

Georgia State University

ScholarWorks @ Georgia State University

---

Mathematics Theses

Department of Mathematics and Statistics

---

5-3-2007

## Omnibus Tests for Comparison of Competing Risks with Covariate Effects via Additive Risk Model

Duytrac Vu Nguyen

Follow this and additional works at: [https://scholarworks.gsu.edu/math\\_theses](https://scholarworks.gsu.edu/math_theses)



Part of the [Mathematics Commons](#)

---

### Recommended Citation

Nguyen, Duytrac Vu, "Omnibus Tests for Comparison of Competing Risks with Covariate Effects via Additive Risk Model." Thesis, Georgia State University, 2007.

doi: <https://doi.org/10.57709/1059681>

This Thesis is brought to you for free and open access by the Department of Mathematics and Statistics at ScholarWorks @ Georgia State University. It has been accepted for inclusion in Mathematics Theses by an authorized administrator of ScholarWorks @ Georgia State University. For more information, please contact [scholarworks@gsu.edu](mailto:scholarworks@gsu.edu).

**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.

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

by

**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

Copyright by  
Duytrac Vu Nguyen  
2007

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

by

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.

## TABLE OF CONTENTS

Acknowledgements.....	iv
List of Tables.....	vi
List of Figures.....	vii
List of Abbreviation.....	viii
Chapter One: Introduction .....	1
Chapter Two: Test Procedure .....	5
2.1 Cumulative cause-specific hazard function .....	5
2.2 Test Process .....	7
2.3 Confidence Bands .....	11
Chapter Three: Simulation Study.....	13
3.1 Simulation example (1).....	15
3.2 Simulation example (2).....	17
3.3 Simulation example (3).....	19
Chapter Four: Application .....	20
Chapter Five: Conclusion .....	32
References.....	34
Appendix.....	36

## List of Tables

Table 3.1: Powers of test for equality of conditional cause-specific hazard rates based on $D_2$ and $D_3$ at nominal level 0.05 with $z_0 = (0.5,0.5)$ , CR = 0.30.....	16
Table 3.2: Powers of test for equality of conditional cause-specific hazard rates based on $D_2$ and $D_3$ at nominal level 0.05 with $z_0 = (0.5,0.5)$ , CR =0.15.....	18
Table 3.3: Powers of test for equality of conditional cause-specific hazard rates based on $D_2$ and $D_3$ at nominal level 0.05 with $z_0 = (0.3,0.3)$ , CR = 0.30.....	19
Table 4.1: Statistics test under additive risk model for failure caused by disease and failure caused by other causes. $H_2$ and $H_3$ as alternative hypotheses.....	21
Table 4.2: Statistics test under Cox regression model for failure caused by disease and failure caused by other causes. $H_2$ and $H_3$ as alternative hypotheses.....	22
Table 4.3: Risk factors in Additive risk model for failure time to death occurring from different causes of 205 malignant melanoma patients .....	25
Table 4.4: Risk factors in Cox regression model for failure time to death occurring from different causes of 205 malignant melanoma patients .....	25



## List of Figures

Figure 4.1a: Cumulative incidence functions plotting.....	23
Figure 4.1b: Hazard rate plotting.....	23
Figure 4.2: The test process $L(t)$ using $W_1$ plotting.....	27
Figure 4.3: The test process $L(t)$ using $W_2$ plotting.....	28
Figure 4.4: The test process $L(t)$ using $W_3$ plotting.....	29
Figure 4.5: The test process $L(t)$ using $W_4$ plotting.....	30
Figure 4.6: The simultaneous confidence bands for the difference of cumulative incidence functions.....	31

**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  $j = 1, \dots, k$ . 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  $\delta \in \{1, \dots, k\}$  is observed along with  $p$ -vector  $Z$  representing the covariate information. We are interested in focusing on the conditional cause-specific hazard rate  $\lambda_j(t | z_0) = \lim_{\Delta t \rightarrow 0} P(t \leq X \leq t + \Delta t, \delta = j | X \geq t, Z = z_0) / \Delta t$ . In other words,  $\lambda_j(t | z_0)$  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  $F_j(t | z_0) = P(X \leq t, \delta = j | Z = z_0)$ .

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  $\lambda_j(t | z_0)$  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

$$H_0 : \lambda_1(t | z_0) = \lambda_2(t | z_0), \quad 0 \leq t \leq \tau,$$

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:

$$H_1 : \lambda_1(t | z_0) \neq \lambda_2(t | z_0), \quad 0 \leq t \leq \tau$$

$$H_2 : F_1(t | z_0) \leq F_2(t | z_0), \quad 0 \leq t \leq \tau$$

$$H_3 : \lambda_1(t | z_0) \leq \lambda_2(t | z_0), \quad 0 \leq t \leq \tau,$$

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

$$F_j(t | z_0) = \int_0^t S_X(u | z_0) \lambda_j(u | z_0) du \quad (\text{Kalbfleisch and Prentice, 1980; Gay, 1988}), \text{ where}$$

$S_X(t | z_0) = P(X > t | Z = z_0)$  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

