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OMNIBUS TESTS FOR COMPARISON OF COMPETING RISKS WITH COVARIATE EFFECTS VIA ADDITIVE RISK MODEL

by

DUYTRAC VU NGUYEN

Under the direction of Yichuan Zhao

ABSTRACT

It is of interest that researchers study competing risks in which subjects may fail from any one of *K* causes. Comparing any two competing risks with covariate effects is very important in medical studies. This thesis develops omnibus tests for comparing cause-specific hazard rates and cumulative incidence functions at specified covariate levels. In the thesis, the omnibus tests are derived under the additive risk model, that is an alternative to the proportional hazard model, with by a weighted difference of estimates of cumulative cause-specific hazard rates. Simultaneous confidence bands for the difference of two conditional cumulative incidence functions are also constructed. A simulation procedure is used to sample from the null distribution of the test process in which the graphical and numerical techniques are used to detect the significant difference in the risks. A melanoma data set is used for the purpose of illustration.

INDEX WORDS: Cause-specific hazard rates, Additive risk model, Cumulative incidence function, Confidence bands, Competing risks.

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DUYTRAC VU NGUYEN

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Science

in the College of Arts and Sciences

Georgia State University

2007

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DUYTRAC VU NGUYEN

Major Professor: Dr. Yichuan Zhao
Committee: Dr. Yu-Sheng Hsu
Dr. Xu Zhang
Dr. Gengsheng (Jeff) Qin

Electronic Version Approval:

Office of Graduate Studies
College of Arts and Sciences
Georgia State University
May 2007

ACKNOWLEDGEMENTS

I would like to acknowledge those who have helped me in the completion of this thesis. First of all, I must thank Dr. Zhao who had been an extraordinary advisor, a great professor, and a great supporter. This thesis cannot be finished without him. It has been a great learning experience for me to work and take his classes for almost two years.

I would like to acknowledge the other members of my committee, Dr. Yu-Sheng Hsu, Dr. Gengsheng (Jeff) Qin, and Dr. Xu Zhang for taking the time to read this thesis and provide useful comments.

I'd also like to thank all other professors in the Mathematics & Statistics Department at Georgia State University for their supports and encouragement. They have been a great helper and very generous. I thank you for everything.

Lastly, I want to acknowledge the support of my parents and my fiancé who endured this long process with me, always offering support and love.

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List of Abbreviation

MM:	Malignant Melanoma
CR:	Censor Rate

Chapter One: Introduction

Competing risks has been arising in many applications in medicine nowadays. In competing risks people can study the cause of risk that each subject may fail in. It is important to discover which cause affects the death of the subject because it will help researchers have a good way of treatment to patients or sometimes they can design a new vaccine for a disease. Each subject is observed with a time to failure and an indicator that tells which of the competing risks causes the failure. The classic example of competing risks is competing causes of death, such as cancer, heart disease, AIDS, etc. For example, in cancer clinical trials, patients being followed up for relapse may die before relapse occurs, so relapse and death without antecedent relapse are associated as competing failure types. Another example, in clinical study that involves 205 patients operated for malignant melanoma, 71 patients died in which 57 patients were recorded as having died of the disease and 14 patients who died from causes unrelated to the disease during the follow-up (Andersen et al., 1993). This thesis develops a method that is called omnibus tests in which competing risks is compared via additive risk model with using nonnegative weight functions. Comparison of cause-specific hazard rates and cumulative incidence functions at specified covariate levels are applied in this method.

As we consider a competing risks framework in which subjects are at risk from k types of failure and covariate measurements on each subject are available. We will propose a testing that provides graphical and numerical methods for comparing any two of the k cause-specific hazard rates, or cumulative incidence functions, at a specified covariate level. Suppose each subject has an underlying failure time X that may be subject to censoring. We assume there is an existence of the latent failure time T_j corresponding to each failure

type $j = 1,...,k$. Then the observed time of failure is given by $X = \min_j T_j$, which may be right censored. When X is uncensored, the cause of failure $\delta \in \{1,...,k\}$ is observed along with $p-vector$ Z representing the covariate information. We are interested in focusing on the conditional cause-specific hazard rate $\lambda_j(t \mid z_0) = \lim_{\Delta t \to 0} P(t \le X \le t + \Delta t, \delta = j \mid X \ge t, Z = z_0) / \Delta t$. In other words, $\lambda_j(t \mid z_0)$ is the instantaneous of failure of type j given z_0 and in the presence of the other failure types. In the presence of dependent competing risks, the conditional cumulative incidence function is defined by $F_j(t \mid z_o) = P(X \le t, \delta = j \mid Z = z_o)$.

According to McKeague, Gilbert, and Kanki (2001), a proposal of omnibus tests for comparison of competing risks with covariate effects has been developed under Cox proportional hazards model (Cox, 1972). Also, nonparametric tests that allow censoring and dependent competing risks but no covariate have been considered by Aly, Kochar, and McKeague (1994), Lam (1998), among others. Although the Cox model has been considered as a major tool for the regression analysis of censored survival data, the proportional hazards assumption may not be appropriate to some data analyses. Therefore, it is of interest for us to investigate an alternative approaches to modeling the association between failure times and risk factors through hazard functions. Additive risk model in various forms which has been developed and successfully utilized by numerous authors (Aalen, 1980, Cox and Oakes, 1984; Lin and Ying, 1994) is one such alternative that has been used to describe different aspects of these associations, and it is suitable in many applications.

Under the additive risk model, we specify each $\lambda_j(t \mid z_o)$ and assume that the censoring is conditionally independent of the latent failure times given *Z*. From these

assumptions, we develop a graphical method, along with a formal procedure, for testing the null hypothesis

$$H_0 : \lambda_1(t \mid z_0) = \lambda_2(t \mid z_0),\ \ 0 \le t \le \tau,$$

where z_0 is a specified *p*-vector of covariate levels and $[0, \tau]$ is the time interval of interest. Then, the following hypotheses will be considered:

$$H_1 : \lambda_1(t \mid z_0) \ne \lambda_2(t \mid z_0),\ \ 0 \le t \le \tau$$

$$H_2 : F_1(t \mid z_0) \le F_2(t \mid z_0),\ \ 0 \le t \le \tau$$

$$H_3 : \lambda_1(t \mid z_0) \le \lambda_2(t \mid z_0),\ \ 0 \le t \le \tau,$$

with strict inequality for some $t \in [0, \tau]$ in H_2 and H_3. The hypothesis H_0 is equality of the corresponding cumulative incidence functions over $[0, \tau]$, because $F_j(t \mid z_o) = \int_0^t S_X(u \mid z_o)\lambda_j(u \mid z_o)du$ (Kalbfleisch and Prentice, 1980; Gay, 1988), where $S_X(t \mid z_o) = P(X > t \mid Z = z_o)$ is the conditional survival function of *X*. The hypotheses H_2 and H_3 are alternative expressing that cause 2 is more serious than cause 1, with H_3 being the more restrictive alternative. H_2 is appropriate for a comparison in terms of absolute risk and H_3 in terms of risks intensity. We develop omnibus tests that are consistent against all departures from H_0 in the directions of H_1, H_2, and H_3.

The rest of this thesis is organized as follows. Chapter two includes a brief introduction to the test procedure in which a formula will be proposed for using comparison based on a comparison of the cumulative cause-specific hazard estimators at the specified covariate level z_0. A sampling from the null distribution of the test process that is used to simulate and detect departure from the null hypothesis is discussed in this chapter. Choice of

weight process that will help the test leads to graphical procedure is also covered. Confidence band for difference of two cumulative incidence functions is constructed in Chapter two. Simulation results, comparing cause-specific hazard rates and cumulative incidence functions are presented in Chapter three. In Chapter four, we apply the proposed test to the real malignant melanoma data for comparing the rate of death. The thesis concludes with a summary of results and potential research.

Chapter Two: Test Procedure

2.1 Cumulative cause-specific hazard function

As shown in Lin and Ying (1994), the regression coefficient estimator in the semiparametric additive risk model has an explicit form, which leads to a simpler mathematical solution in comparison to that of the Cox model. In contrast to the Cox model, the additive risk model specifies the hazard function for a covariate vector Z in the form of

$$\lambda_j(t \mid Z) = \lambda_{0j}(t) + \beta_j^T Z(t), \tag{2.1}$$

where $\lambda_{0j}(.)$ is an unspecified baseline hazard function and β_j is an unknown *p*-vector of regression parameter for the *j*th cause of failure. Here, $Z(t)$ is a *p*-vector of possibly time-varying covariates and to be time independent. Lin and Ying (1994) applied the standard counting process martingale techniques and showed that the estimator is asymptotically normal with mean β_j and a variance-covariance matrix.

Let *C* denote the censoring time. The competing risks model data are assumed to be given by n independent replicated of $(\tilde{X}, \tilde{\delta}, Z)$, where $\tilde{X} = \min(X, C)$, $\tilde{\delta} = \delta I(X \le C)$, and I(.) is indicator function. We also assume that *C* is conditionally independent of $T_1,\ldots,T_k$ given covariates $Z(t)$. The latent failure time T_j do not have to be independent, but we do require that $P(T_j = T_l) = 0$ for $j \ne l$. The cause of failure time $\delta = j$ when $X=T_j$. Let $\Delta_{ji} = I(\tilde{\delta}_i = j)$, and $N_{ji}(t) = \Delta_{ji} I(\tilde{X}_i \le t)$ ($i= 1,\ldots, n$) be a counting process for indicating whether an event of type *j* has been observed for *i*th subject by time *t*. Let $Y_i(t) = I(\tilde{X}_i \ge t)$ denote the predictable process indicating whether or not the *i*th subject is at risk just before

time *t*. Let τ satisfy $P(X_i > \tau) > 0$. Lin and Ying (1994) proposed the following estimation function

$$U_j(\beta) = \sum_{i=1}^{n} \int_0^{\tau} Z_i(t)\left\{dN_{ji}(t) - Y_i(t)d\hat{\Lambda}_{0j}(\beta_j, t) - Y_i(t)\beta_j^T Z_i(t)dt\right\}, \tag{2.2}$$

where

$$\hat{\Lambda}_{0j}(\hat{\beta}, t) = \int_0^{\tau} \frac{\sum_{i=1}^{n}\left\{dN_{ji}(u) - Y_i(u)\hat{\beta}_j^T Z_i(u)du\right\}}{\sum_{j=1}^{n} Y_j(u)}.$$

(2.2) is equivalent to

$$U_j(\beta) = \sum_{i=1}^{n} \int_0^{\tau} \left\{Z_i(t) - \bar{Z}(t)\right\}\left\{dN_{ji}(t) - Y_i(t)\beta_j^T Z_i(t)dt\right\}, \tag{2.3}$$

where

$$\bar{Z}(t) = \frac{\sum_{j=1}^{n} Y_j(t) Z_j(t)}{\sum_{j=1}^{n} Y_j(t)}.$$

The regression coefficients are estimated by solving the equation $U_j(\hat{\beta}) = 0$. That is

$$\left[\sum_{i=1}^{n} \int_0^{\tau} Y_i(t)\left\{Z_i(t) - \bar{Z}(t)\right\}^{\otimes 2} dt\right]\hat{\beta} = \left[\sum_{i=1}^{n} \int_0^{\tau} \left\{Z_i(t) - \bar{Z}(t)\right\} dN_{ji}(t)\right]. \tag{2.4}$$

The resulting estimator of β is

$$\hat{\beta}_j = \left[\sum_{i=1}^{n} \int_0^{\tau} Y_i(t)\left\{Z_i(t) - \bar{Z}(t)\right\}^{\otimes 2} dt\right]^{-1}\left[\sum_{i=1}^{n} \int_0^{\tau} \left\{Z_i(t) - \bar{Z}(t)\right\} dN_{ji}(t)\right], \tag{2.5}$$

where $a^{\otimes 2} = aa'$. The confidence region for the regression parameter β_j has been developed by (Zhao and Hsu, 2005) in which the empirical likelihood method under the semiparametric additive risk model with right censoring had been used.

