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Small Sample Study of Kernel Hazard Ratio Estimator

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ABSTRACT

The hazard ratio may be useful as a descriptive measure to compare the hazard experience of a treatment group with that of a control group. In this paper, we propose a kernel estimator of hazard ratio with censored survival data. The uniform consistency and asymptotic normality of the proposed estimator are proved by using counting process approach. In order to assess the performance of the proposed estimator, we compare the kernel estimator with Cox estimator and the generalized rank estimators of hazard ratio in terms of MSE by Monte Carlo simulation.

1. INTRODUCTION

Being compared survival across treatment groups in a clinical trial, it is useful to have a descriptive measure of the difference in survival between groups. When the hazard functions in two groups are roughly proportional, the ratio of hazard functions has the interpretation of relative risk. The Cox's proportional hazard model (here after will be abbreviated by PHM)

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(Cox, 1972) assumes that the hazard function for the survival time t of an individual with covariate vector z has the form

$$\alpha(t|z) = \alpha_0(t) exp(\beta_0{}' z), \quad t \geq 0$$

where β_0 is a p-vector of unknown regression coefficients and $\alpha_0(t)$ is an unknown and unspecified baseline hazard function. In case that $p = 1$ and covariate z is an indicator for treatment group, the PHM becomes

$$\alpha_2(t) = \theta\alpha_1(t),$$

where the proportionality constant $\theta (= e^{\beta_0})$ is the relative risk, and $\alpha_1(t)$ and $\alpha_2(t)$ are the hazard functions in control and treatment group respectively. Cox(1972, 1975) use the partial likelihood function to estimate the regression coefficient β_0. (see Andersen and Gill, 1982).

Andersen (1983) introduces the generalized rank estimator of the hazard ratio as a new interpretation of the linear nonparametric two sample tests for censored data, and establishes asymptotic normality by using counting process and martingale theory. Dabrowska, Doksum and Song (1989) provide graphs, confidence procedures and tests that could be used with censored survival data to compare the hazard experience of a treatment group with that of a control group. In particular, they considered the relative change $\Delta(t)$ in a cumulative hazard function, which equals to $\theta - 1$ under PHM.

In this paper, we extend Dabrowska et al(1989)'s estimator by smoothing via kernel method. A kernel estimator of hazard ratio is proposed and the asymptotic properties of the proposed estimator are derived using counting processes approaches in Section 2. Section 3 presents the results of a simulation study, comparing this estimator with others.

2. KERNEL ESTIMATION OF HAZARD RATIO

Nelson (1972) and Aalen (1978) suggested the estimator for cumulative hazard function, as follows,

$$\hat{\beta}_i(t) = \int_0^t \frac{dN_i(s)}{Y_i(s)}, \quad i = 1, 2, \tag{2.1}$$

where $N_i(t)$ are the numbers of deaths in the group i in the interval $[0, t]$ and $Y_i(t)$ are the numbers of the individuals at risk at time $t-$ in the group i.

Dabrowska et al (1989) develop a simultaneous confidence band for hazard ratio by using the ratio of the Nelson - Aalen estimators and provide a graphical procedure to check whether the PHM holds or not. A smoothed version of their estimator may be considered, which we now propose a kernel estimator for hazard ratio as follows.

$$\hat{\theta}_{KER}(t) = \frac{\int_0^1 K((t-s)/b)d\hat{\beta}_2(s)}{\int_0^1 K((t-s)/b)d\hat{\beta}_1(s)} , \tag{2.2}$$

where K is a bounded function with integral 1, and $\hat{\beta}_i(t)$, $i = 1,2$ is the Nelson-Aalen estimator of the $i-$th group cumulative hazard function $\int_0^t \alpha_i(s)ds$, and b is the positive number, where plays role of the amount of smoothing. The optimal selection of b is very crucial.

Theorem 1. Assume that the following conditions hold :

(i) $\alpha_i(t), i = 1,2$ are continuous on $[0,1]$.

(ii) There exist funtions y_1, y_2 taking values in $(0,1)$ such that under the PHM

$$\sup_{t\in[0,1]} \left| \frac{Y_i^{(n)}(t)}{n} - y_i(t) \right| \xrightarrow{P} 0, \quad i = 1,2; \quad \text{as} \quad n \to \infty.$$

Then $\hat{\theta}_{KER}^{(n)}(t)$ is uniformly consistent for θ under the PHM. (the proof is given in the Appendix).