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

where  $\lambda_{0j}(\cdot)$  is an unspecified baseline hazard function and  $\beta_j$  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  $\beta_j$  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  $\tilde{X} = \min(X, C)$ ,  $\tilde{\delta} = \mathcal{I}(X \leq C)$ , and  $\mathcal{I}(\cdot)$  is indicator function. We also assume that  $C$  is conditionally independent of  $T_1, \dots, T_k$  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  $j \neq l$ . The cause of failure time  $\delta = j$  when  $X = T_j$ . Let  $\Delta_{ji} = \mathcal{I}(\tilde{\delta}_i = j)$ , and  $N_{ji}(t) = \Delta_{ji} \mathcal{I}(\tilde{X}_i \leq t)$  ( $i = 1, \dots, n$ ) be a counting process for indicating whether an event of type  $j$  has been observed for  $i$ th subject by time  $t$ . Let  $Y_i(t) = \mathcal{I}(\tilde{X}_i \geq t)$  denote the predictable process indicating whether or not the  $i$ th subject is at risk just before

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

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

where

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

(2.2) is equivalent to

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

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

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

The resulting estimator of  $\beta$  is

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

where  $a^{\otimes 2} = aa'$ . The confidence region for the regression parameter  $\beta_j$  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  $N_{ji}(\cdot)$  can be decomposed uniquely so that for every  $i$ th 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  $j$ th cumulative cause-specific hazard function for  $T_j$  given  $Z_i = z_0$  takes the form

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

where

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

where  $\beta_j$  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  $W(\cdot)$ ,

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

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,

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

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

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

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

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

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

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

and  $\hat{S}_X(t | z_0) = \exp \left\{ - \sum_{j=1}^k \hat{\Lambda}_j(t | z_0) \right\}$  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  $F(t | z_0)$ . 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  $W_4(t) = n^{1/2} \hat{S}_X(t- | z_0)$ , which gives the normalized difference of the estimated cumulative incidence functions,

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

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

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

$F_j(t | z_0) = \int_0^t S_X(u | z_0) \lambda_j(u | z_0) du$ . 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

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

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

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

Let

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

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

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

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

$$\begin{aligned} L(t) &= \int_0^t W(u) \left( \hat{\Lambda}_2(du | z_0) - \hat{\Lambda}_1(du | z_0) \right) = \\ &= \int_0^t W(u) \left( \hat{\Lambda}_2(du | z_0) - \Lambda(du | z_0) \right) - \int_0^t W(u) \left( \hat{\Lambda}_1(du | z_0) - \Lambda(du | z_0) \right). \end{aligned}$$

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

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

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  $\{G_{ji}, \tilde{G}_{ji} : j = 1, 2; i = 1, \dots, n\}$  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  $H_3$ :

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

### 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  $\delta(t) = F_2(t | z_0) - F_1(t | z_0)$  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

$\hat{\delta}(t) \equiv \hat{F}_2(t | z_0) - \hat{F}_1(t | z_0) = L(t)/n^{1/2}$  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  $\hat{\delta}(t) \pm ac_{\alpha/2}(t)n^{-\frac{1}{2}}$ ,  $t \in [0, \tau]$ ,

where  $a \geq 1$  and is the critical value of  $\sup_{0 \leq t \leq \tau} \left| \frac{\sqrt{n}(\hat{\delta}(t) - \delta(t))}{c_{\alpha/2}(t)} \right| = \sup_{0 \leq t \leq \tau} \left| \frac{L^*(t)}{c_{\alpha/2}(t)} \right|$ . 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  $\lambda_0(t) = \alpha_j, j = 1, \dots, k$  where  $\alpha_j$  is a various choices of constant, and set  $\beta_1 = \beta_2 = \dots = \beta_p = 1$ , then model (2.1) becomes

$$\lambda_j(t | z) = \alpha_j + [Z_1(t) + Z_2(t) + \dots + Z_p(t)]. \quad (3.1)$$

Simply we denote it as

$$\lambda_j(t | z) = \alpha_j + W, \quad (3.2)$$

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

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  $Z_{pi}(t), i = 1, \dots, n$ .

$Z$ 's are drawn from uniform distribution  $U(0,1)$ . Since  $Z_1, Z_2, \dots, Z_p$  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 $T_j, j = 1, \dots, k$

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  $\lambda_j(t | z) = \alpha_j + W$ , 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

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

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

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

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

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

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

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  $(\tilde{X}_i, \tilde{\delta}_i, W_p)$ ,  $i = 1, \dots, n$ , where  $\tilde{X} = \min(X, C)$ ,  $\tilde{\delta} = \mathcal{I}(X \leq C)$  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  $n = 50, 100, 200, \text{ and } 400$ , 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  $\alpha_2 (1, 1.5, 2.0, 2.5, 3.0)$  in order to generate  $T$  from (3.5). Then we test all weight functions,  $W_1, W_2, W_3, \text{ and } W_4$ , 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,  $z_0 = (0.5, 0.5)$ ,  $CR = 0.30$ .*