Under model (2.1), for each *j*, the counting process $N_{ji}(.)$ can be decomposed uniquely so that for every ith subject at t, $N_{ji}(t) = M_{ji}(t) + \int_0^t Y_i(u) d\Lambda_j(u; Z_i)$, where $M_{ji}(\cdot)$ is a local square integrable martingale (Lin and Ying, 1994). The jth cumulative cause-specific hazard function for T_j given $Z_i = z_0$ takes the form

$$\Lambda_j(t \mid z_0) = \Lambda_{oj}(t) + \int_0^t \beta_j^T z_0 du \,, \tag{2.6}$$

where

$$\hat{\Lambda}_{oj}(t) = \frac{1}{n} \sum_{i=1}^{n} \int_0^t \frac{1}{\bar{Y}(u)} dN_{ji}(u) - \int_0^t \hat{\beta}_j^T \bar{Z}(u) du \,, \tag{2.7}$$

where β_j values are computed from (2.5) and $\bar{Y}(t) = \frac{1}{n} \sum_{j=1}^{n} Y_j(t)$.

2.2 Test process

We use an approach test that is based on a comparison of the cumulative cause-specific hazard estimators at the specified covariate level z_0, using general predictable locally bounded nonnegative weight processes $W(.)$,

$$L(t) = \int_0^t W(u) \left(\hat{\Lambda}_2(du \mid z_0) - \hat{\Lambda}_1(du \mid z_0) \right). \tag{2.8}$$

The weight process provides a flexible way to control the relative importance attached to differences to the cause-specific hazards at different times and is useful for controlling instability in the tails. Thus, it is important to choose the weight function so that the function (2.8) gives a better and nominal level. Aly, Kochar, and McKeague (1994) used weight function for comparing cumulative incidence functions and cause-specific hazard rates, but

the covariate was absent. Then, McKeague, Gilbert, and Kanki (2001) applied weight functions for comparing cause-specific hazard rates and cumulative incidence functions at specified covariate levels. Note that the various choice of weight function was under Cox hazards proportional model.

There are many ways to choose the weight process. First, the simplest choice is $W_1(t) = n^{1/2}$, which reduces the test process to the normalized difference of the estimated cumulative cause-specific hazard functions,

$$L(t) = \sqrt{n}\left(\hat{\Lambda}_2(t \mid z_0) - \hat{\Lambda}_1(t \mid z_0)\right). \tag{2.9}$$

This choice is good and easy to interpret, but the variance of *L(t)* increases with t, so it is preferable to use a decreasing weight process that gives less weight to the tail, such as

$$W_2(t) = \sum_{i=1}^{n} I(\tilde{X}_i \geq t)/\sqrt{n}\,, \tag{2.10}$$

where $I(.) = 1$ when $\left(X_i \wedge C_i \geq t\right)$, otherwise $I(.) = 0$.

Another choice that gives more sophisticated weight process and has a similar effect under the additive risk model is

$$W_3(t) = \hat{S}_X(t- \mid z_0)^{1/2}\left(\frac{2}{S^{(o)}(t)}\right)^{-1/2}, \tag{2.11}$$

where $$S^{(o)}(t) = \sum_{i=1}^{n} Y_i(t)\,,$$

and $\hat{S}_X(t \mid z_0) = \exp\left\{-\sum_{j=1}^{k} \hat{\Lambda}_j(t \mid z_0)\right\}$ is the conditional survival function of *X*. In this case, the asymptotic distribution of *L(t)* is the additive hazards model based on the estimator of a relatively simple form, and the variance function of *V(t)* simplifies to the conditional

cumulative incidence function $F(t \mid z_0)$. For k = 2 and no covariates, $W_3(t)$ reduces to a weight process considered by (Aly et al., 1994) and makes the test statistics asymptotically distribution free.

The last relatively simple choice is $W_4(t) = n^{1/2}\hat{S}_X(t- \mid z_0)$, which gives the normalized difference of the estimated cumulative incidence functions,

$$L(t) = \sqrt{n}\left(\hat{F}_2(t \mid z_0) - \hat{F}_1(t \mid z_0)\right), \tag{2.12}$$

where $F_j(t \mid z_o) = \int_0^t \hat{S}_X(u- \mid z_0)\hat{\Lambda}_j(du \mid z_0)$.

We use a plotting method to demonstrate (2.8) in looking for possible departure from H_0, with a tendency for large absolute values under H_1, large positive values under H_2, and an increasing trend under H_3. This can be seen from the identity $F_j(t \mid z_o) = \int_0^t S_X(u \mid z_o)\lambda_j(u \mid z_o)du$. However, these plots can be difficult to interpret when the test process that occur even under the hypothesis of equal cause-specific hazards. McKeague, Gilbert, and Kanki (2001) showed that *L(t)* from (2.8) converges in distribution under H_0 to a zero mean Gaussian process provided $W(t)/n^{1/2}$ converges uniformly in probability over $[0,\tau]$ to a bounded function. Moreover, the limiting covariance is complicated. Therefore, we develop a simulation method for approximately sampling from the null distribution of *L(t)* under the additive risk model. This procedure was presented in Song, Jeong, and Song (1997) for finding confidence bands for survival curve without using weight function; in Shen and Cheng (1999) for confidence bands for cumulative incidence curves.

In order to sample the null distribution of the test process, we derive the limiting distribution of the cumulative hazard estimator.

Let

$$L_j(t) = n^{1/2}\left\{\hat{\Lambda}_j(t \mid z_0) - \Lambda_j(t \mid z_0)\right\},$$

and $\tau = \inf\{t \geq 0; H(t) = 1\}$,

where *H(.)* is the distribution function of the observed failure time $\tilde{X}_i$.

Let

$$G(t, z_0) = \int_0^t W(u)\left\{z_0(u) - \overline{Z}(u)\right\}du\,, \qquad \overline{Y}(t) = \frac{1}{n}\sum_{j=1}^{n} Y_j(t)\,,$$

$$C^{-1} = \frac{1}{n}\sum_{i=1}^{n}\int_0^{\infty}\left\{Z_i(u) - \overline{Z}(u)\right\}Y_i(u)Z_i^{'}(u)du\,,$$

where $\overline{Z}(t) = \dfrac{\sum_{i=1}^{n} Y_i(t)Z_i(t)}{\sum_{j=1}^{n} Y_j(t)}$.

Under H_0, the form (2.8) is also equivalent to:

$$L(t) = \int_0^t W(u)\left(\hat{\Lambda}_2(du \mid z_0) - \hat{\Lambda}_1(du \mid z_0)\right) =$$
$$\int_0^t W(u)\left(\hat{\Lambda}_2(du \mid z_0) - \Lambda(du \mid z_0)\right) - \int_0^t W(u)\left(\hat{\Lambda}_1(du \mid z_0) - \Lambda(du \mid z_0)\right).$$

Then, the process *L(t)* is asymptotically equivalent to the process $L_2(t) - L_1(t)$, where

$$L_j(t) = \frac{G^{'}(t, z_0)C^{'}}{n}\sum_{i=1}^{n}\int_0^{\infty}\left\{Z_i(u) - \overline{Z}(u)\right\}dM_{ji}(u) + \frac{1}{n}\sum_{i=1}^{n}\int_0^t \frac{W(u)}{\overline{Y}(u)}dM_{ji}(u)\,, \qquad (2.13)$$

where $M_{ji}(t) = N_{ji}(t) - \int_0^t Y_i(u)d\Lambda_j(u, Z_i)$.

The process to simulate *L(t)* is defined by $L^*(t)$ in which we replace $M_{ji}(u)$ in the first and second terms of $L_j(t)$ by $G_{ji}N_{ji}(u)$ and $\tilde{G}_{ji}N_{ji}(u)$, respectively, where $\{G_{ji}, \tilde{G}_{ji} : j = 1,2; i = 1,...,n\}$ are independent standard normal variables. Realizations of $L^*(t)$ are approximate draws from the null distribution of the test process. In other words, under H_0, the conditional distribution of $L^*(t)$ given the observed data is the same in the limit as the unconditional distribution of *L(t)* (McKeague, Gilbert, and Kanki, 2001). The method works essentially because $M_{ji}(t)$ has mean zero and variance $E\{N_{ji}(t)\}$.

With the sampling from the null distribution and the proposal of the test, we have formal procedures that detect departures from H_0 in the direction of H_1, H_2, and H_3:

$$D_1 = \sup_{0 \le t \le \tau} |L(t)|, \qquad D_2 = \sup_{0 \le t \le \tau} L(t), \qquad D_3 = \sup_{0 \le s \le t \le \tau} \{L(t) - L(s)\}, \text{ respectively.}$$

2.3 Confidence Bands

In this section, we construct confidence bands for the difference of two conditional cumulative incidence functions since confidence intervals are used for inference or for making statistical statements about estimates. Gray (1988), Shen and Cheng (1999), developed the confidence bands for cumulative incidence function for each type of failure. However, McKeague, Gilbert, and Kanki, (2001) constructed confidence bands for the difference in two conditional cumulative incidence functions using the weight function W_4 under Cox regression model. Consider the difference $\delta(t) = F_2(t \mid z_0) - F_1(t \mid z_0)$ can be obtained from the *L(t)* (2.12) in which the weight function W_4 is used. Since the process $n^{1/2}(\hat{\delta}(t) - \delta(t))$ converges in distribution to the null limiting distribution of *L(t)*, we can use

$\hat{\delta}(t) \equiv \hat{F}_2(t \mid z_0) - \hat{F}_1(t \mid z_0) = L(t)/n^{1/2}$ to estimate the difference of two conditional cumulative incidence functions. The earlier Monte Carlo procedure based on $L^*(t)$ can be used to estimate an upper $\alpha/2 - quantile$, $c_{\alpha/2}(t)$, of the limiting distribution of $|L(t)|$. An approximate $100(1-\alpha)\%$ pointwise confidence band for $\delta(t)$ is given by $\hat{\delta}(t) \pm c_{\alpha/2}(t) n^{-\frac{1}{2}}$. A simultaneous band for $\delta(t)$ can be found by suitably scaling the pointwise band. For example, we can use $\hat{\delta}(t) \pm a c_{\alpha/2}(t) n^{-\frac{1}{2}}$, $t \in [0, \tau]$,

where $a \geq 1$ and is the critical value of $\sup_{0 \leq t \leq \tau} \left| \frac{\sqrt{n}\left(\hat{\delta}(t) - \delta(t)\right)}{c_{\alpha/2}(t)} \right| = \sup_{0 \leq t \leq \tau} \left| \frac{L^*(t)}{c_{\alpha/2}(t)} \right|$. Monte Carlo procedure is used to adjust the constant a to furnish the desired $100(1-\alpha)\%$ simultaneous confidence level.

