

**INFERENCE ON CENSORED SURVIVAL DATA
UNDER COMPETING RISKS**

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Competing risks is commonly encountered in survival data. While fundamental methods have been established to analyze survival data in the presence of competing risks, some of methods still remain undeveloped. The primary goal of this study is to extend existing methods for survival analysis to the competing risks settings.

In the first study is to determine the optimal cutpoint in the presence of competing risks. A continuous variable often needs to be dichotomized to quantify the prognostic effect. The “outcome-oriented” cutpoint approach is the useful method without any prior knowledge about that variable, which is to seek an optimal cut point that provides the maximum difference in prognostic effect between the splits. The rescaled sequential method is one of the approaches for estimating the optimal cutpoint and for adjusting its significance after the dichotomization. We adapted the concept of improper random variables from Gray’s test and modified log-rank test to apply the rescaled sequential approaches. We present simulation results of the operating characteristics of the proposed method. A real dataset from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 is exemplified.

In the second part, a quantile residual life regression model was developed for competing risks. Residual life analysis provides useful information when the effect of prognostic factors on the distribution of remaining lifetimes is evaluated at several years after the initial diagnosis/therapy. This model allows for meaningful interpretations of covariate effects on not only any quantile residual life but also at a specific time point. Simulation studies are performed to assess the finite sample properties of proposed method in terms of the parameter

estimator, type I error and power of the test statistics at different time points. The new regression method is illustrated with a NSABP B-04 dataset.

Although competing risks have been an important issue in survival analysis research, it is often neglected by clinical researchers due to its complex nature and lack of available methodology. Development of inference procedures suitable for competing risks data would provide more accurate additional information, which has great significance in a public health perspective leading to improved patient care in clinical settings.

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PREFACE

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1.0 INTRODUCTION

1.1 SURVIVAL ANALYSIS

In many biomedical studies an outcome of interest is a time from a pre-defined origin to occurrence of particular event such as disease or death. One distinguishing feature of this time-to-event data is censoring, which is the case when the event does not occur within the study duration and its distribution is assumed to be independent of event time. Special statistical techniques to analyze those data have been widely developed and commonly accepted in the medical literature. Without assumption about underlying distribution of the data, the Kaplan-Meier estimator (Kaplan and Meier, 1958) [18] is the standard estimator of the survival function. This is a step function with jumps at the observed event times, $t_1 < t_2 < \dots < t_D$, taking into account of censored observations, formulated as

$$\hat{S}(t) = \prod_{t_i \leq t} \left(1 - \frac{d_i}{Y_i} \right), \quad (1.1)$$

where d_i is number of events and Y_i is number of subjects at risk at time t_i . Kaplan-Meier curve plotting survival function by time might be a first step for a preliminary evaluation of survival rate. Typically it provides a graphical visual comparison on the survival rate between grouped patients, for instance, treatment and placebo. To test hypotheses about the equality in the survival distribution of two or more groups, log-rank test (Peto, 1972) [23] is commonly used. The log-rank statistic can be calculated by computing the sum of the differences between observed and expected events in one of the group at the observed times, that is,

$$U = \sum \left(d_{1i} - Y_{1i} \frac{d_i}{Y_i} \right) \quad (1.2)$$

where d_{1i} and d_{2i} are the numbers of events in group 1 and group 2, respectively, and Y_{1i} and Y_{2i} are the numbers of subject at risk at time t_i , respectively, then $d_i = d_{1i} + d_{2i}$ and $Y_i = Y_{1i} + Y_{2i}$ in two group comparison. To regress survival time on related prognostic factors, the Cox-proportional hazard regression is one of popular and unique regression techniques (Cox, 1972) [5]. It can be presented with baseline hazard $h_0(t)$ and covariate term $\exp(\beta'X)$ as

$$h(t|X) = h_0(t) \exp(\beta'X) \tag{1.3}$$

Equation (1.3) implies that if $X = 0$, a baseline hazard is observed. Furthermore, the two hazard functions are portional. Those are some of the established methodologies for survival data, which is assumed only one type of event of interest.

1.2 COMPETING RISKS

In many cases in survival data, multiple types of event could exist and actually they “compete” with each other, but we generally observe only one event whichever occurs first. We call this as a competing risks data. Typically, competing risks can be defined as a situation where any other types of events preclude the occurrence of our primary event or modify the probability of it [11]. In a cancer treatment clinical trial, relapse of disease and death is a well known example of competing risks. Cancer patients could die due to any other reason without relapse and this occurrence is a competing risks event that prevents the cancer relapse from happening. Another example can be found in a radiation trial where local recurrence is the primary event of interest, and then distance recurrence is a competing risks event that affects the probability of local recurrence.

In a competing risks setting, unlike regular survival data, subjects would have event of interest, competing risks event, or censored, at the end of study as illustrated in Figure 1, and the analysis approach will be different depending on the goal and hypothesis of the study. In a cancer treatment clinical trial, if investigators focus on the treatment effect in “disease-free survival”, it can be analyzed by standard survival method. Whereas, if the primary interest is in the treatment effect in relapse of disease, death become a competing

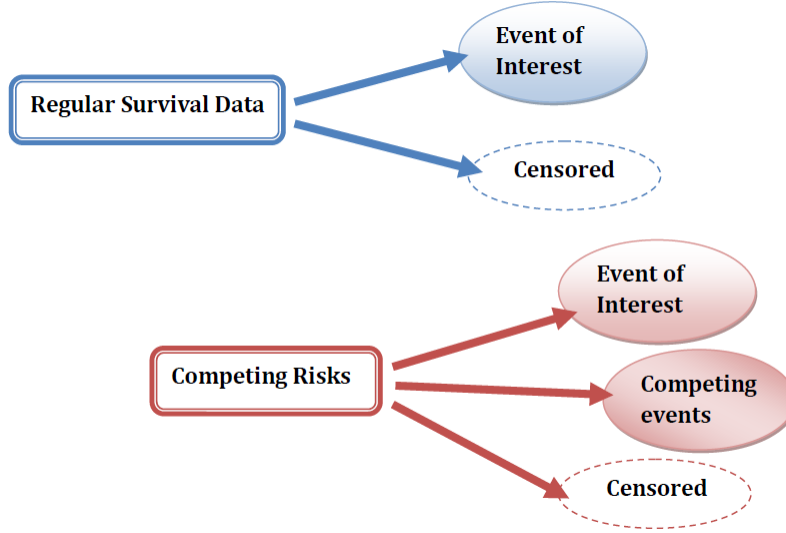


Figure 1: A schematic illustrating survival (top) and competing risks (bottom) data

risks event and standard survival analysis considering death as independent censoring leads to biased results [24]. To analyze survival data with multiple types of event, the time to event need to be defined carefully, and competing risks event should be identified.

It has been suggested by many authors that the cumulative incidence function is the appropriate descriptive quantity under competing risks. The cumulative incidence function (CIF), a joint density function of the specific event type can be defined

$$F_k(t) = P(T \leq t, \epsilon = k) = \int_0^t h_k(u) \exp\{-H_T(u)\} du = \int_0^t h_k(u) S(u) du \quad (1.4)$$

where $h_k(t)$ is a cause specific hazard rate and $H_T(t) = \sum_{k=1}^K \int_0^t h_k(u) du$ is the sum of K cause-specific cumulative hazard rates. Note that the cumulative incidence function depends on not only hazard rate of event type of interest but also the hazard rate of other type of events. This leads to more suitable interpretation that the probability of failure from type k by time t where all other competing events may influence on individual. Whereas, the complement of the Kaplan-Meier (1 - KM) estimator is a naive approach which is often misused

to estimate the cumulative probability of event of interest in the presence of competing risks event. 1 - KM estimate of cumulative incidence of event type k can be denoted as $G_k(t)$,

$$G_k(t) = \int_0^t h_k(u) \exp\left\{-\int_0^t h_k(u)\right\} du = \int_0^t h_k(u) S_k(u) du. \quad (1.5)$$

It tends to overestimate the probability of failure of specific type of event, ignoring the competing risks. This can be explained simply by the fact that $S_k(u) > S(u)$, and $G_k(t) > F_k(t)$ in (1.4) and (1.5) . Figure 2 compares the 1 - KM and cumulative incidence function estimates of the breast cancer related death in the presence of the other types of events of B-04 data, from National Surgical Adjuvant and Bowel Project (NSABP). The amount of overestimation of 1 - KM increases with time.

Gray's test (Gray,1988) [12] and Fine & Gray's subdistribution proportional hazards regression (Fine and Gray, 1999) [7] analogous to log-rank test and Cox proportional hazards model, are known defined methods to account for competing risks. In this study, we revisit Gray and log-rank test statistics for comparison under competing risks and propose a simple modified log-rank test statistic to determine the optimal cutpoint of a continuous risk factors, in the presence of competing risks. Secondly, the quantile residual life regression is developed for competing risks data. The regression model was built based on the conditional cause-specific quantile residual life defined from the cause-specific residual cumulative incidence function. This technique allows for alternative nonparametric inference with meaningful interpretations of covariate effects.