Theorem 2. Assume that the conditions of Theorem 1 are satisfied and that the following conditions hold :

(i) $b_n \in (0,1/2)$ and $b_n \to 0$ as $n \to \infty$.

(ii) The kernel has support within $[-1,1]$ and is symmetric about zero.

(iii) $\frac{1}{b_n}\int_0^1 K^{(n)}(\frac{t-s}{b_n})\alpha_1(s)ds \xrightarrow{P} \alpha_1(t),\ t \in [b_n, 1-b_n]$, as $n \to \infty$.

Then the process $\sqrt{nb_n}(\hat{\theta}_{KER}^{(n)}(t) - \theta)$ converges weakly to a Gaussian process mean zero with variance function $\sigma_{KER}^2(t)$ given by

$$\sigma_{KER}^2(t) = \frac{\theta^2}{\alpha_1(t)} \left(\frac{y_1(t) + \theta y_2(t)}{\theta y_1(t) y_2(t)} \right) \int_{-1}^1 K^2(u)\, du. \tag{2.3}$$

(the proof is given in the Appendix).

Corollary 1. Assume that the condition (ii) of Theorem 1 and the condition (iii) of Theorem 2 are satisfied. Then $\hat{\sigma}^2_{KER}(t)$ is uniformly consistent for $\sigma^2_{KER}(t)$ under the PHM, which is given by

$$\hat{\sigma}^2_{KER}(t) = n(\hat{\theta}^{(n)}_{KER}(t))^2 \times \frac{\int_{-1}^{1} K^2(u)\left(\frac{d[N_1(t-bu)+N_2(t-bu)]}{Y_1(t-bu)\hat{\theta}Y_2(t-bu)}\right)}{\left(\int_{-1}^{1} K(u)\frac{dN_1(t-bu)}{Y_1(t-bu)}\right)^2}, \quad t \in [b, 1-b]. \quad (2.4)$$

(the proof is given in the Appendix).

3. SIMULATION STUDY

In this section we compare the performance of the kernel estimator with others such as Cox and the generalized rank estimators in terms of MSE by Monte Carlo simulation. Crowley, Liu and Voelkel(1982) compare asymptotic variances for the maximum likelihood estimator, the Cox estimator and the generalized rank estimator of relative risk as a large sample measure of efficiency.

The simulation structure adopted here has $n(= n_1 + n_2) = 60, 100$. Lifetimes of control and treatment groups were generated from an exponential distridutions with mean $\frac{1}{\lambda}$ ($Exp(\lambda)$) and a Weibull distribution with parameters δ and λ whose survival function is $exp(-\lambda t^{\delta})$ ($Weib(\lambda, \delta)$), and censoring times from exponential distributions. The values of λ were determined by censoring proportions ranged from 10% *to* 30%. To compare the performances of the kernel estimator in the case of PHM, we took $Exp(\lambda_{11})$ and $Exp(\lambda_{21})$ as the lifetime distributions of control and treatment groups, and $Exp(\lambda_{12})$ and $Exp(\lambda_{22})$ as their corresponding censoring distributions. The true hazard ratio $\theta(t)$ is $\frac{\lambda_{21}}{\lambda_{11}}$.

Similarly for the case that the PHM does not hold (non–PMH), we took $Weib(\lambda_{11}, \delta_1)$ and $Weib(\lambda_{21}, \delta_2)$ as the lifetime distributions of control and treatment groups, and the same censoring distributions as in the PHM case. The true hazard ratio $\theta(t)$ is $\frac{\lambda_{21}}{\lambda_{11}}\frac{\delta_2}{\delta_1}t^{\delta_2-\delta_1}$. For both cases, the values of estimates and their MSE's are tabulated in Table 1 and 2. For each simulation run, there are 200 replications and the values of t at which estimates were evaluated, were selected $5(5)95-th$ quantile points of the control group lifetime distribution. The Cox's estimator $\hat{\theta}_{COX}(= e^{\hat{\beta}_0})$ is obtained iteratively by the Newton-Raphson algorithm with the Mantel-Haenszel estimator of β_0 as an initial value. The weight functions proposed by Mantel-Haenszel, Gehan and Harrington-Fleming are used to obtain the generalized rank estimators $\hat{\theta}_{MH}(t)$, $\hat{\theta}_{GH}(t)$, $\hat{\theta}_{HF}(t)$.(Gill and Schumacher, 1987).