Chapter Three: Simulation Study

In this chapter, we designed simulation to study the performance of the proposed test procedure. We consider if the nominal size accurately matches observed levels at moderate sample size and which weight function that gives the best performance in terms of power. We also want to know whether covariate level and censoring rate have effect on the powers of test.

First, we consider a simple additive risk model with the baseline hazard $\lambda_0(t) = \alpha_j$, j =1,…,k where α_j is a various choices of constant, and set $\beta_1 = \beta_2 = ... = \beta_p = 1,$ then model (2.1) becomes

$$\lambda_j(t \mid z) = \alpha_j + \left[Z_1(t) + Z_2(t) +,...,+ Z_p(t)\right]. \tag{3.1}$$

Simply we denote it as

$$\lambda_j(t \mid z) = \alpha_j + W, \tag{3.2}$$

where $W = Z\beta$, $Z = (Z_1, Z_2, \ldots, Z_p)$ covariate vector, and $\beta = (1,1,...,1)^T$.

Let T denote failure times, C denote the censoring times. We simulate competing risk data sets with right censoring survival time as following steps.

1. Simulating covariates $Z_{pi}(t), i = 1,..., n.$

Z's are drawn from uniform distribution $U(0,1)$. Since $Z_1, Z_2,..., Z_p$ are random independent uniform variables, we randomly choose a matrix with n rows and p columns from uniform distribution as the simulated competing risk data.

2. Simulating failure time T_j, $j = 1,...,k$

To simulate failure time T, we assume the conditional distribution of T given Z in model (3.1) is exponential distribution with parameter $\alpha_j + W$. The survival function related with exponential distribution is derived as $S(x) = e^{-(\alpha_j + W)x}$. Suppose the hazard function for failure time T is known, say $\lambda_j(t \mid z) = \alpha_j + W$, we can derive the survival function $S(t)$ and the distribution function $F(t)$ for T. Since $\lambda(t) = \frac{-d\ln(S(t))}{dt} = -\frac{S'(t)}{S(t)}$, we have

$$S(t \mid z) = e^{-\int_0^t \lambda(s|z)ds} = e^{-\int_0^t (\alpha_j + W)ds} = e^{-(\alpha_j + W)t}, \tag{3.2}$$

$$F(t) = 1 - S(t) = 1 - e^{-(\alpha_j + W)t}, \tag{3.3}$$

$$t = -\frac{\ln(1 - F(t))}{W + \alpha_j}. \tag{3.4}$$

Given a distribution function $F(t)$, we can simulate failure time samples T distributed with such a cumulative function $F(t)$. Suppose U is drawn from uniform distribution $U(0,1)$, then the failure time T is obtained from

$$T_j = -\frac{\ln(1 - U)}{W + \alpha_j} \tag{3.5}$$

3. Simulating censoring time C_i, $i = 1,...,n$

Censoring time C_i's are drawn from exponential distribution with decay parameter adjusted so 15-30% of the observations were censored in $[0, \tau]$.

Finally, the simulated observations from the additive hazard risk model (3.2) are the triples as $\left(\tilde{X}_i, \tilde{\delta}_i, W_p\right)$, $i = 1,...,n$, where $\tilde{X} = \min(X, C)$, $\tilde{\delta} = \delta I(X \le C)$ and $\delta = j$ when $X = T_j$.

3.1 Simulation Example (1)

In this simulation example, we generate a competing risk data set with censoring rate (CR) 0.30, a $p = 2$ dimensional covariate Z. We set covariate level $z_0 = (0.5, 0.5)$, and the sample size n = 50, 100, 200, and 400, respectively. The size and power of test based on D_2 and D_3 at the nominal 0.05 level were estimated from 1000 independent samples, with critical values obtained in each sample from 1000 realizations of $L^*(t)$.

Since we assumed the alternative hypotheses H_2 and H_3 from the proposal test that are expressing the notion of cause (risk) 2 more serious than cause 1, we choose $\alpha_1 = 1$ and various choices of α_2 (1, 1.5, 2.0, 2.5, 3.0) in order to generate T from (3.5). Then we test all weight functions, W_1, W_2, W_3, and W_4, respectively.

Table 3.1

Observed levels and powers of test for equality of conditional cause-specific hazard rates based on D_2 and D_3 at nominal level 0.05, $z_0 = (0.5, 0.5)$, *CR = 0.30.*

n	α_j		D_2				D_3			
	α_1	α_2	W_1	W_2	W_3	W_4	W_1	W_2	W_3	W_4
50	1	1	**0.047**	**0.047**	**0.046**	**0.047**	**0.050**	**0.052**	**0.054**	**0.052**
	1	1.5	0.116	0.123	0.132	0.120	0.131	0.139	0.137	0.133
	1	2.0	0.257	0.273	0.271	0.263	0.261	0.268	0.261	0.258
	1	2.5	0.368	0.387	0.393	0.323	0.377	0.383	0.377	0.330
	1	3.0	0.539	0.564	0.557	0.543	0.509	0.525	0.551	0.522
100										
	1	1	**0.057**	**0.060**	**0.064**	**0.059**	**0.054**	**0.061**	**0.061**	**0.060**
	1	1.5	0.206	0.215	0.216	0.207	0.201	0.209	0.208	0.206
	1	2.0	0.417	0.430	0.441	0.414	0.382	0.397	0.393	0.371
	1	2.5	0.558	0.568	0.588	0.544	0.549	0.557	0.563	0.539
	1	3.0	0.798	0.884	0.814	0.804	0.747	0.786	0.784	0.740
200										
	1	1	**0.049**	**0.057**	**0.057**	**0.053**	**0.050**	**0.052**	**0.052**	**0.052**
	1	1.5	0.283	0.282	0.295	0.233	0.286	0.288	0.296	0.269
	1	2.0	0.614	0.622	0.631	0.615	0.575	0.600	0.589	0.562
	1	2.5	0.865	0.866	0.875	0.866	0.837	0.876	0.866	0.858
	1	3.0	0.953	0.966	0.968	0.957	0.926	0.935	0.938	0.916
400										
	1	1	**0.057**	**0.057**	**0.059**	**0.051**	**0.059**	**0.057**	**0.059**	**0.047**
	1	1.5	0.427	0.439	0.438	0.419	0.392	0.426	0.406	0.402
	1	2.0	0.860	0.867	0.862	0.856	0.839	0.853	0.853	0.851
	1	2.5	0.991	1.000	0.996	0.994	0.986	1.000	0.988	0.970

The results in Table 3.1 show that the observed levels for D_2 and D_3 quite accurately match the 0.05 nominal level of the test. Since we simulate failure times from (3.5) and give value α_1 and α_2 that represent risk-1 and risk-2, respectively, the failure time of risk-2 is always bigger than the failure time of risk-1. Moreover, if the value of α_2 is much bigger

than the value of α_1, then the powers of test is larger. That means the test statistics is much significant.

In the simulation, we find that sample size and weight functions also have appreciable effect on accuracy. For example, if the sample size is increasing, the powers of test are also increasing. For example, the powers of test of sample size n = 200 are bigger than the powers of test of sample size n = 100 (cf., Table 3.1). Especially, when sample size n = 400 and $\alpha_2 = 2.5$, the power of test tends to be one. The weight functions W_2 and W_3 gave better performance overall than W_1 and W_4 in terms of power. This makes sense because both W_1 and W_4 do not down weight observations in the tail, where there tends to be sharp increase in the variance of the cumulative baseline hazard estimate.

3.2 Simulation Example (2)

In this simulation example we want to consider if censoring rate have effect on powers of test. Doing the same as simulation in example (1), we generate a competing risk data set with setting censoring rate 0.15, two covariates, covariate level $z_0 = (0.5, 0.5)$, and the sample size n = 50, 100, 200, respectively.

The results, reported in Table 3.2 show that the censoring rate has effect on powers of test. As the censoring rate decreasing, the powers of test seem to be increasing, but appears not so much difference.

Table 3.2

Observed levels and powers of test for equality of conditional cause-specific hazard rates based on D_2 and D_3 at nominal level 0.05, $z_0 = (0.5, 0.5)$, *CR = 0.15.*

n	CR	α_j		D_2				D_3			
		α_1	α_2	W_1	W_2	W_3	W_4	W_1	W_2	W_3	W_4
50	0.30	1	1	**0.047**	**0.047**	**0.046**	**0.047**	**0.050**	**0.052**	**0.054**	**0.052**
		1	1.5	0.116	0.123	0.132	0.120	0.131	0.139	0.137	0.133
		1	2.0	0.257	0.273	0.271	0.263	0.261	0.268	0.261	0.258
		1	2.5	0.368	0.387	0.393	0.323	0.377	0.383	0.377	0.330
		1	3.0	0.539	0.564	0.557	0.543	0.509	0.525	0.551	0.522
	0.15										
		1	1	**0.059**	**0.054**	**0.060**	**0.057**	**0.057**	**0.056**	**0.054**	**0.059**
		1	1.5	0.142	0.149	0.144	0.137	0.136	0.144	0.147	0.143
		1	2.0	0.285	0.290	0.293	0.288	0.269	0.274	0.273	0.265
		1	2.5	0.412	0.427	0.420	0.418	0.391	0.416	0.419	0.412
		1	3.0	0.540	0.575	0.578	0.562	0.516	0.565	0.560	0.554
100	0.30										
		1	1	**0.057**	**0.060**	**0.064**	**0.059**	**0.054**	**0.061**	**0.061**	**0.060**
		1	1.5	0.206	0.215	0.216	0.207	0.201	0.209	0.208	0.206
		1	2.0	0.417	0.430	0.441	0.414	0.382	0.397	0.393	0.371
		1	2.5	0.558	0.568	0.588	0.544	0.549	0.557	0.563	0.539
		1	3.0	0.798	0.884	0.814	0.804	0.747	0.786	0.784	0.740
	0.15										
		1	1	**0.061**	**0.059**	**0.061**	**0.059**	**0.068**	**0.064**	**0.064**	**0.064**
		1	1.5	0.210	0.222	0.217	0.209	0.208	0.215	0.214	0.208
		1	2.0	0.440	0.445	0.444	0.443	0.376	0.415	0.396	0.408
		1	2.5	0.627	0.639	0.652	0.643	0.588	0.620	0.624	0.616
		1	3.0	0.802	0.891	0.821	0.810	0.750	0.788	0.790	0.784
200	0.30										
		1	1	**0.049**	**0.057**	**0.057**	**0.053**	**0.050**	**0.052**	**0.052**	**0.052**
		1	1.5	0.283	0.282	0.295	0.233	0.286	0.288	0.296	0.269
		1	2.0	0.614	0.622	0.631	0.615	0.575	0.600	0.589	0.562
		1	2.5	0.865	0.866	0.875	0.866	0.837	0.876	0.866	0.858
		1	3.0	0.953	0.966	0.968	0.957	0.926	0.935	0.938	0.916
	0.15										
		1	1	**0.049**	**0.045**	**0.05**	**0.053**	**0.054**	**0.043**	**0.044**	**0.052**
		1	1.5	0.266	0.284	0.298	0.240	0.292	0.282	0.286	0.232
		1	2.0	0.617	0.626	0.649	0.623	0.578	0.593	0.594	0.573
		1	2.5	0.871	0.872	0.883	0.873	0.843	0.880	0.885	0.867
		1	3.0	0.961	0.986	0.977	0.967	0.942	0.956	0.961	0.950

3.3 Simulation Example (3)

Now we consider the effect of covariate level. We want to adjust the covariate level by setting $z_0 = (0.3,0.3)$; two covariates; censoring rate 0.30; the sample size n = 50 and 100. Then, we observe the result of powers of test as shown in Table 3.3. The results show the powers of test seem to be changed a little.

