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Nonparametric Comparison for Multivariate Panel Count Data

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Abstract

Multivariate panel count data often occur when there exist several related recurrent events or response variables defined by occurrences of related events. For univariate panel count data, several nonparametric treatment comparison procedures have been developed. However, it does not seem to exist a nonparametric procedure for multivariate cases. Based on differences between estimated mean functions, this paper proposes a class of nonparametric test procedures for multivariate panel count data. The asymptotic distribution of the new test statistics is established and a simulation study is conducted. Also the new procedures are applied to a skin cancer problem that motivated this study.

Keywords

Counting processes; Medical follow-up study; Nonparametric comparison; Panel count data; Skin cancer study

1. Introduction

This paper discusses nonparametric treatment comparison based on multivariate panel count data. Panel count data commonly refer to the data arising from studies concerning recurrent events in which each subject is observed only at several distinct time points instead of continuously (Kalbfleisch and Lawless, 1985; Zhang, 2002). Examples of recurrent events include disease infections and machine failures (Cook and Lawless, 2007). For panel count data, no information is available on subjects between observation time points and only the numbers of the occurrences of the events between the observation times are known. Also the number of observations and the observation times may vary from subject to subject. The fields that often produce such data include clinical trials, medical follow-up studies, reliability experiments, sociological studies and tumorigenicity experiments. One of the early examples of panel count data was given by Kalbfleisch and Lawless (1985) on school children smoking behavior. Also Thall and Lachin (1988) described a set of panel count data arising from a follow-up study on patients with floating gallstones.

Multivariate panel count data occur if there exist several related recurrent events or response variables defined by the occurrences of related recurrent events. This study was motivated by a skin cancer chemoprevention trial conducted by the University of Wisconsin Comprehensive Cancer Center in Madison, Wisconsin. The primary objective of this trial was to evaluate the overall effectiveness of 0.5g/m²/day PO difluoromethylornithine (DFMO) in reducing new skin cancers in a population of patients with a history of non-melanoma skin cancers: basal cell carcinoma and squamous cell carcinoma. During the

study, the patients were observed from time to time and the observed data include the numbers of occurrences of both basal cell carcinoma and squamous cell carcinoma between observation times. More details about the study will be given below. He et al. (2008) discussed another example of multivariate panel count data from a cohort study, conducted at the University of Toronto Psoriatic Arthritis Clinic, of the patients with psoriatic arthritis on the recurrences of joint damages.

For the analysis of panel count data, it is helpful to note the differences between recurrent event data, generated when study subjects are observed continuously over some intervals, and panel count data. A major one is that unlike the former, the latter involves an observation process governing the time points where the subject is observed. Also it is apparent that the former gives much more information about the underlying counting processes than the latter. There exists an extensive literature on the analysis of recurrent event data (Andersen et al., 1993; Cook and Lawless, 1997; Wang and Chang, 1999; Lin et al., 2000; and so on) but relatively much less literature on the analysis of panel count data (Hu et al., 2009; Sun and Kalbfleisch, 1995; Sun and Wei, 2000; and Zhang, 2002).

Treatment comparison is one of the most asked questions in clinical trials or medical follow-up studies. For univariate panel count data, several nonparametric procedures have been developed in the literature (Balakrishnan and Zhao, 2009; Park et al., 2007; Sun and Fang, 2003; Thall and Lachin 1988; Zhang, 2006; Zhao et al., 2011). For example, Thall and Lachin (1988) suggested to transform the problem to a multivariate comparison problem and then to apply a multivariate Wilcoxon-type rank test. To implement the proposed procedure, one needs to partition the whole study period into several fixed, consecutive and non-overlapping intervals. To overcome this, several procedures that do not require this were developed by Balakrishnan and Zhao (2009), Park et al. (2007), Sun and Fang (2003), and Zhang (2006). However, none of these can be applied to multivariate data. The idea behind all these procedures is similar and is to construct the test statistics based on the differences between estimated mean functions of the underlying counting processes that generate the panel count data. In the following, we will generalize this idea to multivariate panel count data situations.