Finally the following kernel function is used (Epanechnikov, 1969)

$$K(x) = \begin{cases} \frac{3}{4}(1 - x^2), & \text{if } |x| \leq 1; \\ 0, & \text{otherwise}, \end{cases}$$

and the bandwidth is selected at which the MSE is minimized among 0.05 (0.05)0.5 times of range of the generated survival times. The results are summarized in Table 1 and 2. Table 1 provide estimates of $\hat{\theta}(t)$ and their MSE's for the two selected models which hold the PHM, and Table 2 for non-PHM. From Table 1 and 2, the following conclusions may be extracted.

(a) In cases of PHM, the proposed kernel estimator $\hat{\theta}_{KER}(t)$ seems to be better than the generalized rank estimators $\hat{\theta}_{MH}(t)$, $\hat{\theta}_{HF}(t)$ and $\hat{\theta}_{GH}(t)$, and compatible with Cox estimator, $\hat{\theta}_{COX}$ in the sense of MSE.

(b) In cases of non-PHM, $\hat{\theta}_{KER}(t)$ works best among others.

(c) Although we are not tabulated the results due to limited space, $\hat{\theta}_{KER}(t)$ seems to have smaller biases than other estimators in any case.

In most cases $\hat{\theta}_{KER}(t)$ seems to have on the whole smaller biases, MSE's and their standard deviations of MSE's than $\hat{\theta}_{MH}(t)$, $\hat{\theta}_{HF}(t)$, and $\hat{\theta}_{GH}(t)$. Even, in case of PHM, $\hat{\theta}_{KER}(t)$ seems to be as good as Cox estimator which is known to be best asymptotically.

Table 1. Estimates of $\theta(t)$ and their MSE's under the PHM

(1) *When* $\lambda_{11} = 1.0, \lambda_{12} = 0.111, \lambda_{21} = 1.5$ *and* $\lambda_{22} = 0.167$.

n	t	0.288	0.357	0.431	0.598	0.693	0.799	0.916	1.050	1.204
	KER	1.537	1.558	1.536	1.532	1.499	1.496	1.448	1.508	1.382
n_1	COX	1.539	1.539	1.539	1.539	1.539	1.539	1.539	1.539	1.539
	GGH	1.774	1.709	1.650	1.658	1.618	1.609	1.608	1.626	1.612
30	GMH	1.769	1.697	1.651	1.640	1.607	1.593	1.599	1.609	1.577
	GHF	1.770	1.702	1.649	1.647	1.610	1.598	1.594	1.615	1.591
	MSE1	0.183	0.254	0.273	0.204	0.198	0.188	0.162	0.197	0.185
n_2	MSE2	0.188	0.188	0.188	0.188	0.188	0.188	0.188	0.188	0.188
	MSE3	1.091	0.965	0.563	0.663	0.412	0.427	0.364	0.409	0.334
30	MSE4	1.031	0.884	0.561	0.576	0.348	0.361	0.288	0.367	0.267
	MSE5	1.502	0.914	0.555	0.610	0.369	0.382	0.314	0.378	0.287
	KER	1.533	1.518	1.530	1.503	1.501	1.472	1.501	1.510	1.461
n_1	COX	1.533	1.533	1.533	1.533	1.533	1.533	1.533	1.533	1.533
	GGH	1.634	1.659	1.622	1.593	1.554	1.573	1.557	1.570	1.542
50	GMH	1.631	1.659	1.617	1.589	1.548	1.566	1.557	1.563	1.543
	GHF	1.632	1.658	1.619	1.590	1.550	1.568	1.556	1.565	1.541
	MSE1	0.121	0.099	0.126	0.116	0.117	0.115	0.133	0.152	0.146
n_2	MSE2	0.112	0.112	0.112	0.112	0.112	0.112	0.112	0.112	0.112
	MSE3	0.513	0.460	0.370	0.290	0.219	0.220	0.176	0.216	0.187
50	MSE4	0.497	0.462	0.347	0.259	0.194	0.201	0.160	0.179	0.144
	MSE5	0.502	0.458	0.355	0.270	0.201	0.205	0.163	0.189	0.157