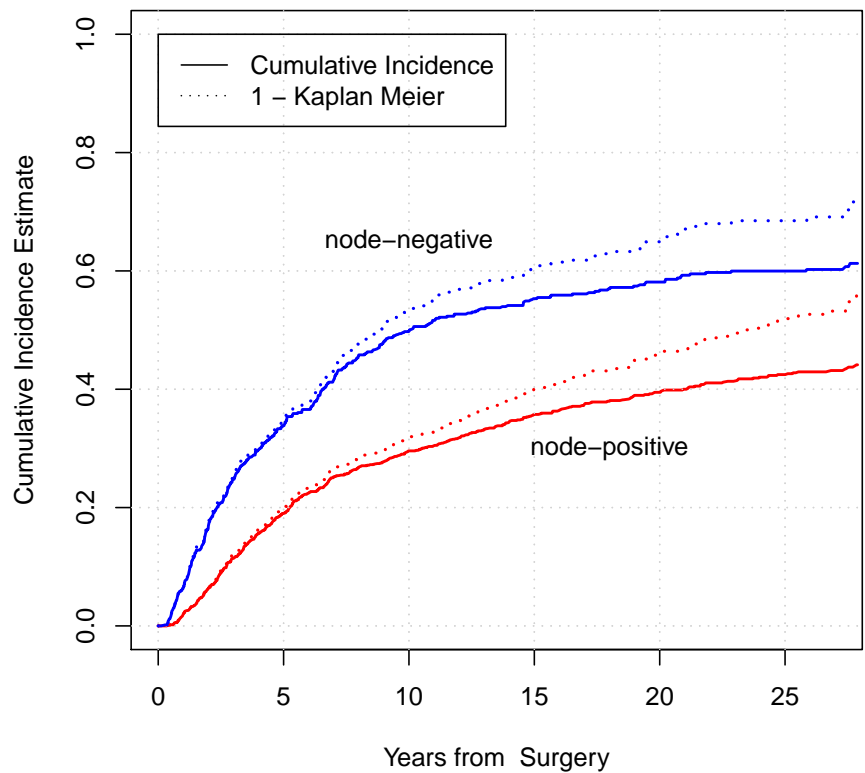


Figure 2: A comparison between the 1-KM and cumulative incidence function (CIF) estimates of the breast cancer related death in B-04

2.0 DETERMINATION OF OPTIMAL CUTPOINT IN COMPETING RISKS

2.1 INTRODUCTION

Although dichotomizing a continuous variable has some drawbacks, such as a loss of information and power (Royston et al., 2006) [26], it is a commonly used method for investigators not only to be free of the linearity assumption but also to quantify the prognostic effects, providing more straightforward interpretation. For instance, in breast cancer clinical trial studies, it is well known that recurrence and estrogen receptor level are highly correlated. A patient with higher estrogen receptor level is more likely to recur breast cancer. Investigators might want to dichotomize this value to quantify the prognostic effect, such as relative risk. However, it is not simple to determine the optimal cut point to split the continuous variable without biological reasoning or prior information. “Data-oriented” cut point, such as median, mean or quantile is frequently used but it is simply because there is no prior information regarding the optimal cut point. A more systematic “outcome-oriented” approach has been considered to select the cut point that leads to maximum difference in effect. Contal and O’Quigley (1999) [4] proposed a method to estimate the optimal cut point and its significance, constructing a statistic that asymptotically follows Brownian bridge. Their application was in survival data, thus the optimal cutpoint is chosen that corresponds to the maximum value of the process based on the log-rank test. However, in cancer clinical studies, when recurrence of disease is the event of interest, then other types of event, such as other types of cancer or death often occur prior to the recurrence. We need to take those competing risks events into account to determine the optimal cutpoint. the log-rank test (Peto, 1972) [23] is used to compare the cause-specific hazard functions after censoring all

uninteresting events. It assumes that the specific risk is the only risk acting on the population. Thus it could cause inaccurate results to use log-rank test under competing risks data. Gray’s method (Gray,1988) [12], one of the most popularly used in competing risk data, compares the subdistribution hazards taking account of uninteresting events.

In this chapter, we propose a modified log-rank test using the notion of the improper random variable from Gray’s test. This way, the log-rank can be applied to the Contal and O’Quigley method improving the accuracy to estimate optimal cutpoint and it’s significance in competing risks data. Simulation studies were carried out to assess the performance of proposed method and it is applied to clinical trail data from NSABP B-14.

2.2 BACKGROUND

2.2.1 Cutpoint Model in Survival Analysis

Let Z be a continuous covariate and T be the outcome, namely time to event in survival data then $(Z_i, T_i), i = 1..n$ is paired observations. One approach to investigating relationship between Z and T is that to split population into two groups; those who have the variable Z smaller than certain cutpoint μ , and those who have the variable Z larger than μ and to test the null hypothesis below

$$H_0 : \Pr(T \leq t | Z \leq \mu) = \Pr(T \leq t | Z > \mu). \quad (2.1)$$

Without the prior information, the choice of the cutpoint, μ is generally based on the maximization of a measure of difference between the groups, which is called “outcome-oriented” method. In survival analysis, the cutpoint can be estimated based on Cox proportional hazards model

$$h(t|Z, \mu) = h_0(t) \exp\{\beta_\mu I [X \leq \mu]\} \quad (2.2)$$

testing the null hypothesis that $H_0 : \beta_\mu = 0$. The point that corresponds to maximize the test statistic (e.g., likelihood-ratio test, Wald test, and score test) or to minimize the p -value of the test among the possible observed Z_i will be the optimal cutpoint. However, since we

have picked the cutpoint that gives the most significant result after multiple testings, it tends to overestimate the significance of the difference based on obtained cutoff values (Miller and Siegmund, 1982) [20]. There has been several approaches to addressing this issue to make inference about β_μ .

Jespersen (1986) [15] used the score statistics to construct a new test statistic W_J defined by

$$W_J = \frac{\sup_{\mu} |U(0, \mu)|}{\sqrt{D}}, \quad (2.3)$$

where $U(0, \mu)$ is the score test statistic and D is the number of events. Using counting process theory, Jespersen showed that this test statistic W_J under the null has a limiting distribution of $\sup |W^0(p)|, 0 \leq p \leq 1$, where $W^0(p)$ is a Brownian Bridge. Using distribution of $\sup |W^0(p)|$ below formula given in Billingsley (1968) [3], Jespersen's adjusted p -value and critical values of the test can be obtained.

$$P \left(\sup_{0 \leq p \leq 1} |W^0(p)| \geq k \right) = 2 \left(\sum_{j=1}^{\infty} (-1)^{j+1} \exp(-2j^2 k^2) \right) \quad (2.4)$$

Lausen and Schumacher (1992, 1996) [19] proposed a method to correct the minimum p -value of the test. It is generalization of theoretical approach of Miller and Siegmund (Miller and Siegmund, 1982) [20] that maximally selected χ^2 statistic in 2×2 tables is the distribution of the supremum of the absolute value of a standardized Brownian Bridge,

$$\sup_{p \in [\epsilon, 1-\epsilon]} \frac{|W^0(p)|}{\sqrt{p(1-p)}} \quad (2.5)$$

with $0 < \epsilon < 0.5$ and $p = F_z(Z)$ where $F_z(Z)$ denote the distribution of Z , and the following approximation for the distribution

$$P \left(\sup_{p \in [\epsilon, 1-\epsilon]} \frac{|W^0(p)|}{\sqrt{p(1-p)}} > b \right) \cong \phi(b) \left(b - \frac{1}{b} \right) \ln \left(\frac{(1-\epsilon)^2}{\epsilon^2} \right) + 4 \left(\frac{\phi(b)}{b} \right) \quad (2.6)$$

Lausen and Schumacher restricted the range of the hypothetical cutpoint, $[Z_{(n\epsilon)}, Z_{(n(1-\epsilon))}]$ where Z_k is the k th order continuous variable, Z_i and $0 < \epsilon < 0.5$. They showed that the maximally selected standardized test statistic converges to the supremum of the absolute value of a standardized Brownian Bridge,

$$\text{Max}\{|C(\mu)|, \mu \in [Z_{(n\epsilon)}, Z_{(n(1-\epsilon))}]\} \xrightarrow{D} \sup_{p \in [\epsilon, 1-\epsilon]} \frac{|W^0(p)|}{\sqrt{p(1-p)}}, \quad \text{as } n \rightarrow \infty. \quad (2.7)$$

and use the Miller and Siegmund approximation to obtain corrected p -value. Let P_{\min} be the smallest p -value among those p -values from the test based on all hypothetical cutpoints, μ , over the range $[Z_{(n\epsilon)}, Z_{n(1-\epsilon)}]$. Then p -value can be adjusted by

$$P_{cor} = \phi(w) \left(w - \frac{1}{w} \right) \ln \left(\frac{(1-\epsilon)^2}{\epsilon^2} \right) + 4 \frac{\phi(w)}{w}, \quad (2.8)$$

where $w = \phi^{-1}(1 - P_{\min}/2)$ with $\phi(w)$ is the standard normal density. Their corrected p -value approach has been recommended and applied by many studies, but the arbitrariness and inconsistency depends on the choice of ϵ can be a limitation.

A third method is a rescaled sequential approach proposed by Contal and O'Quigley (1999) [4]. This method is based on the Billingsley (1968) [3] following result. If the α_i are exchangeable random variables and satisfy the three following conditions, that is called Noether condition:

$$\sum_{i=1}^n \alpha_i \xrightarrow{p} 0, \quad \sum_{i=1}^n \alpha_i^2 \xrightarrow{p} 1, \quad \max_{1 \leq i \leq n} |\alpha_i| \xrightarrow{p} 0, \quad \text{as } n \rightarrow \infty, \quad (2.9)$$

then $S_n(p) = \sum_{i=1}^{\lfloor np \rfloor} \alpha_i$ converges in distribution to the Brownian Bridge, $W^0(p)$ in (2.4) where $0 \leq p \leq 1$ and $\lfloor \cdot \rfloor$ is the greatest integer function. The scores of log-rank test statistic are exchangeable random variable, and then standardized form of the score is also exchangeable and meet the Noether condition. When the observed event, D is equal to total sample size n , the log-rank test is equal to Savage's test, which is a linear rank statistic with exponential scores defined by

$$a_i = 1 - \sum_{j=1}^i \frac{1}{D - j + 1} \quad (2.10)$$

with $\text{var}(a) = \{1/(D-1)\} \sum_{j=1}^D a_j^2$. The process $S_n(p)$ can be constructed by

$$S_n(p) = \frac{1}{\sqrt{\text{var}(a)(D-1)}} \sum_{i=1}^D a_i. \quad (2.11)$$

and it follows Brownian bridge asymptotically. The censoring case, $D \leq n$, log-rank statistics is used and normalized by $\text{var}(a)$. Wu (2001) [31] examined and compared those method with extensive simulation study and suggested that rescaled sequential approach performs more powerful and robust in censoring case. Our extension to estimate the optimal cutpoint in the presence of competing risks will follow the rescaled sequential approach.