Table 3.3

Observed levels and powers of test for equality of conditional cause-specific hazard rates based on D_2 and D_3 at nominal level 0.05, $z_0 = (0.3,0.3)$, *CR = 0.30.*

n	z_0	α_j		D_2				D_3			
		α_1	α_2	W_1	W_2	W_3	W_4	W_1	W_2	W_3	W_4
50	(0.5)	1	1	**0.047**	**0.047**	**0.046**	**0.047**	**0.050**	**0.052**	**0.054**	**0.052**
		1	1.5	0.116	0.123	0.132	0.120	0.131	0.139	0.137	0.133
		1	2.0	0.257	0.273	0.271	0.263	0.261	0.268	0.261	0.258
		1	2.5	0.368	0.387	0.393	0.323	0.377	0.383	0.377	0.330
		1	3.0	0.539	0.564	0.557	0.543	0.509	0.525	0.551	0.522
	(0.3)										
		1	1	**0.071**	**0.063**	**0.059**	**0.065**	**0.060**	**0.067**	**0.063**	**0.066**
		1	1.5	0.134	0.136	0.132	0.130	0.133	0.143	0.142	0.140
		1	2.0	0.273	0.259	0.265	0.263	0.245	0.253	0.256	0.252
		1	2.5	0.414	0.423	0.422	0.420	0.422	0.431	0.429	0.419
		1	3.0	0.528	0.530	0.546	0.518	0.518	0.526	0.533	0.526
100	(0.5)										
		1	1	**0.057**	**0.060**	**0.064**	**0.059**	**0.054**	**0.061**	**0.061**	**0.060**
		1	1.5	0.206	0.215	0.216	0.207	0.201	0.209	0.208	0.206
		1	2.0	0.417	0.430	0.441	0.414	0.382	0.397	0.393	0.371
		1	2.5	0.558	0.568	0.588	0.544	0.549	0.557	0.563	0.539
		1	3.0	0.798	0.884	0.814	0.804	0.747	0.786	0.784	0.740
	(0.3)										
		1	1	**0.053**	**0.055**	**0.052**	**0.050**	**0.051**	**0.051**	**0.054**	**0.054**
		1	1.5	0.230	0.234	0.233	0.231	0.219	0.228	0.224	0.217
		1	2.0	0.410	0.412	0.408	0.404	0.401	0.408	0.404	0.402
		1	2.5	0.593	0.594	0.600	0.592	0.558	0.579	0.583	0.574
		1	3.0	0.802	0.891	0.821	0.810	0.750	0.788	0.790	0.784

Chapter Four: Application

The data consist of measurements made on patients with malignant melanoma. Each patient had their tumors removed by surgery at the Department of Plastic Surgery, University Hospital of Odense, Denmark during the period 1962 to 1977. The surgery consisted of complete removal of the tumors together with about 2.5cm of the surrounding skin. Among the measurements taken were the thickness of the tumors and whether it was ulcerated or not. These are thought to be important prognostic variables in that patients with a thick and/or ulcerated tumors have an increased chance of death from melanoma. Patients were followed until the end of 1977. There were 205 patients involving operated for malignant melanoma, 71 patients died, of whom 57 were recorded as dies of the disease and 14 from causes unrelated to the disease during the follow-up. The remaining 134 patients were censored at the closure of the study since they were still alive at that point in time (Andersen et al., 1993). For time-varying covariate effects to cause of risk were also collected, including sex, age, year entry study, the size of tumor, and ulceration status at the time of operation. The latter faction is dichotomous and is scored as “present” if the surface of the melanoma shows signs of ulcers and as “absent” otherwise. Failure time is defined as the time since operation.

For comparison, we use the proposed test to compare the rate of death by the disease and the rate of death from other causes. Let the failure caused by the disease, melanoma be risk-2 and the failure caused by other factors be risk-1. We assume risk-2 is more serious than risk-1. The follow-up time for the test is ten years. Then we have hypotheses as follow:

$$H_0 : \lambda_1(t \mid z_0) = \lambda_2(t \mid z_0),\ \ 0 \le t \le 10,$$

where z_0 is a specified covariate levels of a four-vector covariate, i.e., sex, age, the size of tumor, and ulceration status. The alternative hypotheses will be considered:

$$H_2 : F_1(t \mid z_0) \le F_2(t \mid z_0),\ \ 0 \le t \le 10$$

$$H_3 : \lambda_1(t \mid z_0) \le \lambda_2(t \mid z_0),\ \ 0 \le t \le 10$$

In our application, the covariate age has mean 52 years and standard deviation 17 years, and tumor thickness covariate has mean 2.9 mm and standard deviation 3 mm. Since the prediction of the cumulative incidence based on the standardize covariates has reduced standard errors, we specified the z_0 levels as $z_0 = \{$ulceration, 2.9 mm, male, 52 years$\}$ for the covariates ulceration, tumor size, sex, and age, respectively. Table 4.1 summarizes the result of test statistics and its *p*-value in which we used the simulation method for sampling from the null distribution of *L(t)*. We also used the four weight functions, W_1, W_2, W_3, and W_4 as described in Section 2.2 to detect departures from H_0.

Table 4.1

Statistical test under additive risk model for failure caused by disease and failure resulting by other causes. H_2 and H_3 as alternative hypotheses.

		W_1	W_2	W_3	W_4
H_2	Test statistics	4.291	2.685	2.350	3.345
	P-value	<0.001	0	0	<0.001
H_3	Test statistics	4.552	2.941	2.531	3.601
	P-value	<0.001	0	0	<0.001

Table 4.2

Statistical test under Cox regression model for failure caused by disease and failure resulting by other causes. H_2 and H_3 as alternative hypotheses.

		W_1	W_2	W_3	W_4
H_2	Test statistics	5.758	3.564	3.731	4.467
	P-value	0.046	0.014	0.019	0.032
H_3	Test statistics	5.921	3.726	3.915	4.630
	P-value	0.045	0.013	0.015	0.027

From Tables 4.1 and 4.2, the *p*-values of W_1, W_2, W_3, and W_4 in both alternative hypotheses, H_2 and H_3 show the test is very consistent and significant under both additive risk model and Cox regression model. That means the failure caused by the disease is overall higher than the failure resulting by other causes unrelated to the disease.

The graphical method is also applied in these alternative hypotheses test. Applying estimation of the cumulative incidence probability directly by the subdistribution approach (Gay, 1988; Fine and Gray, 1999) to estimate the cumulative incidence function of risk-1 and risk-2, and nonparametric Epanechnikov kernel estimates hazard rates. As shown in Figures 4.1a and 4.1b, in which the cumulative incidence of risk-2 (malignant melanoma) overally exceeded the cumulative incidence of risk-1 and the hazard rate of risk-2 is also higher than the hazard rate of risk-1. Thus, the test is satisfied for both alternative hypotheses, H_2 and H_3.

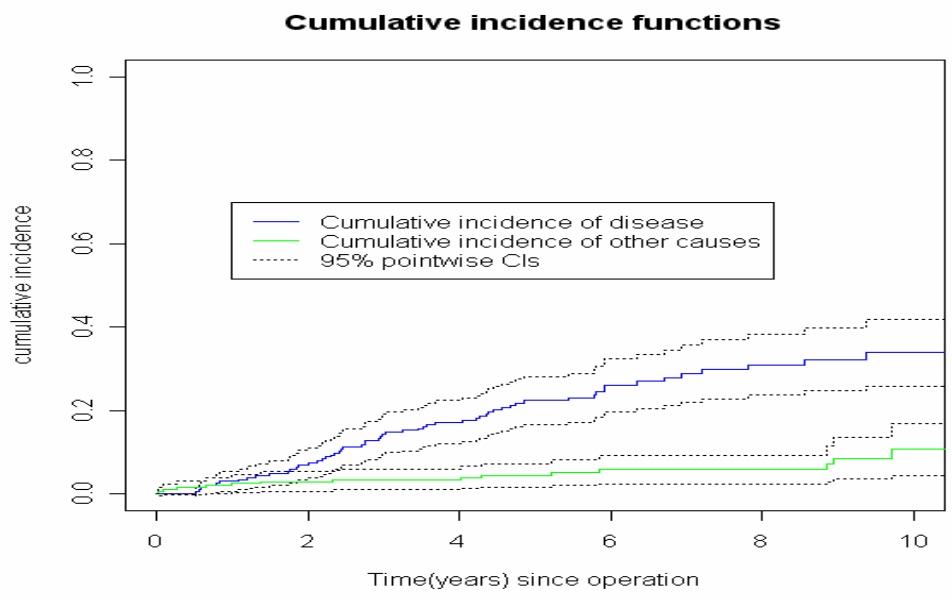

Figure 4.1a. Malignant melanoma cohort study. No adjustment for covariates. Estimated the disease and other causes cumulative incidence functions with 95% pointwise confidence limits.

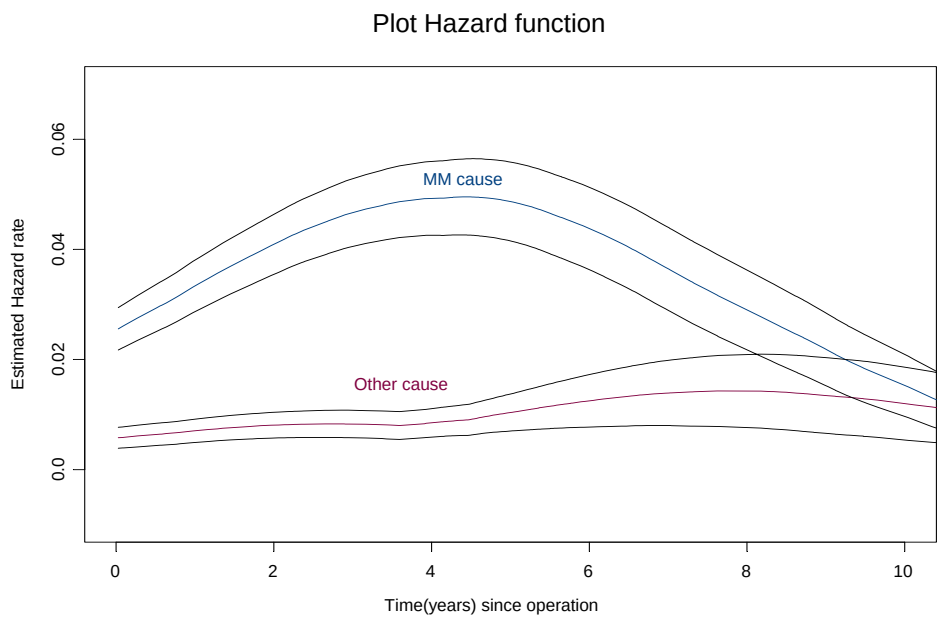

Figure 4.1b. Nonparametric Epanechnikov kernel estimates of the disease and other causes hazard rates based on the smoothed hazard rate estimate with 95% pointwise confidence limits calculated by transforming the symmetric confidence limits.

