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A Covariate-adjusted Logrank Test for Paired Survival Data[1]

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Abstract

In this paper, a covariate adjusted logrank test is considered for censored paired data under the Cox proportional hazard model. The proposed score test resembles the adjusted logrank test of Tsiatis, Rosner and Tritchler (1985), which is derived from the partial likelihood. The dependence structure for paired data is accommodated into the test statistic by using 'sum of square type' variance estimators. Several weight functions are also considered, which produce a class of covariate adjusted weighted logrank tests. Asymptotic normality of the proposed test is established and simulation studies with moderate sample size show the proposed test works well, particularly when there are dependence structure between treatment and covariates.

Keywords : proportional hazard model, score test, restricted maximum partial likelihood estimate

1. Introduction

In analyzing survival data, we are often interested in the comparison of two treatments. According to increasing interest in this area, many important procedures have been developed for a couple of past decades as shown in Fleming and Harrington (1991) and Klein and Moeschberger (1997). Especially the class of weighted logrank tests and its various extensions have been studied extensively and it led the logrank test to become the most widely used one.

Moreover, Cox (1972) proposed the proportional hazard regression model and it was found that the logrank test could be derived from the Cox's model based on the partial likelihood method. Counting on the proportional hazard model and the partial likelihood, the covariate adjusted logrank test was originally proposed by Tsiatis, Rosner and Tritchler (1985). Adjustment of covariates have also been studied by many other researchers such as Lin and Wei (1989), Slud (1991), Gu and Ying (1995), Kong and Slud (1997) and Lin, Yao and Ying (1999) under the proportional hazard model and Lin (1992) under the accelerated life time model.

The procedures proposed by the aforementioned studies can be applied to the independent

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sample case. In many clinical trials, however, we might encounter paired data such as couples of eyes, twins and litters of rats. Jung (1999) and Jeong (1999) treated the logrank test for paired censored data in the absence of covariate. Huster, Brookmeyer and Self (1989) developed a parametric procedure with covariate adjustment for paired data under the Clayton-Oakes model (Clayton 1978, Oakes 1982). For more general multivariate data, Wei, Lin and Weissfeld (1989) presented a marginal approach based on the proportional hazard model., and Lee, Wei and Ying (1993) considered the accelerated life time model.

In this paper, we consider a covariate adjusted logrank test for censored paired data under the Cox proportional hazard model. The proposed score test resembles the adjusted logrank test of Tsiatis, Rosner and Tritchler (1985), which is derived from the partial likelihood. In addition to the idea of Tsiatis et al., a modification of the marginal approach proposed by Wei, Lin and Weissfeld (1989) plays an important role in model construction. This modelling methods are closely explained and examined in section 2. In section 3, test statistics based on score statistics are proposed and their large sample distributional properties are studied. The dependence structure is accommodated into the test statistic by using a 'sum of square type' variance, and then simple consistent estimators of the asymptotic variances are obtained. To assess the moderate sample size properties of the proposed tests, some simulation studies are carried out and the results are reported in section 4. Concluding remarks are presented in section 5.

2. Modelling

Consider a clinical trial with n pairs of subjects. Assume members of a pair are randomly assigned to one of two treatments 1 and 2. Let T and C denote failure time and censoring time of a member. Denote Z to be treatment indicator, $Z=1$ for treatment 1 and $Z=0$ otherwise, and W to be p dimensional covariate vector. Assume T and C are independent given treatment indicator and covariates. Define observable time $X=T\wedge C$, censoring indicator $\delta=I(X=T)$, at-risk process $Y(t)=I(X\geq t)$ and counting process $N(t)=I(X\leq t,\delta=1)$. For the member of pair i associated with treatment k, we observe a random vector $(X_{ki},\delta_{ki},Z_{ki},W_{ki})$, and we assume that the observable random vectors of pair i, $\{(X_{1i},\delta_{1i},Z_{1i},W_{1i}),(X_{2i},\delta_{2i},Z_{2i},W_{2i})\}$, are identically and independently distributed. If the covariate vector W is time-dependent, it is written as $W(t)$. Assume that the members in each pair are exchangeable with a common marginal distribution.