<b>n</b>	$\alpha_j$		$D_2$				$D_3$			
	$\alpha_1$	$\alpha_2$	$W_1$	$W_2$	$W_3$	$W_4$	$W_1$	$W_2$	$W_3$	$W_4$
50	1	1	<b>0.047</b>	<b>0.047</b>	<b>0.046</b>	<b>0.047</b>	<b>0.050</b>	<b>0.052</b>	<b>0.054</b>	<b>0.052</b>
	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	<b>0.057</b>	<b>0.060</b>	<b>0.064</b>	<b>0.059</b>	<b>0.054</b>	<b>0.061</b>	<b>0.061</b>
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	<b>0.049</b>	<b>0.057</b>	<b>0.057</b>	<b>0.053</b>	<b>0.050</b>	<b>0.052</b>	<b>0.052</b>
	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	<b>0.057</b>	<b>0.057</b>	<b>0.059</b>	<b>0.051</b>	<b>0.059</b>	<b>0.057</b>	<b>0.059</b>
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  $\alpha_1$  and  $\alpha_2$  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  $\alpha_2$  is much bigger

than the value of  $\alpha_1$ , 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	$\alpha_j$		$D_2$				$D_3$			
		$\alpha_1$	$\alpha_2$	$W_1$	$W_2$	$W_3$	$W_4$	$W_1$	$W_2$	$W_3$	$W_4$
50	0.30	1	1	<b>0.047</b>	<b>0.047</b>	<b>0.046</b>	<b>0.047</b>	<b>0.050</b>	<b>0.052</b>	<b>0.054</b>	<b>0.052</b>
		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	<b>0.059</b>	<b>0.054</b>	<b>0.060</b>	<b>0.057</b>	<b>0.057</b>	<b>0.056</b>	<b>0.054</b>	<b>0.059</b>
		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	<b>0.057</b>	<b>0.060</b>	<b>0.064</b>	<b>0.059</b>	<b>0.054</b>	<b>0.061</b>	<b>0.061</b>	<b>0.060</b>
		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	<b>0.061</b>	<b>0.059</b>	<b>0.061</b>	<b>0.059</b>	<b>0.068</b>	<b>0.064</b>	<b>0.064</b>	<b>0.064</b>
		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	<b>0.049</b>	<b>0.057</b>	<b>0.057</b>	<b>0.053</b>	<b>0.050</b>	<b>0.052</b>	<b>0.052</b>	<b>0.052</b>
		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	<b>0.049</b>	<b>0.045</b>	<b>0.05</b>	<b>0.053</b>	<b>0.054</b>	<b>0.043</b>	<b>0.044</b>	<b>0.052</b>
		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	$z_0$	$\alpha_j$		$D_2$				$D_3$			
		$\alpha_1$	$\alpha_2$	$W_1$	$W_2$	$W_3$	$W_4$	$W_1$	$W_2$	$W_3$	$W_4$
50	(0.5)	1	1	<b>0.047</b>	<b>0.047</b>	<b>0.046</b>	<b>0.047</b>	<b>0.050</b>	<b>0.052</b>	<b>0.054</b>	<b>0.052</b>
		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	<b>0.071</b>	<b>0.063</b>	<b>0.059</b>	<b>0.065</b>	<b>0.060</b>	<b>0.067</b>	<b>0.063</b>	<b>0.066</b>
		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	<b>0.057</b>	<b>0.060</b>	<b>0.064</b>	<b>0.059</b>	<b>0.054</b>	<b>0.061</b>	<b>0.061</b>	<b>0.060</b>
		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	<b>0.053</b>	<b>0.055</b>	<b>0.052</b>	<b>0.050</b>	<b>0.051</b>	<b>0.051</b>	<b>0.054</b>	<b>0.054</b>
		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:

$$H_0 : \lambda_1(t | z_0) = \lambda_2(t | z_0), \quad 0 \leq t \leq 10,$$

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:

$$H_2 : F_1(t | z_0) \leq F_2(t | z_0), 0 \leq t \leq 10$$

$$H_3 : \lambda_1(t | z_0) \leq \lambda_2(t | z_0), 0 \leq t \leq 10$$

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  $z_0 = \{\text{ulceration, 2.9 mm, male, 52 years}\}$  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**

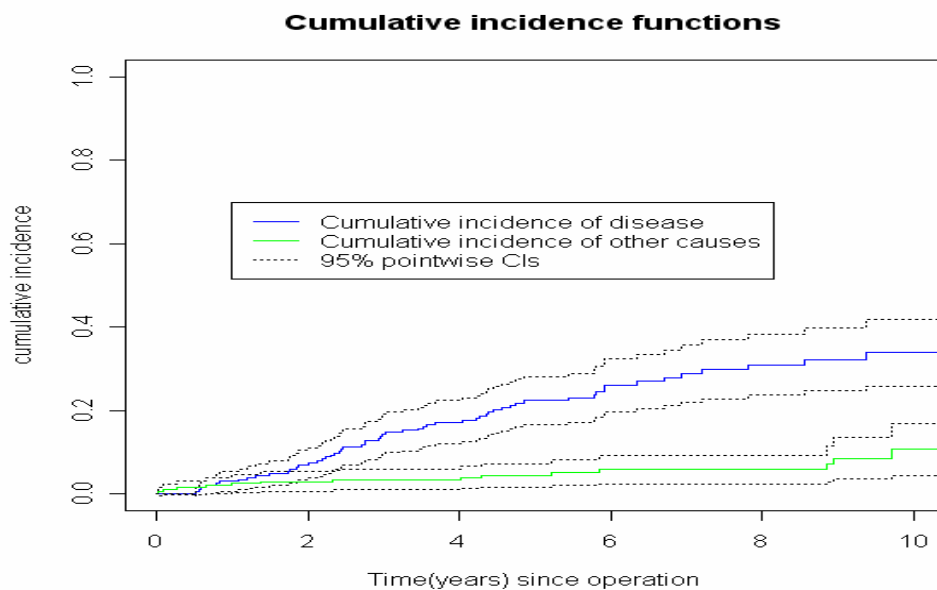
*Statistical test under Cox regression model for failure caused by disease and failure resulting by other causes.  $H_2$  and  $H_3$  as alternative hypotheses.*