2.2.2 Comparison of Test Statistic

In this section we will review the test statistic to compare the survival rate under competing risks. First, log-rank test is the most commonly used test in survival data to compare the hazard rates between groups. However, when it comes to competing risks setting, it compares the cause-specific hazard after censoring other types of events of no interest at the time of occurrence. Let $\epsilon = 1, \dots, K$ be the type of event then type k specific hazard is

$$h_k(t) = \lim_{\delta t \rightarrow 0} \left\{ \frac{P(t < T \leq t + \delta t, \epsilon = k | T > t)}{\delta t} \right\}. \quad (2.12)$$

Let $t_1 < t_2 < \dots < t_D$ be the distinct death times in the pooled sample and d_{ij} be the number of an interesting event and Y_{ij} be the numbers at risk in group j at time t_i , $i = 1, \dots, D, j = 1, \dots, J$. Let d_i and Y_i be the corresponding numbers for combined groups at time t_i . Then the log-rank test is the form of

$$Z_j(\tau) = \sum_{i=1}^D W_j(t_i) \left\{ \frac{d_{ij}}{Y_{ij}} - \frac{d_i}{Y_i} \right\}, \quad j = 1, \dots, J \quad (2.13)$$

In general, weight function is the form of $W_j(t_i) = Y_{ij}L(t_i)$, and when $L(t_i) = 1$, it simplifies

$$Z_j(\tau) = \sum_{i=1}^D \left\{ d_{ij} - Y_{ij} \left(\frac{d_i}{Y_i} \right) \right\}, \quad j = 1, \dots, J \quad (2.14)$$

On the other hand, Gray's method compares subdistributions of cause-specific events among different groups in competing risks data. The subdistribution, also called cumulative incidence function [17], $F_k(t) = Pr(T \leq t, \epsilon = k)$, is a joint probability of observing event type k in the presence of other types of events. Gray defined it as $F_k(t) = Pr(T_k^* \leq t)$ using the improper random variable, $T_k^* = I(\epsilon = k) \times T + I(\epsilon \neq k) \times \infty$. He pointed out that the relationship of cause specific hazards is different from that of cumulative incidence in competing risks setting. That is, even though cause specific hazard for type 1 in group 1 is higher than that for type 1 in group 2, the cumulative incidence for group 2 could be higher than that for group 1 at some point. His method is based on weighted averages of the hazard

of the subdistribution functions for the event of interest, k . Let's assume that there is only two type of events ($K=2$) and the general form of score for group j is

$$U_{jk}(\tau) = \int_0^\tau W_{jk}(t) \{\gamma_{jk}(t) - \gamma_{0k}(t)\} dt, \quad j = 1, \dots, J. \quad (2.15)$$

Where $\gamma_{jk}(t)$ is the hazard of the subdistribution for group j , and $\gamma_{0k}(t)$ is the hazard of the subdistribution for all groups together of our interesting type of event, where hazard of the subdistribution can be defined

$$\gamma_k(t) = \lim_{\delta t \rightarrow 0} \left\{ \frac{P(t < T \leq t + \delta t, \epsilon = k | T > t \cup (T \leq t \cap \epsilon \neq k))}{\delta t} \right\}. \quad (2.16)$$

Without loss of generality, let's assume only two types of events: event of interest and competing event. The test is refer to the event of interest, the index for the type of event will be suppressed. The weight function (Gray,1988) is the form $W_j(t) = R_j(t)L(t)$ and $R_j(t)$ can be estimated

$$R_j(t) = Y_j(t) \frac{1 - \hat{F}_j(t-)}{\hat{S}_j(t-)} \quad (2.17)$$

Where $Y_j(t)$ is number of individuals at risk at time t in group j , $F_j(t-)$ is the left-hand limit of the cumulative incidence function for the event of interest in group j and $S_j(t-)$ is the left-hand limit of the probability of being free of any event in group j , as estimated by the Kaplan-Meier method. When only event of interest occurs then $S_j(t-) = 1 - F_j(t-)$, but once competing risks event occurs, $S_j(t-) < 1 - F_j(t-)$ and the difference will increase as more competing risks events happen. That is, we can say that R_j is the estimated number of individuals at risk adjusted by the number of competing risks event happened.

For simplicity, we present when $J = 2$, and $L(t) = 1$ in the discrete case. Then,

$$R_{i1} = Y_{i1} \frac{1 - \hat{F}_1(t_{i-1})}{\hat{S}_1(t_{i-1})} \quad (2.18)$$

and the score is

$$\begin{aligned}
Z_1^* &= \sum_{i=1}^D W_1(t_i) \left\{ \frac{d_{i1}}{R_{i1}} - \frac{d_{i1} + d_{i2}}{R_{i1} + R_{i2}} \right\} \\
&= \sum_{i=1}^D \left\{ d_{i1} - R_{i1} \left(\frac{d_{i1} + d_{i2}}{R_{i1} + R_{i2}} \right) \right\}
\end{aligned} \tag{2.19}$$

where $W_1(t_i) = R_{i1}$.

This is similar to the form of the log-rank test, except the risk set (denominator) adjusted by the number of event of competing risk already occurred up to time t_i .

2.3 PROPOSED METHOD

2.3.1 Modified Log-rank Test

To find the optimal cutpoint in competing risks, we introduce a modified log-rank test statistic by directly applying the improper random variable concept to the observed dataset rather than estimating the risk process. An improper random variable can be defined by setting time to event of competing risks as infinity. That is, the event of competing risks is considered as the censoring at the end of the study, always being included in the risk set. Let r_{ij} be the number of events of competing risks up to time t_i in j th group and r_i be the corresponding numbers for combined groups. Modified log rank test with improper random variable can be derived in the same way as the ordinal log rank test, by adding the number of competing risks event to a risk set by directly applying the improper random variable concept to the observed dataset rather than estimating the risk process. Improper random variable can be defined by setting time to event of competing risks as infinity. That is the event of competing risks is considered as the censoring at the end of the study, always being included in the risk set. Let r_{ij} is the number of events of competing risks up to time t_i in j th group and r_i is the corresponding numbers for combined groups. Modified log rank test

with improper random variable can be derived in the same way as the ordinal log rank test, by adding the number of competing risks event to a risk set

$$Z_j^* = \sum_{i=1}^D W_j(t_i) \left\{ \frac{d_{ij}}{Y_{ij} + r_{ij}} - \frac{d_i}{Y_i + r_i} \right\}, \quad j = 1, \dots, J, \quad (2.20)$$

where the weight function, $W_j(t_i) = (Y_{ij} + r_{ij})L(t)$ is the same form as above. The variance and covariance can be derived using that d_{ij} follow the hypergeometric distribution with parameter d_i and $P_j = (Y_{ij} + r_{ij})/(Y_i + r_i), j = 1, \dots, J$.

The variance of Z_j^* is

$$\hat{\sigma}_{jj} = \sum_{i=1}^D \left(\frac{Y_{ij} + r_{ij}}{Y_i + r_i} \right) \left(1 - \frac{Y_{ij} + r_{ij}}{Y_i + r_i} \right) \left(\frac{Y_i + r_i - d_i}{Y_i + r_i - 1} \right) d_i, \quad j = 1, \dots, J \quad (2.21)$$

and the covariance of Z_j^*, Z_g^* is given by

$$\hat{\sigma}_{jg} = - \sum_{i=1}^D \left(\frac{Y_{ij} + r_{ij}}{Y_i + r_i} \right) \left(\frac{Y_{ig} + r_{ig}}{Y_i + r_i} \right) \left(\frac{Y_i + r_i - d_i}{Y_i + r_i - 1} \right) d_i, \quad g \neq j \quad (2.22)$$

The test statistic is given by the quadratic form with estimated variance-covariance matrix, $\Sigma_{(J-1) \times (J-1)}$.

$$(Z_1(\tau), \dots, Z_{j-1}(\tau)) \Sigma^{-1} (Z_1(\tau), \dots, Z_{j-1}(\tau))^t \quad (2.23)$$

When the null hypothesis is true, this statistic follow a chi-square distribution, with $J - 1$ degree of freedom. When $J = 2$ the test statistics can be expressed by

$$Z = \frac{\sum_{i=1}^D d_{i1} - (Y_{i1} + r_{i1}) \left(\frac{d_i}{Y_i + r_i} \right)}{\sqrt{\sum_{i=1}^D \left(\frac{Y_{i1} + r_{i1}}{Y_i + r_i} \right) \left(1 - \frac{Y_{i1} + r_{i1}}{Y_i + r_i} \right) \left(\frac{Y_i + r_i - d_i}{Y_i + r_i - 1} \right) d_i}} \quad (2.24)$$

2.3.2 Estimation Procedure

The re-scaled sequential estimation procedure described in Contal and O'Quigley (1999) [4] was applied to our modified log-rank statistic. Let t_1, \dots, t_D be the ordered observed death time and for μ_k be the hypothetical cutpoint of continuous covariate Z , then the number for log-rank statistic at each failure time can be summarized in $D_{2 \times 2}$ tables below.