Two interesting real examples included in such a case were cited in Lee et al. (1993) as follows:

In a litter-matched tumorigenesis experiment (Mantel, Bohidar and Ciminera (1977)), the investigator were interested in assessing whether the tumor appearance for the drug-treated group tend to be shorter than that for the control group. There are two rats (In fact, there are three rats in the experiment.) in each of the 50 female litters in the study. In each litter, one rat is drug-treated and the other is control. Another example is from the Diabetic Retinopathy Study, a randomized trial conducted by the National Eye Institute to evaluate the photocoagulation treatment for proliferative diabetic retinopathy (Diabetic Retinopathy Study Group (1985)). In this study, photocoagulation was randomly assigned to eye for each study patient, with the other eye serving as an untreated control. One of this study's main objectives was to investigate whether the time of occurrence of severe visual loss for the treated eye is longer than that for the control. Some important eye- and patient-specific covariates were also recorded.

To analyse such data, we consider the following proportional hazard model proposed by Cox (1972):

$$\lambda_{ki}(t \mid Z_{ki}, W_{ki}) = \lambda_0(t) e^{\theta Z_{ki}} e^{\beta' W_{ki}}, \qquad k=1,2;\ i=1,\cdots,n, \tag{2.1}$$

where $\lambda(t \mid Z, W)$ denotes the conditional hazard function at time t given treatment indicator Z and covariates W, $\lambda_0(t)$ represents an arbitrary baseline hazard, and β is a common regression parameter. Under this model, we are interested in testing the null hypothesis of no treatment effect $H_0: \theta = 0$. In model (2.1), the exponential link function can be replaced with any other smooth link functions used in Tsiatis et al. (1985), Gu and Ying (1995) and Kong and Slud (1997), but we will consider only the exponential one for simplicity.

Now, we can think more general model than (2.1). First of all, we can separate β into treatment-wise parameters β_1 and β_2 if necessary. In addition, the popular weight function of the logrank test, $q(t)$, such as Gehan-Wilcoxon and Peto-Prentice weights, is able to be included in the model. Such an extended model is given by

$$\lambda_{ki}(t \mid Z_{ki}, W_{ki}) = \lambda_0(t) e^{\theta q(t) Z_{ki}} e^{\beta_k' W_{ki}}, \qquad k=1,2;\ i=1,\cdots,n. \tag{2.2}$$

In this model, we also assume a common baseline hazard.

In the literature, the model (2.1) was originally introduced by Tsiatis et al. (1985) under the sequential analysis setting. It was also used by Gu and Ying (1995) and Kong and Slud (1997). The weight function in the model (2.2) was proposed by Lin et al. (1999) in the sequential tests framework based on the stochastic curtailment. All procedures proposed in the above researches were devised for the independent sample case.

On the contrary, when multivariate data are given, Wei et al. (1989) proposed a marginal approach where the proportional hazard model is applied to each failure type or each member of a pair, not to each treatment. In this approach, they allowed to use different baseline hazards and separate regression parameters. So, their model for paired data can be given by

$$\lambda_{ki}(t \mid W_{ki}) = \lambda_{k0}(t) e^{\beta_k' W_{ki}}, \quad k=1,2;\ i=1,\cdots,n, \tag{2.3}$$

where k indicates kth member in each pair and the treatment indicator is included in the covariate vector W. If the treatment indicator is the first component of W, the null hypothesis of no treatment effect will be expressed by $H_0: \beta_{11} = \beta_{21}$, where $\beta_{k1}\ (k=1,2)$ denote treatment effect for kth member in each pair.

Compared with Wei's model (2.3), the model (2.1) (or (2.2)) is modelling treatment-wise margins and assumes common baseline hazard. It means that the model (2.1) has a stronger assumption that treatment-wise marginal distributions under the null hypothesis are equal. This assumption may, however, be relaxed to some extent if we use separate parameters as shown in the model (2.2). Though the assumptions of model (2.1) are stronger than those of (2.3), we expect model (2.1) gives simpler procedure than (2.3) as long as we are primarily interested in testing the null hypothesis of no treatment effect. In fact, the model (2.1) is directly focused on testing of the treatment effect θ while (2.3) on the inferences for the regression parameter β.

In the sequel, main results will be described mainly based on the model (2.1) for convenience.

3. Test Statistics

We derive the test statistic from the partial likelihood under the assumption that treatment groups are independent. Huster, Brookmeyer and Self (1989) referred it as an independent working model. We will also use this term in the sequel. Denote the partial likelihood as $L(\theta, \beta)$ under the independent working model, then the score statistic for testing the null hypothesis is $n^{-1/2}U_\theta(\hat{\beta})$, where

$$U_\theta(\beta) = [\frac{\partial}{\partial\theta} \log L(\theta, \beta)]_{\theta=0},$$

and $\hat{\beta}$ denotes the restricted maximum partial likelihood estimate of β under H_0. That is, it is the solution of $U_\beta(\hat{\beta})=0$, where $U_\beta(\beta) = \frac{\partial}{\partial\beta} \log L(0, \beta)$.