According to Andersen et al., (1993), the number death patients who involving operated for malignant melanoma is higher than the number death patients from causes unrelated to the disease during the follow-up. The results in Tables 4.1,4.2 and Figures 4.1a, 4.1b show the test satisfies the alternative hypotheses and our assumption. We also want to consider the effect of risk factors on the rate of death under the additive risk models. At the 0.05 significance level, univariable additive risk models identified tumor thickness and ulceration status are highly significant risk factors for death caused by malignant melanoma, whereas both covariates have little effect on the intensity of dying from other causes (Tables 4.3,4.4). In fact, the covariate age has the most significant influence on death caused by other factors. In addition, it is worth mentioning that certain transformations of the continuous covariates may improve the efficiency of estimators under the additive risk model (Shen and Cheng, 1999). In our application, the covariates age (mean: 52 years; standard deviation: 17 years) and tumor thickness (mean: 2.92 mm; standard deviation: 3 mm) are standardized as given in Tables 4.3 and 4.4. We also fit the cause-specific intensity function by the Cox proportional hazards model (Cox, 1972) in order to compare its results with the additive risk model. Although the magnitude of each parameter estimate appears to differ between the two model fittings, it is notable that there is good agreement between the test statistics for subject covariate effects under both models.

Table 4.3

Estimation results of risk factors in additive risk model for failure time to death occurring from different causes of 205 malignant melanoma patients.

	Covariate	Estimate	SE	Estimate/SE	*P*-value
Failure caused by melanoma	**ulceration**	0.05074	0.01577	3.217	**0.001**
	(thickness - 2.92)/3	0.02511	0.01195	2.1014	**0.0356**
	sex	0.0196	0.01457	1.3453	0.1785
	(age -52)/17	0.0105	0.00772	1.3600	0.1738
Failure resulting from other causes	**ulceration**	0.002205	0.007022	0.3141	0.7535
	(thickness - 2.92)/3	0.003441	0.00524	0.6573	0.511
	sex	0.004487	0.007093	0.6326	0.527
	(age -52)/17	0.0110	0.00356	3.0906	**0.002**

Table 4.4

Estimation results of risk factors in Cox regression model for failure time to death occurring from different causes of 205 malignant melanoma patients.

	Covariate	Estimate	SE	Estimate/SE	*P*-value
Failure caused by melanoma	**ulceration**	1.141	0.312	3.657	**<0.001**
	(thickness - 2.92)/3	0.3651	0.0925	3.946	**<0.001**
	sex	0.400	0.269	1.487	0.137
	(age -52)/17	0.2213	0.1411	1.567	0.117
Failure resulting from other causes	**ulceration**	0.1239	0.5842	0.212	0.832
	(thickness - 2.92)/3	0.1646	0.2384	0.690	0.490
	sex	0.3735	0.5455	0.685	0.493
	(age -52)/17	1.136	0.343	3.311	**0.001**

We applied the test to compare cause-specific hazard rates for the full model in which four covariates, ulceration status, tumor thickness, sex, and age have been included, and another model in which only the significant risk factors covariates, ulceration status, tumor thickness, and age (sex was excluded because it has little effect on the intensity of dying the disease and other causes (cf., Tables 4.3, 4.4).

Test of H_0 versus H_2 and H_3 applied at covariate level $z_0 = \{$ulceration, 2.9 mm, male, 52 years$\}$ for the full model and $z_0 = \{$ulceration, 2.9 mm, 52 years$\}$ for other one, indicated a significantly greater type 1 hazard rate and cumulative incidence function, and the weight functions W_2 and W_3 performed better than the weight function W_1 and W_4 as shown in Tables 4.1, 4.2 and Figures 4.2 – 4.5 in both models. Figures 4.2-4.5 also show the model without covariate sex performed better than the full model.

It is of interest to estimate the difference between the risk-1 and risk-2 cumulative incidence functions for various covariate subgroups. The confidence bands displayed in Figure 4.6 were computed via the procedure described in Section 2.3 for the same covariate subgroups as in Figures 4.2-4.5, conditions ***a*** and ***b***, respectively. The constant value *a* is estimated by Monte Carlo procedure in the condition with covariate sex is 1.4, and the condition without covariate sex is 1.9 Based on the 90% simultaneous bands, we find the probability of risk-2 (malignant melanoma) is lower than the probability of risk-1 in the first two years. However, the probability of risk-2 is overall higher than the probability of risk-1 during the follow-up.

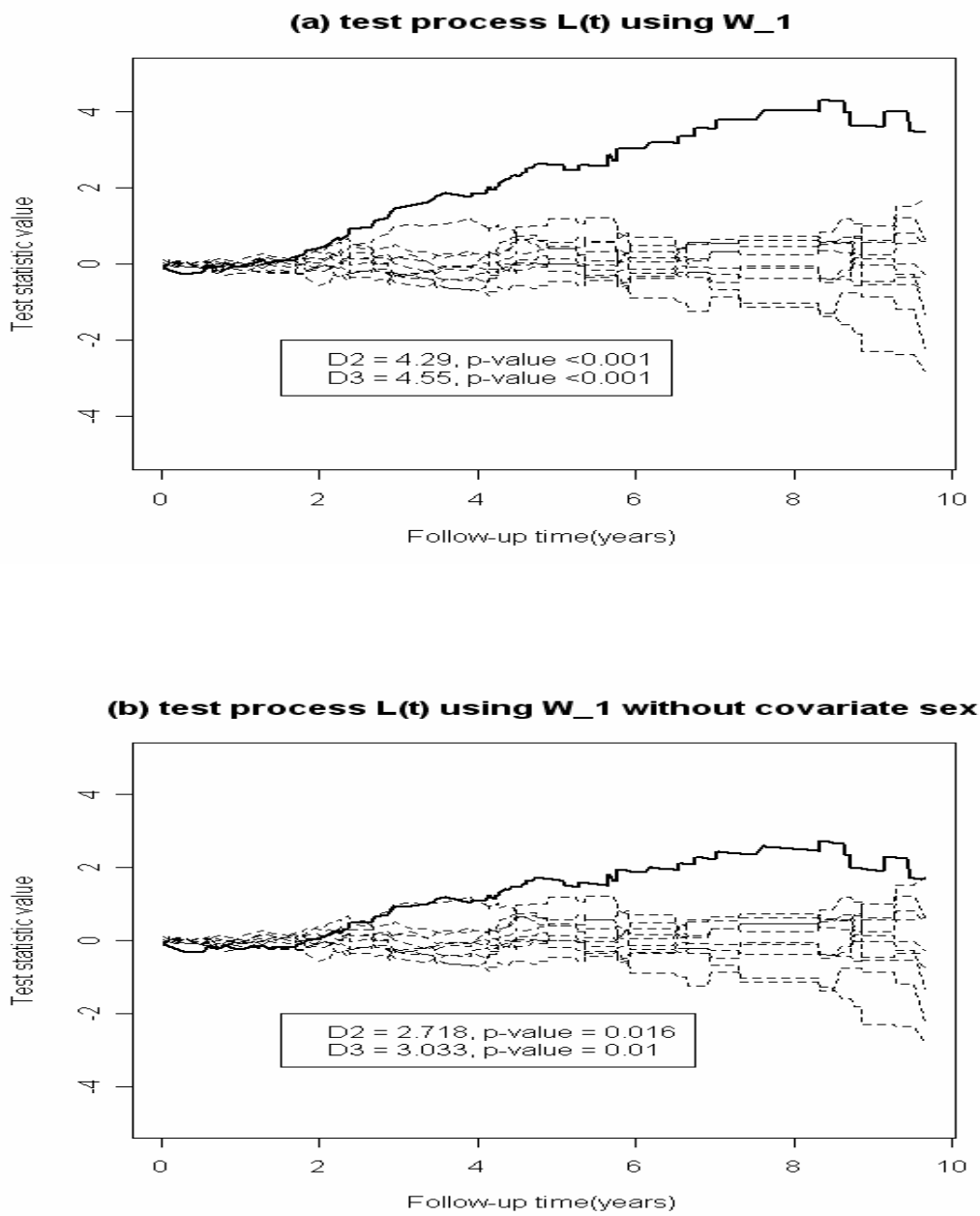

Figure 4.2. The test process *L(t)* (solid line) and 10 realizations of $L^*(t)$ (dash lines) for the weight process $W_1(t)$. **a**. Conditions with covariate {ulceration status, tumor thickness, sex, and age}. **b**. Conditions with covariate {ulceration status, tumor thickness, and age}.

