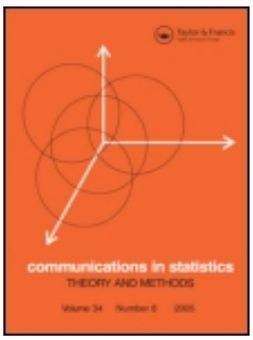

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Nonparametric Inference

A Nonparametric Test for Interval-Censored Failure Time Data with Unequal Censoring

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This article considers nonparametric comparison of survival functions, one of the most commonly required task in survival studies. For this, several test procedures have been proposed for interval-censored failure time data in which distributions of censoring intervals are identical among different treatment groups. Sometimes the distributions may depend on treatments and thus not be the same. A class of test statistics is proposed for situations where the distributions may be different for subjects in different treatment groups. The asymptotic normality of the test statistics is established and the test procedure is evaluated by simulations, which suggest that it works well for practical situations. An illustrative example is provided.

Keywords Interval-censored data; Linear functional; Two sample comparison; Unequal censoring.

Mathematics Subject Classification Primary 62G10; Secondary 34M30.

1. Introduction

In clinical trials and epidemiological studies, one of the primary objectives is often to compare survival functions. In this case, one usually prefers to apply nonparametric methods due to the lack of knowledge about the underlying distributions of the failure time of interest. In this article, we consider such nonparametric comparison problems when only interval-censored failure time data are available. In practice,

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there exist two types of interval-censored data: Case I and II interval-censored data (Anderson and Rønn, 1995; Groeneboom and Wellner, 1992; Sun, 2005). The former, which is also often referred to as current status data, means that each subject is observed only once and thus the failure event of interest is observed only to have occurred before the observation time or not yet. In other words, the failure time of interest is either left- or right-censored. Case II interval-censored data mean that the failure time of interest is known only to belong to an interval. They reduce to Case I interval-censored data if the interval includes either 0 or infinity. Another commonly used formation for Case II interval-censored data is that for each subject, there exist two random observation times and the failure time is known only to be smaller than the first observation time, between the two observation times, or larger than the second observation time (Groeneboom and Wellner, 1992; Zhang et al., 2001).

Interval-censored failure time data occur in many fields including clinical trials and epidemiological studies. In AIDS cohort studies, for example, HIV infection is usually determined through periodic blood tests. Thus, the HIV infection time is known only to belong to an interval given by dates of the last negative blood test and the first positive blood test. Such an example is discussed in detail in Sec. 4.

For survival comparison based on interval-censored data, a few test procedures have been proposed (Fay, 1996; Finkelstein, 1986; Pan, 2000; Petroni and Wolfe, 1994; Self and Grossman, 1986; Zhao and Sun, 2004; Zhang et al., 2001, 2003). However, most of them assume that censoring intervals or observation times for all subjects have the same distribution function, which obviously may not be true in practice. A failure to take into account this difference in distributions could seriously overestimate or underestimate the treatment difference. One exception is given by Sun (1999), who considered survival comparison based on Case I interval-censored data when the distributions of observation times differ among different treatment groups. Note that for right-censored failure time data, there are no censoring intervals involved and thus the corresponding problem does not exist. Of course, there exists a single right-censoring variable for right-censored data and in this case, conditional approaches are usually used for survival comparison (Kalbfleisch and Prentice, 2002).

In the following, we discuss the same problem as that in Sun (1999) for Case II interval-censored data. Specifically, we consider the two-sample survival comparison problem and a class of test statistics is presented in Sec. 2 that allow the distributions of observation times to be different between two treatment groups. The statistics are constructed based on linear functionals of estimated survival functions and are generalizations of those used in Zhang et al. (2001). The asymptotic normality of the test statistic is established. Monte Carlo simulation studies are performed to evaluate the finite sample properties of the proposed approach in Sec. 3 and Sec. 4 applies it to an AIDS cohort study. Some concluding remarks are given in Sec. 5.