	Died	Survived + Competing events	total
$Z \leq \mu_k$	d_i^\ominus	$Y_i^\ominus + r_i^\ominus - d_i^\ominus$	$Y_i^\ominus + r_i^\ominus$
$Z \geq \mu_k$	d_i^\oplus	$Y_i^\oplus + r_i^\oplus - d_i^\oplus$	$Y_i^\oplus + r_i^\oplus$
Total	d_i	$Y_i + r_i - d_i$	$Y_i + r_i$

Where d_i is the number of event of interest at time t_i , Y_i is the number of individual at risk just before t_i and r_i is the number of competing events up to t_i . For a fixed cutpoint μ_k , the modified log-rank statistic based on the groups defined by being less(\ominus) than or greater(\oplus) than μ_k can be computed as

$$S_k = \sum_{i=1}^D \left[d_i^\oplus - d_i \frac{Y_i^\oplus + r_i^\oplus}{Y_i + r_i} \right]. \quad (2.25)$$

The estimated cut point $\hat{\mu}$ is the value of μ_k which corresponds to the maximum $|S_k|$, and the adjusted test statistic for testing any difference between the splits by the optimal cut point is

$$Q = \frac{\max |S_k|}{s\sqrt{D-1}}, \quad (2.26)$$

where s is defined by

$$s^2 = \frac{1}{D-1} \sum_{i=1}^D \left\{ 1 - \sum_{j=1}^i \frac{1}{D-j+1} \right\}^2. \quad (2.27)$$

2.4 SIMULATION

We carried out a Monte Carlo simulation to assess the properties of our proposed test statistic and the behavior of the estimated cutpoint based on this statistic. For simplicity, we considered only two types of competing events, type 1 events being of our interest. Failure time of type 1, T_{1i} , was assumed to follow a Weibull distribution with survival function $S(t) = \exp(-\rho t^\kappa)$, where ρ and κ are scale and shape parameters, respectively. Failure time of type 2, T_{2i} , was assumed to follow a unit exponential distribution for all groups. The true improper subdistribution function for type 1 event can be specified as,

$$F_1(t) = \pi \{1 - \exp(-\rho t^\kappa)\} \Leftrightarrow \Pr(T \leq t, \epsilon = 1) = \Pr(\epsilon = 1) \Pr(T \leq t | \epsilon = 1),$$

To simulate the data set, first we generate ϵ from a Bernoulli distribution with success probability of π , then conditioning on the ϵ value, generate an event time from the proper Weibull distribution $F_1(t)/\pi$ with ρ_1 for group 1 and ρ_2 for group 2. In Figure 3, the estimated cumulative incidence curves (Gray, 1988) [12] were plotted using the R function *cuminc* and compared with the true subdistribution functions.

The first set of simulation is to examine the size of the test and to compare the powers of the tests using different values of κ , hazard ratio between two split groups and the probability of each type of failure, π . Their distribution for failure type 1 is $F_1^{(1)}(t) = 1/2 \{1 - \exp(-\rho_1 t^\kappa)\}$ for group 1, and $F_1^{(2)}(t) = 1/2 \{1 - \exp(-\rho_2 t^\kappa)\}$ for group 2, so that ρ_2/ρ_1 will be the hazard ratio between two groups. The independent censoring times C_i were generated from a uniform and exponential distribution with constant c which controls the censoring proportion. With a fixed total sample size of $n=500$, simulations were performed for various combinations: 0% to 30% censoring proportions, $\rho_1 = 0.1$, $\rho_2 = 0.1$ to 0.4 to make the hazard ratio of 1 through 4, $\kappa = 1, 2$ and $\pi = 0.5, 0.6, 0.7$. The results indicate that empirical size is close to the true nominal level of 5% when the hazard ratio (hr) equal to 1 as shown in Table 1. The power increases with the larger hazard ratio and success probability of type 1 event when the κ is equal to 1 (Table 2) and 2 (Table 3).

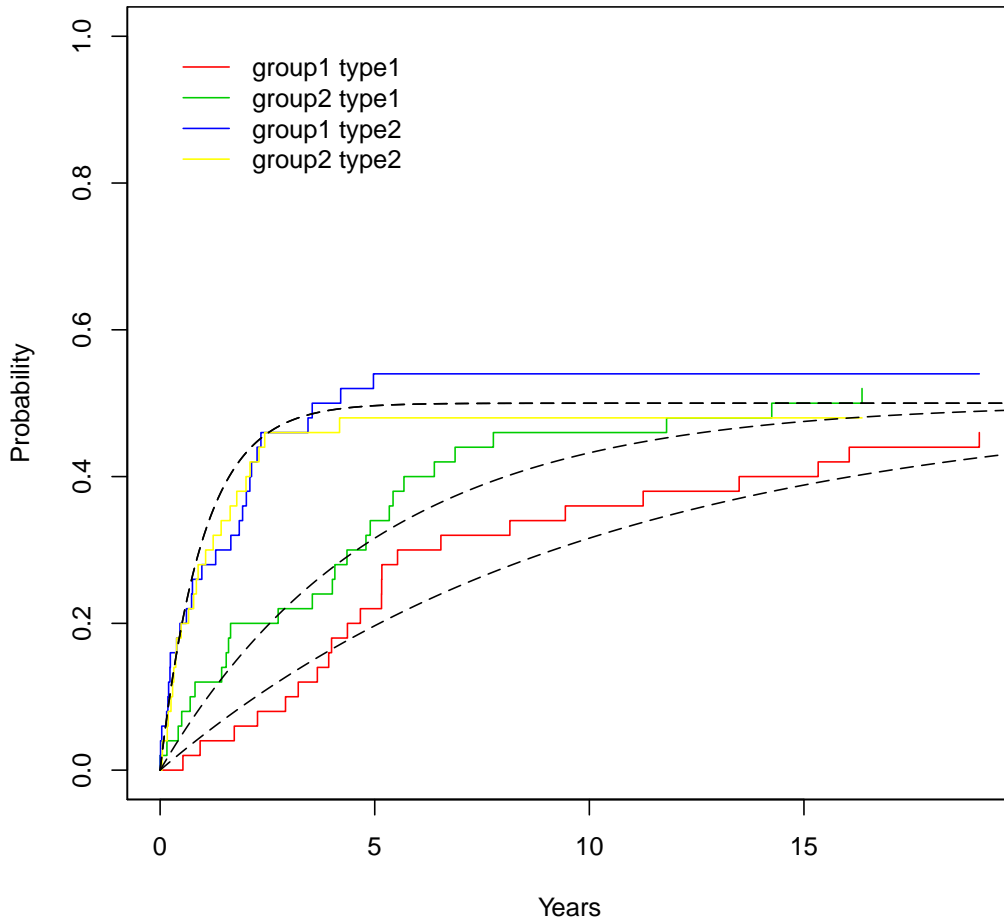


Figure 3: Estimated cumulative incidence curves of simulated data (solid line) and true subdistribution (dotted line) where type 1 event time is from Weibull distribution ($\rho_1 = 0.1, \rho_2 = 0.2$) and type 2 event time is from unit exponential distribution

Table 1: Empirical sizes of a nominal 5% level test for different $\pi(0.5, 0.6, 0.7)$, $\kappa(1, 2)$ and censoring proportion with $n = 500$

$c\%$	$\kappa = 1$			$\kappa = 2$		
	$\pi=0.5$	$\pi=0.6$	$\pi=0.7$	$\pi=0.5$	$\pi=0.6$	$\pi=0.7$
0	4.2	5.1	4.8	5.2	5.0	4.8
10	3.1	4.8	4.4	5.8	4.5	5.3
20	4.3	4.4	4.4	5.5	5.0	4.5
30	4.7	5.6	4.7	5.7	4.8	4.0

Table 2: Empirical powers for different $\pi(0.5, 0.6, 0.7)$, $hr(2, 3, 4)$ and censoring proportion with $\kappa = 1$ and $n = 500$

$c\%$	hr	$\pi=0.5$			$\pi=0.6$			$\pi=0.7$		
		2	3	4	2	3	4	2	3	4
0		17.5	32.3	42.7	29.8	54.8	69.2	49.4	81.9	93.0
10		41.0	68.5	82.3	45.9	85.2	93.7	69.8	95.9	99.6
20		56.9	92.4	98.4	65.9	91.8	99.2	79.5	99.0	99.9
30		66.9	95.8	99.5	74.3	98.1	100	85.5	99.7	100

Table 3: Empirical powers for different $\pi(0.5, 0.6, 0.7)$ and $hr(2, 3, 4)$ and censoring proportion with $\kappa = 2$ and $n = 500$

$c\%$	hr	$\pi=0.5$			$\pi=0.6$			$\pi=0.7$		
		2	3	4	2	3	4	2	3	4
0		17.1	32.0	41.7	28.1	52.9	69.2	49.3	81.7	93.0
10		23.5	44.1	61.2	36.9	68.0	83.1	54.2	86.6	99.6
20		29.5	55.7	75.2	45.3	77.6	92.0	57.8	89.9	99.9
30		35.1	67.0	84.7	49.7	93.7	95.3	59.8	94.0	100

The test statistic Q (2.26) has a limiting distribution of the supremum of the absolute value of a Brownian Bridge under the null hypothesis. In next simulation, we examine the distribution of Q under H_0 . In accordance with the Cox proportional hazard model (Cox, 1972) [5], the outcome variable T_i was generated from $F_1^{(1)}(t)$ or $F_1^{(2)}(t)$ depending on whether the continuous prognostic effect Z (unit uniform distribution) is greater (group 1) or less (group 2) than hypothetical cutpoint at $\mu = 0.5$. Figure 4 presents the simulated relative frequency of the maximum value of the statistic set of potential cutpoints under the null hypothesis ($\rho.1 = \rho.2 = 0.1$) with different sample sizes ($n = 100, 200, 300$), and $\kappa = 1, 2$. The asymptotic values for the test statistic provide a good approximation for the Brownian bridge.

