recurrent serious infections could be overestimated since older patients with serious infections on

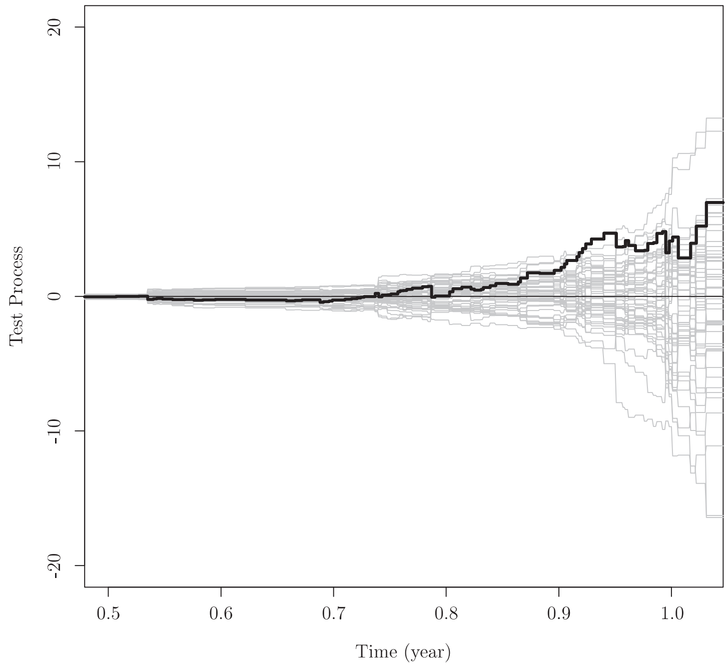

Figure 1. A diagnosis plot for testing marginal independent censoring of the recurrent events for CGD data. The solid line is the observed test process $R^{(1)}(t)$ and the gray lines are 50 realizations from $R^{*(1)}(t)$ conditional on the observed data.

gamma interferon tend to drop out the study more often. Sensitivity analysis can be used to examine how the estimation is affected by dependent censoring, which necessitates further study.

6. Discussion

The proposed test procedures are based on the weighted difference of the two reduced sample estimators $\bar{\mu}^{(Y)}(s)$ and $\hat{\mu}^{(Y)}(s,t)$ for $0 \le s \le t$. In particular, $\hat{\mu}^{(Y)}(\cdot,t)$ does not use information from subjects whose censoring times are before t and thus may have large variance when t is large. We suggest choosing τ such that the percentage of uncensored subjects by τ is not too small. This may cause some concerns on efficiency loss of the tests. This problem needs further investigation.

The proposed test procedures allow the flexibility of choosing different weight processes. One can choose to emphasize early or late differences between the two estimators constructed from sample subsets with different patterns of censoring by selecting the weight processes to be decreasing or increasing. We have, however, used identity weight in our numerical studies. Choosing a weight pro-