For multivariate panel count data, a main difficulty is how to deal with the relationship of different types of recurrent events. Of course, one may separately apply methods for univariate panel count data to each type of event and to make multiple single hypothesis testing. However, it is apparent that this would be less efficient than conducting a joint or multivariate analysis if the different types of recurrent events are related. In this paper, we propose a joint test statistic to do the simultaneous testing for each type of recurrent events based on the differences between estimated mean functions. One major advantage of the proposed methodology is that it leaves the dependence structures for related types of recurrent events completely arbitrary.

The remainder of the article is organized as follows. We will begin in Section 2 with introducing some notation and the problem of interest. Then a class of nonparametric test statistics is presented for comparing two treatment groups with respect to their mean functions. They are generalizations of the test statistics proposed in Park et al. (2007) and represent the integrated weighted difference between the estimated mean functions. Also in Section 2, the asymptotic distribution of the test statistics is given. Section 3 investigates the finite sample properties of the proposed test procedures through simulation studies and Section 4 applies the methodology to the skin cancer study described above. Some concluding remarks are provided in Section 5.

2. Nonparametric treatment comparison

Consider a recurrent event study that involves n independent subjects and in which each subject may experience K different types of recurrent events. Assume that there exist two treatment groups. Also for simplicity assume that the first n_1 subjects are in the control group and the remaining n_2 are in the treatment group, where $n_1 + n_2 = n$. Let $N_{ik}(t)$ denote the cumulative number of the occurrences of the k -th type recurrent event of interest that subject i has experienced up to time t , $i = 1, \dots, n$, $k = 1, \dots, K$. Also let $\Lambda_{k1}(t)$ and $\Lambda_{k2}(t)$ denote the mean functions of $N_{ik}(t)$ for subjects in the control and treatment groups, respectively. That is, $\Lambda_{k1}(t) = E\{N_{ik}(t)\}$ for $i = 1, \dots, n_1$ and $\Lambda_{k2}(t) = E\{N_{ik}(t)\}$ for $i = n_1 + 1, \dots, n$. In the following, suppose that the goal is to test the hypothesis

$$H_0 : \Lambda_{11}(t) = \Lambda_{12}(t), \dots, \Lambda_{K1}(t) = \Lambda_{K2}(t).$$

Suppose that one observes only panel count data on the $N_{ik}(t)$'s. Specifically, for subject i , let $0 < t_{i,1} < \dots < t_{i,m_i}$ denote the observation times on $N_{ik}(t)$ and $n_{i,k,j} = N_{ik}(t_{i,j})$, the observed value of $N_{ik}(t)$ at $t_{i,j}$, $i = 1, \dots, n$, $k = 1, \dots, K$, $j = 1, \dots, m_i$. Then the observed data are $\{t_{i,j}, n_{i,k,j}\}$. Note that here for simple presentation, we assume that the observation times for different types of recurrent events from the same subject are the same. The methodology given below can be easily generalized to the situation where the observation times for different types of recurrent events are different. To test the hypothesis H_0 , let $\hat{\Lambda}_{k1}$ and $\hat{\Lambda}_{k2}$ denote some consistent estimates of Λ_{k1} and Λ_{k2} , respectively, which will be discussed below, $k = 1, \dots, K$. Then motivated by the test statistics used in Park et al. (2007), we propose to use the statistic

$$U_n = \sqrt{\frac{n_1 n_2}{n}} \sum_{k=1}^K \int_0^\tau W_{nk}(t) \left\{ \hat{\Lambda}_{k1}(t) - \hat{\Lambda}_{k2}(t) \right\} dG_n(t)$$

where τ is the largest observation time, $W_{nk}(t)$ is a bounded weight process and

$$G_n(t) = \frac{1}{n} \sum_{i=1}^n \sum_{j=1}^{m_i} I(t_{i,j} \leq t).$$

It can be easily seen that the statistic U_n is the integrated weighted differences between estimated mean functions and should be sensitive to stochastically ordered mean functions. Similar test statistics can be found in many other fields such as survival analysis. For two sample survival comparison with right-censored data, for example, Pepe and Fleming (1989) proposed some test statistics that have the same format as U_n with replacing the estimates by estimated survival functions. Note that for testing H_0 , the statistic U_n compares estimates of individual mean functions directly. As an alternative, one could construct some test statistics that compare the estimates of individual mean functions with the estimate of the overall mean function under the hypothesis (Sun and Fang, 2003). In general, it is natural to expect that the statistic U_n may give a better power although the two are asymptotically equivalent.

