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A GENERAL CLASS OF FUNCTION-INDEXED NONPARAMETRIC TESTS FOR SURVIVAL ANALYSIS[1]

BY CHIN-YU LIN AND MICHAEL R. KOSOROK

University of Alabama at Birmingham and University of Wisconsin, Madison

Many of the popular nonparametric test statistics for censored survival data used in two-sample, k-sample trend and continuous covariate situations are special cases of a general statistic, differing only in the choice of the covariate-based label and the weight function. A weight function determines the asymptotic efficiency of its corresponding statistic in this general class. Since the true alternatives are often unknown, we may not be able to foresee which weight function is the best for a particular data set. We show in this paper that certain large families of these statistics form stochastic processes, doubly indexed by both the weight function and the time scale, which converge weakly to Gaussian processes also indexed by both the weight function and the time scale. These asymptotic properties allow development of versatile test procedures which are simultaneously sensitive to a reasonably large collection of alternatives. Due to the complexity of the Gaussian processes, a Monte Carlo approach is proposed to obtain the distributional characteristics of these statistics under the null hypothesis.

1. Introduction. In clinical studies involving time-to-event outcomes, how to select a statistic sensitive to a variety of treatment effects is of great concern. Many popular nonparametric two-sample test statistics such as the log-rank, Peto and Peto (1972) and Gehan–Wilcoxon [Gehan (1965)] statistics have been shown to be special cases of two-sample weighted log-rank statistics, differing only in the choice of weight function [Tarone and Ware (1977), Gill (1980)]. A poorly chosen weight function can result in less sensitivity to the actual observed treatment effects. Consider, for example, the $G^{\rho,\gamma}$ family of statistics proposed by Fleming and Harrington [(1991), Definition 7.2.1] which are weighted log-rank statistics with weights of the form $\{\hat{S}_p(t-)\}^{\rho}\{1-\hat{S}_p(t-)\}^{\gamma}$, where $\hat{S}_p(t-)$ is the left-continuous Kaplan–Meier estimate based on the pooled survival data. Kosorok and Lin (1999) observe in the β-Blocker Heart Attack Trial (BHAT) that the beneficial effect of propranolol

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hydrochloride on patients having at least one episode of myocardial infarction can be detected with the $G^{20,0}$ weighted log-rank statistic at a much earlier calendar time than with the log-rank ($G^{0,0}$) statistic, where the log-rank was the statistic originally chosen by the investigators [β-Blocker Heart Attack Trial Research Group (1982)]. To resolve difficulties like this, test procedures sensitive to a range of alternatives have been developed [Bose and Slud (1995), Fleming and Harrington (1991), Fleming, Harrington, and O'Sullivan (1987), Gastwirth (1985), Kosorok (1998), Tarone (1981)].

Although we usually cannot foresee the true alternative hypothesis, we may be able to select a collection of possible alternatives of interest. For any given weight satisfying mild regularity conditions, there exists a contiguous alternative hypothesis for which the corresponding weighted log-rank statistic has maximum asymptotic relative efficiency (ARE) over all other weighted log-rank tests. Based on this property, we can conversely obtain a collection of most efficient weights corresponding to any given collection of alternatives. Tarone (1981) and Fleming and Harrington [(1991), Chapter 7] suggested selecting a finite number of relevant contiguous alternatives and then using the maximum of the corresponding collection of maximum ARE weighted log-rank statistics as the test statistic. Gastwirth (1985) proposed a similar idea; however, instead of taking the maximum, he used the linear combination of the same collection of statistics which maximized the minimum ARE over the set of alternatives. This maximin efficiency-robust test (MERT) procedure can be applied to certain infinite collections of alternatives and has been demonstrated to be the minimax hypothesis test within an action space of score-test statistics with loss function equivalent to the asymptotic power [Bose and Slud (1995)]. For stochastic ordering alternatives with crossing hazards, Fleming, Harrington and O'Sullivan (1987) recommended a Renyi-type statistic which takes the supremum over time of the weighted log-rank statistics.

Two-sample weighted log-rank statistics can be formulated as integrated, weighted differences of the estimated intensity processes from the two samples, with weights composed of nonnegative bounded predictable processes of bounded variation. Kosorok (1998) proposed a "function-indexing" scheme which considers these stochastic processes as being doubly indexed by both the weight function and the time scale, and then he showed that these processes jointly converge weakly over time and over all weight functions in a usefully large compact set. This result allows us to develop more efficient testing procedures and offers us greater flexibility in selecting the collection of the weighted log-rank statistics over the Tarone, Fleming and Harrington or MERT approaches. Kosorok also showed that the MERT and Renyi-type approaches are special cases of the function-indexing approach.

In the BHAT study mentioned earlier, we may be interested in knowing the impact of weight, hypertension and/or cigarette smoking on survival rates after adjusting for treatment effect in order to develop interventions for prolonging patients' lives. The previously described class of statistics cannot let us do this, nor do they permit us to investigate the differences in survival rates for multiple treatment groups. Jones and Crowley (1989, 1990) proposed a class of single-covariate nonparametric tests for right-censored survival data that includes the Tarone and Ware (1977) two-sample class, the Cox (1972) score test, the Tarone (1975) k-sample trend statistics, the Brown, Hollander, and Korwar (1974) modification of the Kendall rank statistic, the Prentice (1978) linear rank statistics and the logit rank statistic of O'Brien (1978) as special cases. Certain large families of these statistics form stochastic processes doubly indexed by both the weight function and the time scale. We will in this paper generalize these single-covariate processes to allow for multiple covariates, and utilize the "function-indexing" scheme proposed in Kosorok (1998) to establish their weak convergence over a useful function space and over the time scale. This class of statistics can be applied to address the BHAT intervention question raised above. It includes the class of Kosorok (1998) as a special case and also shares the merits of the function-indexing scheme: flexibility in choosing the collection of weight functions and the potential to develop efficient versatile test procedures.

The formulation of multicovariate nonparametric tests as well as hypotheses of interest are given in Sections 2.1 and 2.2, respectively. In Section 2.3, we propose two test procedures which are simultaneously sensitive to ordered hazard and stochastic ordering alternatives for applying to the data analysis setting. The main weak convergence results for these statistics are then given in Section 3. In Section 4, we propose a Monte Carlo approach to obtain the P-values of the newly proposed test procedures. These newly proposed methods are then applied to analyze the β-Blocker Heart Attack Trial data in Section 5, and a brief discussion is given in Section 6.

2. Function-indexed stochastic processes. We will introduce the general class of nonparametric tests mentioned above, describe the hypotheses of interest and propose test statistics for application to data analysis settings in this section.

2.1. *The class of nonparametric tests.* For a sample of survival data of size n, let T_j and C_j represent the times to failure and censoring, respectively, and let $Z_j(t)$ be the covariates measured at time t for individual j. Define the observed failure counting process

$$N_j(t) = I_{\{T_j \wedge C_j \le t,\ \delta_j = 1\}}$$

and the at-risk process

$$Y_j(t) = I_{\{T_j \wedge C_j \ge t\}},$$

where I is the indicator function and $j = 1, \dots, n$. Let

$$\overline{N}(t) = \sum_{j=1}^{n} N_j(t) \quad \text{and} \quad \overline{Y}(t) = \sum_{j=1}^{n} Y_j(t).$$

We will work only under the general random censorship model, that is,

$$P\{T \in [t, t+\Delta t),\ C \in [t, t+\Delta t) | \underline{Z}(t)\}$$
$$= P\{T \in [t, t+\Delta t) | \underline{Z}(t)\} P\{C \in [t, t+\Delta t) | \underline{Z}(t)\},$$

where $\underline{Z}(t) = \{Z(s)\colon 0 \le s \le t\}$.

Denote the cumulative hazard by Λ and allow it to depend on n. Throughout, the covariate is assumed to be well constructed so that the jth individual's hazard at time t is a function of $Z_j(t)$, that is, $d\Lambda_j(t) = d\Lambda(t|\underline{Z}_j(t)) = d\Lambda(t|Z_j(t))$. Under the above assumptions and certain regularity conditions, Dolivo (1974) showed that

$$M_j(t) = N_j(t) - \int_0^t Y_j(s)\, d\Lambda_j(s) \tag{2.1}$$

are square integrable martingales over $[0, \infty)$ with predictable covariation

$$\langle M_i, M_j \rangle(t) = I_{\{i=j\}} \int_0^t Y_j(s) \left[1 - \Delta\Lambda_j(s)\right] d\Lambda_j(s), \tag{2.2}$$

where $\Delta\Lambda_j(s) = \Lambda_j(s) - \Lambda_j(s-)$.

Jones and Crowley (1989) proposed a class of single-covariate nonparametric tests

$$X^n(t) = n^{-1/2} \int_0^t w(s) \sum_{j=1}^n Y_j(s)\left[Z_j(s) - \overline{Z}(s)\right] dN_j(s), \tag{2.3}$$

where $w(s)$ is a locally bounded, predictable weight function, and $\overline{Z}(s) = \overline{Y}^{-1}(s)\Sigma Y_j(s) Z_j(s)$. By "predictable," we mean predictable with respect to the filtration $\mathscr{F}^n \equiv \{\mathscr{F}_t^n,\ t \ge 0\}$, where

$$\mathscr{F}_t^n = \sigma\left\{N_j(s),\ Y_j(s+),\ Z_j(s+),\ j = 1 \cdots n,\ s \le t\right\}, \tag{2.4}$$

are the histories of the study up to and including time t, and where $\sigma\{A\}$ is the smallest σ-field making all of A measurable. This statistic requires no further assumptions on the hazard rates and will be large if the failure mechanism favors large values of the covariates. They showed that the X^n, specified by particular choices of covariates and weight functions, are equivalent to several well-known test statistics. For example, if the Z_j are either 0 or 1 (group indicator), then the X^n are two-sample weighted log-rank statistics. They also proposed a variance estimator for $X^n(t)$,

$$\begin{aligned} V^n(t) = n^{-1} \int_0^t w^2(s) \sum_{j=1}^n Y_j(s)\left[Z_j(s) - \overline{Z}(s)\right]^2 \\ \times \frac{\overline{Y}(s) - \Delta\overline{N}(s)}{\overline{Y}(s) - 1} \frac{d\overline{N}(s)}{\overline{Y}(s)}, \end{aligned} \tag{2.5}$$

where $\Delta\overline{N}(s) = \overline{N}(s) - \overline{N}(s-)$.