The simulated distributions of the estimated cutpoint with various effect, $\exp(\beta)$ in the proportional Cox hazards model are represented in Figure 5. The simulation model has a true cutpoint at 25th (0.25) and 50th (0.5) percentile of Z , which follows uniform distribution with sample size $n = 200$, $\kappa = 1((a),(c))$, 2 ((b),(c)), with 30% censoring. As $\rho.2$ values has various values (1 4, 6, 8), hazard ratio changes from 1 to 4, 6 and 8. We extend the same simulation in the case that Z follows the standard normal distribution with true cut point at -0.67 and 0 in Figure 6. We observe that the larger the hazard ratio, the smaller confidence interval of $\hat{\mu}$, as expected.

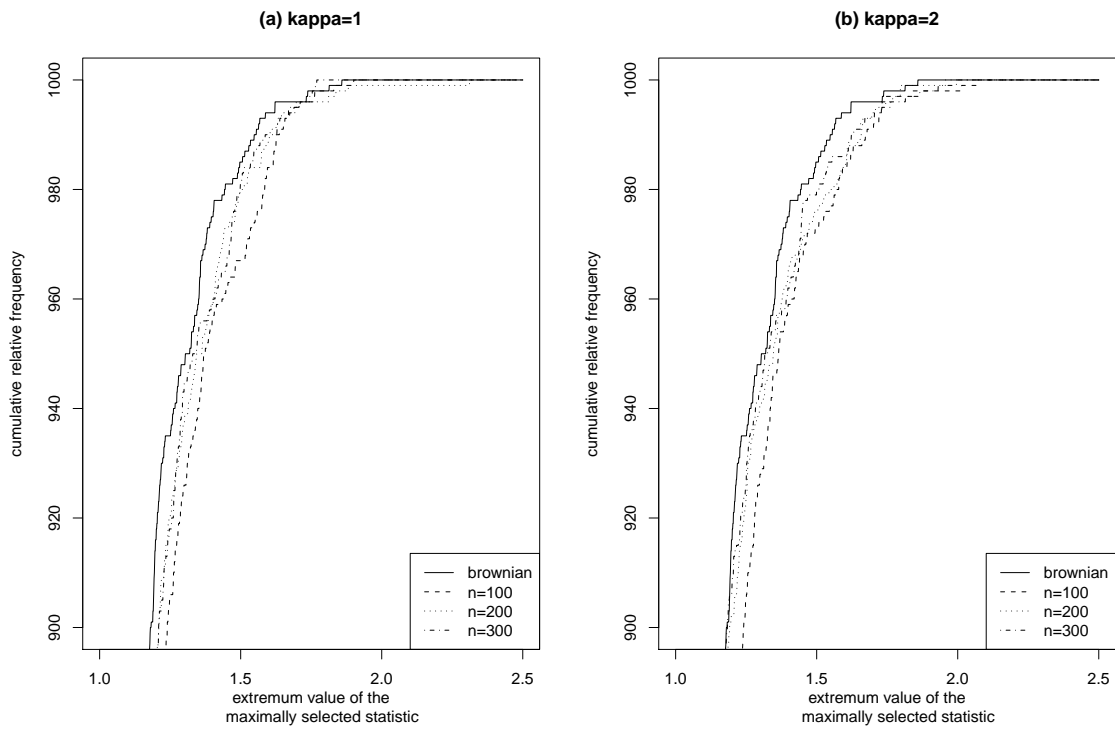


Figure 4: Upper part of the simulated distribution of the extremum value of the standardized process under the null hypothesis

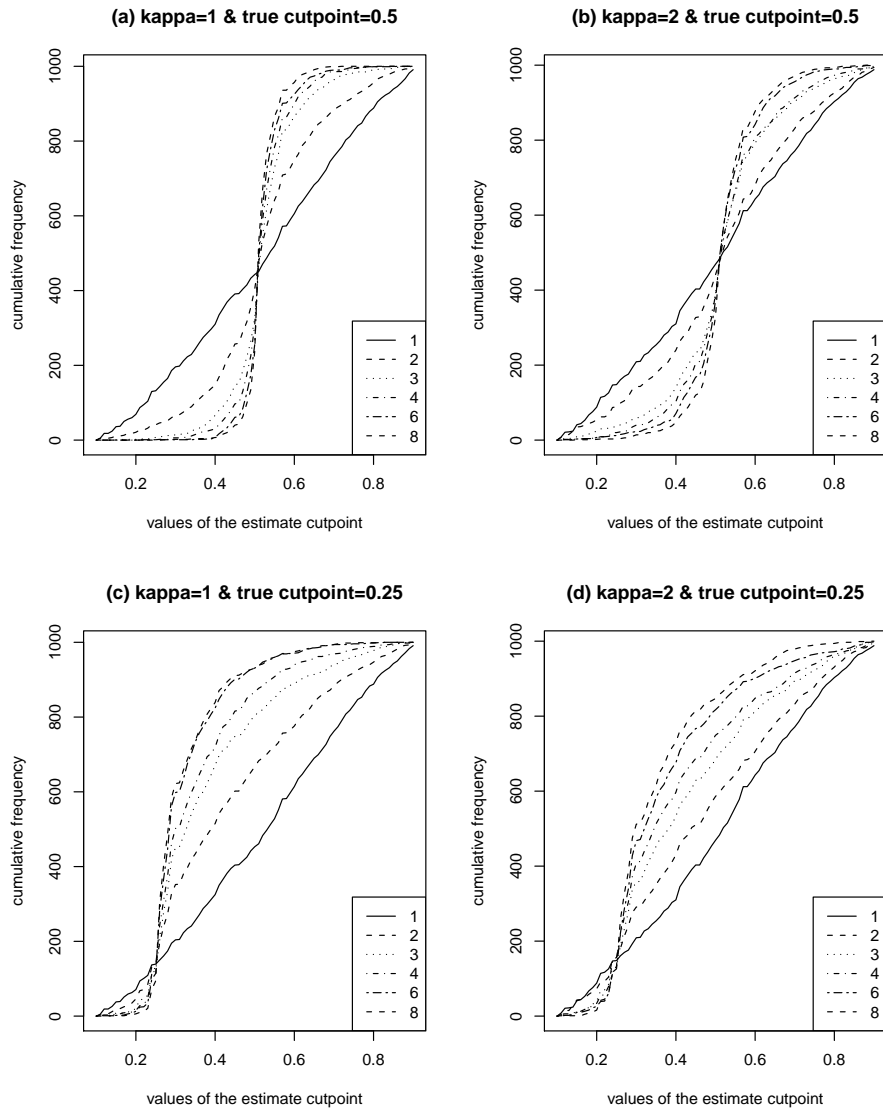


Figure 5: Distribution of the simulated cutpoint estimator where $\kappa = 1$ ((a),(c)), $\kappa = 2$ ((b),(c)) the true cutpoint is equal to 0.5 ((a),(b)) and 0.25 ((c),(d)) under Uniform Z.

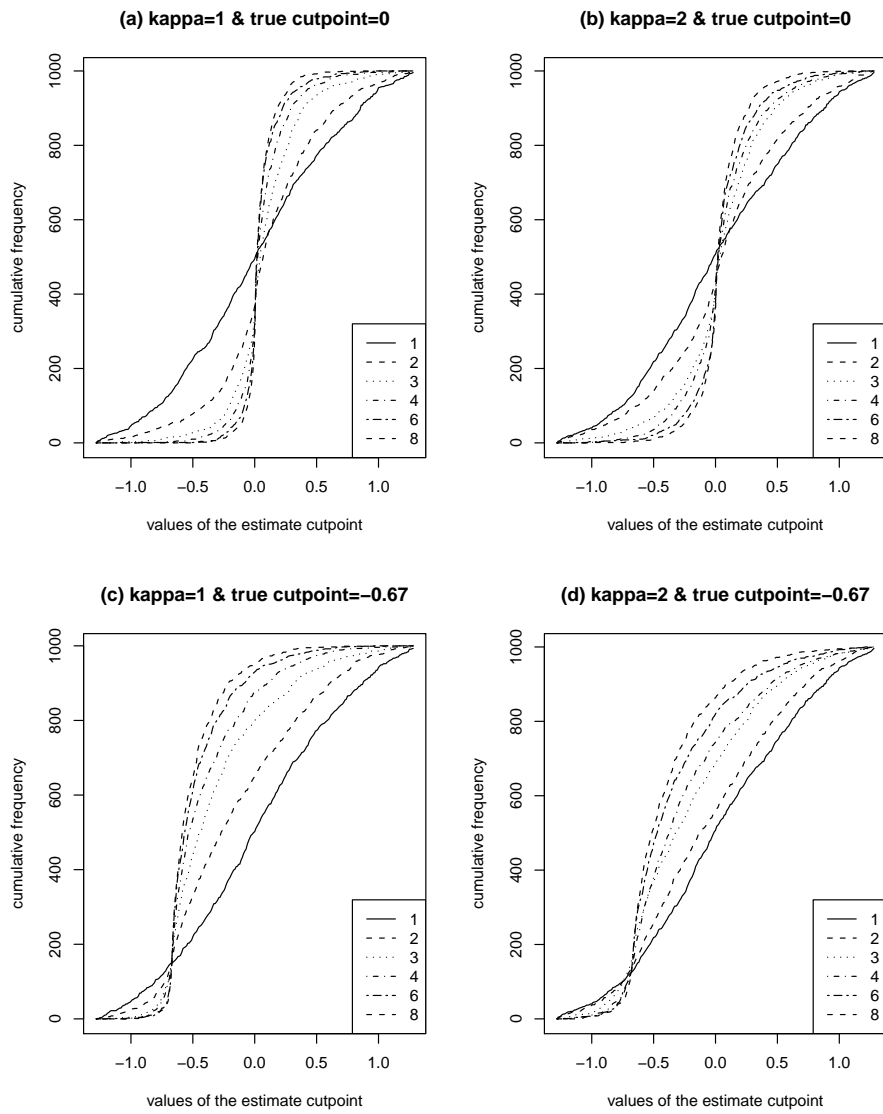


Figure 6: Distribution of the simulated cutpoint estimator under Normal Z.