It is easy to see that the test statistic U_n can be rewritten as

$$U_n = \sqrt{\frac{n_1 \cdot n_2}{n^3}} \sum_{i=1}^n \sum_{k=1}^K \sum_{j=1}^{m_i} W_{nk}(t_{i,j}) \left\{ \hat{\Lambda}_{k1}(t_{i,j}) - \hat{\Lambda}_{k2}(t_{i,j}) \right\}.$$

By following the same arguments as those in Park et al. (2007), one can show that under some regular condition, for large n , the distribution of U_n can be approximated by the normal distribution with mean zero and the variance that can be consistently estimated by

$$\begin{aligned} \hat{\sigma}_n^2 = & \frac{n_2}{n \cdot n_1} \sum_{i=1}^{n_1} \left[\sum_{k=1}^K \sum_{j=1}^{m_i} W_{nk}(t_{i,j}) \left\{ N_{ik}(t_{i,j}) - \hat{\Lambda}_{k1}(t_{i,j}) \right\} \right]^2 \\ & + \frac{n_1}{n \cdot n_2} \sum_{i=n_1+1}^n \left[\sum_{k=1}^K \sum_{j=1}^{m_i} W_{nk}(t_{i,j}) \left\{ N_{ik}(t_{i,j}) - \hat{\Lambda}_{k2}(t_{i,j}) \right\} \right]^2. \quad (1) \end{aligned}$$

The proof of the results above is sketched in the Appendix. It thus follows that the test of the hypothesis H_0 can be carried out by using the statistic $U_n^* = U_n / \hat{\sigma}_n$ based on the standard normal distribution.

To apply the test procedure given above, one needs some consistent estimates of $\Lambda_{k1}(t)$ and $\Lambda_{k2}(t)$. In the literature, one such estimate, which will be used below, is the isotonic regression estimator given in Sun and Kalbfleisch (1995) and Wellner and Zhang (2000). To introduce the isotonic regression estimator, for simplicity, assume that all mean functions $\Lambda_{kl}(t)$ are the same and equal to $\Lambda(t)$. Let $s_1, \dots, s_m$ denote the ordered distinct observation times in the set $\{t_{i,j}; j = 1, \dots, m_i, i = 1, \dots, n\}$ and w_l and $\bar{n}_l$ the number and mean value, respectively, of the observations made at $s_l, l = 1, \dots, m$. Then the isotonic regression estimator $\hat{\Lambda}(t)$ is defined as a nondecreasing step function with possible jumps at the s_l 's that minimizes

$$\sum_{l=1}^m w_l \left\{ \bar{n}_l - \Lambda(s_l) \right\}^2$$

subject to the nondecreasing restriction. It can be shown that $\hat{\Lambda}(t)$ has a closed expression given by

$$\begin{aligned} \hat{\Lambda}(s_l) &= \max_{r \leq l} \min_{s \geq l} \frac{\sum_{v=r}^s w_v \bar{n}_v}{\sum_{v=r}^s w_v} \\ &= \min_{s \geq l} \max_{r \leq l} \frac{\sum_{v=r}^s w_v \bar{n}_v}{\sum_{v=r}^s w_v}, \quad l=1, \dots, m \end{aligned}$$

(Robertson et al., 1988).

Another aspect related to the use of the proposed test statistic is the selection of the weight process $W_{nk}(t)$. It is clear that a simple and natural choice is to set all $W_{nk}(t)$ to be the same with $W_{nk}(t) = 1$. Another natural choice is to let $W_{nk}(t) = \sum_{i=1}^n I(t \leq t_{i,m_i}) / n$ and in this case, the weights are proportional to the number of subjects under observation. Of course, many other choices could be used and one may want to employ different weight processes for different types of recurrent events.