2. Two-Sample Survival Comparison

Consider a survival study that consists of n independent subjects randomly assigned to one of two treatments. For subject i, let T_i denote the failure time of interest and assume that only an interval-censored observation on it is available. Specifically, suppose that the observed information includes two random variables U_i and V_i with $U_i \leq V_i$ and the indicator variables $\delta_{1i} = I(T_i \leq U_i)$, $\delta_{2i} = I(U_i < T_i \leq V_i)$

and $\delta_{3i} = 1 - \delta_{1i} - \delta_{2i}$, where I is the indicator function. It will be assumed that U_i and V_i are independent of T_i. The variables δ_{1i}, δ_{2i}, and δ_{3i} indicate whether the survival event of interest for subject i has occurred before U_i, within the interval $(U_i, V_i]$, or after V_i.

Define $N_i(t) = I(T_i \le t)$, a counting process indicating if the survival event of interest has occurred by time t, and let z_i be 0-1 treatment indicator, $i = 1, \ldots, n$. Also, let $F_l(t)$ denote the failure time distribution function for subjects with $z_i = l$, $l = 0, 1$. Then the observed data consist of $\{(U_i, V_i, \delta_{1i}, \delta_{2i}, \delta_{3i}, z_i); i = 1, \ldots, n\}$ or $\{(U_i, V_i, N_i(U_i), N_i(V_i), z_i); i = 1, \ldots, n\}$ and the goal is to test the hypothesis $H_0 : F_0(t) = F_1(t)$.

To construct a test statistic for H_0, let $H_1^{(l)}(u)$, $H_2^{(l)}(v)$, and $H^{(l)}(u, v)$ denote marginal and joint distribution functions of the U_i's and V_i's for subjects with $z_i = l$, respectively, $l = 0, 1$. Assume that the support of F_0 and F_1 is given by a finite interval $[0, \tau]$. Motivated by the weighted Kaplan-Meier test statistics for right-censored data (Fleming and Harrington, 1991) and the statistics given in Zhang et al. (2001), we consider the functional

$$g(F) = \iint_{0 \le u \le v \le \tau} \{F(u)\eta(u) + F(v)\eta(v)\} dH^{(1)}(u, v), \tag{1}$$

where $\eta(u)$ is an arbitrary known bounded function. Let $\widehat{F}_0$ and $\widehat{F}_1$ denote the estimates of F_0 and F_1, respectively. Then a natural test statistic for H_0 is given by

$$Q = n^{1/2}\{g(\widehat{F}_0) - g(\widehat{F}_1)\}$$

for given $\eta(u)$. It is apparent that under H_0, Q should be around zero.

For estimation of F_0 and F_1, note that we can divide the observed data into two sets of current status data given below:

$$\{(U_i, N_i(U_i), z_i); i = 1, \ldots, n\}, \quad \{(V_i, N_i(V_i), z_i); i = 1, \ldots, n\}.$$

One way to estimate F_0 and F_1 is to combine these two data sets together, but treat them as independent samples. Then we have a single larger set of current status data and can define $\widehat{F}_l$ to be the maximum likelihood estimator based on this larger data set from subjects with $z_i = l$, $l = 0, 1$. The same idea was used by Zhang et al. (2001) among others and one advantage of this approach is that $\widehat{F}_0$ and $\widehat{F}_1$ have closed forms. More comments on this are given below.

To test H_0 using statistic Q, we need to derive the null asymptotic distribution of Q. To this end, let $h_1^{(l)}(u)$ and $h_2^{(l)}(v)$ denote the marginal density functions of the U_i's and V_i's for subjects with $z_i = l$, respectively, $l = 0, 1$. It will be assumed that these functions are positive and satisfy

$$\frac{h_1^{(1)}(\cdot)}{h_1^{(0)}(\cdot)} = \frac{h_2^{(1)}(\cdot)}{h_2^{(0)}(\cdot)} = R(\cdot). \tag{2}$$

Let $\xi = \eta \cdot R$. Then we have the following result.