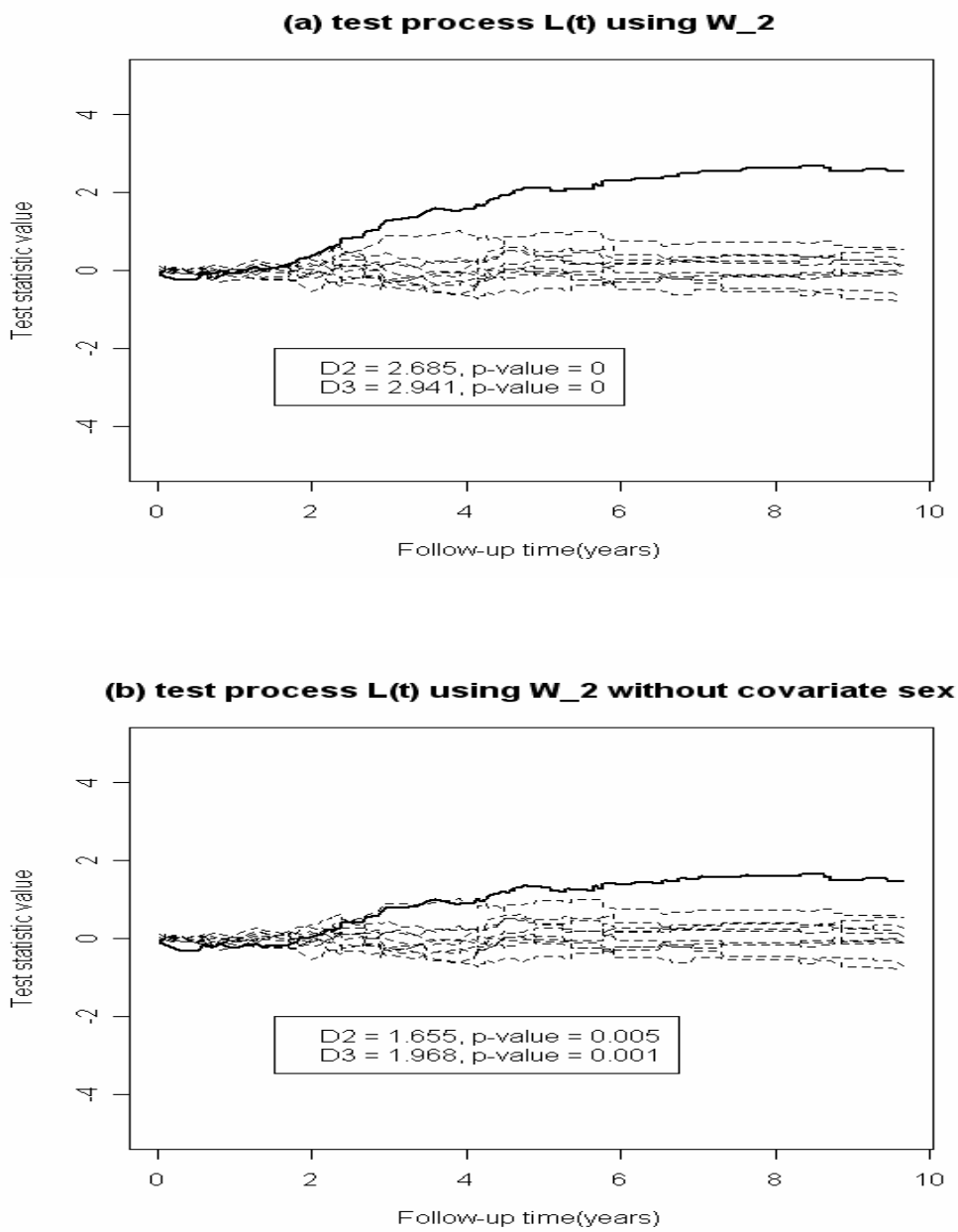

Figure 4.3. The test process *L(t)* (solid line) and 10 realizations of $L^*(t)$ (dash lines) for the weight process $W_2(t)$. **a**. Conditions with covariate {ulceration status, tumor thickness, sex, and age}. **b**. Conditions with covariate {ulceration status, tumor thickness, and age}.

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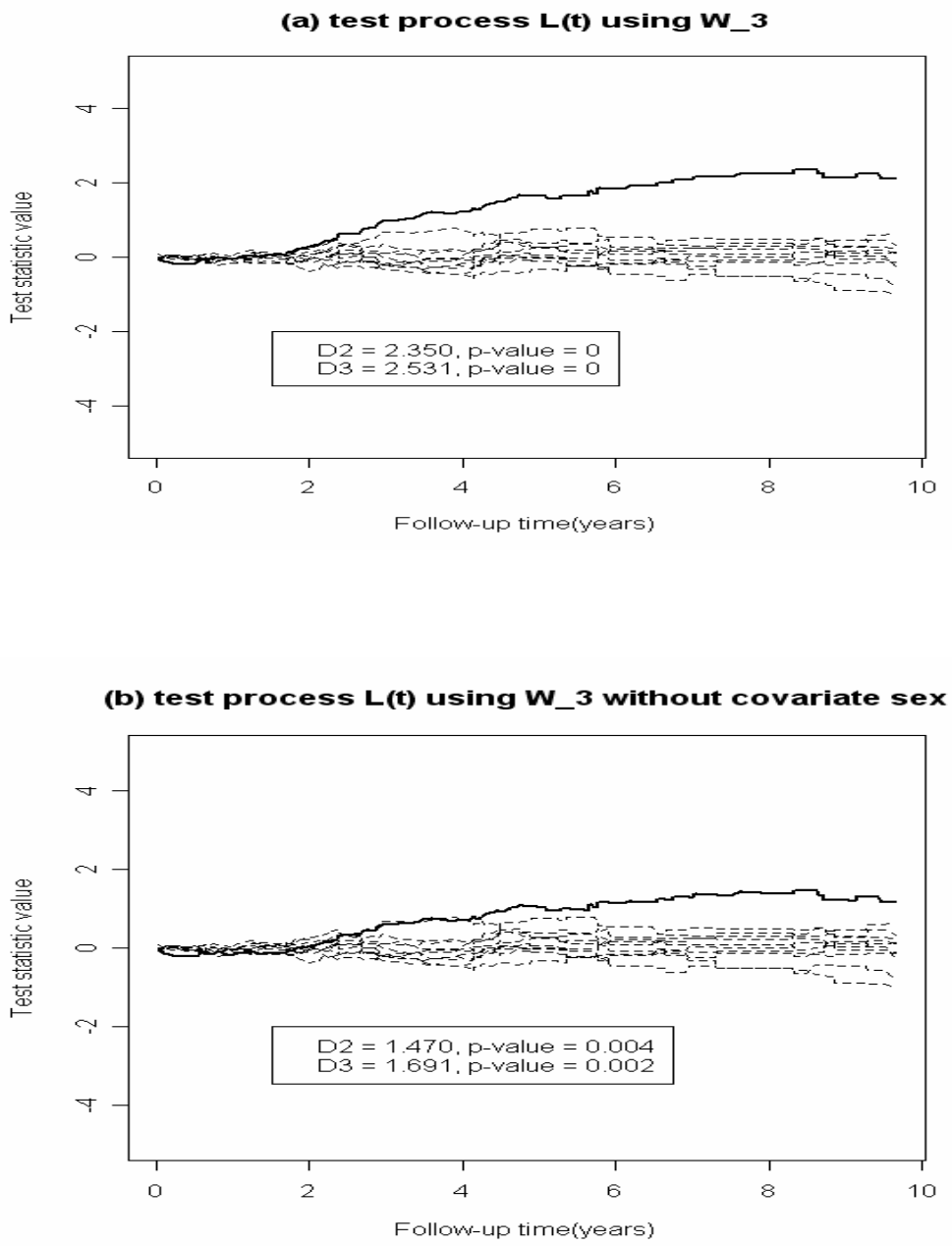
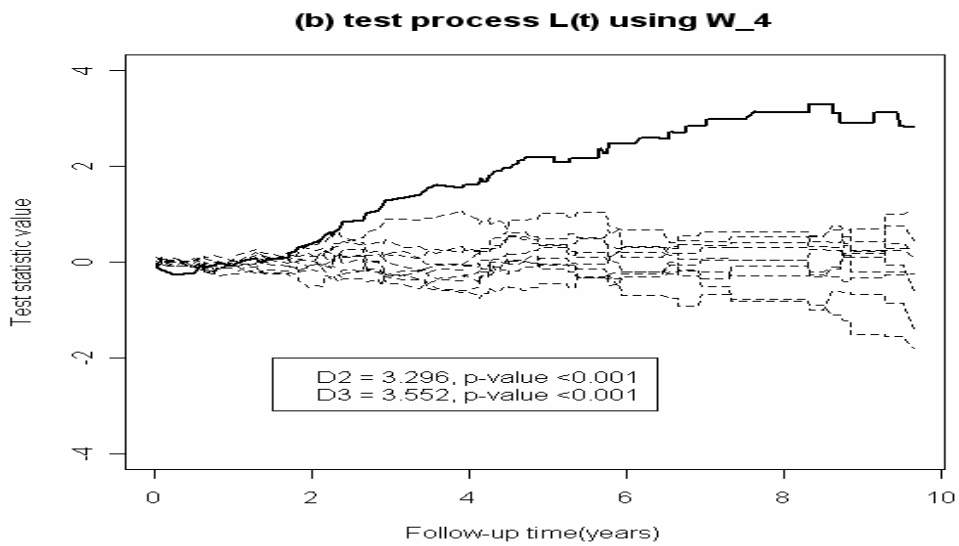


Figure 4.4. The test process *L(t)* (solid line) and 10 realizations of $L^*(t)$ (dash lines) for the weight process $W_3(t)$. **a**. Conditions with covariate {ulceration status, tumor thickness, sex, and age}. **b**. Conditions with covariate {ulceration status, tumor thickness, and age}.



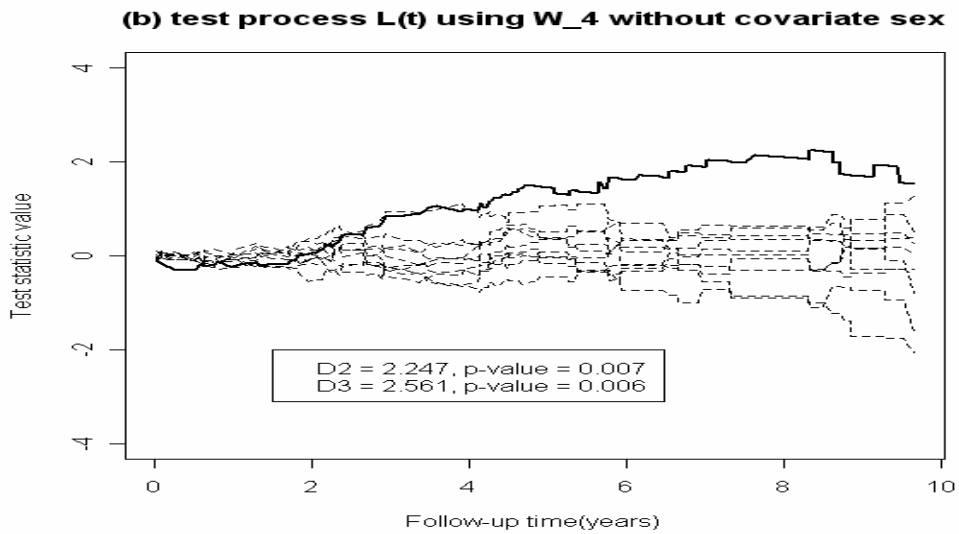
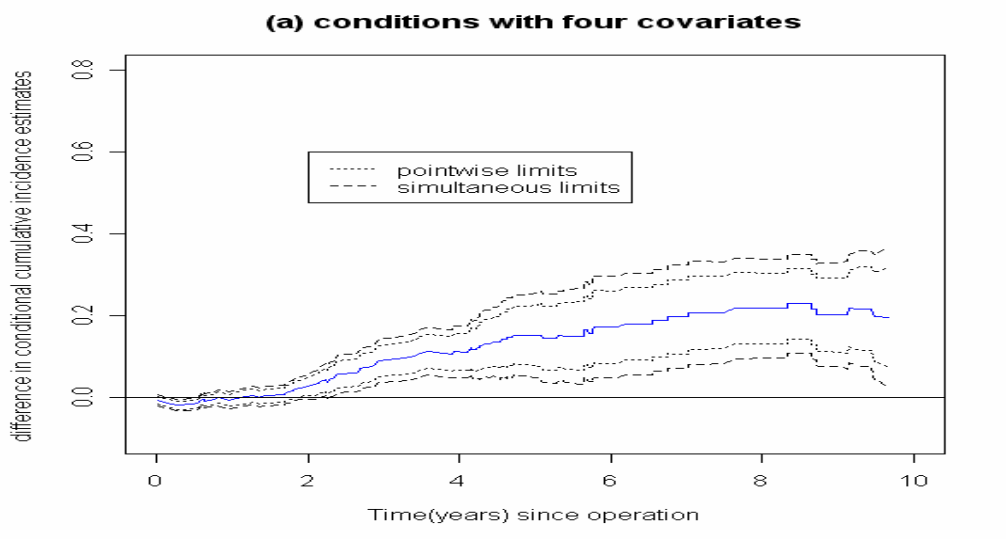


Figure 4.5. The test process *L(t)* (solid line) and 10 realizations of $L^*(t)$ (dash lines) for the weight process $W_4(t)$. **a**. Conditions with covariate {ulceration status, tumor thickness, sex, and age}. **b**. Conditions with covariate {ulceration status, tumor thickness, and age}.