We generalize Jones and Crowley's single-covariate statistics to accommodate the multiple-covariate situation. Suppose p covariates are obtained from each subject. Let the covariate vector of the jth subject be $\mathbf{Z}_j(t) =$

$\{Z_{j1}(t), \dots, Z_{jp}(t)\}^T$, $j = 1, \dots, n$, where superscript T denotes transpose, and define statistics $\mathbf{X}^n(\mathbf{f}, t) = \{X_1^n(\mathbf{f}, t), \dots, X_p^n(\mathbf{f}, t)\}^T$ with the kth element

$$X_k^n(\mathbf{f}, t) = n^{-1/2} \int_0^t f_k\{\mathbf{b}^n(s)\} \sum_{j=1}^n Y_j(s)\big[Z_{jk}(s) - \bar{Z}_k(s)\big]\, dN_j(s), \tag{2.6}$$

where $\bar{Z}_k(s) = \bar{Y}^{-1}(s)\Sigma Y_j(s) Z_{jk}(s)$; $\mathbf{f} = [f_1, \dots, f_p]^T$ is the "function-index," where f_k: $[0,1]^r \mapsto [0,1]$ is an element of a function space having certain compactness and continuity properties (e.g., having square-integrable derivatives); $t \in [0, \infty]$, and $\mathbf{b}^n(s) = \{b_1^n(s), \dots, b_r^n(s)\}^T$, where b_i^n: $[0, \infty) \mapsto [0,1]$ are $\mathscr{F}^n$-predictable processes, $i = 1, \dots, r$ and r is finite. The sequence $\{\mathbf{b}^n,\ n \geq 1\}$ needs to converge in probability to a constant function $\mathbf{b}$. Notice that we allow the statistics X_k^n, $k = 1, \dots, p$ to have different weight functions since the associations between different covariates and survival rates may be different. Examples of weight function spaces that fit these criteria are:

1. The Tarone–Ware weights $\{\bar{Y}(s)/n\}^{\rho}$, where $\bar{Y}(s)/n$ is the pooled at-risk estimator, $\rho \in \{0\} \cup [\varepsilon, \tau]$, $0 < \varepsilon \leq \tau < \infty$ and $s \in [0, \infty]$. Note that $\rho = 0$ and $\rho = 1$ correspond to the log-rank and the Gehan–Wilcoxon [Gehan (1965)] weights.
2. The $G^{\rho, \gamma}$ weights $\{\hat{S}_p(s-)\}^{\rho}\{1 - \hat{S}_p(s-)\}^{\gamma}$ defined in Fleming and Harrington (1991), where $\hat{S}_p(s)$ is the pooled Kaplan–Meier estimator, $\rho \in \{0\} \cup [\varepsilon_1, \tau_1]$, $\gamma \in \{0\} \cup \{\varepsilon_2, \tau_2]$, and $0 < \varepsilon_i \leq \tau_i < \infty$, $i = 1, 2$. When $\gamma = 0$, this family reduces to the G^{ρ} weights introduced by Harrington and Fleming (1982), and $\rho = 0$ and $\rho = 1$ correspond to the log-rank and the Prentice–Wilcoxon [Prentice (1978)] weights, respectively.

Denote $\mathbf{V}_{\mathbf{fg}}^n(s, t)$ to be the estimator of the covariance of $\mathbf{X}^n(\mathbf{f}, s)$ and $\mathbf{X}^n(\mathbf{g}, t)$ of the form

$$\begin{aligned} \mathbf{V}_{\mathbf{fg}}^n(s, t) = n^{-1} \int_0^{s \wedge t} \mathbf{f}\{\mathbf{b}^n(x)\} \mathbf{g}^T\{\mathbf{b}^n(x)\} \sum_{j=1}^n Y_j(x)\big[\mathbf{Z}_j(x) - \bar{\mathbf{Z}}(x)\big] \\ \times \big[\mathbf{Z}_j(x) - \bar{\mathbf{Z}}(x)\big]^T \frac{\bar{Y}(x) - \Delta \bar{N}(x)}{\bar{Y}(x) - 1} \frac{d\bar{N}(x)}{\bar{Y}(x)}, \end{aligned} \tag{2.7}$$

where $s, t \in [0, \infty]$. We will show in Section 3 that the function-indexed process $\mathbf{X}^n$ converges weakly to a Gaussian process over $[0, \infty] \times \mathbf{H}$ and that the covariance estimator $\mathbf{V}^n$ is uniformly consistent.

2.2. *Hypotheses of interest*. The asymptotic properties of the function-indexed processes are developed under both the null and the following alternative hypotheses. Let $\mathscr{Z}$ represent the space of potential covariate paths or some subspace of it. All the processes in $\mathscr{Z}$ are assumed to be adapted, bounded and left continuous with right-hand limits without loss of practical generality. Let Λ_z denote the cumulative hazard for the path $z \in \mathscr{Z}$.

We are interested in testing the null hypothesis H_0: $\Lambda_z^n = \Lambda$ over $[0, \infty)$ for all $z \in \mathscr{Z}$, against the proportional odds contiguous alternatives of the form

$$(2.8)\qquad d\Lambda^n(t|z(t)) = \frac{\exp\left[\left(\beta^T z(t)/\sqrt{n}\right)g(t)\right]\, d\Lambda(t)}{1 + \left(\exp\left[\left(\beta^T z(t)/\sqrt{n}\right)g(t)\right] - 1\right)\Delta\Lambda(t)},$$

for some finite $\boldsymbol{\beta} = [\beta_1, \dots, \beta_p]^T$, some baseline hazard $\Lambda(t)$ and some real function g such that g is bounded by $G < \infty$. Note that (2.8) becomes the proportional hazards contiguous alternative model when the baseline hazard is continuous and becomes the null hypothesis when $\boldsymbol{\beta} = \mathbf{0}$.

2.3. *Test procedures*. The joint weak convergence of the function-indexed stochastic processes permits us to develop efficient versatile test procedures. We here propose two test statistics for application to data analysis settings.

Define $\mathscr{C}$ to be collections of standardized statistics

$$(2.9)\qquad \mathscr{C} = \left\{\mathbf{W}^n(\mathbf{f}, t) \equiv \left[\mathbf{V}_{\mathbf{ff}}^n(\infty, \infty)\right]^{-1/2}\mathbf{X}^n(\mathbf{f}, t),\ t \in [0, \infty],\ \mathbf{f} \in \mathbf{H}\right\},$$

where $\mathbf{H}$ is a chosen compact index set. We will show in Section 3 that $\mathbf{W}^n$ converges weakly to a multivariate Gaussian process. The test procedures we propose are

$$(2.10)\qquad \sup_{\mathbf{f}\in\mathbf{H}}\left[\mathbf{W}^n(\mathbf{f}, \infty)\right]^T\left[\mathbf{W}^n(\mathbf{f}, \infty)\right] \quad \text{and} \quad \sup_{\mathbf{f}\in\mathbf{H}}\ \sup_{t\in[0,\infty]}\ \left[\mathbf{W}^n(\mathbf{f}, t)\right]^T\left[\mathbf{W}^n(\mathbf{f}, t)\right].$$

Note that if $\mathbf{f} \equiv 1$ and $\mathbf{H} \equiv \{\mathbf{1}\}$, the first statistic is the Cox score statistic to test whether $\boldsymbol{\beta} = \mathbf{0}$ in the proportional hazard model,

$$\lambda(t) = \lambda_0(t)\exp(\boldsymbol{\beta}'\mathbf{Z}).$$

These newly proposed statistics should be sensitive to both the ordered hazard and the stochastic ordering alternatives since the supremum-over-function-space statistics give sensitivity to broad ordered hazards alternatives and the supremum-over-time statistics to stochastic ordering alternatives. Kosorok and Lin (1999) studied the size and power properties of these two statistics under the two-sample weighted log-rank statistics setting utilizing $G^{\rho,\gamma}$-weights. The performance of these two statistics appeared to be adequate when there were no differences between the two survival curves. For ordered hazards alternatives with early differences, the first statistic with index set $(\rho, \gamma) \in [0, 4] \times [0, 1]$ performs very well. Both statistics with the same index set also do well for ordered hazards alternatives with either early or late difference, for stochastic ordering alternatives and for stochastic crossing alternatives. See Kosorok and Lin (1999) for details.

Because of the complexity of the Gaussian processes, we generally are not able to obtain the P-values of these statistics through analytical means. Therefore, a Monte Carlo approach is proposed in Section 4 to simulate the null distribution of the processes $\mathbf{W}^n$ and thereby estimate the P-values of these statistics.