Table 1.(continued)

(2) *When* $\lambda_{11} = 1.5, \lambda_{12} = 0.167, \lambda_{21} = 1.0$ *and* $\lambda_{22} = 0.111$.

n	t	0.149	0.192	0.287	0.399	0.462	0.532	0.611	0.7	0.803
	KER	0.688	0.668	0.712	0.668	0.680	0.704	0.679	0.677	0.724
n_1	COX	0.704	0.704	0.704	0.704	0.704	0.704	0.704	0.704	0.704
	GGH	0.842	0.732	0.712	0.726	0.706	0.673	0.716	0.699	0.704
30	GMH	0.837	0.737	0.715	0.721	0.697	0.671	0.709	0.694	0.702
	GHF	0.839	0.734	0.713	0.723	0.701	0.672	0.712	0.696	0.702
	MSE1	0.038	0.051	0.047	0.041	0.047	0.048	0.047	0.054	0.058
n_2	MSE2	0.037	0.037	0.037	0.037	0.037	0.037	0.037	0.037	0.037
	MSE3	0.674	0.225	0.146	0.127	0.114	0.082	0.112	0.076	0.053
30	MSE4	0.653	0.232	0.142	0.111	0.109	0.082	0.098	0.068	0.049
	MSE5	0.663	0.228	0.143	0.117	0.110	0.081	0.103	0.070	0.050
	KER	0.678	0.671	0.695	0.684	0.690	0.699	0.694	0.681	0.672
n_1	COX	0.687	0.687	0.687	0.687	0.687	0.687	0.687	0.687	0.687
	GGH	0.747	0.766	0.746	0.712	0.712	0.671	0.706	0.690	0.688
50	GMH	0.747	0.768	0.745	0.711	0.710	0.670	0.701	0.686	0.688
	GHF	0.747	0.767	0.745	0.711	0.711	0.670	0.703	0.688	0.687
	MSE1	0.026	0.026	0.025	0.026	0.026	0.030	0.031	0.028	0.031
n_2	MSE2	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019
	MSE3	0.262	0.208	0.117	0.054	0.068	0.052	0.051	0.057	0.040
50	MSE4	0.261	0.205	0.116	0.054	0.065	0.050	0.047	0.053	0.033
	MSE5	0.261	0.206	0.116	0.054	0.066	0.050	0.048	0.054	0.035

Table 2. Estimates of $\theta(t)$ and their MSE's under the non-PHM

(1) *When* $\lambda_{11} = 1.0, \delta_1 = 0.5, \lambda_{12} = 0.067$
and $\lambda_{21} = 1.15, \delta_2 = 2.0, \lambda_{22} = 0.49$

n	t	0.127	0.186	0.261	0.481	0.638	0.839	1.102	1.450
	$\theta(t)$	0.209	0.368	0.613	1.532	2.342	3.539	5.322	8.028
	KER	0.266	0.373	0.589	1.503	2.082	3.207	4.411	5.916
n_1	COX	0.989	1.009	0.988	0.891	0.930	0.902	0.928	0.970
	GGH	0.048	0.076	0.147	0.270	0.347	0.465	0.540	0.587
30	GMH	0.051	0.083	0.166	0.327	0.453	0.660	0.839	1.001
	GHF	0.050	0.080	0.159	0.304	0.409	0.576	0.702	0.799
	MSE1	0.031	0.030	0.060	0.247	0.610	1.503	4.567	16.734
n_2	MSE2	0.723	0.525	0.235	0.455	2.051	7.025	19.372	49.866
	MSE3	0.030	0.094	0.235	1.613	4.008	9.490	22.925	55.415
30	MSE4	0.029	0.092	0.222	1.479	3.613	8.358	20.198	49.454
	MSE5	0.030	0.093	0.227	1.532	3.771	8.837	21.422	52.319
	KER	0.247	0.370	0.645	1.494	2.085	3.160	4.607	5.958
n_1	COX	1.109	1.025	1.021	1.033	1.078	0.994	1.042	1.045
	GGH	0.047	0.081	0.127	0.261	0.364	0.451	0.539	0.575
50	GMH	0.051	0.088	0.144	0.319	0.474	0.644	0.851	0.988
	GHF	0.049	0.085	0.137	0.296	0.430	0.562	0.709	0.792
	MSE1	0.010	0.019	0.035	0.143	0.327	0.957	3.106	9.833
n_2	MSE2	0.941	0.475	0.209	0.278	1.697	6.506	18.367	48.778
	MSE3	0.029	0.086	0.242	1.629	3.929	9.560	22.912	55.570
50	MSE4	0.028	0.083	0.228	1.490	3.516	8.425	20.057	49.605
	MSE5	0.028	0.084	0.233	1.544	3.680	8.896	21.328	52.401