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

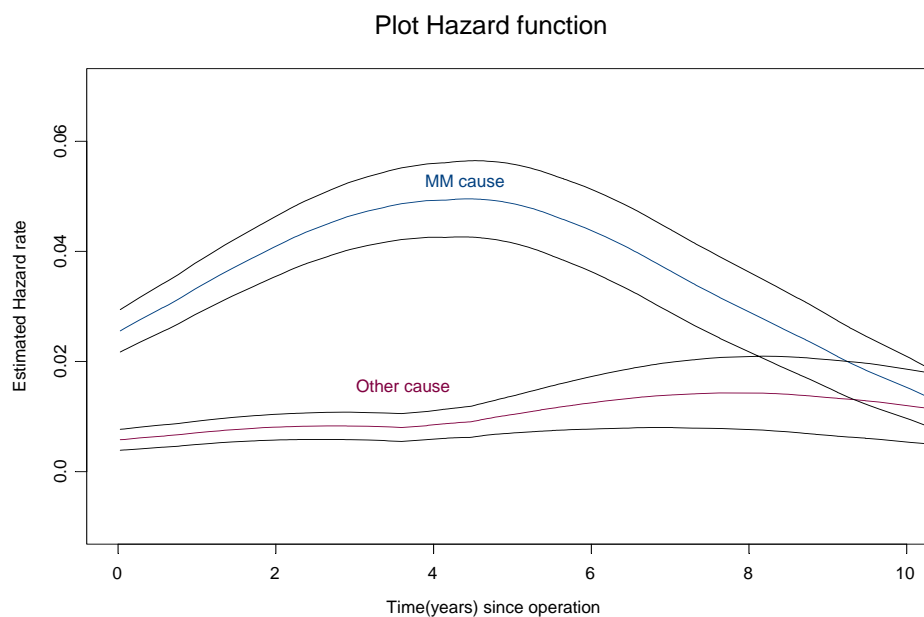
From Tables 4.1 and 4.2, the *p*-values of  $W_1$ ,  $W_2$ ,  $W_3$ , and  $W_4$  in both alternative hypotheses,  $H_2$  and  $H_3$  show the test is very consistent and significant under both additive risk model and Cox regression model. That means the failure caused by the disease is overall higher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

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

**Table 4.4**

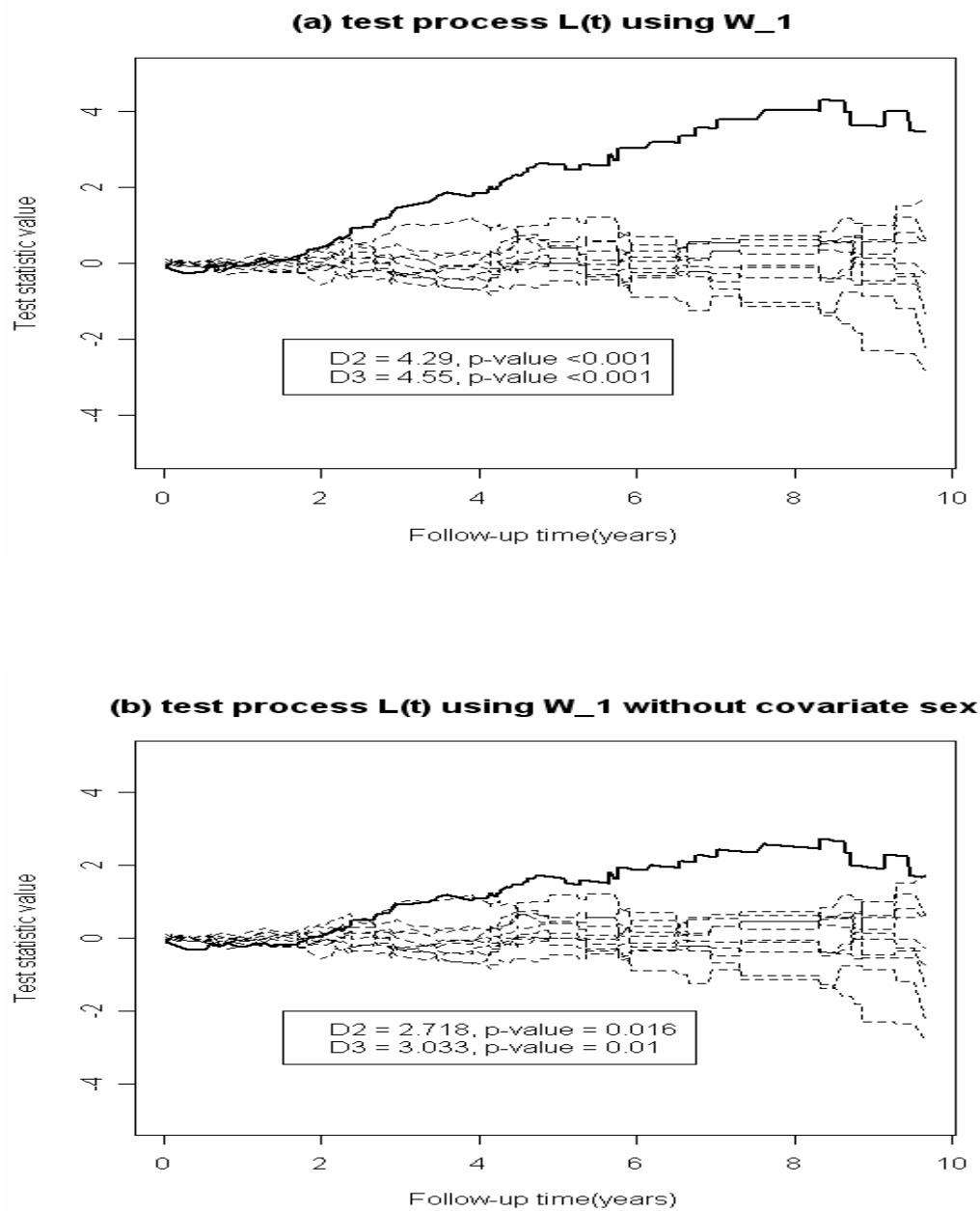
*Estimation results of risk factors in Cox regression model for failure time to death occurring from different causes of 205 malignant melanoma patients.*