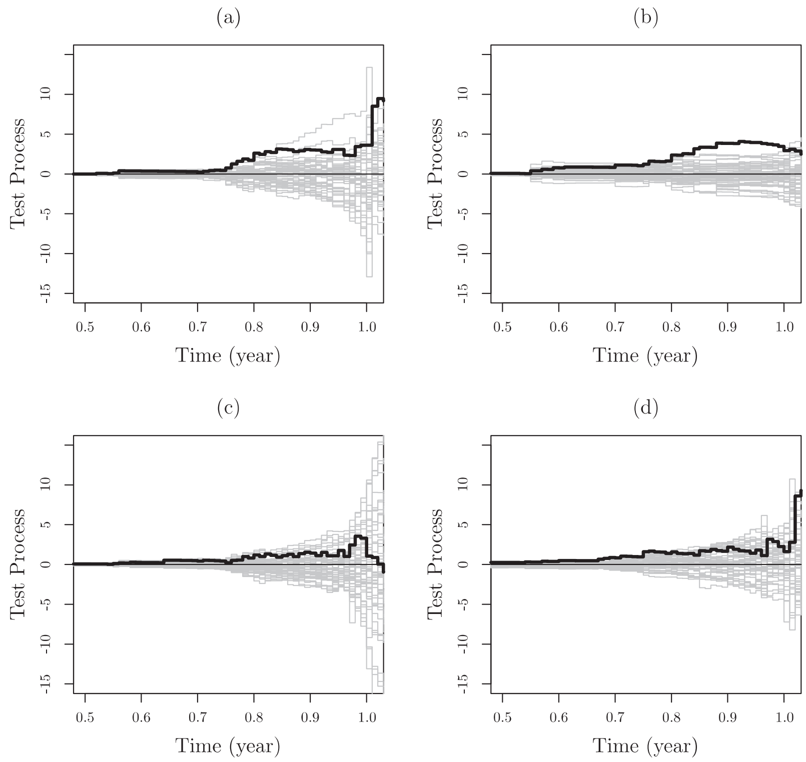

Figure 2. A diagnosis plot for testing conditional independent censoring of the recurrent events given treatment and age for CGD data. The solid lines are the observed test process $R_Z^{(1)}(t)$ and the gray lines are 50 realizations from $R_Z^{*(1)}(t)$ conditional on the observed data corresponding to the four strata of the covariate space. Figure (a) is for patients on gamma interferon treatment and under the average age of 14.64 years, (b) is for patients on gamma interferon treatment and over 14.64 years old, (c) is for patients on placebo and under 14.64 years old, and (d) is for patients on placebo and over 14.64 years old.

cess that optimizes the power against given alternatives is challenging and needs further exploration.

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Appendix

Proof of Theorem 1. Let $\bar{M}(t) = \sum_{i=1}^n \int_0^t [Y_i(u)dN_i(u) - I(C_i \geq u)\alpha_1^c(u)du]$. By an application of the Central Limit Theorem for empirical processes (cf. Theorem 19.5 of van der Vaart (1998)), $n^{-1/2}\bar{M}(t)$ converges weakly to a mean zero Gaussian process on $t \in [0, \tau]$. By the uniform convergence $H(t) \xrightarrow{P} h(t)$ and $n^{-1}\bar{\xi}(t) \xrightarrow{P} G(t)$ over $t \in [0, \tau]$, and by Lemma A.1 of Lin and Ying (2001), we have

$$
\begin{aligned}
n^{1/2} & \int_0^t H(u)\, d(\bar{\mu}^{(Y)}(u) - \mu_1^c(u)) \\
&= n^{1/2} \sum_{i=1}^n \int_0^t \frac{H(u)[Y_i(u)dN_i(u) - I(C_i \geq u)\alpha_1^c(u)du]}{\bar{\xi}(u)} + o_p(1) \\
&= n^{-1/2} \sum_{i=1}^n \int_0^t \frac{h(u)[Y_i(u)dN_i(u) - I(C_i \geq u)d\mu_1^c(u)]}{G(u)} + o_p(1). \qquad \text{(A.1)}
\end{aligned}
$$

Similarly,

$$
\begin{aligned}
n^{1/2} & \int_0^t H(u)\, (\hat{\mu}^{(Y)}(du, t) - \mu_2^c(du, t)) \\
&= n^{1/2} \sum_{i=1}^n \int_0^t \frac{H(u)[Y_i(u)dN_i(u) - \alpha_2^c(u, t)du]I(C_i \geq t)}{\bar{\xi}(t)} + o_p(1) \\
&= n^{-1/2} \sum_{i=1}^n \int_0^t \frac{h(u)[Y_i(u)dN_i(u) - \mu_2^c(du, t)]I(C_i \geq t)}{G(t)} + o_p(1). \qquad \text{(A.2)}
\end{aligned}
$$

Combining (A.1) and (A.2), we have

$$
\begin{aligned}
R^{(Y)}(t) &= n^{1/2} \int_0^t H(u)\, (\bar{\mu}^{(Y)}(du) - \hat{\mu}^{(Y)}(du, t)) \\
&= n^{-1/2} \sum_{i=1}^n \int_0^t \frac{h(u)[Y_i(u)dN_i(u) - I(C_i \geq u)d\mu_1^c(u)]}{G(u)} \\
&\quad - n^{-1/2} \sum_{i=1}^n \int_0^t \frac{h(u)[Y_i(u)dN_i(u) - \mu_2^c(du, t)]I(C_i \geq t)}{G(t)} \\
&\quad + n^{1/2} \int_0^t H(u)(\mu_1^c(du) - \mu_2^c(du, t)) + o_p(1). \qquad \text{(A.3)}
\end{aligned}
$$

Under independent censoring NIC2, $\mu_1^c(u) = \mu_2^c(u, t)$ for $0 \leq u \leq t$. By an application of the Central Limit Theorem for empirical processes, $R^{(Y)}(t)$ converges weakly to a mean zero Gaussian process.