Table 2.(continued)

(2) *When* $\lambda_{11} = 1.15, \delta_1 = 2.0, \lambda_{12} = 0.49$
and $\lambda_{21} = 1.0, \delta_2 = 0.5, \lambda_{22} = 0.067$

n	t	0.612	0.721	0.833	0.893	0.955	1.023	1.284	1.415
	$\theta(t)$	0.454	0.355	0.286	0.258	0.233	0.210	0.149	0.129
	KER	0.551	0.395	0.322	0.296	0.289	0.258	0.214	0.217
n_1	COX	1.145	1.118	1.114	1.211	1.032	1.085	1.136	1.169
	GGH	3.594	2.889	2.446	2.404	2.251	2.246	1.954	2.009
30	GMH	2.723	2.137	1.703	1.643	1.478	1.435	1.141	1.144
	GHF	3.015	2.394	1.958	1.903	1.741	1.712	1.418	1.447
	MSE1	0.052	0.030	0.023	0.022	0.022	0.018	0.016	0.028
n_2	MSE2	0.574	0.664	0.768	1.028	0.729	0.841	1.043	2.220
	MSE3	13.540	8.475	5.577	5.430	2.647	5.079	3.905	4.114
30	MSE4	6.998	4.275	2.456	2.268	1.803	1.795	1.129	1.165
	MSE5	8.836	5.508	3.370	3.181	4.793	2.706	1.862	1.981
	KER	0.505	0.367	0.306	0.285	0.246	0.237	0.198	0.185
n_1	COX	1.026	0.975	1.002	1.041	1.029	0.998	0.970	0.985
	GGH	3.357	2.753	2.550	2.416	2.282	2.092	1.931	1.887
50	GMH	2.594	2.017	1.788	1.632	1.506	1.327	1.121	1.082
	GHF	2.853	2.262	2.042	1.895	1.769	1.582	1.396	1.355
	MSE1	0.028	0.016	0.012	0.0135	0.009	0.0089	0.009	0.0097
n_2	MSE2	0.357	0.413	0.554	0.644	0.686	0.695	0.697	0.766
	MSE3	10.445	6.548	5.844	5.171	4.636	3.963	3.529	3.426
50	MSE4	5.667	3.157	2.578	2.100	1.781	1.379	1.031	0.981
	MSE5	7.082	4.139	3.506	2.967	2.588	2.085	1.702	1.635

APPENDIX

A.1. Uniform consistency of $\hat{\theta}_{KER}(t)$

Lemma 1. (Lenglart's inequality; Andersen & Gill, 1982) Let M be a local square integrable martingale. Then for all $\delta, \eta > 0$

$$P\left\{ \sup_{t\in[0,1]} |M(t)| > \eta \right\} \leq \frac{\delta}{\eta} + P\{< M, M > (1) > \delta\}.$$