3. Main weak convergence results. Before giving the main result, we need to introduce several concepts and definitions.

Clearly, $\mathbf{X}^n$ is a stochastic process on $\mathbf{H} \times (\mathbf{D}[0,\infty])^p$, where $\mathbf{D}[0,\infty]$ is the space of all right-continuous real functions on $[0,\infty]$ with left-hand limits such that their limits at ∞ exist. In order to resolve measurability problems in the nonseparable metric space on $(\mathbf{D}[0,\infty])^p$ endowed with the uniform metric, we will utilize Hoffman–Jørgensen–Dudley (HJD) weak convergence theory as described in van der Vaart and Wellner (1996). The corresponding theorems for stochastic processes defined on the complete, Borel measurable metric space on $(\mathbf{D}[0,\infty])^p$ endowed with the Skorohod metric are given in Lin (1998). For the weak convergence of $\mathbf{X}^n$, we will use the uniform topology on the space $\mathbf{A}(\mathbf{H}, (\mathbf{D}[0,\infty])^p)$; where for metric spaces $\{H, \rho\}$ and $\{G, \gamma\}$, $\mathbf{A}(H, G)$ is the metric space of continuous mappings $H \mapsto G$ endowed with the metric

$$a(x, y) = \sup_{f \in H} \gamma(x(f), y(f)),$$

where $\{A, a\}$ denotes the metric space defined on A endowed with the metric a. In our setting, $H = \mathbf{H}$, $G = (\mathbf{D}[0,\infty])^p$, $h = \rho$, where ρ is the uniform metric on $\mathbf{H}$, and $\gamma = d$, where d is defined as follows: for $\mathbf{u} \equiv \{u_1, \ldots, u_p\}$ and $\mathbf{v} \equiv \{v_1, \ldots, v_p\}$ in $(\mathbf{D}[0,\infty])^p$, $d(\mathbf{u}, \mathbf{v}) \equiv \max_{1 \le k \le p} d_u(u_k, v_k)$, where d_u is a bounded version of the uniform metric on $\mathbf{D}[0,\infty]$. Also define $\mathscr{D}$ to be the Borel σ-field of $\{(\mathbf{D}[0,\infty])^p, d\}$ and let $\mathscr{D}^*$ be the Borel σ-field of the product metric space $\{\mathbf{D}[0,\infty], d_s\}^p$, where d_s is a complete and bounded version of the Skorohod metric on $\mathbf{D}[0,\infty]$.

We also require that the function space $\mathbf{H}$ of weight indices to be the Cartesian product of p sets which are either equal to or closed subsets of $\mathbf{G}_r^+(K)$ (defined below) for some $K < \infty$. Before defining $\mathbf{G}_r^+(K)$, we need to introduce some additional notation. Let N_1^r be the set of all multiindexes $\boldsymbol{\alpha} = \{\alpha_1, \ldots, \alpha_r\}$, where α_l is either 0 or 1, $l = 1, \ldots, r$ and define the first cross-partial derivative linear operator

$$D_0^{\boldsymbol{\alpha}} \equiv \prod_{l=1}^{r} \left(\frac{\partial}{\partial x_l} \right)^{\alpha_l},$$

evaluated at $\mathbf{y} = \{y_1, \ldots, y_r\}^T$, where $y_l = \alpha_l x_l$, $l = 1 \ldots r$. For each f: $[0,1]^r \mapsto [0,1]$, also define

$$\|f\|_*^r \equiv \left(\sum_{\boldsymbol{\alpha} \in N_1^r} \int_{[\mathbf{0},\mathbf{1}]} \left[D_0^{\boldsymbol{\alpha}} f(\mathbf{s}) \right]^2 d\mathbf{s} \right)^{1/2},$$

where $[\mathbf{0}, \mathbf{1}] = [0,1]^r$ and $\mathbf{s} = \{s_1, \ldots, s_r\}^T$.

DEFINITION 1. Let $\mathbf{G}_r^+(K)$ denote the space of bounded, absolutely continuous functions f mapping from $[0,1]^r$ to $[0,1]$ for which all first cross-partial derivatives are square integrable and their total L_2-norms are bounded by K, in the sense that $\|f - f(\mathbf{0})\|_*^r \le K$.

Now we present the main result.

THEOREM 1. *Assume the statistic* $\mathbf{X}^n$ *has the form given in* (2.6). *Also assume* $\mathbf{f}$ *is restricted to the set* $\mathbf{H}$, *where* $\mathbf{H}$ *is the Cartesian product of* $\mathbf{H}_1, \dots, \mathbf{H}_p$, *and* $\mathbf{H}_k$ *is either equal to or a closed subset of* $\mathbf{G}_{\mathbf{r}}^{+}(K_k)$ *for some* $K_k < \infty$, $k = 1, \dots, p$. *Under the general random censorship model and the "contiguous alternative" sequence* (2.8), *suppose the following conditions also hold*:

(i) *There exists a function* $\pi\colon [0,\infty) \mapsto [0,1]$ *such that*

$$\sup_{t \in [0,\infty)} \left| \frac{\overline{Y}(t)}{n} - \pi(t) \right| \to_P 0 \quad \text{as } n \to \infty.$$

(ii) *The covariate processes are adapted, uniformly bounded and left continuous with right-hand limits.*

(iii) *Set* $\mathscr{I} = \sup\{t\colon \pi(t) > 0\}$ *and* $u_0 = \sup \mathscr{I}$. *For any* $t \in \mathscr{I}$, *there exist left-continuous functions* v_{kl}, $k, l = 1, \dots, p$, *with right-hand limits such that for all* $t \in \mathscr{I}$,

$$\sup_{s \in [0,t]} \left| \frac{1}{\overline{Y}(s)} \sum_{j=1}^{n} Y_j(s) \big[Z_{jk}(s) - \overline{Z}_k(s) \big] \big[Z_{jl}(s) - \overline{Z}_l(s) \big] - v_{kl}(s) \right| \to_P 0$$

and $v_{kl}(s)$ *are zero outside of* $\mathscr{I}$.

(iv) *For* $i = 1 \dots r$, *each* $b_i^n\colon [0,\infty) \mapsto [0,1]$ *is* $\mathscr{F}^n$*-predictable and, for each closed subinterval of* $\mathscr{I}$, $\mathscr{I}^* \subset \mathscr{I}$, *the following holds*:

$$\sup_{s \in \mathscr{I}^*} |b_i^n(s) - b_i(s)| \to_P 0$$

as $n \to \infty$, *for some deterministic* $b_i\colon [0,\infty) \mapsto [0,1]$, *where* b_i *is left continuous with right-hand limits, and* $db_i^+(t)$, *with* b_i^+ *being the right-continuous version of* b_i, *changes sign only a finite number of times over* $[0,\infty)$.

Then:

(a) $\mathbf{X}^n(\cdot,\cdot)$ *converges HJD-weakly in the uniform topology on* $\mathbf{A}(\mathbf{H}, (\mathbf{D}[0,\infty])^p)$ *to a multivariate Gaussian process* $\mathbf{X}(\cdot,\cdot)$ *with mean function*

$$\boldsymbol{\mu}(\mathbf{f}, t) = \int_0^t \operatorname{diag}[\mathbf{f}\{\mathbf{b}(s)\}][\mathbf{v}(s)\boldsymbol{\beta}] g(s)\, d\Lambda(s) \tag{3.1}$$

and covariance function

$$\mathbf{V}_{\mathbf{fg}}(s,t) = \int_0^{s \wedge t} \mathbf{f}\{\mathbf{b}(x)\} \mathbf{g}^T\{\mathbf{b}(x)\} \mathbf{v}(x) \pi(x) [1 - \Delta\Lambda(x)]\, d\Lambda(x), \tag{3.2}$$

for all $\mathbf{f}, \mathbf{g} \in \mathbf{H}$ *and* $s, t \in [0,\infty]$, *where* $\mathbf{v}$ *is a* $p \times p$ *matrix with* (k,l)*th element* v_{kl}.

(b) *The covariance estimators* $\mathbf{V}^n_{\mathbf{fg}}(\cdot,\cdot)$ *defined in* (2.7) *and* $\tilde{\mathbf{V}}^n_{\mathbf{fg}}(\cdot,\cdot)$ *defined as*

$$\begin{aligned}\tilde{\mathbf{V}}^n_{\mathbf{fg}}(s,t) = n^{-1}\int_0^{s\wedge t}\mathbf{f}\{\mathbf{b}^n(x)\}\mathbf{g}^T\{\mathbf{b}^n(x)\}\sum_{j=1}^n Y_j(x)\big[\mathbf{Z}_j(x)-\overline{\mathbf{Z}}(x)\big]\\ \times\big[\mathbf{Z}_j(x)-\overline{\mathbf{Z}}(x)\big]^T\frac{\overline{Y}(x)-\Delta\overline{N}(x)}{\overline{Y}(x)-1}dN_j(x)\end{aligned} \tag{3.3}$$

are uniformly consistent for $\mathbf{V}_{\mathbf{fg}}$ *over all* $\mathbf{f},\mathbf{g}\in\mathbf{H}$ *and all* $s,t\in[0,\infty]$.

(c) *Provided that* $\inf_{\mathbf{f}\in\mathbf{H}}\mathbf{c}^T\mathbf{V}_{\mathbf{f},\mathbf{f}}(\infty,\infty)\mathbf{c}>0$ *for every nonzero* $\mathbf{c}\in\Re^p$, *then* $[\mathbf{V}^n_{\mathbf{ff}}(\infty,\infty)]^{-1/2}\mathbf{X}^n(\mathbf{f},t)$ *converges HJD-weakly in the uniform topology on* $\mathbf{A}(\mathbf{H},(\mathbf{D}[0,\infty])^p)$ *to* $\mathbf{V}_{\mathbf{ff}}^{-1/2}(\infty,\infty)\mathbf{X}(\mathbf{f},t)$.