Table 4: Estimated Cutpoint of AGE

	Placebo (n=1450)	Treatment (n=1435)
Mean	54.6	54.9
Median	56	56
Range	25-71	25-75
Selection Interval	31-70	33-70
Estimate, $\hat{\mu}$	41	47
P-value	0.05	0.26

2.5 EXAMPLE

A dataset from National Surgical Adjuvant Breast and Bowel Project (NSABP) trial, Protocol B-14, was used to illustrate our proposed method. In this phase III trial, over a 6-year period, patients with primary breast cancer, negative axillary lymph nodes, and estrogen receptor positive tumors were randomized to receive either tamoxifen ($n = 1453$) or placebo ($n = 1439$) following surgery and has been followed more than 20 years. The event of interest (type 1) was local-regional recurrence as first event, while all other events such as distant recurrences, other types of cancer, or death prior to any disease were considered to be competing events (type 2). In this dataset, our continuous prognostic variables (Z) of interest are age and estrogen receptor level. Outer 1% of the distribution in each side was excluded, thus the potential cutpoints are those within inner 98% of the distribution. We estimated the cutpoint which maximized the absolute value of proposed log-rank statistics under competing risks among the potential cutpoints. Table 3 and Table 4 summarize the result. The estimated optimal cutpoint of age is 41 in tamoxifen group and 47 point in placebo group. The adjusted p-value shows that the age effect is significant on survival for placebo group but not for treatment group. For estrogen receptor level, the estimated cutpoint was 610 in tamoxifen group and 580 in placebo group. Age effect was not significant in neither groups.

Table 5: Estimated Cutpoint of Estrogen Receptor Level (fm/mole)

	Placebo (n=1449)	Treatment (n=1435)
Mean	1213.7	1178.1
Median	580	610
Range	0-15910	0-31870
Selection Interval	100-9760	100-7800
Estimate, $\hat{\mu}$	185	415
P-value	> 0.3	0.16

2.6 SUMMARY

In medical research, dichotomizing continuous variables based on a cutpoint is a common strategy to quantifying the prognostic factors. In some situations, however, a cutpoint of continuous measurement is not obvious. Recent increasing study of using biomarker is one instance that is required a cut-point to dichotomize a biomarker level but none of definite point exist. Much of effort has been done to analyze competing risk data, not much attention has been drawn to determine the optimal cutpoint in a continuous variable under competing risks. Here we proposed a modified log-rank test, adapting the notion of improper random variable from Gray's test by adding the number of competing events to risk sets rather than estimating it. This way it can be applied to the method of Contal and O'Quigley (1999) [4], preserving the properties of the log-rank statistic. Simulation results indicate the adequacy of our method using proposed statistics and it was applied to a real dataset, B-14 to estimating a optimal cutpoint of age and estrogen receptor level and adjusted p-value by treatment status in the presence of competing risks.

3.0 COMPETING RISKS QUANTILE RESIDUAL LIFE REGRESSION

3.1 INTRODUCTION

Residual life analysis provides useful information when the effect of prognostic factors on the distribution of remaining lifetimes is evaluated at several years after the initial diagnosis/therapy. For instance, in a long-term breast cancer clinical trial where the secondary therapy being considered for patients who remain recurrence free after the initial treatment, the residual life analysis would provide a straightforward prediction of a patient's lifetime that could be prolonged by the new therapy. However, the residual life regression has not been studied in the competing risks setting commonly encountered in medical data. In this study we propose competing risks quantile residual life regression model based on the conditional cause-specific quantile residual life defined from the cause-specific residual cumulative incidence function. We describe the estimation procedure to obtain the parameter estimates and test statistic which does not require estimation of the variance-covariance matrix of the regression estimators. This model provides meaningful interpretations of covariate effects on not only any quantile residual life but also at a specific time point. Simulation studies are performed to assess the finite sample properties of proposed method in terms of the parameter estimator, type I error and power of the test statistics at different time point. In addition, new regression method is illustrated with a real dataset protocol B-04 from a breast cancer clinical trial that was performed by the National Surgical Adjuvant Breast and Bowel Project (NSABP).

3.2 BACKGROUND

3.2.1 Quantile Residual Life Function (Median Residual Life Function)

As mean and median are commonly used statistical measurement to summarize the distribution of the data, mean residual life (MRL) function and median residual life (MERL) function are useful function to describe the remaining life time in survival data. Although MRL function has been of much interest in the actuarial science, survival studies and reliability theory, MERL function has several advantages over MRL function especially when data are censored or has fat-tailed distribution (Schmittlein and Morris,1981) [27]. A more general concept of MERL function is a α -quantile residual life function $\theta^{(\alpha)}(t) = \alpha - \text{quantile}(T - t|T > t)$, that is a α quantile of remaining life times among survivals beyond time t can be presented as followings.

$$\begin{aligned}P\{T - t > \theta^{(\alpha)}(t)|T > t\} &= 1 - \alpha \\P\{T > t + \theta^{(\alpha)}(t)\} &= (1 - \alpha)P(T > t) \\S\{t + \theta^{(\alpha)}(t)\} &= (1 - \alpha)S(t)\end{aligned}$$

MERL function has been extensively studied by many authors. Wang and Hettmansperger (1990) [29] introduced a confidence interval approach to compare two quantiles from failure time distributions under censoring and Su and Wei (1993) introduced a nonparametric test statistic to improve Wang and Hettmansperger's procedure by using the minimum dispersion statistic (Basawa and Koul, 1988) [1]. Berger, Boos and Guess (1982) [2] proposed a modified test statistic based on Fligner and Rust's approach (1982) [9] to compare two median residual life times under censoring, which involves a nonparametric estimation of the pdf of the failure time distribution under censoring. Jeong, Jung and Costantino (2008) [14] extended Su and Wei's method to compare median residual lifetime at any fixed time point during the follow-up period.

3.2.2 Regression on Quantile Residual Life

There has been a few studies in regression model for the residual life function. Rao, Damara-
 raju, and Alhumoud (1993) [25] inferred the covariate effects on the quantile residual life
 function under the parametric accelerated failure time (AFT) and Cox proportional hazard
 models. Regression model for the simple median originally introduced by Ying, Jung and
 Wei(1995) [32]. It is a semiparametric approach to examine the covariate effects on median
 survival, analog to AFT model, alternative to traditional Cox proportional hazard. As the
 AFT model regresses the logarithm of the survival time on its covariates, they regress the
 median of failure time on the covariates. Unlike AFT model that relates the mean of the
 logarithm of the failure time to the covariates, it linearly relates the median of failure time.
 Gelfand and Kottas (2003) [10] modeled the median residual life function induced by the
 AFT assumption under the Bayesian framework. Jung, Jeong and Bandos (2009) [16] re-
 cently developed a semiparametric regression method on a quantile residual life to assess
 the effect of covariates at a given time point. This is a generalized form of Ying's (1995)
 [32] method to time-specific quantile regression, where the quantile residual function can be
 modeled at any specific time point. They consider a linear regression model for a τ -quantile
 of residual lifetimes at time t_0 , on a log-scale,

$$\tau - \text{quantile}\{\log(T_i - t_0) | T_i \geq t_0, Z_i\} = \beta_{\tau|t_0} Z_i \quad (3.1)$$

This model specifies a linear relationship between the τ -quantile residual lifetime on a log-
 scale and the vector of covariates at a specific time t_0 . The special type of estimating equation
 which is modification of least absolute deviations(LAD) method is used to estimate for $\beta_{\tau|t_0}$.
 Let T_i and C_i denote failure and censoring time for i th patient and $Y_i = \min(T_i, C_i)$. Without
 censoring, the LAD estimate can be obtained by minimizing $\sum_{i=1}^n |\log(T_i - t_0) - \beta_{\tau|t_0} Z_i|$,
 which is equivalent to solving the equation

$$U_n(\beta_{\tau|t_0}) = \sum_{i=1}^n Z_i [I\{T_i \geq t_0 + \exp(\beta_{\tau|t_0} Z_i)\}] = 0. \quad (3.2)$$

For censored case, where Y_i is observed survival time and \hat{G} is the Kaplan-Meier estimate

of the survival function of the censoring distribution, the estimating equation is following.

$$S_{\tau|t_0,n}(\beta_{\tau|t_0}) = \sum_{i=1}^n Z_i \left[\frac{I\{Y_i \geq t_0 + \exp(\beta_{\tau|t_0} Z_i)\}}{\hat{G}\{t_0 + \exp(\beta_{\tau|t_0} Z_i)\}} - (1 - \tau) \frac{I(Y_i \geq t_0)}{\hat{G}(t_0)} \right] = 0 \quad (3.3)$$

Due to the discontinuity of the function $S_{\tau|t_0,n}(\beta_{\tau|t_0})$, the estimating equation does not always have an exact solution, therefore, an estimator $\hat{\beta}_{\tau|t_0}$ is defined as a minimizer of the Euclidean norm of the function $\|S_{\tau|t_0,n}(\beta_{\tau|t_0})\|$. To test the null hypothesis $H_0 : \beta_{\tau|t_0} = \beta_{\tau|t_0,0}$, they use the estimating function $S_{\tau|t_0,n}(\beta_{\tau|t_0})$ directly, without estimating covariance matrix depending on the unknown density function.