Proof of Theorem 1. From the definition (2.2) of the kernel estimator $\hat{\theta}^{(n)}_{KER}(t)$, we have, under PHM

$$\hat{\theta}^{(n)}_{KER}(t) - \theta = \frac{\int_0^1 K^{(n)}\left(\frac{t-s}{b_n}\right)\frac{dN_2^{(n)}(s)}{Y_2^{(n)}(s)}}{\int_0^1 K^{(n)}\left(\frac{t-s}{b_n}\right)\frac{dN_1^{(n)}(s)}{Y_1^{(n)}(s)}} - \theta$$

$$= \frac{\int_0^1 K^{(n)}(\frac{t-s}{b_n})(\frac{dM_2^{(n)}(s)}{Y_2^{(n)}(s)} - \theta\frac{dM_1^{(n)}(s)}{Y_1^{(n)}(s)})}{\int_0^1 K^{(n)}(\frac{t-s}{b_n})\frac{dN_1^{(n)}(s)}{Y_1^{(n)}(s)}},$$

where the last equality follows from the facts that $dN_i^{(n)}(s) = dM_i^{(n)}(s) + \alpha_i(s)Y_i^{(n)}(s)$ and $\alpha_2(s) = \theta\alpha_1(s)$ under the PHM. Here $K/Y_i, i = 1,2$ is interpreted as 0 whenever $Y_i = 0, i = 1,2$. Hence $\hat{\theta}^{(n)}_{KER}(t) - \theta$ can be represented by a stochastic integral as follows :

$$\hat{\theta}^{(n)}_{KER}(t) - \theta = \int_0^1 B_2^{(n)}(s)dM_2^{(n)}(s) - \int_0^1 B_1^{(n)}(s)dM_1^{(n)}(s)$$

where

$$B_1^{(n)}(s) = \left(\int_0^1 K^{(n)}\left(\frac{t-s}{b_n}\right)\frac{dN_1^{(n)}(s)}{Y_1^{(n)}(s)}\right)^{-1}\frac{K^{(n)}\left(\frac{t-s}{b_n}\right)}{Y_1^{(n)}(s)}$$

and

$$B_2^{(n)}(s) = \left(\int_0^1 K^{(n)} \left(\frac{t-s}{b_n} \right) \frac{dN_1^{(n)}(s)}{Y_1^{(n)}(s)} \right)^{-1} \frac{K^{(n)} \left(\frac{t-s}{b_n} \right)}{Y_2^{(n)}(s)},$$

are the stochastic integrals. Since $B_1^{(n)}$ and $B_2^{(n)}$ are the predictable processes and $M_1^{(n)}$ and $M_2^{(n)}$ are the martingales.

By using Lemma 1, we have, for all $\delta, \eta > 0$,

$$P\left(\sup_{t\in[0,1]} |\hat{\theta}_{KER}^{(n)}(t) - \theta| > \eta \right) \leq \frac{\delta}{\eta^2} + P(< \hat{\theta}_{KER}^{(n)} - \theta > (1) > \delta) = \frac{\delta}{\eta^2}$$

$$+P\left(\left(\int_0^1 [B_2^{(n)}(s)]^2 d < M_2^{(n)} > (s) + \int_0^1 [B_1^{(n)}(s)]^2 d < M_1^{(n)} > (s) \right) > \delta \right)$$

By using $\frac{Y_i^{(n)}(t)}{n} \xrightarrow{P} y_i(t) > 0$, for each t, we complete the proof.

A.2. Asymptotic property of

$\hat{\theta}_{KER}(t)$

Lemma 2. (Martingale CLT; Andersen & Gill, 1982) Let $p \geq 1$ be fixed , and consider a sequence $N^{(n)}$ of k_n-variate counting processes with intensity processes $\Lambda^{(n)}$,and a sequence $H^{(n)}$ of $p \times k_n$-matrices of predictable processes, such that the stochastic integrals

$$U_j^{(n)}(t) = \int_0^t \sum_{h=1}^{k_n} H_{jh}^{(n)}(s)\{dN_h^{(n)}(s) - \Lambda_h^{(n)}(s)\, ds\};\ j = 1, \cdots, p;$$

are well defined. If, as $n \to \infty$,

$$< U_j^{(n)}, U_l^{(n)} > (t) \longrightarrow C_{jl}(t);\ j,l = 1, \cdots, p,\ t \in [0,1], \qquad (A.1)$$

where C is $p \times p$ matrix of continuous functions on [0,1] forming the covariance function of a p-variate Gaussian martingale $U^{(\infty)}$ with $U^{(\infty)}(0) = 0$, and if for all $\epsilon > 0$, as $n \to \infty$,

$$\int_0^1 \sum_{h=1}^{k_n} [H_{jh}^{(n)}(t)]^2 \Lambda_h^{(n)}(t) I\{|H_{jh}^{(n)}(t)| > \epsilon\}\, dt \xrightarrow{P} 0;\ j = 1, \cdots, p; \quad (A.2)$$

then

$$U^{(n)} \xrightarrow{\mathcal{D}} U^{(\infty)}, \quad \text{as } n \to \infty, \quad in \;\; D([0,1]^p).$$