REMARK 1. (i) The unusual changes-of-sign restriction in condition (iv) will be needed later in the proofs to insure that the total variation of $f\{\mathbf{b}^n(\cdot)\}$ for any $f\in\mathbf{G}^+_r(K)$ is finite, where $K<\infty$. Two commonly used weight functions, the left-continuous version of the pooled Kaplan–Meier estimator $\hat{S}_p(t-)$ and the pooled at-risk estimator $\hat{\pi}_p(t)=\overline{Y}(t)/n$, satisfy this condition.

(ii) Result (c) and the continuous mapping theorem establish weak convergence in the uniform topology of the test procedures described in Section 2.3 and give us confidence that we will not lose too much power while using these supreme-type statistics over a reasonable large function space $\mathbf{H}$.

(iii) Although both $\mathbf{V}^n_{\mathbf{fg}}$ and $\tilde{\mathbf{V}}^n_{\mathbf{fg}}$ are uniformly consistent for $\mathbf{V}_{\mathbf{fg}}$, for small or moderate sample size, $\mathbf{V}^n_{\mathbf{fg}}(s,t)$ tends to estimate the covariance of $\mathbf{X}^n(\mathbf{f},s)$ and $\mathbf{X}^n(\mathbf{g},t)$ more accurately, for all $\mathbf{f},\mathbf{g}\in\mathbf{H}$ and $s,t\in[0,\infty]$.

Under some regularity conditions, the above results can be generalized to the contiguous alternative sequences discussed in Jones and Crowley (1990):

$$\sup_{\mathbf{z}}\sup_{t\in[0,\infty)}|d\Lambda^n(t|\mathbf{z}(t))-d\Lambda(t)|\to 0\quad\text{as } n\to\infty. \tag{3.4}$$

COROLLARY 1. *Under the contiguous alternative submodel* (3.4), *suppose conditions* (i)–(iv) *of Theorem* 1 *obtain and for any predictable process* h^n *with* $|h^n|\le c$, $c<\infty$,

$$\sup_{1\le k\le p}E\left\{n^{-1/2}\int_0^t h^n(s)\sum_{j=1}^n Y_j(s)\big[Z_{jk}(s)-\overline{Z}_k(s)\big]\,d\Lambda^n_j\right\}^2\le C,$$

for all $n\ge 1$, $t\in[0,\infty]$, *and some* $C<\infty$. *Then*, *results* (a)–(c) *of Theorem* 1 *apply to* $\mathbf{X}^n(\cdot,\cdot)$ *except that the mean function of the limiting process* $\mathbf{X}$ *is of a different form which depends on* Λ^n_j.

The proof of this corollary, which will not be given here, follows along the lines of the proof of Theorem 1 given below.

Before giving the proof of Theorem 1, we need an additional theorem and two lemmas. The following theorem of Kosorok (1998) establishes weak convergence of stochastic processes in $\mathbf{A}(H, G)$ (defined above).

THEOREM 2. *Suppose a sequence of stochastic processes* $\{X^n(\cdot)\}$ *in* $\mathbf{A}(H, G)$, *where* $\{H, \rho\}$ *is compact and* $\{G, \gamma\}$ *is complete with Borel* σ-*field* $\mathscr{G}$, *satisfies the following conditions*:

(i) $X^n(f)$ *is a* $\mathscr{G}^*$-*measurable random variable for all* $f \in H$ *and all* $n \geq 1$, *where the* σ-*field* $\mathscr{G}^* \subset \mathscr{G}$, *and all finite-dimensional distributions of the form* $\{X^n(f_1), \dots, X^n(f_m)\}$, *for* $m < \infty$, *converge HJD-weakly on* $(\{G, \gamma\})^m$ *to some tight* $\{X(f_1), \dots, X(f_m)\}$ *as* $n \to \infty$.

(ii) $\forall f, g \in H$,

$$\gamma(X^n(f), X^n(g)) \leq q(h(f, g))Q_n,$$

where

(a) γ *is a bounded, continuous,* $\mathscr{G}^* \times \mathscr{G}^*$-*measurable mapping from* $G \times G$ *to* $[0, \infty)$;

(b) q *is continuous and nondecreasing with* $q(0) = 0$ *and*

(c) $\{Q_n\}$ *is a stochastically bounded sequence of real random variables, that is, for any* $\varepsilon > 0$, *there exists a* $\tau < \infty$ *such that* $P\{Q_n \leq \tau\} > 1 - \varepsilon$, $\forall$ $n \geq 1$.

Then $X^n(\cdot)$ *converges HJD-weakly on* $\{\mathbf{A}(H, G), a\}$ *to tight* $X(\cdot)$ *as* $n \to \infty$.

The proof is given in Kosorok (1998).

The following lemma establishes Condition (i) of Theorem 2 for the statistic $\mathbf{X}^n$.

LEMMA 1. *Under the conditions of Theorem* 1, $\mathbf{X}^n(\mathbf{f})$ *is* $\mathscr{D}^*$-*measurable for all* $\mathbf{f} \in \mathbf{H}$ *and all* $n \geq 1$, *and all finite-dimensional distributions of the form* $\{\mathbf{X}^n(\mathbf{f}_1), \dots, \mathbf{X}^n(\mathbf{f}_m)\}$, *for* $m < \infty$, *converge HJD-weakly in the uniform topology on* $(\mathbf{D}[0, \infty])^{pm}$ *to* $\{\mathbf{X}(\mathbf{f}_1), \dots, \mathbf{X}(\mathbf{f}_m)\}$ *as* $n \to \infty$, *where* $\mathbf{X}$ *is the limiting Gaussian process defined in result* (a) *of Theorem* 1.

The proof is given in the Appendix.

The following lemma is helpful in establishing Condition (ii) of Theorem 2 for the statistic $\mathbf{X}^n$.

LEMMA 2. *For each* $\mathbf{f} \in \mathbf{H}$, *where* $\mathbf{H}$ *is the Cartesian product of* $\mathbf{H}_1, \dots, \mathbf{H}_p$ *and* $\mathbf{H}_k$ *is either equal to or a closed subset of* $\mathbf{G}_r^+(K_k)$ *for some* $K_k < \infty$, $k = 1, \dots, p$, *let* $\mathbf{X}^n(\mathbf{f})$ *be a* p-*dimensional vector of stochastic processes with* k*th element*

$$X_k^n(\mathbf{f}) \equiv X_k^n(\mathbf{f}, \cdot) = \int_0^{(\cdot)} f_k\{\mathbf{b}^n(s)\}\, dU_k^n(s), \tag{3.5}$$

where $\mathbf{b}^n = \{b_1^n, \ldots, b_r^n\}^T$ *and* r *is finite. Suppose we have the following conditions for each* $n \geq 1$, *where* $\tilde{\mathscr{F}}^n = \{\tilde{\mathscr{F}}_t^n, t \geq 0\}$ *is a filtration*:

(i) *For each* $k = 1, \ldots, p$, U_k^n *is an* $\tilde{\mathscr{F}}_t^n$*-adapted process on* $[0, \infty]$ *and is right continuous with left-hand limits such that*:

(a) U_k^n *is locally of bounded variation on* $[0, \infty]$ *and* $\Delta U_k^n(0) = 0$, $\forall$ $n \geq 1$, *and*

(b) $\exists C_k < \infty$ *such that for any* $\tilde{\mathscr{F}}_t^n$*-predictable* h^n, *with* $|h^n| \leq c$, *there exists a nonnegative* $\tilde{\mathscr{F}}_t^n$*-adapted right-continuous submartingale* $G_k^n(h^n, t)$ *such that*

$$\left\{\int_0^t h^n(s)\, dU_k^n(s)\right\}^2 \leq G_k^n(h^n, t)$$

$\forall$ $t \in [0, \infty]$ *and* $E[G_k^n(h^n, u)] \leq c^2 C_k$, $\forall$ $n \geq 1$.

(ii) $\forall n \geq 1$, *each* b_j^n, *for* $1 \leq j \leq r$, *is an* $\tilde{\mathscr{F}}_t^n$*-predictable process mapping from* $[0, \infty)$ *to* $[0, 1]$.

(iii) $\mathbf{X}^n(\mathbf{f})$ *is measurable with respect to the Skorohod topology on* $(\mathbf{D}[0, \infty])^p$ *for all* $\mathbf{f} \in \mathbf{H}$ *and all* $n \geq 1$.

Then $\forall \mathbf{f}, \mathbf{g} \in \mathbf{H}$,

$$d(\mathbf{X}^n(\mathbf{f}), \mathbf{X}^n(\mathbf{g})) \leq q(\rho(\mathbf{f}, \mathbf{g}))Q_n,$$

where d, q *and* Q_n *satisfy condition* (*ii*) *of Theorem* 2 *with* $h = \rho$, $\gamma = d$, $\mathscr{G} = \mathscr{D}$ *and* $\mathscr{G}^* = \mathscr{D}^*$.