Theorem 2.1. *Suppose that* $\eta \circ F^{-1}$ *and* $\xi \circ F^{-1}$ *are bounded Lipschitz functions and* $n_0 n \to p$ $(0 < p < 1)$ *as* $n \to \infty$, *where* $n_0 = \sum_{i=1}^{n}(1 - z_i)$. *Then under* H_0

and $n \to \infty$,

$$Q \to N\left(0, \frac{A_0}{p} + \frac{A_1}{1-p}\right)$$

in distribution, where

$$A_0 = \int_0^\tau F_0(u)(1-F_0(u))\xi^2(u)\, dH_1^{(0)}(u) + \int_0^\tau F_0(v)(1-F_0(v))\xi^2(v) dH_2^{(0)}(v) + 2\iint_{0\le u\le v\le\tau} F_0(u)(1-F_0(v))\xi(u)\xi(v) dH^{(0)}(u,v)$$

and

$$A_1 = \int_0^\tau F_1(u)(1-F_1(u))\eta^2(u) dH_1^{(1)}(u) + \int_0^\tau F_1(v)(1-F_1(v))\eta^2(v) dH_2^{(1)}(v) + 2\iint_{0\le u\le v\le\tau} F_1(u)(1-F_1(v))\eta(u)\eta(v) dH^{(1)}(u,v).$$

The proof of the above theorem is sketched in the Appendix. Condition (2) means that the ratio of the density functions of the first observation times across the two groups is the same as that of the second observation times across the two groups. In other words, the mechanism that governs the observation times in the two groups is same for the first and second observation times. This is usually the case for medical studies as long as patients follow the same pattern of observations. Note that condition (2) can be equivalently replaced by $h_1^{(1)}(\cdot)/h_2^{(1)}(\cdot) = h_1^{(0)}(\cdot)/h_2^{(0)}(\cdot)$. This means that the ratio of the density functions of the two observation times in one group is the same as that in the other group, which would be the case if the variation of the observation times in the two groups is due to treatment. Of course, condition (2) holds if $H^{(0)}(u,v) = H^{(1)}(u,v)$. That is, the observation times have the same distribution and in this case, $R(u) = 1$. Some comments about checking condition (2) are given in Sec. 4.

Using the above theorem, for large n, one can test H_0 by the statistic

$$T_\eta = \frac{n^{1/2}\int_0^\tau \left\{\left[\widehat{F}_0(u) - \widehat{F}_1(u)\right]\eta(u) d\widehat{H}_1^{(1)}(u) + \left[\widehat{F}_0(v) - \widehat{F}_1(v)\right]\eta(v) d\widehat{H}_2^{(1)}(v)\right\}}{\left(n_0 n^{-1}\widehat{A}_0 + n_1 n^{-1}\widehat{A}_1\right)^{1/2}}$$

based on the standard normal distribution, where $n_1 = n - n_0$,

$$\widehat{A}_0 = \int_0^\tau \widehat{F}_0(u)(1-\widehat{F}_0(u))\hat{\xi}^2(u) d\widehat{H}_1^{(0)}(u) + \int_0^\tau \widehat{F}_0(v)(1-\widehat{F}_0(v))\hat{\xi}^2(v) d\widehat{H}_2^{(0)}(u) + 2\iint_{0\le u\le v\le\tau} \widehat{F}_0(u)(1-\widehat{F}_0(v))\hat{\xi}(u)\hat{\xi}(v) d\widehat{H}^{(0)}(u,v)$$

and

$$\widehat{A}_1 = \int_0^\tau \widehat{F}_1(u)(1-\widehat{F}_1(u))\eta^2(u) d\widehat{H}_1^{(1)}(u) + \int_0^\tau \widehat{F}_1(v)(1-\widehat{F}_1(v))\eta^2(v) d\widehat{H}_2^{(1)}(v) + 2\iint_{0\le u\le v\le\tau} \widehat{F}_1(u)(1-\widehat{F}_1(v))\eta(u)\eta(v) d\widehat{H}^{(1)}(u,v).$$

In the above, $\widehat{H}_1^{(l)}$, $\widehat{H}_2^{(l)}$, and $\widehat{H}^{(l)}$ denote the empirical distributions of U_i's, V_i's, and (U_i, V_i)'s for subjects with $z_i = l$, respectively, $l = 0, 1$, and $\hat{\xi}(\cdot)$ is an estimate of $\xi(\cdot)$.