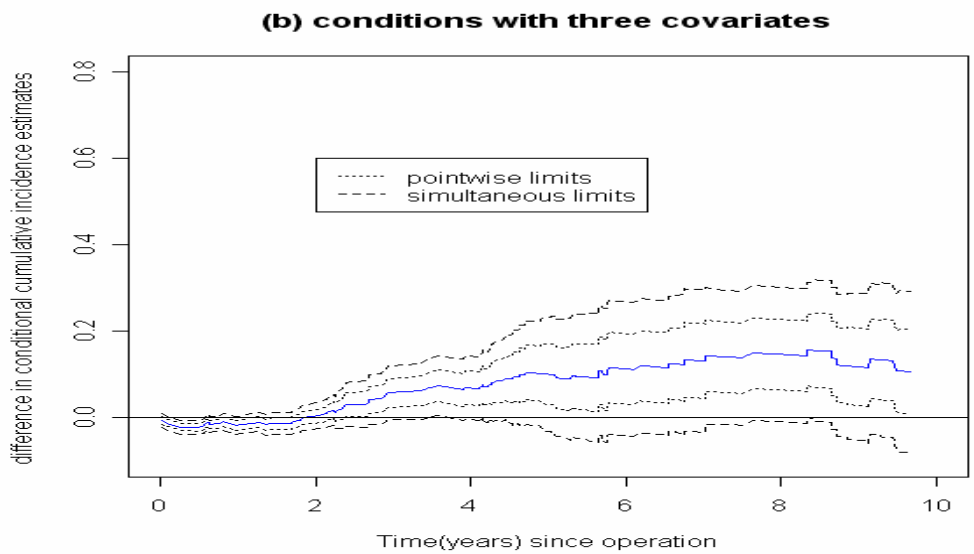


Figure 4.6. Ninety-five percent pointwise and 90% simultaneous confidence bands for the difference in conditional rate of death cumulative incidence functions. **a**. Conditions with covariate {ulceration status, tumor thickness, sex, and age} at level z_0 = {ulceration, 2.9 mm, male, 52 years}. **b**. Conditions with covariate {ulceration status, tumor thickness, and age} at level z_0 = {ulceration, 2.9 mm, 52 years}.

Chapter Five: Conclusion

The main purpose of this thesis was to develop omnibus tests for comparison of competing risks with covariate effects via semiparametric additive risk model that is used for alternative of the Cox regression model. It has shown how useful it is to compare cause-specific hazard rate and cumulative incidence in competing risks data. The graphical method is also applied for illustration of the comparison.

The simulation results and the applied problem verify that the additive risk model is to be fit with competing risk data. The developing of the simulation method for approximately sampling the null distribution of $L(t)$ under the additive risk models to detect the hypotheses is consisted. Beside formal omnibus tests that are consistent against all departures from H_0 in the directions of H_1, H_2, and H_3, we used graphical method as shown in Figures 4.1a - 4.1b and Figures 4.2 – 4.6 to illustrate the comparison risk-1 and risk-2. An adjustment of covariate level and censoring rate are also used in simulation of this thesis. It is very important to know which covariate has effect on the intensity of dying because it will help the researcher to determine the cause of death and its rate of death, or in the designing of a new vaccine. For example, McKeague, Gilbert, and Kanki, (2001) have mentioned about designing a new vaccine for the human immunodeficiency virus (HIV) in which they needed to compare the infection rate HIV type1 and HIV type2 with adjustment for covariate effects because in order for an HIV vaccine to be efficacious in a particular geographic region, it may be necessary to match the genotypes of the HIV antigens contained in the vaccine to the local HIV genotype that pose the greatest risk of HIV infection. This thesis has shown it to be a reliable and useful tool for comparison of competing risk data where covariate has possibly time-varying.

Future research could extend this to comparing of more than two competing risks under the additive risk model or the Cox regression model. Sun (2001) studied the nonparametric test procedures for comparing multiple cause-specific hazard rates. We will investigate the challenging problem in the future. Another area of the research could be to develop a goodness-of-fit test for the model in which a comparison between the additive risk model and the Cox regression model is considered.