3.2.3 Cause-Specific Quantile Residual Life Function

Residual life analysis has been introduced in the competing risks setting, with multiple and potentially dependent failure types (Jeong and Fine 2009) [13]. We previously described that the cumulative incidence function correctly quantifies the proportion of the event of interest in the presence of competing risks. They brought the “residual” concept into cumulative incidence function and defined the residual cumulative incidence function for all-cause,

$$F_{t_0} = \Pr(T - t_0 \leq t | T > t_0) = \{S(t_0) - S(t + t_0)\} / S(t_0), \quad t > 0 \quad (3.4)$$

and extended this to the cause specific residual cumulative incidence function to quantify the residual cumulative probability of event of interest, considering the existence of the competing risks.

$$F_{k,t_0} = \Pr(T - t_0 \leq t, \epsilon = k | T > t_0) = \{F_k(t + t_0) - F_k(t_0)\} / S(t_0), \quad t > t_0 \quad (3.5)$$

Inverting this function, a τ -th quantile of event of interest(k) residual life distribution, $Q_{k,t_0}(\tau)$ was defined, that is $Q_{k,t_0}(\tau) = \inf\{q : F_{k,t_0}(q) \geq \tau\}, \tau < F_{k,t_0}(\infty)$. For the case $t_0 = 0$, Q_{k,t_0} is identical to Q_k in Peng & Fine (2007) [21] based on F_k . Assuming F_{k,t_0} is absolutely continuous and it's derivative, f_{k,t_0} is positive around Q_{k,t_0} , then $Q_{k,t_0}(\tau)$ can

be estimated with nonparametric estimate of $\hat{F}_k(\cdot)$ and Kaplan-Meier estimator $\hat{S}(\cdot)$ for all causes.

$$\hat{u}\{Q_{k,t_0}(\tau)\} = \hat{F}_k\{t_0 + Q_{k,t_0}(\tau)\} - \hat{F}_k(t_0) - \tau\hat{S}(t_0) = 0, \quad (3.6)$$

Nonparametric inference was performed without estimation of f_{k,t_0} . To test the null hypothesis, $H_0 : Q_{k,t_0}(\tau) = q$, the statistic $T(q) = n\{\hat{F}_{k,t_0}(q) - \tau\}^2/\hat{\sigma}^2\{\hat{Q}_{k,t_0}(\tau)\}$ which follows χ_1^2 distribution was used and inverted to construct a confidence interval.

3.3 PROPOSED METHOD

3.3.1 Estimation Procedure

Let $Y_i, i = 1, 2, \dots, n$, denote the minimum of the failure time T_i and censoring time C_i . Let ϵ_i be the cause of failure and $\delta_i = I(T_i \leq C_i)\epsilon_i$. Without covariates, we denote $F_{k,t_0}(t)$ for the cause-specific residual cumulative incidence function (CIF) for type k events at time t_0 and $Q_{k,t_0}(\tau)$ for the corresponding cause-specific quantile residual life function (Jeong and Fine, 2009) [13]. Given a vector of covariates Z , we similarly define $Q_{k,t_0}(\tau|Z) = \inf\{t : F_{k,t_0}(t|Z) \geq \tau\}$ ($k = 1, \dots, K$). Without loss of generality, it will be assumed that there are only two types of competing events, so that $\delta_i = 0, 1$, or 2 , type 1 events being of primary interest. Note that the associated cause-specific residual cumulative incidence function given survival up to t_0 can be defined as

$$\begin{aligned} F_{1,t_0}(t|Z) &= \Pr(T - t_0 \leq t, \epsilon_i = 1 | T > t_0, Z) \\ &= \{F_1(t + t_0|Z) - F_1(t_0|Z)\} / S(t_0|Z), \quad t > t_0 \end{aligned} \quad (3.7)$$

where $F_1(\cdot)$ is the cause-specific CIF for type 1 events and $S(\cdot)$ is the all-cause survival function. Defining $Q_{1,t_0}(\tau|Z)$ as the τ^{th} quantile of the residual life distribution of type 1 events at a given time t_0 , we have

$$u\{Q_{1,t_0}(\tau|Z)\} = F_1\{t_0 + Q_{1,t_0}(\tau|Z)|Z\} - F_1(t_0|Z) - \tau S(t_0|Z) = 0. \quad (3.8)$$

We propose a regression model that assumes the log-linear relationship between $Q_{1,t_0}(\tau)$ and a covariate vector, i.e. $Q_{1,t_0}(\tau|Z) = \exp(\beta'_{1,t_0|\tau}Z)$, where $\beta_{1,t_0|\tau}$ is a $(p+1) \times 1$ vector of the regression coefficients, and Z is a $(p+1) \times 1$ vector of covariates. Then the equation (3.8) implies

$$\Pr(T_i \leq t_0 + \exp(\beta'_{1,t_0|\tau}Z_i), \epsilon_i = 1 | Z_i) - \Pr(T_i \leq t_0, \epsilon_i = 1 | Z_i) = \tau \Pr(T_i \geq t_0 | Z_i). \quad (3.9)$$

Assuming conditional independence between (T_i, ϵ_i) and C_i given Z (Peng and Fine, 2009) [22], the first term of the left hand side of equation (3.9) is equivalent to

$$\begin{aligned} & E \left\{ \frac{I(Y_i \leq t_0 + \exp(\beta'_{1,t_0|\tau}Z_i), \delta_i = 1)}{G(Y_i|Z_i)} \Big| Z_i \right\} \\ &= E \left[E \left\{ \frac{I(T_i \leq t_0 + \exp(\beta'_{1,t_0|\tau}Z_i), \epsilon_i = 1, C_i \geq T_i)}{G(T_i|Z_i)} \Big| T_i, \epsilon_i, Z_i \right\} \Big| Z_i \right] \\ &= E \left[\frac{I(T_i \leq t_0 + \exp(\beta'_{1,t_0|\tau}Z_i), \epsilon = 1)G(T_i|Z_i)}{G(T_i|Z_i)} \Big| Z_i \right] \\ &= \Pr(T_i \leq t_0 + \exp(\beta'_{1,t_0|\tau}Z_i), \epsilon_i = 1 | Z_i) \end{aligned} \quad (3.10)$$

where $G(\cdot)$ is the survival function of the censoring distribution. Similarly, the second term of the left hand side in equation (3.9) has the following equivalence:

$$\Pr(T_i \leq t_0, \epsilon_i = 1 | Z_i) = E \left\{ \frac{I(Y_i \leq t_0, \delta_i = 1)}{G(Y_i|Z_i)} \Big| Z_i \right\}.$$

Therefore the equation (3.9) can be reexpressed as

$$E \left[\frac{[I\{Y_i \leq t_0 + \exp(\beta'_{1,t_0|\tau}Z_i)\} - I(Y_i \leq t_0)] I(\delta_i = 1)}{G(Y_i|Z_i)} \Big| Z_i \right] = E \left\{ \tau \frac{I(Y_i \geq t_0)}{G(t_0|Z_i)} \Big| Z_i \right\}, \quad (3.11)$$

which leads to an estimating equation for the regression parameter $\beta_{1,t_0|\tau}$,

$$S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}) = 0, \quad (3.12)$$

where

$$S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}) = \sum_{i=1}^n Z_i \left[\frac{[I\{Y_i \leq t_0 + \exp(\beta'_{1,t_0|\tau}Z_i)\} - I(Y_i \leq t_0)] I(\delta_i = 1)}{\hat{G}(Y_i|Z_i)} - \tau \frac{I(Y_i \geq t_0)}{\hat{G}(t_0|Z_i)} \right] \quad (3.13)$$

where $\hat{G}(\cdot|Z)$ is the Kaplan-Meier estimator of the conditional censoring distribution given covariates. However, throughout this study, we will assume that the censoring distribution is independent of the covariates since in a well-designed clinical trial, important prognostic factors are balanced across the treatment groups, featured with administrative censoring.

Due to the discontinuity of $S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau})$, the estimating equation would not always have the exact solution, thus a solution $\hat{\beta}_{1,t_0|\tau}$ is defined as a minimizer of the function, Euclidean norm $\|S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau})\|$, defined as the square root of sum of squares. For optimization, we use a grid search method to minimize an $\|S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau})\|$. Following is the iterative algorithm to obtain the solution, supposing $\beta_{1,t_0|\tau}$ is the 2-dimensional parameter case.

- step1: Based on initial value (x_0, y_0) , initial region $[x_0 \pm a] \times [y_0 \pm b]$ are given
- step2: Compute $\|S(\cdot)\|$ with all intersected points of equi-distance grid within initial region
- step3: Obtain $S^{(1)}$ which has a minimum $\|S(\cdot)\|$ and set the corresponding (x_i, y_i) as a second initial value
- step4: Consider the equi-distance grid within $[x_0 \pm 0.75 * a] \times [y_0 \pm 0.75 * b]$ region
- step5: Obtain $S^{(2)}$ which has a minimum $\|S(\cdot)\|$ among the intersected points within second grid
- step6: Iterate step2 - step5 until $S^{(1)} - S^{(2)} < 0.001$ and corresponding (x_j, y_j) of $S^{(2)}$ is the solution $(\hat{\beta}_0, \hat{\beta}_1)$.