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

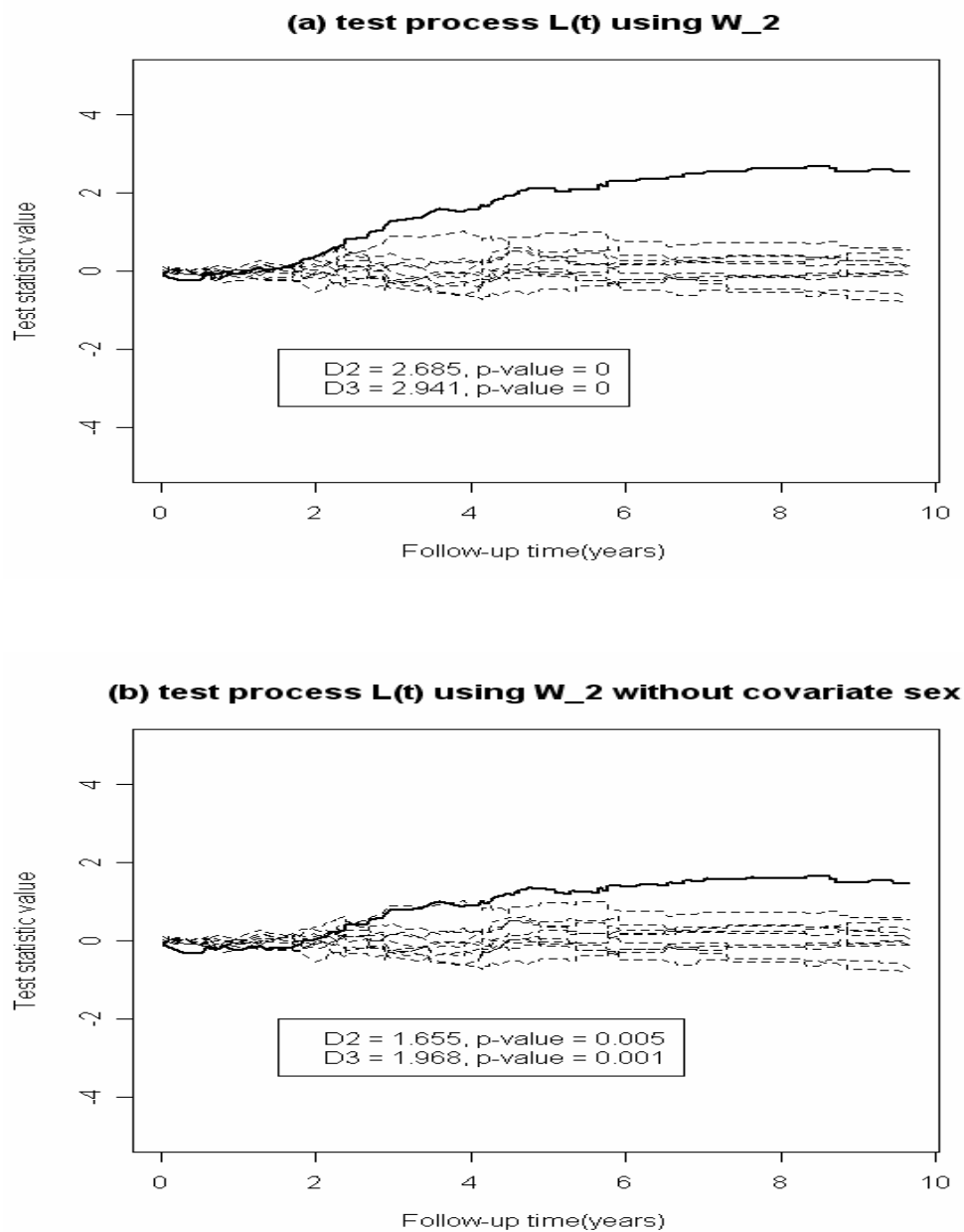
We applied the test to compare cause-specific hazard rates for the full model in which four covariates, ulceration status, tumor thickness, sex, and age have been included, and another model in which only the significant risk factors covariates, ulceration status, tumor thickness, and age (sex was excluded 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  $z_0 = \{\text{ulceration, 2.9 mm, male, 52 years}\}$  for the full model and  $z_0 = \{\text{ulceration, 2.9 mm, 52 years}\}$  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.