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Appendix A

FORTRAN Code for comparison competing risk in simulation

```
c
c    This program is to implement tests of ordering
c    of two conditional cause-specific hazard functions
c    and two cumulative incidence functions.
c    Simulated data example.
c
c    Test H_0: g_1(t|z)=g_2(t|z) on [t1,t2]
c           where z, t1 and t2 need to be specified
c    versus
c        H_1:  F_1(t|z)<=F_2(t|z) on [t1,t2]
c    OR
c        H_2: g_1(t|z)<=g_2(t|z) on [t1,t2]
c      (with strict inequality for some t)
c  Note:  H_1 and H_2 are denoted H_2 and H_3 in the paper.
c


      program pvalues
      parameter(mxnsmp=1000,mxncov=2)

c
c     ncov  : number of covariates
c
c     set mxncov=ncov in the subroutine ESTP as well!!
c
c     nsamp : sample size
c     time(i)  :  failure time for subject i
c     censor(i) : cause-of-failure = 0 (censored), 1 or 2
c     covar(j,i,k) :  covariate j for subject i at k-th event time
c     clevel(j)  :  specified level of covariate j
c     nboot:  number of simulated test processes used
c             to find P-value (nboot=1000 gives good results)
c     nsim:  number of runs (only needed for a simulation study
c            to check accuracy of the tests;
c

      integer ncov,nsamp,indx(mxnsmp),seeda,seedb,seedc,seedd,
     $        nsim,nboot
      real censor(mxnsmp),covar(mxncov,mxnsmp,mxnsmp),
     $   time(mxnsmp),dat(14),ccensor(mxnsmp),cov(mxncov,mxnsmp),
     $   ctime(mxnsmp), s0(mxnsmp),
     $   U(mxncov),copy(mxnsmp),nrej,nreja,
     $   U2(mxncov),s1(mxncov,mxnsmp),s2(mxncov,mxncov),
     $   var(mxncov,mxncov),beta(mxncov),base2(2,0:mxnsmp),
     $   beta2(2,mxncov),s02(2,mxnsmp),clevel(mxncov),phi(0:mxnsmp),
     $   stt(0:mxnsmp),betav1,betav2,cbeta,clev,cc,
```

```
     $   s12(2,mxncov,mxnsmp),w(mxnsmp),censor1(mxnsmp),
     $   censor2(mxnsmp),aa, bb(0:mxnsmp), phiboot(mxnsmp),
     $   v1(mxncov,mxncov),v2(mxncov,mxncov),
     $   uu(mxncov,0:mxnsmp),zt(mxnsmp,mxncov),
     $   g(mxncov,0:mxnsmp),gt(1,mxncov,mxnsmp),Yi,sumYi,
     $   cvalue(mxncov,mxncov),ctemp(mxncov,mxnsmp),
     $   cinv(mxncov,mxncov),ct(mxncov,mxncov),
     $   gcvalue(1,mxncov,mxnsmp),Zbar(mxncov,mxnsmp),
     $   temp1(mxncov,mxnsmp),temp2(mxncov,mxnsmp),
     $   value11,value22, value2(2,0:mxnsmp),
     $   value3(2,0:mxnsmp), cumulative(2,0:mxnsmp),delta(mxnsmp),
     $   uu1(mxncov),uu2(mxncov),b1(0:mxnsmp),b2(0:mxnsmp)

c     *** Give some values to simulate data ***
c     Use these input values for the numerical example:
c        42 37 45 51  1.  1. .3  400 .5 1000  0. 0.15


      seeda=42.
      seedb=37.
      seedc=45.
      seedd=51.
      betav1=1.
      betav2=1.
      cbeta=.3
      nsamp=200
      clev=.5
      nboot=1000
      t1=0.
      t2=0.15

      nsim=1000

      call rstart(seeda,seedb,seedc,seedd)
      ncov=2
      do 5 j=1,ncov
        clevel(j)=clev
 5    continue
c
      rcounta=0.
      rcount=0.
      do 1000 isim=1,nsim
c
      do 10 i=1,nsamp
         zz=uni()
         zzz=uni()

         cov(1,i)=zz
         cov(2,i)=zzz
```

```
      tim1=-alog(uni())/(betav1*zz+betav1*zzz+1)

      tim2=-alog(uni())/(betav2*zz+betav2*zzz+2.5)

      cc=-alog(uni())*exp(-cbeta*zz-cbeta*zzz)

      if ((tim1.lt.tim2).and.(tim1.lt.cc)) then
         censor(i)=1.
         time(i)=tim1
      endif
      if ((tim2.lt.tim1).and.(tim2.lt.cc)) then
         censor(i)=2.
         time(i)=tim2
      endif
      if  ((tim1.ge.cc).and.(tim2.ge.cc)) then
         censor(i)=0.
         time(i)=cc
      endif

 10   continue
     print *, ' '

c ***************************************************

c     print*,'data simulated'

c      *** order the data by time ***

c ***************************************************

     call indexx(nsamp,time,indx)
     do 20 i=1,nsamp
        copy(i)=time(i)
 20   continue
     do 40 i=1,nsamp
        time(i)=copy(indx(i))
 40   continue
     do 60 i=1,nsamp
        copy(i)=censor(i)
 60   continue
     do 80 i=1,nsamp
        censor(i)=copy(indx(i))
 80   continue
     do 95 j=1,ncov
        do 90 i=1,nsamp
           copy(i)=cov(j,i)
 90      continue
        do 95 i=1,nsamp
```

```
          cov(j,i)=copy(indx(i))
          do 94 ii=1,nsamp
          covar(j,i,ii)=cov(j,i)
 94      continue
 95      continue

c
c ------------------------------------------------
c  Find indices iii and jjj corr to time > t1 and
c       first failure time <= t2)
c ------------------------------------------------
c
      iii=1
      jjj=1
      do 100 i=1,nsamp
        if (time(i).lt.t1) then
          iii=i+1
        endif
        if (time(i).le.t2) then
          jjj=i
        endif
 100  continue
      do 105 i=1,nsamp
         copy(i)=censor(i)
         if (censor(i).gt.1.5) then
           censor(i)=0.
         endif
         censor1(i)=censor(i)
c          print*, i, censor(i)
 105   continue
c
c -------------------------------------------------------
c
       do 200 j=1,ncov

        beta(j)=0.

 200   continue

c  ***  CALL SUBROUTINE estp to get beta hat value ***

       call estp(nsamp,ncov,time,covar,censor,s0,s1,s2,beta,

     $    CL,var,NDEAD,NMIS)

      print *, 'beta1=', (beta(j),j=1,ncov)

      do 205 j=1,ncov
```

```
      beta2(1,j)=beta(j)

 205  continue
      print*, ' '
c ----------------------------------------------------

c   Find the first cumulative function
c   for first cause-of-failure
c ----------------------------------------------------

      do 210 i=1,nsamp
            do 208 j=1,ncov
               base2(j,i)=0.
               cumulative(j,i)=0.0
          value2(j,i)=0.0
          value3(j,i)=0.0
 208      continue
 210  continue

      start=0.0
      sumYi=nsamp
      value11=0.0
      bb1=0.0
      tempvalue1=0

      do 215 j=1,ncov
        bb1=bb1+beta2(1,j)*clevel(j)
 215  continue


      do 225 i=1,nsamp
        s02(1,i)=s0(i)
        value11= value11 +censor1(i)/sumYi
        diff=time(i)-start

        do 220 j=1,ncov
          s12(1,j,i)=s1(j,i)
          Zbar(j,i)= S1(j,i)/S0(i)
          tempValue1=tempValue1 +beta2(1,j)*Zbar(j,i)*diff
 220      continue

        value2(1,i)=tempValue1

        value3(1,i)=value3(1,i) + time(i)*bb1

        base2(1,i)=base2(1,i-1)+value11-value2(1,i)

            cumulative(1,i)=cumulative(1,i)+value11 -value2(1,i)+value3(1,i)
```

```
      start=time(i)
      sumYi=nsamp -i


      do 225 k=1,ncov

        s12(1,k,i)=s1(k,i)

 225  continue

c ---------------------------------------------------------------------
c    Now consider second cause of failure:
c ---------------------------------------------------------------------

     do 300 j=1,ncov

      beta(j)=0.

 300  continue


     do 305 i=1,nsamp

      if (copy(i).ge.2.) then

        censor(i)=1.

      else

        censor(i)=0.

      endif

      censor2(i)=censor(i)

 305  continue

c  ***  CALL SUBROUTINE estp to get second cause of failure ***
      call estp(nsamp,ncov,time,covar,censor,s0,s1,s2,beta,

    $   CL,var,NDEAD,NMIS)


     print *, 'beta2=', (beta(j),j=1,ncov)

     do 310 j=1,ncov

      beta2(2,j)=beta(j)
```

```
 310  continue

c ---------------------------------------------------
c    Find the second cumulative function ***
c ---------------------------------------------------


      value22=0
      start=0.0
      sumYi=nsamp
      bb2=0.0
      tempvalue2=0

      do 315 j=1,ncov
        bb2=bb2+beta2(2,j)*clevel(j)
 315  continue


      do 330 i=1,nsamp
         s02(2,i)=s0(i)
         value22= value22 +censor2(i)/sumYi
         diff=time(i)-start

         do 320 j=1,ncov
           s12(2,j,i)=s1(j,i)
           Zbar(j,i)= S1(j,i)/S0(i)
           tempValue2=tempValue2 + beta2(2,j)*Zbar(j,i)*diff
 320       continue

         value2(2,i)=tempValue2

         value3(2,i)=value3(2,i) + time(i)*bb2

         base2(2,i)=base2(2,i-1)+value22-(value2(2,i))


             cumulative(2,i)=cumulative(2,i)+value22 -value2(2,i)+value3(2,i)

         start=time(i)
             sumYi=nsamp-i


         do 330 k=1,ncov

           s12(2,j,i)=s1(j,i)

 330  continue
c
c ******************************************************************
```

```
c
      st=1.
      st1=1.
      st2=1.
      st0=1.
      phi(0)=0.0
      do 350 i=nsamp
        phi(i)=0
 350  continue

      bb1=0.
      bb2=0.
      do 400 j=1,ncov
        bb1=bb1+beta2(1,j)*clevel(j)
        bb2=bb2+beta2(2,j)*clevel(j)
 400  continue

      sumYi=nsamp
      do 450 i=1,jjj
        st0=st
        st = st*(exp(-(cumulative(1,i)-cumulative(1,i-1) +
     $                          cumulative(2,i)-cumulative(2,i-1))))

        st1 = st1*(exp(-(cumulative(1,i)-cumulative(1,i-1))))
        st2 = st2*(exp(-(cumulative(2,i)-cumulative(2,i-1))))

        if (i.ge.iii) then

c   for constant weight function W_1 use:
        w(i)=sqrt(float(nsamp))

c   for weight function W_2 use
c         w(i)=float(nsamp-i+1)/sqrt(float(nsamp))

c   for weight function W_3 use
c         w(i)=1./sqrt(2./sumYi)

c   for weight function W_4 use
c        w(i)=sqrt(float(nsamp))*st0
c        phi(i)=sqrt(float(nsamp))*(st1-st2)



        phi(i)=phi(i-1)+((cumulative(2,i)-cumulative(2,i-1))-
     $            (cumulative(1,i)-cumulative(1,i-1)))*w(i)

        else
           phi(i)=phi(i-1)
```

```
        endif
        sumYi=nsamp-i
c        print*, time(i), cumulative(1,i),cumulative(2,i),st
 450  continue
c
c ************************************************************
c   **** compute the test statistics ****
c
c*************************************************************
c
      stata=phi(iii)
      stat=phi(iii)
       do 460 i=iii,jjj-1
        xx=phi(i)
        if (xx.gt.stata) then
           stata=xx
        endif
        do 460 j=i+1,jjj
        xxx=phi(j)-phi(i)
        if (xxx.gt.stat) then
           stat=xxx
        endif
 460  continue
c     N.B.  the sqrt(nsamp) in front of the test statistic
c           is merged into the weight function;
c           this avoids having to normalize s^{(0)}
c           by nsamp in various places.
      print*, ' '
      print*, 'The output of sample size ',nsamp
      print *,'Test statistic (H_0 vs H_1) =', stata
      print *,'Test statistic (H_0 vs H_2) =', stat
      print*,' '
c -------------------------------------------------------
c
c   **** simulation to determine P-value ****
c -------------------------------------------------------

      b1(iii-1)=0
      b2(iii-1)=0
      nreja=0.
      nrej=0.

      do 900 iboot=1,nboot

      sumYi=nsamp
      do 510 i=nsamp
         do 505 j=1,ncov
            uu1(j)=0
            uu2(j)=0
```

```
          ctemp(j,i)=0
          g(j,i)=0
 505      continue
 510  continue
c -------------------------------------
c    Find the second term of L(t)
c -------------------------------------

c *** culculate G' value ***

      start=0.
      g(1,0)=0

      do 520 i=1, jjj
            diffvalue=time(i)- start

            do 515 j=1,ncov
              g(j,i)=g(j,i-1)+ w(i)*(clevel(j)- zbar(j,i))*diffvalue
 515      continue
        start=time(i)
 520      continue
c ------------------------------------------

      start2=0

      do 580 i=1,nsamp
        diffvalue2=time(i)- start2
            do 525 j=1,ncov
              gt(1,j,i)=g(j,i)
 525    continue
c        print*, i, (gt(1,j,i), j=1,2)

c *** transpose of Z value ***

      do 530 j=1,ncov
              zt(i,j)=covar(j,i,i)
 530  continue

      do 535 j=1,ncov
        ctemp(j,i)=ctemp(j,i)+ (covar(j,i,i)-zbar(j,i))*diffvalue2
 535  continue


      start2=time(i)

      do 550 K=1,ncov
        do 545 L=1,ncov
          temp10=zero
          do 540 M=1,1
```

```
            temp10= temp10 + ctemp(L,i)*zt(i,K)/float(nsamp)
 540        continue
          cvalue(L,K)=cvalue(L,K)+temp10
 545      continue
 550  continue
 580  continue
c ---------------------------------------------
c *** get C inverse    ***
c ---------------------------------------------
      call MATINV(cvalue,ncov,ncov,IFLAG)

      do 620 K = 1, ncov
         do 610 J = 1, ncov
          cinv(K,J)=cvalue(K,J)
 610      continue
 620  continue
c ----------------------------------------
c *** get C transpose    ***
c ----------------------------------------
      do 640 k=1,ncov
             do 630 L=1,ncov
          ct(K,L)=cinv(L,K)
 630      continue
 640  continue
c      print*, ct(1,1), ct(1,2)
c      print*, ct(2,1), ct(2,2)

      do 680 i=1,nsamp
             do 660 k=1,ncov
          temp15=zero
               do 650 j=1,ncov
            temp15= temp15 + gt(1,j,i)*ct(j,k)/float(nsamp)
 650        continue
          gcvalue(1,k,i)=temp15
 660       continue
 680  continue

c
c ---------------------------------------------------------
c    Find phiboot(i) then p-value
c ---------------------------------------------------------

      do 750 i=iii,jjj
         b1(i)=b1(i-1)+w(i)*rnor()*censor1(i)/(sumYi)
         b2(i)=b2(i-1)+w(i)*rnor()*censor2(i)/(sumYi)

         a1=0
         a2=0
```

```
      yy1=rnor()*censor1(i)
      yy2=rnor()*censor2(i)
      do 710 j=1,ncov
        uu1(j)=uu1(j)+ yy1*(covar(j,i,i)-zbar(j,i))
        uu2(j)=uu2(j)+ yy2*(covar(j,i,i)-zbar(j,i))

        a1=a1 + gcvalue(1,j,i)*uu1(j)
        a2=a2 + gcvalue(1,j,i)*uu2(j)

710     continue

          sumYi=nsamp-i

      phiboot(i)=b1(i)+b2(i) + (a1+a2)/float(nsamp)
750    continue
c ---------------------------------------------------------

    bstata=phiboot(iii)
    bstat=phiboot(iii)

    do 800 i=iii,jjj-1
    xx=phiboot(i)
    if (xx.gt.stata) then
       bstata=xx
    endif
    do 800 j=i+1,jjj
      xxx=phiboot(j)-phiboot(i)
       if (xxx.gt.bstat) then
         bstat=xxx
       endif
800  continue
    if (bstata.gt.stata) then
      nreja=nreja+1.
    endif
    if (bstat.gt.stat) then
      nrej=nrej+1.
    endif

900  continue

    print*, ' '
    print*, 'P-value (vs H_1) = ', nreja/float(nboot)
    print*, 'P-value (vs H_2) = ', nrej/float(nboot)
    print *,'(H_1 and H_2 are denoted H_2 and H_3 in the paper!)'
    print*,'Completed simulation',isim, ', runs with nboot = ', nboot
    print*,'*****************************************************'

    if (nreja/float(nboot).lt.0.05) then
      rcounta=rcounta+1.
```

```
      endif
      if (nrej/float(nboot).lt.0.05) then
        rcount=rcount+1.
      endif
 1000 continue
       print*,'Completed simulation ',nsim, ' runs with nboot = ', nboot
       print*,'Rej. at 0.05 level (vs H_1)= ',rcounta/float(nsim)
       print*,'Rej. at 0.05 level (vs H_2)= ',rcount/float(nsim)
      end
c
c ***********************************************************************
c                        ending main program
c ***********************************************************************
```