Proof of Theorem 2. Let $J_n(\beta)=S^{(2)}(t,\beta)/S^{(0)}(t,\beta)-\left(S^{(1)}(t,\beta)/S^{(0)}(t,\beta)\right)^{\otimes 2}$, $A_n(\beta)=n^{-1}\sum_{i=1}^n\int_0^\tau J_n(\beta)\ dN_i^c(t)$, and $O_i^c(t)=N_i^c(t)-\int_0^t I(C_i\geq s)\lambda_c(s|Z_i)\,ds$. A routine analysis following Sun and Wu (2005, Appendix, p.42) shows that

$$n^{1/2}(\hat\beta-\beta)=n^{-1/2}A^{-1}\sum_{i=1}^n\int_0^\tau(Z_i-\bar z(t))\,dO_i^c(t)+o_p(1), \tag{A.4}$$

$$\begin{aligned}
&n^{1/2}(\hat\Lambda_0(t)-\Lambda_0(t))\\
&=n^{-1/2}\sum_{i=1}^n\int_0^t(S^{(0)}(s,\beta))^{-1}dO_i^c(s)-n^{1/2}\int_0^t(\hat\beta-\beta)^T\bar Z(s)\lambda_0(s)\,ds+o_p(1)\\
&=n^{-1/2}\sum_{i=1}^n\int_0^t(s^{(0)}(s))^{-1}dO_i^c(s)-n^{1/2}(\hat\beta-\beta)^T\int_0^t\bar z(s)\lambda_0(s)\,ds+o_p(1). \qquad (A.5)
\end{aligned}$$

By using the delta method,

$$\begin{aligned}
&\hat G_i(t)-G_i(t)=\exp\{-\hat\Lambda_0(t)\exp(\hat\beta^TZ_i)\}-\exp\{-\Lambda_0(t)\exp(\beta^TZ_i)\}\\
&\quad=-\hat G_i(t)\exp(\beta^TZ_i)(\hat\Lambda_0(t)-\Lambda_0(t))-G_i(t)\Lambda_0(t)\exp(\beta^TZ_i)Z_i^T(\hat\beta-\beta)\\
&\qquad+o_p\left(n^{-1/2}\right)\\
&\quad=-n^{-1}\hat G_i(t)\exp(\beta^TZ_i)\sum_{j=1}^n\int_0^t(s^{(0)}(s))^{-1}dO_j^c(s)\\
&\qquad+(\hat\beta-\beta)^TG_i(t)\exp(\beta^TZ_i)\left[\int_0^t\bar z(s)\lambda_0(s)ds-Z_i\Lambda_0(t)\right]+o_p(n^{-1/2}). \qquad (A.6)
\end{aligned}$$

Let $\psi_i(t)=\int_0^t\bar z(s)\lambda_0(s)\,ds-Z_i\Lambda_0(t)$,

$$\begin{aligned}
B_{1k}(s,t)&=\lim_{n\to\infty}\frac1n\sum_{i=1}^n\left(\int_s^t h_k(u)I(Z_i\in\Delta_k)(G_i(u))^{-1}\exp(\beta^TZ_i)Y_i(u)dN_i(u)\right),\\
C_{1k}(t)&=\lim_{n\to\infty}\frac1n\sum_{i=1}^n\left[\int_0^t h_k(u)I(Z_i\in\Delta_k)(G_i(u))^{-1}\exp(\beta^TZ_i)\psi_i(u)Y_i(u)dN_i(u)\right],\\
B_{2k}(t)&=\lim_{n\to\infty}\frac1n\sum_{i=1}^n I(Z_i\in\Delta_k)(G_i(t))^{-1}\exp(\beta^TZ_i)\int_0^t h_k(u)Y_i(u)N_i(du,t),\\
C_{2k}(t)&=\lim_{n\to\infty}\frac1n\sum_{i=1}^n I(Z_i\in\Delta_k)(G_i(t))^{-1}\exp(\beta^TZ_i)\psi_i(t)\int_0^t h_k(u)Y_i(u)N_i(du,t).
\end{aligned}$$