Proof of Theorem 2. Let $Z^{(n)}(t) \equiv \sqrt{nb_n}(\hat{\theta}^{(n)}_{KER}(t) - \theta)$. Then, the process $Z^{(n)}(t)$ is simply

$$Z^{(n)}(t) = \frac{\sqrt{nb_n}\int_0^1 K^{(n)}\left(\frac{t-s}{b_n}\right)\left(\frac{dM_2^{(n)}(s)}{Y_2^{(n)}(s)} - \theta\frac{dM_1^{(n)}(s)}{Y_1^{(n)}(s)}\right)}{\int_0^1 K^{(n)}\left(\frac{t-s}{b_n}\right)\frac{dN_1^{(n)}(s)}{Y_1^{(n)}(s)}}$$
$$= \int_0^1 H_2^{(n)}(s)dM_2^{(n)}(s) - \int_0^1 H_1^{(n)}(s)dM_1^{(n)}(s)$$

where

$$H_i^{(n)}(s) = \sqrt{nb_n}B_i^{(n)}(s), i = 1, 2,$$

and $B_1^{(n)}(s)$, $B_2^{(n)}(s)$ are defined in the proof of Theorem 1. Since $H_1^{(n)}(s)$ and $H_2^{(n)}(s)$ are the predictable processes and $M_1^{(n)}(s)$ and $M_2^{(n)}(s)$ are the martingales, $Z^{(n)}(t)$ is the stochastic integral with respect to $M_1^{(n)}(t)$ and $M_2^{(n)}(t)$.

Now, we need check two conditions (A.1) and (A.2) to apply Lemma 2. Since

$$\{|H_i^{(n)}(s)| > \epsilon\} =$$
$$\left\{\left|\frac{1}{\sqrt{n}}\left(\int_0^1 K^{(n)}\left(\frac{t-s}{b_n}\right)\frac{dN_i^{(n)}(s)}{Y_i^{(n)}(s)}\right)^{-1}\frac{K^{(n)}(\frac{t-s}{b_n})}{Y_i^{(n)}(s)/n}\right| > \epsilon\right\}$$

and the condition (ii) of Theorem 1, we have

$$I\{|H_i^{(n)}(s)| > \epsilon\} \xrightarrow{p} 0 \quad \text{uniformly on} \quad [0,1], i = 1, 2.$$

That shows that the condition (A.2) of Lemma 2 is satisfied.

Next, from the definition of the variance process $< Z^{(n)} > (t)$, we have

$$< Z^{(n)} > (t)$$

$$= \frac{\theta^2}{\left(\int_{-1}^{1} K^{(n)}(u)\frac{dN_1^{(n)}(t-b_n u)}{Y_1^{(n)}(t-b_n u)}\right)^2}$$

$$\times \int_{-1}^{1} K^{(n)}(u)^2\left(\frac{n}{Y_1^{(n)}(t-b_n u)} + \frac{n}{\theta Y_2^{(n)}(t-b_n u)}\right)\alpha_1(t-b_n u)du$$

$$\xrightarrow{p} \frac{\theta^2}{\alpha_1(t)}\left(\frac{1}{\theta y_2(t)} + \frac{1}{y_1(t)}\right)\int_{-1}^{1} K(u)^2 du.$$

because of the conditions of Theorem 2 and (i), (ii) of Theorem 1. Hence, $< Z^{(n)} > (t)\xrightarrow{p}\sigma_{KER}^2(t)$. Therefore, by Lemma 2, $Z^{(n)}(t)$ converges in distribution to $N(0,\sigma_{KER}^2(t))$. So, we complete the proof.