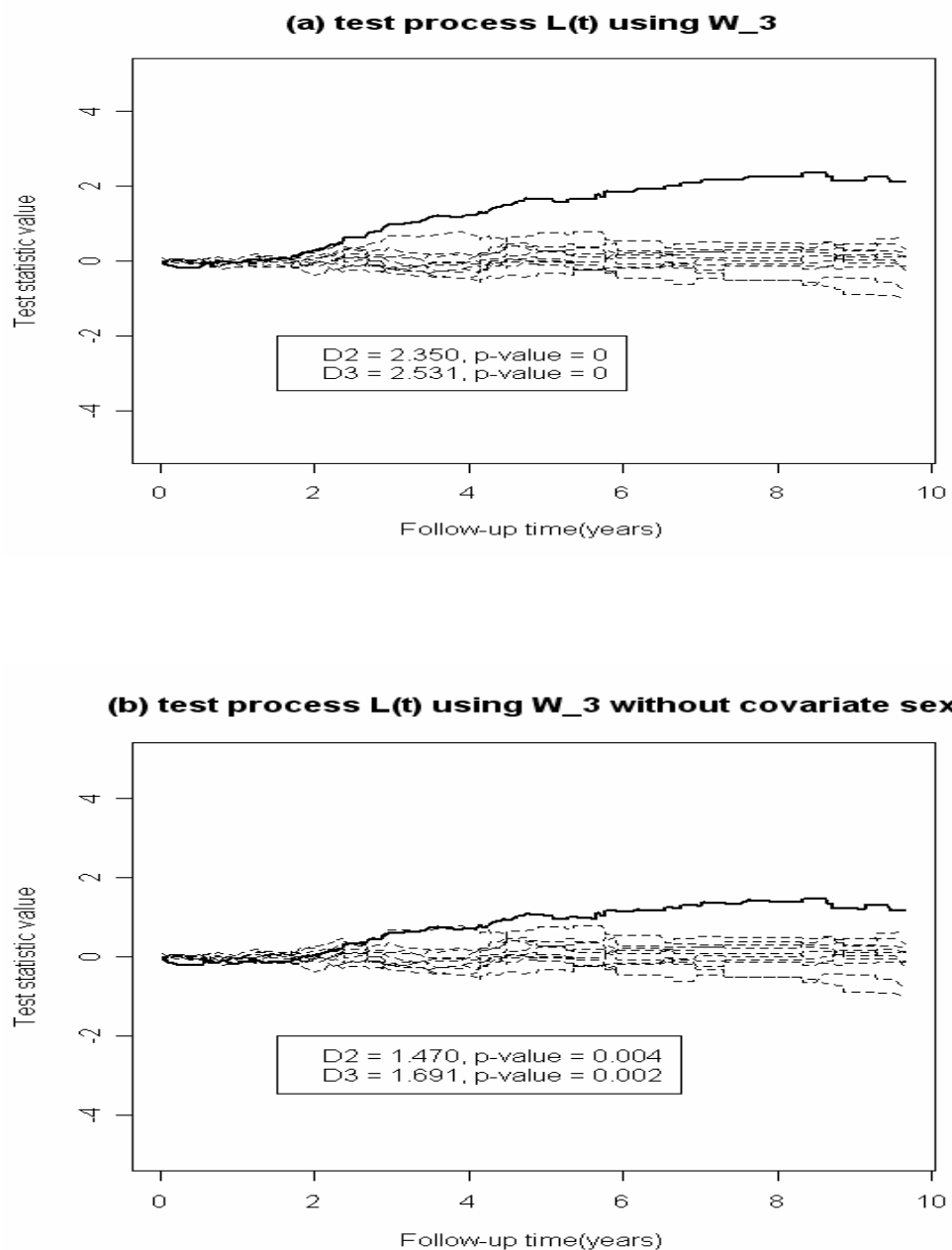
It is of interest to estimate the difference between the risk-1 and risk-2 cumulative incidence functions for various covariate subgroups. The confidence bands displayed in Figure 4.6 were computed via the procedure described in Section 2.3 for the same covariate subgroups as in Figures 4.2-4.5, conditions **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.