3. A simulation study

An extensive simulation study was conducted for investigating the finite sample properties of the proposed test statistic U_n . In the study, we considered the bivariate panel count data case with $K = 2$ and first generated m_i , the number of observation times for subject i , from the uniform distribution $U\{1, \dots, 10\}$. For given m_i , the observation times t_{ij} 's were also generated from the same uniform distribution for simplicity. Note that one could generate the t_{ij} 's from more general uniform distributions and the results should be similar.

To generate the bivariate panel count data, we assumed that the N_{ik} 's were non-homogeneous mixed Poisson processes. Specifically, for given t_{ij} 's and a latent variable Q_i , we generated $N_{ik}(t_{ij})$ based on

$$N_{ik}(t_{i,j}) = N_{ik}^*(t_{i,1}) + N_{ik}^*(t_{i,2} - t_{i,1}) + \dots + N_{ik}^*(t_{i,j} - t_{i,j-1})$$

for $j = 1, \dots, m_i$. In the above, all N_{ik}^* were assumed to follow Poisson distributions with the mean functions defined as, given Q_i and some baseline cumulative mean function $\Lambda_k(t)$,

$$\begin{aligned} E\{N_{ik}^*(t_{i,1})\} &= Q_i \Lambda_k(t_{i,1}), \\ E\{N_{ik}^*(t_{i,j} - t_{i,j-1})\} &= Q_i \{\Lambda_k(t_{i,j}) - \Lambda_k(t_{i,j-1})\} \end{aligned}$$

for $j = 2, \dots, m_i$ and $i = 1, \dots, n_1$, and

$$\begin{aligned} E\{N_{ik}^*(t_{i,1})\} &= Q_i \Lambda_k(t_{i,1}) \exp(\beta), \\ E\{N_{ik}^*(t_{i,j} - t_{i,j-1})\} &= Q_i \{\Lambda_k(t_{i,j}) - \Lambda_k(t_{i,j-1})\} \exp(\beta) \end{aligned}$$

for $j = 2, \dots, m_i$ and $i = n_1 + 1, \dots, n$. Here β is a parameter representing the treatment difference and the Q_i 's were generated from a Gamma distribution with mean one and variance 0.1. For $\Lambda_k(t)$, we considered three choices and they are $\Lambda_k(t) = t$, t^2 , and $\log(t)$. All results reported below are based on $W_{nk} = 1$ and 1000 replications.

Table 1 presents the estimated sizes and powers of the proposed test statistic U_n at significance level $\alpha = 0.05$ with the true value of β being $-0.2, -0.1, 0, 0.1$ or 0.2 and $n_1 = n_2 = 50, 100$ or 200 , respectively. Here we assumed that the baseline mean functions $\Lambda_1(t)$ and $\Lambda_2(t)$ are the same. The results indicate that the proposed test procedure seems to have the right size and reasonable power. Especially, as expected, the procedure performs better when the sample size increases and the power could depend on the underlying baseline mean functions. In Table 2, we studied similar situations to those considered in Table 1 except that we assumed that the underlying baseline mean functions $\Lambda_1(t)$ and $\Lambda_2(t)$ for different types of recurrent events are different. It can be seen that they gave similar conclusions to those suggested in Table 1.

To evaluate the normal distribution approximation to the distribution of U_n , we studied the quantile plots of the standardized test statistic U_n^* against the standard normal distribution. Figure 1 presents the plot for the situation considered in Table 1 with $\beta = 0$, $\Lambda_1(t) = \Lambda_2(t) = t$, and $n_1 = n_2 = 100$, while Figure 2 gives the plot for the situation considered in Table 2 with $\beta = 0$, $\Lambda_1(t) = t$, $\Lambda_2(t) = t^2$, and $n_1 = n_2 = 100$. They suggest that the approximation seems good. We also considered other simulation set-ups and obtained similar results.

4. Application to the skin cancer chemoprevention trial

Now we apply the nonparametric comparison procedure proposed in the previous sections to the skin cancer chemoprevention trial described above. As mentioned before, the study focused on the patients with a history of non-melanoma skin cancers and the primary objective of the trial was to evaluate the overall effectiveness of DFMO in reducing the recurrence rates of new skin cancers, basal cell carcinoma and squamous cell carcinoma, in these patients. During the study, the patients were scheduled to be assessed or observed every six months, however, as expected, the real observation and follow-up times differ from patient to patient. The study consists of 291 patients randomized to either a placebo group (147) or the DFMO group (144) and the observed data include the numbers of occurrences of both basal cell carcinoma and squamous cell carcinoma between observation times. For the analysis below, we will focus on the 290 patients (147 in the placebo group and 143 in the DFMO group) with at least one observation.