A.3. Uniform consistancy of $\hat{\sigma}_{KER}(t)$

Proof of Corollary 1. For convenience, denote $\hat{\theta}_{KER}^{(n)}(t)$ by $\hat{\theta}$. Furthermore, by Lemma 1, we have

$$\frac{1}{b_n}\int_0^1 K^{(n)}\left(\frac{t-s}{b_n}\right)\frac{dN_1^{(n)}(s)}{Y_1^{(n)}(s)} \xrightarrow{p} \alpha_1(t), \quad \text{as} \quad n\to\infty. \qquad (A.3)$$

From the (2.3) and (2.4) , we have

$$\sup_{t\in[0,1]} |\hat{\sigma}_{KER}^{(n)^2}(t) - \sigma_{KER}^2(t)| \leq$$

$$\sup_{t\in[0,1]}\left|\hat{\theta}^2\frac{\int_{-1}^{1} K^{(n)^2}(u)(\frac{n}{\hat{\theta}Y_2^{(n)}(t-b_n u)} + \frac{n}{Y_1^{(n)}(t-b_n u)})\alpha_1(t-b_n u)du}{\left(\int_{-1}^{1} K^{(n)}(u)\frac{dN_1^{(n)}(t-b_n u)}{Y_1^{(n)}(t-b_n u)}\right)^2}\right.$$

$$\left. - \frac{\hat{\theta}^2\int_{-1}^{1} K^{(n)^2}(u)\left(\frac{1}{\theta y_2(t)} + \frac{1}{y_1(t)}\right)\alpha_1(t)du}{\left(\int_{-1}^{1} K^{(n)}(u)\frac{dN_1^{(n)}(t-b_n u)}{Y_1^{(n)}(t-b_n u)}\right)^2}\right|$$

$$+ \sup_{t\in[0,1]} \left| \left[\left(\frac{\hat{\theta}}{\int_{-1}^{1} K^{(n)}(u) \frac{dN_1^{(n)}(t-b_n u)}{Y_1^{(n)}(t-b_n u)}} \right)^2 - \left(\frac{\theta}{\alpha_1(t)} \right)^2 \right] \right.$$

$$\left. \times \left(\frac{1}{\theta y_2(t)} + \frac{1}{y_1(t)} \right) \alpha_1(t) \int_{-1}^{1} K^{(n)^2}(u) du \right|$$

$= (I) + (II).$

It is sufficient to show that $(I) \xrightarrow{p} 0$ and $(II) \xrightarrow{p} 0$. Using Theorem 1 and Theorem 2, we have

$$\int_{-1}^{1} K^{(n)^2}(u) \left(\frac{\alpha_1(t-b_n u)}{\theta Y_2^{(n)}(t-b_n u)/n} - \frac{\alpha_1(t)}{\theta y_2(t)} \right) du$$
$$+ \int_{-1}^{1} K^{(n)^2}(u) \left(\frac{\alpha_1(t-b_n u)}{Y_1^{(n)}(t-b_n u)/n} - \frac{\alpha_1(t)}{y_1(t)} \right) du \xrightarrow{p} 0 \quad \text{as } n \to \infty.$$

Therefore $(I) \xrightarrow{p} 0$ is satisfied.

Also,

$$(II) = \sup_{t\in[0,1]} \left| \left(\frac{\hat{\theta}}{\int_{-1}^{1} K^{(n)}(u) \frac{dN_1^{(n)}(t-b_n u)}{Y_1^{(n)}(t-b_n u)}} - \frac{\theta}{\alpha_1(t)} \right) \right.$$

$$\times \left(\frac{\hat{\theta}}{\int_{-1}^{1} K^{(n)}(u) \frac{dN_1^{(n)}(t-b_n u)}{Y_1^{(n)}(t-b_n u)}} + \frac{\theta}{\alpha_1(t)} \right)$$

$$\left. \times \left(\frac{1}{\theta y_2(t)} + \frac{1}{y_1(t)} \right) \alpha_1(t) \int_{-1}^{1} K^{(n)^2}(u)\, du \right|.$$

By Theorem 1 and (A.3), we have

$$\frac{\hat{\theta}}{\int_{-1}^{1} K^{(n)}(u)\frac{dN_1^{(n)}(t-b_n u)}{Y_1^{(n)}(t-b_n u)}} \quad \xrightarrow{p} \quad \frac{\theta}{\alpha_1(t)}.$$

Hence $(II) \xrightarrow{p} 0$ as $n \to \infty$.
Therefore we complete the proof.

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