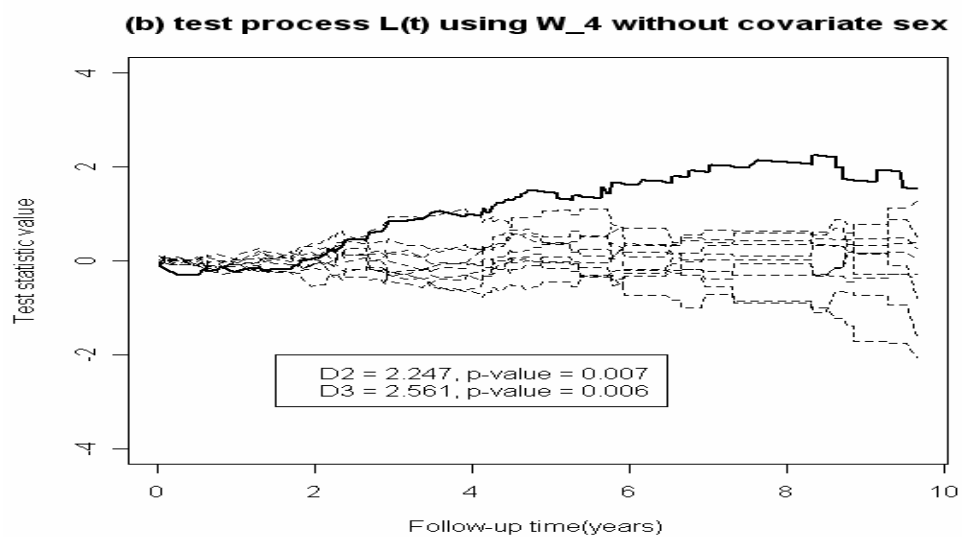
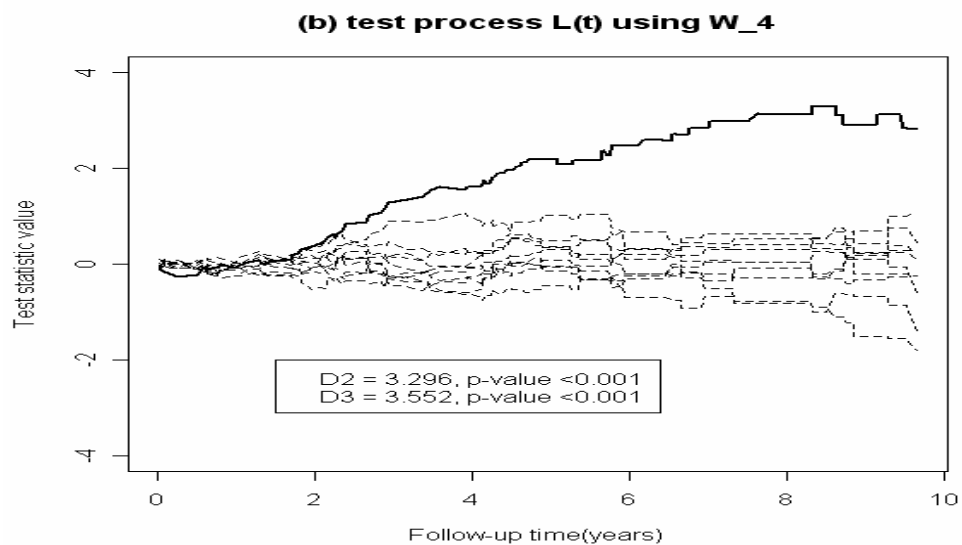
**Figure 4.2.** The test process  $L(t)$  (solid line) and 10 realizations of  $L^*(t)$  (dash lines) for the weight process  $W_1(t)$ . **a.** Conditions with covariate {ulceration status, tumor thickness, sex, and age}. **b.** Conditions with covariate {ulceration status, tumor thickness, and age}.