To test the effect of DFMO on the recurrence rates of both basal cell carcinoma and squamous cell carcinoma together, let $N_{i1}(t)$ denote the total number of occurrences of basal cell carcinoma up to time t for the patients given the treatment DFMO and $N_{i2}(t)$ the total number of occurrences of squamous cell carcinoma up to time t also for the patients given the treatment DFMO, $i = 1, \dots, 143$. Correspondingly, for $i = 144, \dots, 290$, we let $N_{i1}(t)$ and $N_{i2}(t)$ denote the total numbers of occurrences of basal cell carcinoma and squamous cell carcinoma, respectively, up to time t for the patients in the placebo group. Thus Λ_{11} and Λ_{21} represent the cumulative mean functions of the occurrences of basal cell carcinoma and squamous cell carcinoma, respectively, under the DFMO treatment, while Λ_{12} and Λ_{22} are the same cumulative mean functions under the placebo treatment instead of the DFMO.

For the assessment of the overall DFMO treatment effect, we first obtained the isotonic regression estimates of all four mean functions $\Lambda_{jk}(t)$ and present them in Figure 3. One can easily see that the DFMO treatment seems to have some effects in reducing the recurrences of basal cell carcinoma but does not seem to have any effect on the recurrences of squamous cell carcinoma. The application of the proposed test procedure with $W_{nk}(t) = 1$ to the data gave $U_n^* = -1.748$. If using $W_{nk}(t) = \sum_{i=1}^n I(t \leq t_{i,m_i})/n$, we got $U_n^* = -1.660$. They suggest that overall the DFMO treatment seems to have some mild effects in reducing the recurrence rates of the two types of skin cancers considered here.

Of course, if one is only interested in the DFMO treatment effect on the recurrent rate of an individual type of skin cancer, the proposed test procedure could also be applied with a modification $K = 1$ for each type of skin cancer. For the skin cancer trial here, the application of the procedure to the two types of skin cancers separately indicated that the DFMO treatment seems to significantly reduce the recurrence rate of basal cell carcinoma but have no significant effect on the recurrence of squamous cell carcinoma. This is similar to that seen in Figure 3.

5. Concluding Remarks

In the previous sections, we discussed the nonparametric treatment comparison based on multivariate panel count data, which are often observed in many fields including clinical trials, medical follow-up studies and tumorigenicity experiments. For the problem, a class of test procedures was proposed and evaluated by numerical studies, which suggested that the proposed method works well for practical situations. The presented approach is a generalization of the procedure given in Park et al. (2007) for univariate panel count data and was applied to a set of bivariate panel count data that motivated this study. It is worth noting that although the two procedures have similar formats, the new one has to take into

account the correlation among related events implicitly, while the procedure given in Park et al. (2007) does not have the issue. One main advantage of the proposed methodology is that it leaves the relationship of different types of recurrent events completely unspecified.

We note that for the simplicity, we have assumed that the observation times or processes for different types of recurrent events are the same. It can be easily seen that this is usually the case in practice as in the example discussed in Section 4. On the other hand, the proposed approach is still valid if they are different. Specifically, if $\{t_{i,k,1}, \dots, t_{i,k,m_{ik}}\}$ are the observation times on $N_{ik}(t)$, then U_n can be modified to

$$U_n = \sqrt{\frac{n_1 n_2}{n}} \sum_{k=1}^K \int_0^\tau W_{nk}(t) \left\{ \hat{\Lambda}_{k1}(t) - \hat{\Lambda}_{k2}(t) \right\} dG_n^{(k)}(t),$$

where $G_n^{(k)}(t) = n^{-1} \sum_{i=1}^n \sum_{j=1}^{m_{ik}} I(t_{i,k,j} \leq t)$. One can show that the modified test statistic also has the asymptotic normal distribution.