As shown in Tsiatis et al. (1985) and Gu and Ying (1995), the asymptotic distribution of the score statistic $n^{-1/2}U_\theta(\hat{\beta})$ is derived by approximating $U_\theta(\hat{\beta})$ with $U_\theta(\beta)$ and $U_\beta(\beta)$. When Z and W are independent, Tsiatis et al. (1985) showed that $n^{-1/2}[U_\theta(\hat{\beta}) - U_\theta(\beta)]$ converges to zero in probability, and that under H_0, $n^{-1/2}U_\theta(\beta)$ is asymptotically normally distributed with mean zero and variance σ_{zz}, which is the limit of $Var[n^{-1/2}U_\theta(\beta)]$. More generally, Gu and Ying (1995) showed that $n^{-1/2}U_\theta(\hat{\beta})$ is asymptotically equivalent to $n^{-1/2}[U_\theta(\beta) - \sigma_{zw}\sigma_{ww}^{-1}U_\beta(\beta)]$, and that under H_0, it is asymptotically normally distributed with mean zero and variance $\sigma^2 = \sigma_{zz} - \sigma_{zw}\sigma_{ww}^{-1}\sigma_{wz}$, where σ_{zw} and σ_{ww} are the limits of $Cov[n^{-1/2}U_\theta(\beta), n^{-1/2}U_\beta(\beta)]$ and $Var[n^{-1/2}U_\beta(\beta)]$ respectively. Here σ_{wz} is the transpose of vector σ_{zw}. Note that σ_{zw} equals zero when Z and W are independent.

The arguments discussed under the independent working model are applied to the paired data case in the same manner. Only difference is that we should construct consistent estimators of variance and covariance terms accommodating dependence structure of paired data in it. To do this, we rewrite the score statistic $U_\theta(\beta)$ in the counting process notations:

$$\begin{aligned} U_\theta(\beta) &= \sum_i \sum_k \int [Z_{ki} - \bar{Z}(t)] dN_{ki}(t) \\ &= \sum_i \int \frac{S_1(\beta, t) S_2(\beta, t)}{S_1(\beta, t) + S_2(\beta, t)} [\frac{dN_{1i}(t)}{S_1(\beta, t)} - \frac{dN_{2i}(t)}{S_2(\beta, t)}], \end{aligned} \tag{3.1}$$

where

$$\begin{aligned} \bar{Z}(t) &= \sum_i \sum_k Z_{ki} Y_{ki}(t) \exp[\beta' W_{ki}(t)] / \{ \sum_i \sum_k Y_{ki}(t) \exp[\beta' W_{ki}(t)] \} \\ &= S_1(\beta, t) / [S_1(\beta, t) + S_2(\beta, t)] \end{aligned} \tag{3.2}$$

and

$$S_k(\beta, t) = n^{-1} \sum_i Y_{ki}(t) \exp[\beta' W_{ki}(t)].$$

The second equations of (3.1) and (3.2) are obtained by replacing Z_{1i} and Z_{2i}. with 1 and 0.

Define the martingales

$$M_{ki}(t) = N_{ki}(t) - \int_0^t Y_{ki}(s) \exp[\beta' W_{ki}(s)] d\Lambda_0(s), \qquad k = 1, 2,$$

where $\Lambda_0(t)$ is the cumulative baseline hazard function, then it is shown that $N_{ki}(t)$ in (3.1) can be replaced by $M_{ki}(t)$ under H_0. Hence by observing $S_k(\beta, t)$ converges in probability to $s_k(\beta, t) = E[S_k(\beta, t)]$, $U_\theta(\beta)$ is approximated by sum of iid martingales under H_0 and the asymptotic normality is established by the martingale central limit theorem.