PROOF. Lemma 2 of Kosorok (1998) establishes for each $k = 1, \ldots, p$, that if $\mathbf{G}_r^+(K_k)$ is compact in the uniform metric, so is its closed subset $\mathbf{H}_k$. Therefore, the product space $\mathbf{H}$ is compact in the uniform metric $\rho(\mathbf{f}, \mathbf{g}) \equiv \max_{1 \leq k \leq p} \sup_{\mathbf{x} \in [\mathbf{0}, \mathbf{1}]} |f_k(\mathbf{x}) - g_k(\mathbf{x})|$. Theorem 2 of Kosorok (1998) demonstrates that for each $k = 1, \ldots, p$, there exists a sequence (in n) of stochastically bounded random variables $\{Q_{kn}\}$ such that $\forall \mathbf{f}, \mathbf{g} \in \mathbf{H} \cup \{\mathbf{0}\}$ and $t \in (0, \infty]$,

$$d_u(X_k^n(\mathbf{f}), X_k^n(\mathbf{g})) \leq [\rho(\mathbf{f}, \mathbf{g})]^{1/4} Q_{kn} \qquad \forall\ n \geq 1. \tag{3.6}$$

Let $Q_n = \max_{1 \leq k \leq p} Q_{kn}$. Then,

$$d(\mathbf{X}^n(\mathbf{f}), \mathbf{X}^n(\mathbf{g})) \leq [\rho(\mathbf{f}, \mathbf{g})]^{1/4} Q_n \qquad \forall\ n \geq 1, \tag{3.7}$$

and $\{Q_n\}$ is also a sequence of stochastically bounded random variables. □

PROOF OF THEOREM 1. Theorem 2 will be employed to prove this theorem. Condition (i) of Theorem 2 for $\mathbf{X}^n$ follows by Lemma 1. Now let

$$U_k^n(\cdot) = n^{-1/2} \int_0^{(\cdot)} \sum_{j=1}^n Y_j(s)\left[Z_{jk}(s) - \bar{Z}_k(s)\right] dN_j(s);$$

then

$$X_k^n(\mathbf{f}, \cdot) = \int_0^{(\cdot)} f_k\{\mathbf{b}^n(s)\}\, dU_k^n(s).$$

For each $k = 1, \ldots, p$, the processes $Y_j(Z_{jk} - \bar{Z}_k)$, $j = 1, \ldots, n$, are adapted, bounded and left continuous with right-hand limits; so is U_k^n and U_k^n is of bounded variation on $[0, \infty]$. In addition, $\Delta U_k^n(0) = 0$, $\forall$ $n \geq 1$ and $\forall$ k.

Since

$$U_k^n(t) = n^{-1/2} \int_0^t \sum_{j=1}^n Y_j(s)\big[Z_{jk}(s) - \overline{Z}_k(s)\big]\, dM_j(s)$$
$$+ n^{-1/2} \int_0^t \sum_{j=1}^n Y_j(s)\big[Z_{jk}(s) - \overline{Z}_k(s)\big]\, d\Lambda_j^n(s),$$

for any predictable h^n with $|h^n| \le c$, where $c < \infty$,

$$\begin{aligned}\left\{\int_0^t h^n\, dU_k^n\right\}^2 &\le 2\left\{n^{-1/2}\int_0^t h^n \sum_{j=1}^n Y_j\Big(Z_{jk} - \overline{Z}_k\Big)\, dM_j\right\}^2 \\ &\quad + 2\left\{n^{-1/2}\int_0^t h^n \sum_{j=1}^n Y_j\Big(Z_{jk} - \overline{Z}_k\Big)\, d\Lambda_j^n\right\}^2, \\ &\equiv G_k^n(h^n, t) \qquad \forall\, t \in [0, \infty],\end{aligned}$$

where $G_k^n(h^n, t)$ is a nonnegative right-continuous $\mathscr{F}_t^n$-submartingale, for $k = 1, \dots, p$. For the first term of $G_k^n(h^n, t)$,

$$\begin{aligned}\operatorname{Exp}&\left[n^{-1/2}\int_0^t h^n \sum_{j=1}^n Y_j\Big(Z_{jk} - \overline{Z}_k\Big)\, dM_j\right]^2 \\ &\le c^2 \operatorname{Exp}\left[n^{-1}\int_0^t \sum_{j=1}^n Y_j\Big(Z_{jk} - \overline{Z}_k\Big)^2\, d\Lambda_j^n\right] \\ &= c^2 \operatorname{Exp}\left[n^{-1}\int_0^t \sum_{j=1}^n \Big(Z_{jk} - \overline{Z}_k\Big)^2\, dN_j\right] \le c^2(2M)^2,\end{aligned}$$

for all $t \in [0, \infty]$, where $\sup_{j,k} \sup_{t \in [0,\infty)} |Z_{jk}(t)| \le M < \infty$.

Observe that if $\Lambda_j^n = \Lambda$, the second term of $G_k^n(h^n, t)$,

$$n^{-1/2}\int_0^t h^n \sum_{j=1}^n Y_j\Big(Z_{jk} - \overline{Z}_k\Big)\, d\Lambda = 0 \qquad \forall\, t \in [0, \infty].$$

Therefore, condition (i) of Lemma 2 holds under the null hypothesis. Now,

$$\begin{aligned}n^{-1/2}&\int_0^t h^n \sum_{j=1}^n Y_j\big[Z_{jk} - \overline{Z}_k\big]\, d\Lambda_j^n \\ &= n^{-1}\int_0^t h^n \sum_{j=1}^n Y_j\big[Z_{jk} - \overline{Z}_k\big]\sqrt{n}\,\big[d\Lambda_j^n - d\Lambda\big].\end{aligned}$$

Note that $x^{-1}|e^{ax} - 1| \le |a|e^{|a|}$, $\forall\ x \in (0,1]$ and any real a. Hence,

$$\begin{aligned}
&\sqrt{n}\,|d\Lambda_j^n(s) - d\Lambda(s)| \\
&\quad = \sqrt{n}\left|\exp\left[\frac{\boldsymbol{\beta}^T z(s)g(s)}{\sqrt{n}}\right] - 1\right| \\
&\qquad \times \left|1 - \frac{\exp\left[\boldsymbol{\beta}^T z(s)g(s)/\sqrt{n}\,\right]\Delta\Lambda(s)}{[1-\Delta\Lambda(s)] + \exp\left[\boldsymbol{\beta}^T z(s)g(s)/\sqrt{n}\,\right]\Delta\Lambda(s)}\right| d\Lambda(s) \\
&\quad \le 2MG\sum_{l=1}^{p}|\beta_l|\exp\left(MG\sum_{l=1}^{p}|\beta_l|\right) d\Lambda(s),
\end{aligned}$$

where G is an upper bound of the function $|g|$. Thus

$$\begin{aligned}
\operatorname{Exp}\left[n^{-1/2}\int_0^t h^n \sum_{j=1}^n Y_j\left[Z_j - \bar{Z}\right] d\Lambda_j^n\right]^2 &\le c^* \operatorname{Exp}\left[n^{-1}\int_0^t \sum_{j=1}^n Y_j\, d\Lambda\right]^2 \\
&\le c^{**} \operatorname{Exp}\left[n^{-1}\int_0^\infty \sum_{j=1}^n Y_j\, d\Lambda_j^n\right]^2 \\
&\le c^{**} \operatorname{Exp}\left[\frac{\sum_{j=1}^n \Lambda_j^n(T_j)}{n}\right]^2 \\
&\le c^{**} \operatorname{Exp}\left[\frac{\sum_{j=1}^n \left\{\Lambda_j^n(T_j)\right\}^2}{n}\right],
\end{aligned} \tag{3.8}$$

for some finite c^* and c^{**}. The third inequality follows by (2.8) and the last by the Cauchy inequality. For any failure time distribution F with corresponding survival function $S \equiv 1 - F$ and cumulative hazard Λ [defined by integrating $d\Lambda(t) \equiv dF(t)/S(t-)$] and any $t \in [0,\infty)$, we can show that $\int_0^t \Lambda^2(s)\,dF(s) \le 2\int_0^t \Lambda(s)\,dF(s)$ and $\int_0^t \Lambda(s)\,dF(s) \le 1$ by the integration by parts technique and by the relationship between F, S and Λ. Thus, (3.8) is bounded above by $2c^{**}$ and Lemma 2 now yields that condition (ii) of Theorem 2 is established and part (a) of Theorem 1 now follows by Theorem 2. Arguments for establishing that

$$\sup_{s,t\in[0,\infty]}\left|\mathbf{V}_{\mathbf{fg}}^n(s,t) - \mathbf{V}_{\mathbf{fg}}(s,t)\right| \to_P 0,$$

can be found on pages 31 and 32 of Lin (1998). Let

$$\begin{aligned}
U_{kl}^n(t) = n^{-1}\int_0^t \sum_{j=1}^n Y_j(s)&\left[Z_{jk}(s) - \bar{Z}_k(s)\right] \\
&\times\left[Z_{jl}(s) - \bar{Z}_l(s)\right]\frac{\bar{Y}(s) - \Delta\bar{N}(s)}{\bar{Y}(s) - 1}\,\frac{d\bar{N}(s)}{\bar{Y}(s)}.
\end{aligned}$$

Following the same argument used above to prove part (a) of Theorem 1, for any predictable process h^n with $|h^n| \le c$, we can show that

$$\mathrm{E}\big[G_{kl}^n(h^n, t)\big] \equiv \mathrm{E}\left[\int_0^t h^n(s)\, dU_{kl}^n(s)\right]^2 \le c^*$$

for some $c^* < \infty$. Reapplication of Theorem 2 via Lemma 2 gives us the desired uniform convergence in probability of $\mathbf{V}^n$ to $\mathbf{V}$. Similar arguments can be used to obtain the uniform consistency of $\tilde{\mathbf{V}}^n$, and part (b) of Theorem 1 is established. Part (c) follows from the version of Slutsky's lemma given in Example 1.4.7 of van der Vaart and Weller (1996). □

4. Monte Carlo estimation of P-values. Due to the complexity of the limiting distribution of the statistics in (2.10) proposed for use in data analysis, we generally are not able to obtain the P-values through analytical means. Therefore, a Monte Carlo approach is now proposed to simulate the null distribution of the processes W and to estimate the P-values of these statistics.