Also we have assumed that observation times follow the same distribution for subjects in different treatment groups. Again this seems to be the case for the example discussed in Section 4 and actually holds for most of medical studies with periodic follow-up such as clinical trials. In this situation, subjects are usually supposed to be observed at prespecified observation time points. Although actual observation times may vary from these prespecified time points and from subject to subject, the variation can often be regarded as being independent of treatments. The same could be said for many of reliability experiments and sociological studies in which panel count data commonly occur. For this, it is worth pointing out that the distributions of the observation times cannot be allowed to be completely different among treatment groups as otherwise, it would be not possible to compare them.

The focus of the paper has been on nonparametric comparison. An alternative to this is to define some treatment indicators and employ some regression procedures. It is clear that in this approach, some assumption has to be made about the regression model and it may not be possible to verify the appropriateness of the model. Thus if the interest is purely comparison, a nonparametric comparison procedure may be preferred. Of course, sometimes, there may exist other covariates that are of interest and in this case, regression procedures would be better employed.

To employ the proposed procedure, one needs to choose some consistent estimates of the underlying cumulative mean functions. In this paper, we used the isotonic regression estimate since it is much simpler than the maximum likelihood estimate in this situation. Of course, the use of the latter may have some efficiency gain, but the gain may not be significant.

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Appendix

Asymptotic properties of U_n

Let $\Lambda_{k0}(t)$ be the true mean function of the $N_{ik}(t)$'s under H_0 . Firstly suppose that M is an integer-value random variable and $T = \{T_{mj}, j = 1, \dots, m; m = 1, 2, \dots\}$ is a random triangular array, and let m_i and $t_{ij} = t_{m_i j}$ are realizations of them. Then denote

$G(t) = E \left\{ \sum_{j=1}^M I(T_{M,j} \leq t) \right\}$ and assume that $\{(M_i; T_{M_{i,1}}, \dots, T_{M_i, M_i}); i = 1, \dots, n\}$ are iid and independent of the N_{ik} 's. Finally we propose the following regularity conditions.

(C1). $n_1/n \rightarrow p_1$ and $n_2/n \rightarrow p_2$ as $n \rightarrow \infty$, where $0 < p_1, p_2 < 1$ and $p_1 + p_2 = 1$.

(C2). There exists a constant M_0 such that $P\{M \leq M_0\} = 1$, and the random variables T_{mj} 's take values in a bounded set $[0, \tau]$, where $\tau \in (0, \infty)$.

(C3). There exists some positive constant C_0 such that $\max_k \Lambda_{k0}(\tau) \leq C_0$.

(C4). $P\{\limsup_{n \rightarrow \infty} \max_{i,k} N_{i,k}(\tau) < \infty\} = 1$ and $E(N_{ik}(t))^2 \leq C_1$ for all $k = 1, \dots, K$ and $t \leq \tau$, where C_1 is a constant.

(C5). For all $k = 1, \dots, K$, $\{W_{nk}(t)\}$ are bounded weight processes and that there exist bounded functions $\{W_k(t)\}$ such that $\{W_k \circ \Lambda_{k0}^{-1}\}$ are bounded Lipschitz functions and

$$\sup_n E \int_0^\tau |\sqrt{n} \{W_{nk}(t) - W_k(t)\}|^2 dG_n(t) < \infty.$$

To establish the asymptotic properties about U_n , we decompose U_n into

$$U_n = \sum_{k=1}^K \left\{ \sqrt{\frac{n_2}{n}} U_{nk}^{(1)} - \sqrt{\frac{n_1}{n}} U_{nk}^{(2)} \right\},$$

where

$$U_{nk}^{(l)} = \sqrt{n_l} \int_0^\tau W_{nk}(t) \left\{ \hat{\Lambda}_{kl}(t) - \Lambda_{k0}(t) \right\} dG_n(t),$$

and $l = 1, 2$ is the treatment group indicator.