**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}.

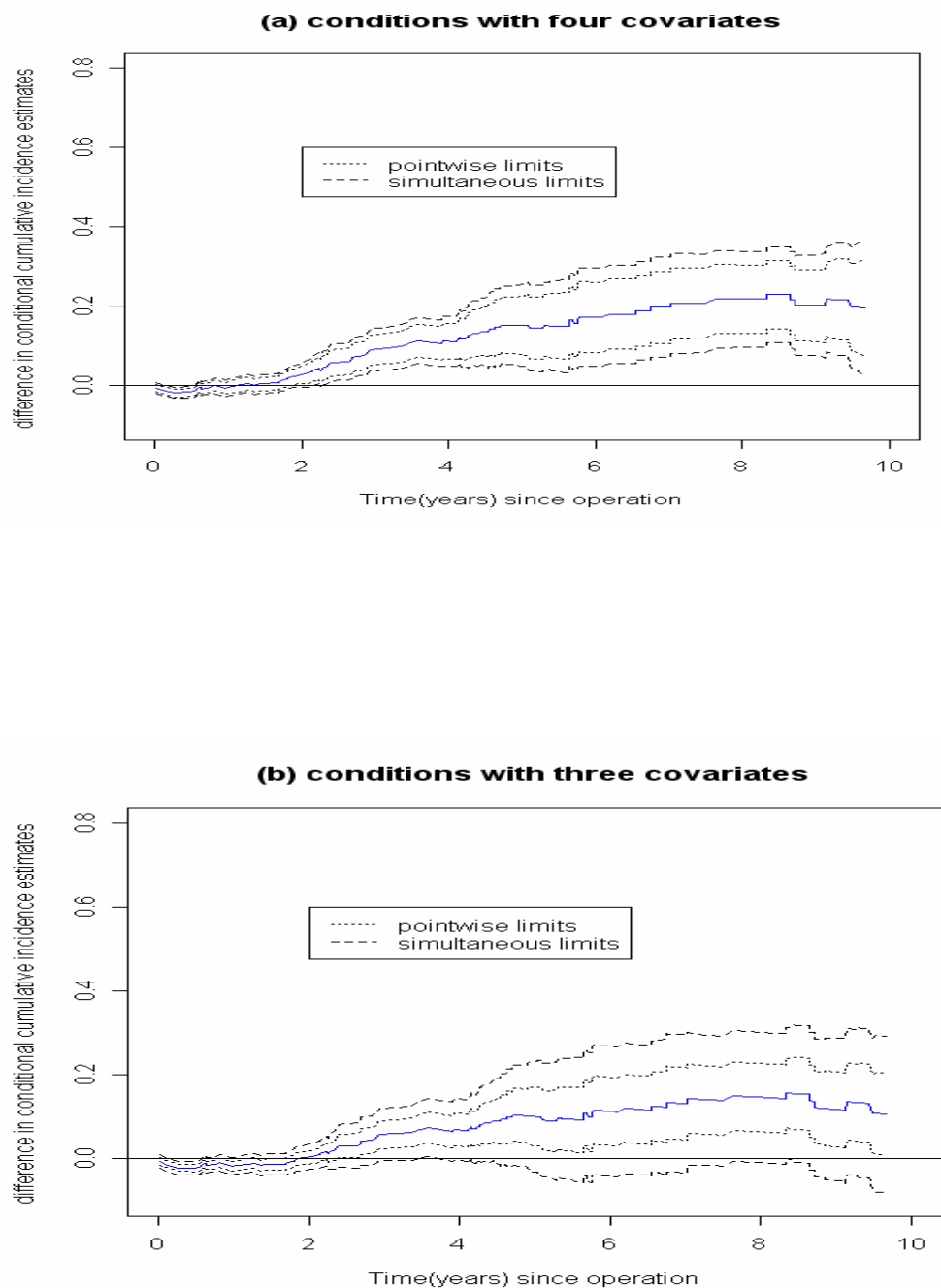


**Figure 4.4.** The test process  $L(t)$  (solid line) and 10 realizations of  $L^*(t)$  (dash lines) for the weight process  $W_3(t)$ . **a.** Conditions with covariate {ulceration status, tumor thickness, sex, and age}. **b.** Conditions with covariate {ulceration status, tumor thickness, and age}.



**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  $z_0 = \{\text{ulceration}, 2.9 \text{ mm}, \text{male}, 52 \text{ years}\}$ . **b.** Conditions with covariate {ulceration status, tumor thickness, and age} at level  $z_0 = \{\text{ulceration}, 2.9 \text{ mm}, 52 \text{ years}\}$ .

## 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.

### References

- Aalen, O.O. (1980). *A Model for Non-parametric Regression Analysis of Counting Processes*. In *Lecture Notes on Mathematical Statistics and Probability*, 2, W. Klonecki, A. Kozek, and J. Rosiski, eds. New York: Springer-Verlag, pp. 1-25.
- Andersen, P. K., Borgan, O., Gill, R. D., and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. New York: Springer-Verlag.
- Aly, E.-E., Kochar, S. C., and McKeague, I. W. (1994). *Some tests for comparing cumulative incidence functions and cause-specific hazard rates*. *Journal of the American Statistical Association* 89, 994-999.
- Cheng, M., Hall, P., and Tu, D. (2006). *Confidence bands for hazard rates under random censorship*. *Biometrika* 93, 357-366.
- Cox, D. R (1972). *Regression models and life tables (with discussion)*. *Journal of the Royal Statistical Society, Series B*, 34, 187-220.
- Cox, D. R and Oakes, D. (1984). *Analysis of Survival Data*. London: Chapman & Hall.
- Fine, J. P. and Gray, R. J. (1999). *A Proportional Hazards Model for the Subdistribution of a Competing Risk*. *JASA*. 94, 496-509.
- Gray, R. J. (1988). *A class of k-sample tests for comparing the cumulative incidence of a competing risk*. *Annals of Statistics* 16, 1140-1154.
- Kalbfleisch, J. D. and Prentice, R. L. (1980). *The Statistical Analysis of Failure Time Data*. New York: Wiley.
- Klein, J.P., and Moeschberger, M.L. (2003). *Survival analysis techniques for censored and truncated data*. New York: Spring Verlag, 2<sup>nd</sup> Edition.
- Lam, K. F. (1998). *A class of tests for the equality of k cause-specific hazard rates in a competing risks model*. *Biometrika*, 85, 179-188.
- Lin, D.Y. and Ying, Z.L. (1994). *Semiparametric analysis of the additive model*. *Biometrika*, 81, 61-71.
- Lin, D.Y. and Ying, Z.L. (1997). *Additive hazards regression models for survival data*. In: *proceeding of the First Seattle Symposium in biostatistics: Survival Analysis*.
- Martinussen, T. and Scheike, T. H. (2006). *Dynamic Regression Models for Survival Data*. Springer.

- McKeague, I.W., Gilbert, P.B., and Kanki, P.J. (2001). *Omnibus test for comparison of competing risks with adjustment for covariate effects*. *Biometrics* 57, 818-828.
- Shen, Y. and Cheng, S.C. (1999). *Confidence bands for cumulative incidence curves under the additive risk model*. *Biometrics* 55, 1093-1100.
- Song, M., Jeong, D., and Song, J. (1997). *Confidence bands for survival curve under the additive risk model*. *Journal of the Korean, Statistical Society*, Vol. 26, No. 4.
- Sun, Y. (2001). *Generalized Nonparametric Test Procedures for Comparing Multiple Cause-Specific Hazard Rates*. *Journal of Nonparametric Statistics*, 13, 171—207.
- Zhao, Y. and Hsu, Y.S. (2005). *Semi-parametric analysis for additive risk model via empirical likelihood*. *Communications in Statistics---Simulation and Computation*, 34, 135-143.

## 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:  $F_1(t|z)\leq F_2(t|z)$  on  $[t1,t2]$ 
c OR
c H_2:  $g_1(t|z)\leq g_2(t|z)$  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
cleve=.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)=cleve
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
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 *** culcuate 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
c           ending main program
c *****
```