Let $\tilde{\mathbf{X}}_q^n$, $q = 1, \dots, Q$, be Q "artificial" realizations of $\mathbf{X}^n$ generated as follows. Obtain nQ independent standard normal random deviates, χ_{jq}, $j = 1 \dots n$, $q = 1 \dots Q$, and construct the corresponding artificial realization of $\mathbf{X}^n, \tilde{\mathbf{X}}_q^n$, with the kth element

$$\tilde{X}_{kq}^n(\mathbf{f}, \cdot) = n^{-1/2} \int_0^{(\cdot)} f_k\{\mathbf{b}^n(s)\} \sum_{j=1}^n Y_j(s)\big[Z_{jk}(s) - \bar{Z}_k(s)\big]\, d\tilde{M}_{jq}^n(s), \tag{4.1}$$

where

$$\tilde{M}_{jq}^n(t) = \chi_{jq} \int_0^t \left\{\frac{\bar{Y}(s) - \Delta\bar{N}(s)}{\bar{Y}(s) - 1}\right\}^{1/2} dN_j(s). \tag{4.2}$$

Define

$$\tilde{\mathscr{F}}_t^n = \sigma\Big\{\mathscr{F}_t^n, \tilde{M}_{jq}^n(s),\ s \le t,\ j = 1 \cdots n,\ q = 1, \dots, Q\Big\}.$$

REMARK 2. $\tilde{M}_{jq}$ are $\tilde{\mathscr{F}}_t^n$-martingales since

$$\begin{aligned} E\big[\tilde{M}_{jq}^n(t) | \tilde{\mathscr{F}}_{t-}^n\big] &= \tilde{M}_{jq}^n(t-) + \mathrm{E}\left[\chi_{jq}\left\{\frac{\bar{Y}(t) - \Delta\bar{N}(t)}{\bar{Y}(t) - 1}\right\}^{1/2} \Delta N_j(t) | \tilde{\mathscr{F}}_{t-}^n\right] \\ &= \tilde{M}_{jq}^n(t-). \end{aligned}$$

THEOREM 3. *Suppose that the conditions of Theorem* 1 *hold. Then*:

(a) *The collection* $\{\tilde{\mathbf{X}}_q^n(\cdot, \cdot),\ q = 1, \dots, Q\}$, *where* $\tilde{\mathbf{X}}_q^n(\mathbf{f}, \cdot)$ *are as given in* (4.1), *converges HJD-weakly in the uniform topology on* $\{\mathbf{A}(\mathbf{H}, \mathbf{D}[0, \infty])^p), a\}^Q$ *to a collection of* Q *independent multivariate Gaussian processes*, $\{\mathbf{X}_q(\cdot, \cdot),\ q$

$= 1, \dots, Q\}$, *such that each* $\mathbf{X}_q$ *has mean* $\mathbf{0}$ *and covariance function* $\mathbf{V}_{\mathbf{fg}}$, *for all* $\mathbf{f}, \mathbf{g} \in \mathbf{H}$, *where* $\mathbf{V}_{\mathbf{fg}}$ *is as defined in* (3.2), *and*

(b) *Let* $\tilde{\mathbf{W}}_q^n = [\tilde{\mathbf{V}}_{\mathbf{ff}}^n(\infty,\infty)]^{-1/2}\tilde{\mathbf{X}}_q^n$ *and* $\mathbf{W}_q^n = [\mathbf{V}_{\mathbf{ff}}(\infty,\infty)]^{-1/2}\mathbf{X}_q$, *where* $\tilde{V}_{\mathbf{ff}}^n$ *is as defined in* (3.3). *Then the collection* $\{\tilde{\mathbf{W}}_q^n(\cdot,\cdot),\ q = 1 \cdots Q\}$ *converges HJD-weakly in the uniform topology on* $\{\mathbf{A}(\mathbf{H}, (\mathbf{D}[0,\infty])^p), a\}^Q$ *to the collection* $\{\mathbf{W}_q(\cdot,\cdot),\ q = 1 \cdots Q\}$.

PROOF. For $q = 1, \dots, Q$, define p-dimensional processes $\tilde{\mathbf{X}}_q^{\diamond}$ with kth element

$$\tilde{X}_{kq}^{\diamond}(\mathbf{f}, \cdot) = n^{-1/2}\int_0^{(\cdot)} f_k\{\mathbf{b}^n(s)\}\sum_{j=1}^n Y_j(s)\big[Z_{jk}(s) - \bar{Z}_k(s)\big]\, d\tilde{M}_{jq}^{\diamond}(s),$$

where

$$\tilde{M}_{jq}^{\diamond}(t) = \chi_{jq}\int_0^t \{1 - \Delta\Lambda(s)\}^{1/2}\, dN_j(s).$$

It is not difficult to see that $\tilde{M}_{jq}^{\diamond}(t)$, $j = 1 \cdots n$, $q = 1 \cdots Q$, are uncorrelated square-integrable $\tilde{\mathscr{F}}_t^n$-martingales. By Theorem 1.5.1 of Fleming and Harrington (1991), $\tilde{X}_{kq}^n$, $\tilde{X}_{kq}^{\diamond}$ and $\tilde{X}_{kq}^n - \tilde{X}_{kq}^{\diamond}$ are also martingales. We can then show that the supremum norm of the difference between $\{\tilde{\mathbf{X}}_q^n,\ q = 1, \dots, Q\}$ and $\{\tilde{\mathbf{X}}_q^{\diamond},\ q = 1, \dots, Q\}$ converges to 0 in outer probability, so that weak convergence of $\{\tilde{\mathbf{X}}_q^n,\ q = 1, \dots, Q\}$ can be established by verifying that of $\{\tilde{\mathbf{X}}_q^{\diamond},\ q = 1, \dots, Q\}$. We can employ the same techniques used in the proof of Theorem 1 to show (a) and (b). The verification of the asymptotic equivalence of $\{\tilde{\mathbf{X}}_q^n,\ q = 1, \dots, Q\}$ and $\{\tilde{\mathbf{X}}_q^{\diamond},\ q = 1, \dots, Q\}$ as well as the main differences in proof between Theorem 1 and Theorem 3 are outlined in pages 41–44 of Lin (1998). After establishing convergence of finite-dimensional distributions, the remainder of the proof follows along the lines of the proof of Theorem 1. □

REMARK 3. (i) The continuous mapping theorem applied to Theorem 3 implies that the limiting distribution, under the null hypothesis of no covariate effect, for the supremum statistics given in Section 2.3 can be accurately estimated by the sample distribution of a collection of the proposed Monte Carlo replicates conditional on the data.

(ii) In contrast to Remark (iii), $\tilde{\mathbf{V}}_{\mathbf{fg}}^n$ tends to estimate the variance of the Monte Carlo realizations $\tilde{\mathbf{X}}^q$ more accurately than $\mathbf{V}_{\mathbf{fg}}^n$ for small or moderate sample sizes; thus it will be the estimator of choice for the Monte Carlo simulations used to obtain the null distribution of $\mathbf{W}^n$.

5. Example: β-Blocker Heart Attack Trial. The β-Blocker Heart Attack Trial (BHAT) mentioned in the Introduction was a randomized, double-blind, placebo-controlled clinical trial designed to test whether the β-blocker propranolol hydrochloride would reduce total mortality among people who had experienced at least one episode of myocardial infarction. By the time the study was stopped in 1980, a total of 3,837 patients (1,916 in the propranolol group and 1,921 in the placebo group) had been accrued, and 337 (142 propranolol, 195 placebo) of them had died. Eleven patients (4 propranolol, 7 placebo) had unknown mortality status and were omitted from the analyses presented here.

The test procedures proposed in Section 2.3, for the special case involving treatment indicator covariates, were utilized by Kosorok and Lin (1999) to assess difference in survival rates between the two treatment groups. We now present an extension of this analysis which uses the more general version of the newly proposed statistics to assess the risk factors: age, systolic blood pressure (SBP) and history of hypertension (DH) with survival rates for patients in the placebo group at the final analysis time. The two function-indexed test procedures described in the previous section with $G^{\rho,\gamma}$ weights were used in this analysis and are denoted G and GS, respectively. We employed these two tests with several weight index sets including $(\rho, \gamma) \in \{(0,0)\}$ (log-rank weight), $\{(1,0)\}$, $[0,1] \times \{0\}$, $[0,4] \times \{0\}$, $[0,20] \times \{0\}$, $[0,4] \times [0,1]$, and $[0,20] \times [0,1]$. The first three are commonly used in practice; $[0,4] \times [0,1]$ was suggested by the simulation studies in Kosorok and Lin (1999) and $[0,20] \times [0,1]$ was used because the optimal weight may be far afield from what we would expect. To save on computing time, a discrete approximation of the intervals $[0, \rho_0]$ and $[0, \gamma_0]$, consisting only of the numbers $k \times 1 \in [0, \rho_0]$ and $l \times 0.5 \in [0, \gamma_0]$, where k and l are nonnegative integers, were used to calculate the function-indexed statistics. P-values were calculated based on 10,000 Monte Carlo realizations. Analysis results are presented in Table 5.1.