By (A.4), (A.6), and Lemma A.1 of Lin and Ying (2001), we have

$$
\begin{aligned}
&\int_0^t H_k(u)\, d\bar{\mu}_k^{(Y)}(u) - \int_0^t H_k(u) d\mu_{1k}^c(u) \\
&= -n^{-1} \sum_{i=1}^n \Big[\int_0^t H_k(u) I(Z_i \in \Delta_k)(\hat{G}_i(u))^{-1}(G_i(u))^{-1} \\
&\quad \times[(\hat{G}_i(u)) - (G_i(u))]Y_i(u) dN_i(u) \Big] \\
&\quad + n^{-1} \sum_{i=1}^n \Big[\int_0^t H_k(u) I(Z_i \in \Delta_k)(G_i(u))^{-1} Y_i(u) dN_i(u) - \int_0^t H_k(u) d\mu_{1k}^c(u) \Big] \\
&= n^{-1} \sum_{j=1}^n \int_0^t B_{1k}(u,t)(s^{(0)}(u))^{-1} dO_j^c(u) \\
&\quad - n^{-1}(C_{1k}(t))^T A^{-1} \sum_{i=1}^n \int_0^\tau (Z_i - \bar{z}(u))\, dO_i^c(u) \\
&\quad + n^{-1} \sum_{i=1}^n \Big[\int_0^t h_k(u) I(Z_i \in \Delta_k)(G_i(u))^{-1} Y_i(u) dN_i(u) - \int_0^t h_k(u) d\mu_{1k}^c(u) \Big] \\
&\quad + o_p\left(n^{-1/2}\right). \qquad\qquad (A.7)
\end{aligned}
$$

Similarly,

$$
\begin{aligned}
&\int_0^t H_k(u) \hat{\mu}_k^{(Y)}(du,t) - \int_0^t H_k(u) \mu_{2k}^c(du,t) \\
&= n^{-1} \sum_{i=1}^n \Big[I(Z_i \in \Delta_k)[(\hat{G}_i(t))^{-1} - (G_i(t))^{-1}] \int_0^t H_k(u) Y_i(u) N_i(du,t) \Big] \\
&\quad + n^{-1} \sum_{i=1}^n \Big[I(Z_i \in \Delta_k)(G_i(t))^{-1} \int_0^t H_k(u) Y_i(u) N_i(du,t) - \int_0^t H_k(u) \mu_{2k}^c(du,t) \Big] \\
&= n^{-1} B_{2k}(t) \sum_{j=1}^n \int_0^t (s^{(0)}(u))^{-1} dO_j^c(u) \\
&\quad - n^{-1}(C_{2k}(t))^T A^{-1} \sum_{i=1}^n \int_0^\tau (Z_i - \bar{z}(u))\, dO_i^c(u) \\
&\quad + n^{-1} \sum_{i=1}^n \Big[I(Z_i \in \Delta_k)(G_i(t))^{-1} \int_0^t h_k(u) Y_i(s) N_i(du,t) - \int_0^t h_k(u) \mu_{2k}^c(du,t) \Big] \\
&\quad + o_p\left(n^{-1/2}\right). \qquad\qquad (A.8)
\end{aligned}
$$

Combining (A.7) and (A.8), we have

$$\int_0^t H_k(u)(\bar{\mu}_k^{(Y)}(du) - \hat{\mu}_k^{(Y)}(du,t))$$
$$= n^{-1}\sum_{i=1}^n r_{ki}(t) + \int_0^t H_k(u)(\mu_{1k}^c(du) - \mu_{2k}^c(du,t)) + o_p\left(n^{-1/2}\right), \qquad (A.9)$$

where

$$\begin{aligned} r_{ki}(t) = &\int_0^t B_{1k}(u,t)(s^{(0)}(u))^{-1}dO_i^c(u) - (C_{1k}(t))^T A^{-1}\int_0^\tau (Z_i - \bar{z}(u))\, dO_i^c(u) \\ &-B_{2k}(t)\int_0^t (s^{(0)}(u))^{-1}dO_i^c(u) + (C_{2k}(t))^T A^{-1}\int_0^\tau (Z_i - \bar{z}(u))\, dO_i^c(u) \\ &+\int_0^t h_k(u)I(Z_i \in \Delta_k)(G_i(u))^{-1}Y_i(u)dN_i(u) \\ &-I(Z_i \in \Delta_k)(G_i(t))^{-1}\int_0^t h_k(u)Y_i(u)N_i(du,t). \end{aligned} \qquad (A.10)$$

Under NIC2, $\mu_{1k}^c(u) = \mu_{2k}^c(u,t)$ for $0 \le u \le t$. By an application of the Central Limit Theorem for empirical processes, $R_Z^{(Y)}(t)$ converges weakly to a vector of K-dimensional mean zero Gaussian processes. This proves Theorem 2.

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