In the application of the above test procedure, different η gives different test statistics and it is apparent that the simplest one is $\eta(u) = 1$. For estimation of $\xi(u) = \eta(u)R(u)$, a simple approach, which is used in the following numerical studies, is to replace $h_1^{(1)}$ and $h_1^{(0)}$ in (2) with their empirical estimates for given η. In general, one can replace them by their consistent estimates such as kernel estimates or other smooth estimates in estimation of R.

3. Simulation Studies

Monte Carlo simulation studies were conducted to investigate the performance of the proposed test procedure. In these studies, it was assumed that there are two treatment groups and they have the same number of subjects. The failure time T_i was generated from Weibull distributions with the shape and scale parameters α_1 and β for group 1 and α_2 and $\theta\beta$ for group 2, respectively. For observation times, for $l = 0, 1$, we first independently generated U_i and W_i from Gamma(p_l, λ_l) and Gamma(q, λ_l), respectively, where

$$\lambda_l = \lambda\left[\frac{\Gamma(p_l + q)}{\Gamma(p_l)}\right]^{1/q}$$

with p_l, q, and λ being some constants. Then we took $V_i = U_i + W_i$, which follows Gamma$(p_l + q, \lambda_l)$. This gives

$$\frac{h_2^{(l)}(t)}{h_1^{(l)}(t)} = \frac{\lambda_l^{p_l+q} t^{p_l+q-1} e^{-\lambda_l t}/\Gamma(p_l + q)}{\lambda_l^{p_l} t^{p_l-1} e^{-\lambda_l t}/\Gamma(p_l)} = \lambda_l^q t^q \cdot \frac{\Gamma(p_l)}{\Gamma(p_l + q)} = (\lambda t)^q,$$

and thus condition (2) holds. For the results reported below, we took $\eta(\cdot) = 1$, $p_1 = 0.2$, $p_2 = 0.4$, $q = 3$, and $\lambda = 0.8$.

Tables 1 and 2 present the estimated size and power at the significance level 0.05 of the proposed test procedure (NPTU) based on 1,000 sets of simulated data with $n_1 = n_2 = 50$ or 100, $\beta = 0.5$ or 1, $\theta = 1, 1.5, 2$, or 3, and α_1 and α_2 taking value 0.5, 1 or 1.5. Here the three different values of α_1 and α_2 give decreasing, constant, and increasing hazard rates, respectively. Note that under the model used here, the null

Table 1
Empirical sizes of the proposed test procedure

Parameters				$n_1 = n_2 = 50$			$n_1 = n_2 = 100$		
β	θ	α_1	α_2	NPTU	PLRT	NPT	NPTU	PLRT	NPT
0.5	1.0	0.5	0.5	3.8	4.5	8.6	4.4	4.5	8.1
0.5	1.0	1.0	1.0	5.3	5.0	8.5	5.2	5.1	7.6
0.5	1.0	1.5	1.5	7.4	5.8	9.8	6.2	5.4	9.0
1.0	1.0	0.5	0.5	4.8	5.4	7.3	4.5	5.4	7.1
1.0	1.0	1.0	1.0	3.6	5.0	7.9	4.0	5.2	8.0
1.0	1.0	1.5	1.5	4.2	6.0	7.6	5.2	5.4	7.3