TABLE 5.1

Monte Carlo P-values (based on 10,000 *Monte Carlo replicates) of the statistics testing the effects of risk factors on survival rates for patients in the BHAT placebo group*

Test procedure	**Index set**	**Overall test**	**Age**	**Age^2**	**DH**	**SBP**
G	$\{(0,0)\}$	0.0169	0.0258	0.0261	0.0168	0.0637
	$\{(1,0)\}$	0.0180	0.0281	0.0281	0.0151	0.0690
	$\{(16,1)\}$	0.0120	0.0200	0.0180	0.0348	0.0250
	$[0,1] \times \{0\}$	0.0179	0.0269	0.0267	0.0160	0.0651
	$[0,4] \times \{0\}$	0.0192	0.0286	0.0290	0.0135	0.0693
	$[0,20] \times \{0\}$	0.0267	0.0371	0.0378	0.0131	0.0879
	$[0,4] \times [0,1]$	0.0271	0.0285	0.0251	0.0242	0.0507
	$[0,20] \times [0,1]$	0.0334	0.0377	0.0330	0.0223	0.0547
GS	$\{(0,0)\}$	0.0268	0.0415	0.0414	0.0151	0.1186
	$\{(1,0)\}$	0.0285	0.0455	0.0451	0.0138	0.1284
	$\{(16,1)\}$	0.0181	0.0327	0.0302	0.0262	0.0421
	$[0,1] \times \{0\}$	0.0279	0.0428	0.0425	0.0141	0.1216
	$[0,4] \times \{0\}$	0.0305	0.0461	0.0461	0.0127	0.1283
	$[0,20] \times \{0\}$	0.0408	0.0651	0.0663	0.0135	0.1588
	$[0,4] \times [0,1]$	0.0396	0.0460	0.0401	0.0210	0.0947
	$[0,20] \times [0,1]$	0.0507	0.0635	0.0547	0.0209	0.1011

DH = 1 if diagnosed with hypertension, = 0 otherwise.
SBP = systolic blood pressure.

The Renyi-type statistics GS are less sensitive than G in testing all risk factors except the history of hypertension. G statistics yield a strong association of survival rates with age and history of hypertension regardless of the index sets chosen, but indicate only a borderline significant association with systolic blood pressure. Systolic blood pressure is significantly related to survival when we analyzed it with the whole sample after adjusting for treatment effect. Its insignificance in this analysis may result from an improper choice of index sets or insufficient sample size. We examined the P-values of the corresponding G statistics for all values of ρ in the interval $[0, 40]$ and γ in the interval $[0, 10]$, in an increment of size 1 and obtained the minimum P-value of 0.0250 attained at $(\rho, \gamma) = (16, 1)$. Although $(16, 1)$ is in $[0, 20] \times [0, 1]$, the increase in variability with the latter index set demerits its achievement of the largest noncentrality parameter. For testing the effect of systolic blood pressure, the G statistic with index set $[0, 4] \times [0, 1]$ appears to be a good choice and is more sensitive than the G with the log-rank weight.

We also calculated the P-values of the same function-indexed tests with a finer increment in ρ and γ. They turn out to be fairly close to the ones we reported here. The sensitivity of the function-indexed tests seem to depend more on the extreme weights incorporated in the index set. Another important observation is that enlarging the index set too much for testing the effect of a continuous covariate can result in a substantial reduction in sensitivity. For example, when we enlarge the index set from the log-rank weight $\{(0, 0)\}$ to $[0, 20] \times [0, 1]$, the P-values of the GS statistics testing the overall associations of age, history of hypertension, and systolic blood pressure with survival rates changed from 0.0268 to 0.0507.

Kosorok and Lin (1999) showed that the variability of the two-sample function-indexed tests does not increase dramatically with an enlargement of the weight index set. However, this may not be true in testing the associations of continuous covariates with survival rates. In this example, the G statistic with the index set $[0, 20] \times [0, 1]$ which incorporates the optimal weight $(16, 1)$ is less sensitive than G with $[0, 4] \times [0, 1]$ in detecting the effect of systolic blood pressure due to the increase in variability. However, they are both more sensitive than G with the log-rank weight. Other weight functions such as G^{ρ} with ρ varying from negative to positive may be a good alternative to the $G^{\rho,\gamma}$ weight. Further studies are needed to obtain appropriate index sets under various alternative settings.

6. Discussion. We generalized the class of single-covariate nonparametric test procedures proposed by Jones and Crowley (1989) to multicovariate situations. These statistics can, in clinical trials, be applied to investigate the treatment effects or k-sample trend after adjusting for possible confounding factors, as well as to explore the potential interventions after influential factors are controlled for. Considering these stochastic processes indexed by both the time scale and the weight function, we showed that certain large families of these processes converge HJD-weakly in the uniform topology to multivariate Gaussian processes also doubly indexed by both time and weight function. This result permits us to develop more powerful test procedures than the current ones for versatile alternatives. Via simulation studies for the two-sample problems in Kosorok and Lin (1999), we have shown that our newly proposed statistics using $G^{\rho,\gamma}$ weight functions with $\rho \in [0,4]$ and $\gamma \in [0,1]$ can increase power under ordered hazards alternatives and stochastic ordering alternatives as well as stochastic crossing alternatives. However, the general behavior of these statistics with covariates present and the criterion for an appropriate choice of weight functions in practice have not been fully explored. Further studies need to be performed for a better understanding of these issues.

The simulation study in Kosorok and Lin also evaluates the performance of a Monte Carlo approach closely related to the one proposed in the present paper. This approach seems quite effective for moderate sample sizes. There are other martingale-type statistics, such as the weighted Kaplan–Meier statistics of Pepe and Fleming (1989), to which the theory in the present paper could potentially be applied. Further research on the relative efficiencies of these martingale-type statistics can give us guidelines on the choice of the type of statistics to use in different situations and would thus be very beneficial in practice.

APPENDIX

Proof of Lemma 1. The kth element of $\mathbf{X}^n(\mathbf{f},t)$ can be written as the sum of a martingale and a mean process

$$\begin{aligned} X_k^n(\mathbf{f},t) &= n^{-1/2}\int_0^t f_k\{\mathbf{b}^n(s)\}\sum_{j=1}^n Y_j(s)\big[Z_{jk}(s)-\bar{Z}_k(s)\big]\,dM_j(s)\\ &\quad + n^{-1/2}\int_0^t f_k\{\mathbf{b}^n(s)\}\sum_{j=1}^n Y_j(s)\big[Z_{jk}(s)-\bar{Z}_k(s)\big]\,d\Lambda_j^n(s) \\ &\equiv X_{\diamond k}^n(\mathbf{f},t)+\mu_k^n(\mathbf{f},t). \end{aligned} \tag{A.1}$$

Note that

$$\mu_k^n(\mathbf{f},t) = n^{-1/2}\int_0^t f_k\{\mathbf{b}^n(s)\}\sum_{j=1}^n Y_j(s)\big[Z_{jk}(s)-\bar{Z}_k(s)\big]\big[d\Lambda_j^n(s)-d\Lambda(s)\big]$$

and

$$\begin{aligned} &d\Lambda_j^n(s)-d\Lambda(s)\\ &\quad= \frac{\exp\big\{\beta^T Z_j(s)g(s)/\sqrt{n}\big\}-1}{1+\big(\exp\big\{\beta^T Z_j(s)g(s)/\sqrt{n}\big\}-1\big)\Delta\Lambda(s)}\,[1-\Delta\Lambda(s)]\,d\Lambda(s). \end{aligned}$$

Since each $\{b_i^n: n \geq 1\}$, $i = 1, \ldots, r$, satisfies Condition (iv) of Theorem 1 and since f_k is continuous on $[0, 1]^r$,

$$\max_{1 \leq k \leq p} \sup_{s \in [0, t]} |f_k\{\mathbf{b}^n(s)\} - f_k\{\mathbf{b}(s)\}| \to_P 0, \tag{A.2}$$

for all $t \in \mathscr{I}$. The boundedness of Z_{jk}, β_k, $k = 1, \ldots, p$ and g yields

$$\lim_{n \to \infty} \sup_{s \in [0, \infty)} \left| n^{1/2}\left[d\Lambda_j^n(s) - d\Lambda(s)\right] - \boldsymbol{\beta}^T \mathbf{Z}_j(s) g(s)\left[1 - \Delta\Lambda(s)\right] d\Lambda(s)\right| = 0.$$

Therefore $\mu_k^n(\mathbf{f}, t)$ converges uniformly on $[0, \infty]$ in probability to $\mu_k(\mathbf{f}, t)$, since

$$\sum_{j=1}^n Y_j\left[Z_{jk} - \bar{Z}_k\right] Z_{jl} = \sum_{j=1}^n Y_j\left[Z_{jk} - \bar{Z}_k\right]\left[Z_{jl} - \bar{Z}_l\right]$$

converges uniformly to v_{kl}, $k, l = 1, \ldots, p$. The finite-dimensional convergence of $\mathbf{X}^n$ can be established by verifying the finite-dimensional weak convergence of $\mathbf{X}_\diamond^n = [X_{\diamond 1}^n, \ldots, X_{\diamond p}^n]^T$, where $X_{\diamond k}^n$ are as given in (A.1), to a Gaussian process with mean $\mathbf{0}$ and covariance function $\mathbf{V}_{\mathbf{fg}}$, where $\mathbf{f}, \mathbf{g} \in \mathbf{H}$. Because the distribution of failure times may not be absolutely continuous as a result of possible ties in the failure times, an adaption of the time-transformed method used in the proof of Theorem 4.2.1 in Gill (1980) will be employed in this proof.

For any collection of m-bounded left-continuous step functions on $[0, \infty]$, $\{c_h, h = 1, \ldots, m\}$ and $\mathbf{h} = [\mathbf{f}_1, \ldots, \mathbf{f}_m] \subset \mathbf{H}$, $m < \infty$, let

$$C_k^n(t) = \sum_{h=1}^m c_h(t) f_{hk}\{\mathbf{b}^n(t)\} \quad \text{and} \quad C_k(t) = \sum_{h=1}^m c_h(t) f_{hk}\{\mathbf{b}(t)\},$$

$k = 1, \ldots, p$. By (A.2), for all $t \in \mathscr{I}$,

$$\max_{1 \leq k \leq p} \sup_{s \in [0, t]} |C_k^n(s) - C_k(s)| \to_P 0. \tag{A.3}$$

Define a p-dimensional process $\tilde{\mathbf{U}}^n$ with the kth element

$$\tilde{U}_k^n(t) = n^{-1/2} \int_0^t C_k^n(s) \sum_{j=1}^n Y_j(s)\left[Z_{jk}(s) - \bar{Z}_k(s)\right] dM_j(s),$$

and $H_{jk}^{(n)}(s) = n^{-1/2} C_k^n(s) Y_j(s)[Z_{jk}(s) - \bar{Z}_k(s)]$, for $k = 1, \ldots, p$ and $j = 1, \ldots, n$.