Moreover, following Lin et al. (1999), we can show that the asymptotic normality also holds if we have a random weight function $Q(t)$ which converges in probability to the deterministic weight function $q(t)$ uniformly in t. But, the assumption of common baseline hazard seems to be inevitable. That is, under the model (2.2) with a common β, the asymptotic normality of $U_\theta(\beta)$ is established simply by plugging the weight function $Q(t)$ into the score statistic. In this case, the score statistic in (3.1) becomes

$$U_\theta(\beta) = \sum_i \int Q(t) \frac{S_1(\beta, t) S_2(\beta, t)}{S_1(\beta, t) + S_2(\beta, t)} [\frac{dN_{1i}(t)}{S_1(\beta, t)} - \frac{dN_{2i}(t)}{S_2(\beta, t)}]. \tag{3.3}$$

The logrank statistic uses $Q(t) = 1$. Lin et al. (1999) suggested each two weights with and without covariate adjustment for the Gehan - Wilcoxon and the Prentice - Wilcoxon statistic. For the Gehan - Wilcoxon statistic, $Q(t) = n^{-1} \sum_i \sum_k Y_{ki}(t)$ or $Q(t) = S_1(\beta, t) + S_2(\beta, t)$, where β can be replaced with its common estimator if necessary. For the Prentice - Wilcoxon statistic, one choice of $Q(t)$ is the left continuous version of the usual Kaplan-Meier estimator $\hat{S}^-(t)$ for the marginal survival function of T based on $\{X, \delta\}$ in the pooled sample. The other is the baseline survival function estimator $e^{-\widehat{\Lambda}_0(t)}$, where

$$\widehat{\Lambda}_0(t) = \sum_i \sum_k \int_0^t \frac{dN_{ki}(u)}{n[S_1(\widehat{\beta}, u) + S_2(\widehat{\beta}, u)]},$$

which is the Breslow estimator of $\Lambda_0(t)$.

From the above arguments, when Z and W are independent, $n^{-1/2}U_\theta(\widehat{\beta})$ is asymptotically normally distributed under H_0 with mean zero and variance σ_{zz}, which can be estimated consistently with

$$\hat{\sigma}_{zz} = n^{-1}\sum_i [\widehat{U}^i_\theta(\widehat{\beta})]^2, \tag{3.4}$$

where $U^i_\theta(\beta)$ denotes the ith component score of $U_\theta(\beta) = \sum_i U^i_\theta(\beta)$ in (3.1) or (3.3), and $\widehat{U}^i_\theta(\widehat{\beta})$can be obtained by replacing $\Lambda_0(t)$ with the Breslow estimator $\widehat{\Lambda}_0(t)$ in the martingales $M_{ki}(t)$. Similarly, $\widehat{U}^i_\beta(\widehat{\beta})$ can also be obtained.

When Z and W are dependent, applying the similar arguments to $U_\beta(\beta)$, we obtain the asymptotic results that $n^{-1/2}U_\theta(\widehat{\beta})$ is asymptotically normally distributed under H_0 with mean zero and variance σ^2, which can be estimated consistently with

$$\hat{\sigma}^2 = \hat{\sigma}_{zz} - \hat{\sigma}_{zw}\ \hat{\sigma}_{ww}^{-1}\ \hat{\sigma}_{wz}, \tag{3.5}$$

where

$$\hat{\sigma}_{zw} = n^{-1}\sum_i [\widehat{U}^i_\theta(\widehat{\beta})][\widehat{U}^i_\beta(\widehat{\beta})]', \quad \hat{\sigma}_{ww} = n^{-1}\sum_i [\widehat{U}^i_\beta(\widehat{\beta})][\widehat{U}^i_\beta(\widehat{\beta})]'.$$

Here we denote

$$U_\beta(\beta) = \sum_i \sum_k \int [W_{ki}(t) - \overline{W}(t)]dN_{ki}(t) = \sum_i U^i_\beta(\beta),$$

$$\overline{W}(t) = \sum_i \sum_k W_{ki}(t)\, Y_{ki}(t) \exp[\beta' W_{ki}(t)] / \{\sum_i \sum_k Y_{ki}(t) \exp[\beta' W_{ki}(t)]\}.$$

Until now, we proposed two test statistics, $n^{-1/2}U_\theta(\widehat{\beta})/\sqrt{\hat{\sigma}_{zz}}$ when Z and W are independent and $n^{-1/2}U_\theta(\widehat{\beta})/\hat{\sigma}$ when Z and W are dependent, and we showed that they have the standard normal distribution as their asymptotic distributions. The proposed statistics can also be used in independent sample case as alternatives to those in Tsiatis et al. (1985) and Gu and Ying (1995).