Table 2
Empirical powers of the proposed test procedure

Parameters				$n_1 = n_2 = 50$		$n_1 = n_2 = 100$	
β	θ	α_1	α_2	NPTU	PLRT	NPTU	PLRT
0.5	1.5	0.5	0.5	10.3	10.6	15.0	18.6
0.5	1.5	1.0	1.0	17.4	22.4	28.6	41.4
0.5	1.5	1.5	1.5	27.5	35.3	42.8	53.5
0.5	2.0	0.5	0.5	22.5	26.6	42.4	43.9
0.5	2.0	1.0	1.0	48.1	60.4	77.2	88.0
0.5	2.0	1.5	1.5	61.8	75.1	90.8	95.7
0.5	3.0	0.5	0.5	48.9	54.2	83.6	88.2
0.5	3.0	1.0	1.0	89.4	94.3	100.0	100.0
0.5	3.0	1.5	1.5	97.2	100.0	100.0	100.0
1.0	1.5	0.5	0.5	9.2	10.6	12.6	17.1
1.0	1.5	1.0	1.0	23.0	27.5	38.0	49.8
1.0	1.5	1.5	1.5	35.4	40.3	63.7	70.4
1.0	2.0	0.5	0.5	21.4	24.6	40.1	44.4
1.0	2.0	1.0	1.0	55.3	67.2	84.0	92.3
1.0	2.0	1.5	1.5	84.6	91.2	97.6	100.0
1.0	3.0	0.5	0.5	44.8	51.4	81.1	87.6
1.0	3.0	1.0	1.0	94.0	95.6	100.0	100.0
1.0	3.0	1.5	1.5	99.8	100.0	100.0	100.0
1.0	2.0	0.5	1.0	59.7	73.0	86.8	96.4
1.0	2.0	1.5	0.5	35.8	99.3	55.3	100.0

hypothesis H_0 is equivalent to $\alpha_1 = \alpha_2$ and $\theta = 1$. For comparison, by assuming that the underlying true model is known, we also calculated the estimated size and power of the parametric likelihood ratio test (PLRT) for H_0 and included them in Tables 1 and 2. In addition, Table 1 gives the estimated size of the test procedure (NPT) given in Zhang et al. (2001) by assuming that the distributions of observation times are the same between the two groups. That is, $H^{(0)}(u, v) = H^{(1)}(u, v)$.

It can be seen from Tables 1 and 2 that the proposed test has reasonable size and power. Especially, its size and power are quite close to those of the parametric likelihood ratio test for most situations, which is optimal for the situations considered here. As expected, both size and power become better when the sample size increases. On the other hand, the test that ignores the difference between the distributions of observation times does not seem to have the proper size.

4. An Application

In this section, we apply the proposed method to the AIDS cohort study discussed in De Gruttola and Lagakos (1989) and Kim et al. (1991). The study consists of 257 individuals with Type A or B hemophilia who were at risk for HIV infection through the contaminated blood factor they received for their treatment. The subjects were classified into two groups, lightly and heavily treated groups,

according to the amount of blood they received. By the end of the study (1988), 197 patients were confirmed as infected with HIV, and among them 25 were found infected at the time of their first blood tests. Since HIV infection status was determined through periodic blood tests, only interval-censored HIV infection times were observed for most patients. One objective of the study was to compare the HIV infection rates between the two groups.

To apply the proposed approach to test if survival functions of the time to HIV infection between the two treatment groups are identical, we first check if the distributions of censoring intervals are the same. For this, we obtained empirical estimates of the joint distributions $H^{(0)}(u, v)$ and $H^{(1)}(u, v)$ based on subjects within each treatment separately and display them in Fig. 1. It seems from the figure that the two distributions are quite different and this suggests that the proposed test procedure should be used. Also, we obtained smooth estimates of the four marginal density functions for checking condition (2) and plotted the two ratio estimates. The plot indicated that the condition seems reasonable.

The application of the proposed test gave $T_{\eta=1} = 3.603$, yielding a p-value of <0.001. The result indicates that the patients in the two different groups had significantly different risk to become HIV infected. To confirm this, Fig. 2 presents the nonparametric estimators $\widehat{F}_0$ and $\widehat{F}_1$ used in the test statistic of the distribution functions of time to HIV infection for patients in the two groups. It seems to be consistent with the result given by the test procedure.