Under the regularity conditions (C1-C5) and using some empirical process results (Van der Vaart and Wellner, 1996) and the proofs of Theorems 1 and 2 in Park et al. (2007), we have

$$U_{nk}^{(l)} = \sqrt{n_l} \int_0^\tau W_k(t) \left\{ \hat{\Lambda}_{kl}(t) - \Lambda_{k0}(t) \right\} dG(t) + o_p(1),$$

Then U_n can be rewritten as

$$U_n = \sqrt{\frac{n_2}{n}} V_{n_1} - \sqrt{\frac{n_1}{n}} V_{n_2} + o_p(1),$$

where

$$\begin{aligned} V_{n_1} &= \sqrt{n_1} \sum_{k=1}^K \int_0^\tau W_k(t) \left\{ \hat{\Lambda}_{k1}(t) - \Lambda_{k0}(t) \right\} dG(t) + o_p(1) \\ &= \frac{1}{\sqrt{n_1}} \sum_{i=1}^{n_1} \sum_{j=1}^{m_i} \sum_{k=1}^K W_k(t_{ij}) \{N_{ik}(t_{ij}) - \Lambda_{k0}(t_{ij})\} + o_p(1), \end{aligned}$$

and

$$\begin{aligned} V_{n_2} &= \sqrt{n_2} \sum_{k=1}^K \int_0^\tau W_k(t) \left\{ \hat{\Lambda}_{k2}(t) - \Lambda_{k0}(t) \right\} dG(t) + o_p(1) \\ &= \frac{1}{\sqrt{n_2}} \sum_{i=n_1+1}^n \sum_{j=1}^{m_i} \sum_{k=1}^K W_k(t_{ij}) \{N_{ik}(t_{ij}) - \Lambda_{k0}(t_{ij})\} + o_p(1). \end{aligned}$$

By the central limit theorem, V_{n_1} and V_{n_2} converge in distribution to two independent mean-zero normal random variables. Then it follows that U_n converges in distribution to a normal random variable that has zero mean and variance that can be estimated by formula (1).

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Figure 1.
The quantile plot of the standardized test statistic with $\beta = 0$, $\Lambda_1(t) = \Lambda_2(t) = t$.

Figure 2.

The quantile plot of the standardized test statistic with $\beta = 0$, $\Lambda_1(t) = t$, $\Lambda_2(t) = t^2$.

Figure 3. Estimated DFMO treatment effects on the recurrent rates of basal cell carcinoma and squamous cell carcinoma.

Table 1

Estimated sizes and powers with the same mean functions.

True β	-0.2	-0.1	0	0.1	0.2
$\Lambda_1(t) = \Lambda_2(t) = t$					
$n_1 = n_2 = 50$	0.609	0.217	0.058	0.248	0.646
$n_1 = n_2 = 100$	0.875	0.363	0.05	0.366	0.916
$n_1 = n_2 = 200$	0.992	0.608	0.054	0.636	0.995
$\Lambda_1(t) = \Lambda_2(t) = t^2$					
$n_1 = n_2 = 50$	0.788	0.356	0.053	0.287	0.798
$n_1 = n_2 = 100$	0.960	0.507	0.052	0.513	0.977
$n_1 = n_2 = 200$	0.999	0.771	0.050	0.766	1.000
$\Lambda_1(t) = \Lambda_2(t) = \log(t)$					
$n_1 = n_2 = 50$	0.345	0.15	0.0587	0.135	0.361
$n_1 = n_2 = 100$	0.569	0.223	0.057	0.223	0.617
$n_1 = n_2 = 200$	0.858	0.356	0.050	0.356	0.893

Table 2

Estimated sizes and powers with different mean functions.

True β	-0.2	-0.1	0	0.1	0.2
$\Lambda_1(t) = t, \Lambda_2(t) = t^2$					
$n_1 = n_2 = 50$	0.798	0.255	0.062	0.305	0.777
$n_1 = n_2 = 100$	0.959	0.484	0.049	0.483	0.972
$n_1 = n_2 = 100$	1.000	0.754	0.050	0.759	1.000
$\Lambda_1(t) = t, \Lambda_2(t) = \log(t)$					
$n_1 = n_2 = 50$	0.520	0.183	0.062	0.205	0.554
$n_1 = n_2 = 100$	0.794	0.310	0.050	0.310	0.847
$n_1 = n_2 = 200$	0.972	0.548	0.050	0.545	0.978