In fact, properties of these tests are found in two sum of square type variance estimators in (3.4) and (3.5). Their simple forms provide a relatively simple but unified variance estimators to paired data and reduce amount of calculations in computing variance formulas. For paired data, a few applications of this method are found in Lam and Longnecker (1983) for constructing Wilcoxon test in the absence of censoring, in O'Brien and Fleming (1987), Jung (1999) and Jeong (1999) for the logrank tests, and in Hsu and Prentice (1996) for the independence test.

4. Simulation Studies

In section 3, we proposed testing procedures based on the partial likelihood under the model (2.1) and (2.2), and investigated their large sample properties. To assess their moderate sample size properties, we carried out simulation studies. The simulation schemes and results here are based on the model (2.2).

The empirical rejection probabilities under the null and the empirical powers under alternative $\theta=0.5$ are computed for the five weight functions described in section 3, the logrank (LR), Gehan-Wilcoxon without and with covariates (GW1, GW2), and Prentice-Wilcoxon without and with covariates (PW1, PW2). For comparison, we considered 4 tests. Test 1 and 2 are for adjusted and unadjusted ones considering dependence between members of a pair, whereas test 3 and 4 denote adjusted and unadjusted ones ignoring dependence, respectively. Test 3 among 4 tests is the same as Gu and Yang's (1995).

We consider a single covariate W, and assume Z and W are both $B(1,0.5)$ variables with the correlation, γ, of 0 and 0.5, and the common regression parameters β is taken as 0 and 0.5. To generate a pair of random numbers of Z and W, first generate two uniform random numbers u_1 and u_2 from $U(0,1)$, and then,

Table 1. Empirical type 1 errors of simulation results ($\theta=0$)

			$\rho=0$				$\rho=0.5$			
γ	β	weight	test 1	2	3	4	test 1	2	3	4
0	0	LR	0.069	0.065	0.072	0.069	0.057	0.052	0.018	0.017
		GW1	0.060	0.058	0.062	0.058	0.046	0.045	0.016	0.016
		GW2	0.060	0.058	0.062	0.058	0.046	0.044	0.016	0.016
		PW1	0.058	0.057	0.058	0.058	0.050	0.049	0.015	0.015
		PW2	0.060	0.059	0.061	0.059	0.051	0.051	0.015	0.015
	0.5	LR	0.057	0.052	0.061	0.057	0.053	0.050	0.016	0.016
		GW1	0.056	0.056	0.053	0.052	0.051	0.050	0.013	0.012
		GW2	0.056	0.055	0.054	0.053	0.048	0.047	0.013	0.012
		PW1	0.055	0.052	0.057	0.056	0.053	0.050	0.015	0.014
		PW2	0.061	0.060	0.060	0.059	0.057	0.054	0.016	0.014
0.5	0	LR	0.059	0.029	0.062	0.032	0.059	0.042	0.016	0.012
		GW1	0.057	0.035	0.057	0.037	0.050	0.033	0.013	0.009
		GW2	0.057	0.035	0.057	0.037	0.049	0.033	0.013	0.009
		PW1	0.058	0.032	0.057	0.034	0.050	0.031	0.013	0.009
		PW2	0.056	0.033	0.062	0.034	0.046	0.031	0.014	0.010
	0.5	LR	0.058	0.026	0.061	0.025	0.067	0.039	0.017	0.014
		GW1	0.060	0.030	0.063	0.031	0.055	0.045	0.024	0.016
		GW2	0.059	0.031	0.064	0.028	0.058	0.044	0.025	0.017
		PW1	0.059	0.029	0.061	0.028	0.060	0.043	0.018	0.015
		PW2	0.057	0.024	0.062	0.025	0.065	0.046	0.021	0.013

Table 2. Empirical powers of simulation results ($\theta=0.5$)