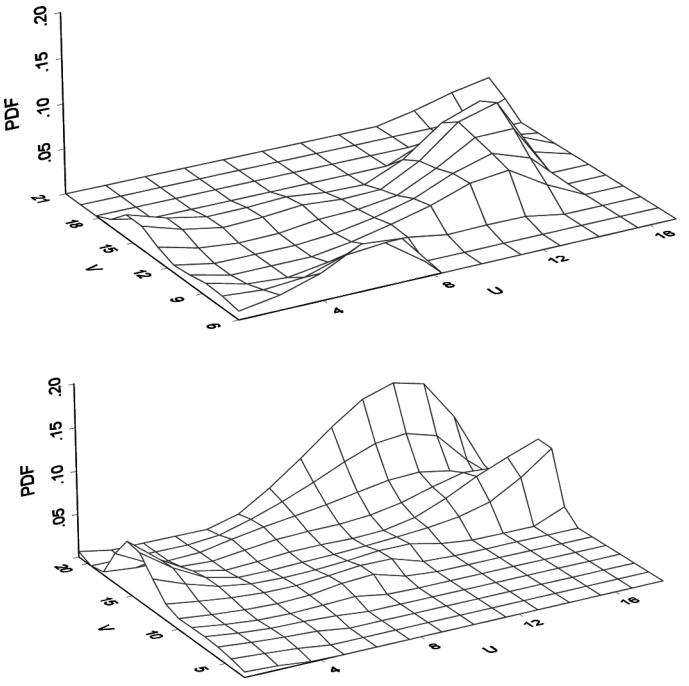

Figure 1. Joint empirical distributions of observation times for the AIDS cohort study: top – heavily treated group; bottom – lightly treated group.

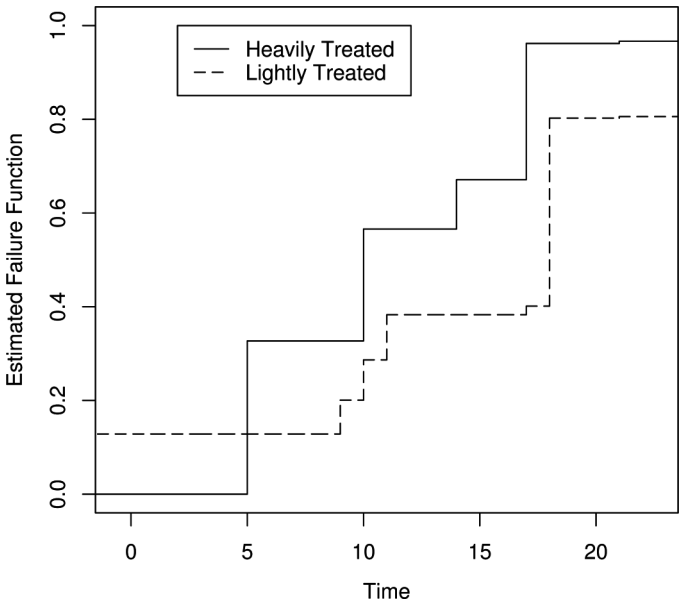

Figure 2. Nonparametric estimators of the distribution functions of time to HIV infection for the AIDS cohort study.

5. Concluding Remarks

In the preceding sections, a class of test statistics was proposed for two-sample survival comparison based on interval-censored failure time data. The key advantage of the approach over existing test procedures is that it allows different distributions of censoring intervals or observation times between two treatment groups, which often occurs in practice. Failure to take into account such differences in treatment comparison can either underestimate or overestimate treatment difference (Sun, 1999). The simulation results suggest that the presented approach works reasonably well for practical situations.

A limitation of the approach presented in the previous sections is condition (2). As discussed before, it requires that the difference or relationship between observation times is same from one group to the other or from the first observation time to the second observation time, and this is the case for many controlled medical studies. Without condition (2), the test statistic Q could be biased and one needs to adjust for the resulting bias in order to apply the procedure.