We can enumerate all the discontinuities of Λ_j^n and Λ, for all $n \geq 1$, in a single sequence $t_1, t_2, \ldots,$ say. Choose $\delta_h > 0$, $h = 1, 2, \ldots,$ such that $\sum_{h=1}^\infty \delta_h < \infty$. Define the time transformation ϕ^*: $[0, \infty] \mapsto [0, \infty]$ by

$$\phi^*(t) = t + \sum_{h:\, t_h \leq t} \delta_h.$$

Let $\mathscr{I}^* = [0, \phi^*(u_0 -))$ if $u_0 \notin \mathscr{I}$ and $\mathscr{I}^* = [0, \phi^*(u_0 -)]$ if $u_0 \in \mathscr{I}$.

The processes $N_j^*, Y_j^*, N_j^*, H_{jk}^{*(n)}$ are defined as follows. First, if $t^* = \phi^*(t)$ for some t, we let $N_j^*(t^*) = N_j(t)$, $Y_j^*(t^*) = Y_j(t)$ and $H_{jk}^{*(n)}(t^*) = H_{jk}^{(n)}(t)$.

Next, we define N_j^* on the intervals $[\phi^*(t_h-), \phi^*(t_h))$ by letting N_j^*, conditional on $Y_j(t_h)$, make a single jump at the point R_{jh} with probability $Y_j(t_h)\Delta\Lambda_j^n(t_h)$, where R_{jh} is an independent variable uniformly distributed on $(\phi^*(t_h-), \phi^*(t_h))$. Also, for $t^* \in [\phi^*(t_h-), \phi^*(t_h))$, $h = 1, 2, \dots,$ we define $Y_j^*(t^*) = Y_j(t_h)$, $H_{jk}^{*(n)}(t^*) = H_{jk}^{(n)}(t_h)$ and

$$M_j^*(t^*) = M_j(t_h-) + N_j^*(t^*) - N_j(t_h-) - Y_j(t_h)I_{\{R_{jh} \le t^*\}}\Delta\Lambda_j^n(t_h).$$

Let

$$\mathscr{E}_{t^*}^{*n} \equiv \sigma\{R_{jh} \text{ for all } h\colon \phi^*(t_h-) \le t^*;\ N_j^*(s^*),\ s^* \le t^*;\ j = 1 \dots n\}$$

and

$$\mathscr{F}_{t^*}^{*n} \equiv \begin{cases} \sigma\{\mathscr{F}_t^n, \mathscr{E}_{t^*}^{*n}\}, & \text{if } t^* = \phi^*(t), \\ \sigma\{\mathscr{F}_{t-}^n, \mathscr{E}_{t^*}^{*n}\}, & \text{if } \phi^*(t-) \le t^* < \phi^*(t). \end{cases}$$

We can see that $M_j^*(t^*)$, $j = 1 \dots n$, are square integrable $\mathscr{F}_{t^*}^{*n}$-martingales, with $H_{jk}^{*(n)}(t^*)$ and $Y_j^*(t^*)$ being $\mathscr{F}_{t^*}^{*n}$-predictable.

Define

$$\tilde{U}_k^{*n}(t^*) = \int_0^{t^*} \sum_{j=1}^n H_{jk}^{*(n)}(s)\, dM_j^*(s)$$

and obtain the predictable covariations $\langle M_j^*, M_{j'}^* \rangle(\cdot) = 0$, for $j \neq j'$, $\langle M_j^*, M_j^* \rangle(t^*) = \langle M_j, M_j \rangle(t)$, for $t^* = \phi^*(t)$ and

$$\langle M_j^*, M_j^* \rangle(t^*) = \langle M_j, M_j \rangle(t_h-) + Y_j(t_h)I_{\{R_{jh} \le t^*\}}[1 - \Delta\Lambda_j^n(t_h)]\,\Delta\Lambda_j^n(t_h),$$

for $\phi^*(t_h-) \le t^* < \phi^*(t_h)$. Then $\tilde{U}_k^*$ is a square integrable $\mathscr{F}^{*n}$-martingale with predictable covariation

$$\langle \tilde{U}_k^{*n}, \tilde{U}_{k'}^{*n} \rangle(t^*) = \begin{cases} \displaystyle\int_0^t \sum_{j=1}^n H_{jk}^{(n)}(s)H_{jk'}^{(n)}(s)\, d\langle M_j, M_j \rangle(s), & \text{if } t^* = \phi^*(t), \\ \displaystyle\int_{t_h-}^0 \sum_{j=1}^n H_{jk}^{(n)}(s)H_{jk'}^{(n)}(s)\, d\langle M_j, M_j \rangle(s) & \\ \displaystyle\quad + \sum_{j=1}^n H_{jk}^{(n)}(t_h)H_{jk'}^{(n)}(t_h)Y_j(t_h)I_{\{t^* \le R_{jh}\}} & \\ \qquad \times[1 - \Delta\Lambda_j^n(t_h)]\,\Delta\Lambda_j^n(t_h), & \\ & \text{if } \phi^*(t_h-) \le t^* < \phi^*(t_h). \end{cases}$$

By (A.3) and condition (iii), we have

$$\sup_{s \in [0,t]} \left| \sum_{j=1}^n H_{jk}^{(n)}(s)H_{jk'}^{(n)}(s) - h_{kk'}(s) \right| \to_P 0, \tag{A.4}$$

for all $k, k' = 1, \dots, p$, and $t \in \mathscr{I}$, where $h_{kk'}(s) = C_k(s)C_{k'}(s)\pi(s)v_{kk'}(s)$; by Definition 1 and condition (iv), $h_{kk'}$ is left continuous with right-hand limits and $h_{kk'}(s+)$ has bounded variation on all closed subintervals of $\mathscr{I}$. Therefore, for every $t^* \in \mathscr{I}^*$,

$$\langle \tilde{U}_k^{*n}, \tilde{U}_{k'}^{*n}\rangle(t^*) \tag{A.5}$$
$$\to_P \begin{cases} \int_0^t h_{kk'}(s)[1-\Delta\Lambda(s)]\,d\Lambda(s), & \text{if } t^* = \phi^*(t), \\ \int_0^{t_h-} h_{kk'}(s)[1-\Delta\Lambda(s)]\,d\Lambda(s) & \\ \quad + h_{kk'}(t_h)\dfrac{t^*-\phi^*(t_h-)}{\delta_h}[1-\Delta\Lambda(t_h)]\,\Delta\Lambda(t_h), & \\ \qquad\qquad \text{if } \phi^*(t_h-) \le t^* < \phi^*(t_h). & \end{cases}$$

Using techniques outlined on pages 28 and 29 of Lin (1998), we can obtain that the convergence in (A.5) is uniform over $\mathscr{I}^*$ and that

$$\langle \tilde{U}_k^{*n}, \tilde{U}_{k'}^{*n}\rangle(t^*) \to_P 0$$

uniformly over the complement of $\mathscr{I}^*$.

Thus Rebolledo's theorem [Theorem II.5.1 of Anderson, Borgan, Gill and Keiding (1993)] combined with the Cramér–Wold device for stochastic processes [Lemma C.3.1 of Fleming and Harrington (1991)] now yields weak convergence in the Skorohod topology on $(\mathbf{D}[0,\infty])^{mp}$ of finite-dimensional collections $\{\mathbf{X}_\diamond^{*n}(\mathbf{f}),\ \mathbf{f}\in\mathbf{h}\}$, where $\mathbf{h}=\{\mathbf{f}_1,\dots,\mathbf{f}_m\}$ and the kth element of $\mathbf{X}_\diamond^{*n}(\mathbf{f})$ is

$$n^{-1/2}\int_0^{(\cdot)} f_k^*\{\mathbf{b}^n(s)\}\sum_{j=1}^n Y_j^*(s)\big[Z_{jk}^*(s)-\bar{Z}_k^*(s)\big]\,dM_j^*(s),$$

where f_k^* and Z_{jk}^* are the time-transformed versions of f_k and Z_{jk} [as was done for $H_{jk}^{*(n)}$] to m-tight Gaussian processes with mean $\mathbf{0}$ and covariance function

$$\mathbf{V}_{fg}^*(t^*) \equiv \begin{cases} \mathbf{V}_{\mathbf{fg}}(t), & \text{if } \phi^*(t)=t^*, \\ \mathbf{V}_{\mathbf{fg}}(t_h-)+\dfrac{t^*-\phi^*(t_h-)}{\delta_h}\Delta\mathbf{V}_{\mathbf{fg}}(t_h), & \text{if } \phi^*(t_h-)\le t^*<\phi^*(t_h), \end{cases}$$

for $\mathbf{f},\mathbf{g}\in\mathbf{h}$.

Since we have weak convergence to a continuous limit, there exists a new probability space where the above convergence can be replaced with outer almost sure convergence in the uniform topology. This implies HJD-weak convergence in the uniform topology for the original probability space. Since the mapping of a process back on the original time scale is continuous in the uniform topology, the continuous mapping theorem yields our desired HJD-weak convergence. □

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DEPARTMENT OF MEDICINE
UNIVERSITY OF ALABAMA
BIRMINGHAM, ALABAMA 35294-3300

DEPARTMENT OF STATISTICS
AND BIOSTATISTICS
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN 53706