			$\rho=0$				$\rho=0.5$			
γ	β	weight	test 1	2	3	4	test 1	2	3	4
0	0	LR	0.803	0.800	0.815	0.811	0.935	0.935	0.857	0.856
		GW1	0.719	0.716	0.724	0.718	0.862	0.862	0.763	0.757
		GW2	0.719	0.716	0.724	0.717	0.862	0.861	0.763	0.758
		PW1	0.750	0.745	0.760	0.754	0.893	0.892	0.813	0.812
		PW2	0.751	0.745	0.763	0.760	0.895	0.894	0.810	0.807
	0.5	LR	0.825	0.818	0.818	0.813	0.946	0.945	0.883	0.880
		GW1	0.713	0.709	0.721	0.716	0.864	0.856	0.768	0.765
		GW2	0.703	0.700	0.713	0.709	0.852	0.848	0.758	0.754
		PW1	0.754	0.752	0.760	0.760	0.901	0.899	0.811	0.807
		PW2	0.772	0.766	0.777	0.770	0.916	0.915	0.834	0.830
0.5	0	LR	0.689	0.583	0.689	0.590	0.819	0.777	0.667	0.616
		GW1	0.562	0.484	0.572	0.489	0.704	0.665	0.555	0.517
		GW2	0.556	0.482	0.571	0.490	0.702	0.663	0.553	0.516
		PW1	0.606	0.519	0.619	0.527	0.756	0.708	0.599	0.562
		PW2	0.612	0.530	0.620	0.528	0.771	0.721	0.605	0.568
	0.5	LR	0.678	0.612	0.681	0.625	0.826	0.780	0.686	0.646
		GW1	0.575	0.511	0.588	0.522	0.707	0.675	0.559	0.533
		GW2	0.557	0.502	0.568	0.509	0.687	0.652	0.543	0.517
		PW1	0.616	0.545	0.628	0.561	0.757	0.713	0.610	0.573
		PW2	0.641	0.565	0.648	0.580	0.775	0.737	0.635	0.598

if $u_1 \geq (1-\gamma)/2$, set $W_1=1$, otherwise, set $W_1=0$

if $u_2 \geq (1+\gamma)/2$, set $W_2=1$, otherwise, set $W_2=0$.

Given Z and W, the pairs of survival times, (T_1, T_2), were generated from bivariate exponential distributions by Moran (1967) with marginal failure rates $\lambda_{ki}=\lambda(Z_{ki}, W_{ki})=\exp(\theta Z_{ki}+\beta W_{ki})$, $k=1,2; i=1,\cdots,n$ and the correlation coefficient $\rho=0,0.5$.

For the censoring times, we considered $C_{ki}\sim U(0,3/\lambda_{ki})$ for $k=1,2; i=1,\cdots,n$ which gives about 30% censoring in each group. For each combinations of simulation parameters, 1000 samples of size $n=100$ were generated.

Empirical type 1 errors are shown in Table 1. The logrank weight is slightly anti-conservative in many cases, specifically under dependence. It seems, as noted in Jeong(1999) because both the logrank weight and the sum of squared type variance estimator put more weight on late time than Prentice - Wilcoxon and Gehan - Wilcoxon weights. Empirical type 1 errors of adjusted tests, test 1 and 3, are close to the nominal level. Unadjusted tests, test 2 and 4, are also good for $\gamma=0$, but are conservative for $\gamma=0.5$. This occurs, of course, since the unadjusted tests ignore the covariates when there exists dependence between treatment and covariates. Under dependence ($\rho=0.5$), tests 3 and 4 are also showing conservativeness because of ignoring dependence. Any special difference is not found according to the value of β.

Empirical powers are reported in Table 2. For independence and no covariate, all 4 tests have good powers. As expected, under dependence, test 1 and 2 are more powerful than the others and comparable each other. With covariates, adjusted tests, test 1 and 3 have larger power and comparable each other. In empirical power, the logrank weight dominate the others and Prentice - Wilcoxon weight is next for all cases studied in this simulation. From this, we guess that the logrank weight is optimal for the exponential distributions.

5. Remarks

In the model (2.1) and (2.2), we were primarily interested in the treatment effect parameter θ. We proposed a score statistic and established its asymptotic normality under the model (2.2) with a common β. The same results will be obtained from the martingale framework when we use separate parameters β_1 and β_2. If we want inferences on the regression parameters β_1 and β_2, we have mentioned that Wei et al.'s (1989) marginal model is proper. In this case, the model (2.2) could be used as an alternative to Wei's model. Furthermore the model (2.2) can be applied to detecting the interaction effect between treatment and covariates in the sense that the hypothesis of no interaction effect will be expressed by $H_0: \beta_1 = \beta_2$. Study on this topic will be useful in a clinical trial where the side effects of a treatment are concerned.

In the independent sample problem, power of the adjusted logrank tests were evaluated analytically in the aforementioned studies such as Tsiatis et al. (1985), Gu and Ying (1995), Kong and Slud (1997) and Lin et al. (1999). For paired data, however, a bivariate hazard function is involved in evaluating power, and as pointed out in Jung (1999), it makes the power evaluation difficult up to now.

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