In constructing the test statistic Q, it is easy to see that the functional $g(F)$ can be equivalently defined as

$$\iint_{0\le u\le v\le \tau} \{F(u)\eta(u) + F(v)\eta(v)\} dH^{(0)}(u, v).$$

In the development of the test procedure given above, as an alternative, one may use the maximum likelihood estimators of F_0 and F_1 based on observed interval-censored data instead of $\widehat{F}_0$ and $\widehat{F}_1$. As commented before, one disadvantage of this approach is that the maximum likelihood estimators do not have closed forms, which would make the implementation of the test procedure much harder.

Also, the derivation of asymptotic distribution of the resulting test statistics is not easy to obtain (Zhang et al., 2001). Of course, one advantage of such test procedures is that they may be more efficient. However, the efficiency gain may not be significant based on the simulated results given in Sec. 3.

This article discussed the situation where the distributions of censoring intervals or observation times may differ between two treatment groups, but the observation times are independent of the survival time of interest. A more complicated situation that may occur in practice is that the observation times and the survival time of interest are correlated. In this case, for treatment comparison based on interval-censored data, a different test procedure would be needed that can take into account the correlation.

Appendix

Proof of Theorem 2.1. To prove the asymptotic normality of Q, first note that under H_0, we can rewritten it as

$$Q = \left(\frac{n}{n_0}\right)^{1/2} Q_0 - \left(\frac{n}{n_1}\right)^{1/2} Q_1,$$

where

$$Q_0 = n_0^{1/2}\{g(\widehat{F}_0) - g(F_0)\}$$

and

$$Q_1 = n_1^{1/2}\{g(\widehat{F}_1) - g(F_1)\}.$$

Thus, it is sufficient to show that Q_0 and Q_1 converge in distribution to independent normal random variables with mean zero and variances A_0 and A_1, respectively.

Define $S_l = \{i : z_i = l\}$, $l = 0, 1$. For Q_1, following the proof of Theorem 1 of Zhang et al. (2001), it can be easily shown that we have

$$Q_1 = U_1 + o_p(1),$$

where

$$U_1 = n_1^{-1/2} \sum_{i \in S_1} \{[\delta_{1i} - F_1(u_i)]\eta(u_i) + [\delta_{1i} + \delta_{2i} - F_1(v_i)]\eta(v_i)\},$$

which clearly has an asymptotic normal distribution with mean zero and variance A_1.

For Q_0, under condition (2), we have

$$\begin{aligned} Q_0 &= n_0^{1/2} \int_0^\tau \{[\widehat{F}_0(u) - F_0(u)]\eta(u) dH_1^{(1)}(u) + [\widehat{F}_0(v) - F_0(v)]\eta(v)\, dH_2^{(1)}(v)\} \\ &= n_0^{1/2} \int_0^\tau \left\{[\widehat{F}_0(u) - F_0(u)]\eta(u) \frac{h_1^{(1)}(u)}{h_1^{(0)}(u)}\, dH_1^{(0)}(u) \right. \\ &\qquad \left. + [\widehat{F}_0(v) - F_0(v)]\eta(v) \frac{h_2^{(1)}(v)}{h_2^{(0)}(v)} dH_2^{(0)}(v)\right\} \end{aligned}$$

$$= n_0^{1/2} \iint_{0 \le u \le v \le \tau} \{[\widehat{F}_0(u) - F_0(u)]\eta(u)R(u)dH_1^{(0)}(u) + [\widehat{F}_0(v) - F_0(v)]\eta(v)R(v)dH_2^{(0)}(v)\}$$

$$= n_0^{1/2} \iint_{0 \le u \le v \le \tau} \{[\widehat{F}_0(u) - F_0(u)]\xi(u) + [\widehat{F}_0(v) - F_0(v)]\xi(v)\}dH^{(0)}(u, v).$$

Then as Q_1, we have that

$$Q_0 = U_0 + o_p(1),$$

where

$$U_0 = n_0^{-1/2} \sum_{i \in S_0} \{[\delta_{1i} - F_0(u_i)]\xi(u_i) + [\delta_{1i} + \delta_{2i} - F_0(v_i)]\xi(v_i)\},$$

which obviously has an asymptotic normal distribution with mean zero and variance A_0. It is apparent that U_0 and U_1 are independent and this completes the proof.

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