3.3.2 Test Statistics

As Jeong and Fine (2009) noted, the asymptotic variance of the quantile estimator would involve the probability density function of the failure time distribution under censoring, which is improper under competing risks. Since our model assumes the log-linear relationship $Q_{1,t_0}(\tau|Z) = \exp(\beta'_{1,t_0|\tau}Z)$, evaluation of the asymptotic variance of the test statistic for the null hypothesis $H_0 : \beta_{1,t_0|\tau} = \beta_{1,t_0|\tau,0}$ would also involve estimation of the probability density

function. To avoid it, we will form our test statistic based on the estimating equation $S_{1,t_0|\tau}(\beta_{1,t_0|\tau})$ directly, as in Su and Wei (1993) [28]. We have shown, in the Appendix B, that the distribution $n^{-1/2}S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}^0)$ is approximately normal with mean zero and variance-covariance matrix $\Gamma_{1,t_0|\tau} = n^{-1} \sum_{i=1}^n \xi_{1,t_0|\tau,i} \xi_{1,t_0|\tau,i}'$, where

$$\begin{aligned} \xi_{1,t_0|\tau,i} = & \left[\frac{\{I(Y_i \leq t_0 + \exp(\hat{\beta}_{1,t_0|\tau} Z_i)) - I(Y_i \leq t_0)\} I(\delta_i = 1)}{G(Y_i)} - \tau \frac{I(Y_i \geq t_0)}{G(t_0)} \right] Z_i \\ & + \int_{-\infty}^{\infty} G^{-1}(s) \int_{-\infty}^s h^{-1}(v) \{dI(Y_i \leq v, \delta_i = 0) - I(Y_i \geq v) d\Lambda_G(v)\} dq_1(s) \\ & - q_2(t_0) \int_{-\infty}^{t_0} h^{-1}(s) \{dI(Y_i \leq s, \delta_i = 0) - I(Y_i \geq s) d\Lambda_G(s)\}, \end{aligned}$$

where $\Lambda_G(\cdot)$ is the cumulative hazard function for the censoring variable,

$$q_1(s) = \lim_{n \rightarrow \infty} n^{-1} \sum_{i=1}^n Z_i [I(t_0 + \exp(\beta_{1,t_0|\tau}^{0'} Z_i)) \geq \min(s, Y_i) - I(t_0 \geq \min(s, Y_i))] I(\delta_i = 1),$$

$$q_2(t_0) = \lim_{n \rightarrow \infty} (\tau/n) G(t_0)^{-1} \sum_{i=1}^n I(Y_i \geq t_0) Z_i, \text{ and } h(v) = \lim_{n \rightarrow \infty} \sum_{i=1}^n I(Y_i \geq v)/n.$$

Here $\xi_{1,t_0|\tau,i}$ can be consistently estimated by

$$\begin{aligned} \hat{\xi}_{1,t_0|\tau,i} = & \left[\frac{[I\{Y_i \leq t_0 + \exp(\hat{\beta}'_{1,t_0|\tau} Z_i)\} - I(Y_i \leq t_0)] I(\delta_i = 1)}{\hat{G}(Y_i)} - \tau \frac{I(Y_i \geq t_0)}{\hat{G}(t_0)} \right] Z_i \\ & + \sum_{l=1}^n \left[Z_l \frac{[I\{Y_l \leq t_0 + \exp(\hat{\beta}'_{1,t_0|\tau} Z_l)\} - I(Y_l \leq t_0)] I(\delta_l = 1)}{\hat{G}(Y_l)} \right] \\ & \left[\frac{I(\delta_i = 0) I\{Y_i \leq t_0 + \exp(\hat{\beta}'_{1,t_0|\tau} Z_i)\}}{\sum_{m=1}^n I(Y_m \geq Y_i)} - \sum_{j=1}^n \frac{I(\delta_j = 0) I[Y_j \leq \min\{t_0 + \exp(\hat{\beta}'_{1,t_0|\tau} Z_l), Y_j\}]}{\sum_{m=1}^n I(Y_m \geq Y_j)^2} \right] \\ & - \sum_{l=1}^n \left\{ Z_l \frac{\tau I(Y_l \geq t_0)}{n \hat{G}(t_0)} \right\} \left[\frac{I(\delta_i = 0) I(Y_i \leq t_0)}{\sum_{m=1}^n I(Y_m \geq Y_i)} - \sum_{j=1}^n \frac{I(\delta_j = 0) I\{Y_j \leq \min(t_0, Y_i)\}}{\sum_{m=1}^n I(Y_m \geq Y_j)^2} \right]. \end{aligned}$$

Denoting $\hat{\Gamma}_{1,t_0|\tau}$ for the consistent estimator of $\Gamma_{1,t_0|\tau}$, the test statistic

$$n^{-1} S'_{1,t_0|\tau,n}(\beta_{1,t_0|\tau,0}) \hat{\Gamma}_{1,t_0|\tau}^{-1} S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau,0}), \quad (3.14)$$

asymptotically follows a χ^2 -distribution with $p + 1$ degrees of freedom. A large observed value of this statistic would result in rejection of the null hypothesis.

Now suppose that we are interested in a local test for a subset of the regression coefficients. Given a partition of the regression coefficients, $\beta_{1,t_0|\tau} = (\beta_{1,t_0|\tau}^{(1)'} , \beta_{1,t_0|\tau}^{(2)'})$, where $\beta_{1,t_0|\tau}^{(1)}$ is a $r \times 1$ vector, let us consider testing the null hypothesis of $H_0 : \beta_{1,t_0|\tau}^{(1)} = \beta_{1,t_0|\tau,0}^{(1)}$. To eliminate the subset of the nuisance parameters $\beta_{1,t_0|\tau}^{(2)}$, we form a variation of the minimum dispersion statistic (Basawa and Koul, 1988) [1],

$$V(\beta_{1,t_0|\tau,0}^{(1)}) = \min_{\beta_{1,t_0|\tau}^{(2)}} \{n^{-1} S_{1,t_0|\tau,n}((\beta_{1,t_0|\tau,0}^{(1)'} , \beta_{1,t_0|\tau}^{(2)'})) \hat{\Gamma}_{1,t_0|\tau}^{-1} S_{1,t_0|\tau,n}((\beta_{1,t_0|\tau,0}^{(1)'} , \beta_{1,t_0|\tau}^{(2)'}))\}. \quad (3.15)$$

Following the arguments in Wei et al.(1990) [30] (Appendix 2) and Ying et al. (1995) [32] (APPENDIX C), it can be shown that the statistic $V(\beta_{1,t_0|\tau,0}^{(1)})$ has approximately a χ^2 -distribution with r degrees of freedom.

3.4 SIMULATION

We have performed numerical studies to evaluate the finite sample properties of our estimator and test statistic, based on the median residual regression, $\tau = 0.5$. For simplicity, we assume two type of competing events, and type 1 events being of our interest. A simple regression model with one binary covariate $x^{(1)}$ is considered as follows:

$$Q_{1,t_0} = \exp(\beta_{1,t_0}^{(0)} + \beta_{1,t_0}^{(1)} x^{(1)}). \quad (3.16)$$

Failure time T_i was assumed to follow a Weibull distribution with survival function $S(t) = \exp\{-(\rho t)^\kappa\}$. When π is the probability of type 1 event, the cumulative incidence functions for type 1 and type 2 events can be expressed as $F_1(t) = \pi\{1 - \exp\{-(\rho_1 t)^{\kappa_1}\}\}$ and $F_2(t) = (1 - \pi)\{1 - \exp\{-(\rho_2 t)^{\kappa_2}\}\}$, respectively. Under the hypothesis of $\tilde{H}_0 : \beta_{1,t_0}^{(1)} = 0$, the median residual for type 1 event distribution is given by

$$\begin{aligned} Q_{1,t_0} &= \exp(\beta_{1,t_0}^{(0)}) = F_1^{-1}\{\tau S(t_0) + F_1(t_0)\} - t_0 \\ &= (1/\rho_1) [-\log\{1 - \{\tau S(t_0) + F_1(t_0)\}/\pi\}]^{1/\kappa} - t_0, \quad t_0 \geq 0. \end{aligned} \quad (3.17)$$

At the origin of time ($t_0 = 0$), $Q_{1,0} = (1/\rho_1) [-\log\{1 - \{\tau S(0) + F_1(0)\}/\pi\}]^{1/\kappa}$ and then ρ_1 can be determined as

$$\begin{aligned}\rho_1 &= \frac{[-\log\{1 - \{\tau S(0) + F_1(0)\}/\pi\}]^{1/\kappa}}{Q_{1,0}} \\ &= \frac{\{-\log(1 - \frac{\tau}{\pi})\}^{1/\kappa}}{\exp(\beta_{1,0}^{(0)})}\end{aligned}\quad (3.18)$$

where $S(0) = 1$ and $F_1(0) = 0$. Now assuming $\rho_2 = 0.4$, $\kappa_1 = \kappa_2 = 1.5$ and $\exp(\beta_{1,0}^{(0)}) = 5$, event times were generated from $T_{i1} = (1/\rho_1)\{-\log(1 - u_i)\}^{1/\kappa_1}$ for type 1 and from $T_{i2} = (1/\rho_2)\{-\log(1 - u_i)\}^{1/\kappa_2}$ for type 2 in both comparison groups using the probability integral transformation where $u_i \sim \text{UNIF}(0, 1)$. Censoring times C_i were from $\text{UNIF}(0, c)$, where c is a constant that controls for the censoring proportion. The observed survival times were determined by $Y_i = \min(T_i, C_i)$, where $T_i = (T_{i1}, T_{i2})'$.

The first part of simulation is to evaluate the empirical distribution of regression parameter estimates at different time points in terms of mean (median) and standard error (SE) at different time points for the censoring proportions of 0%, 10%, and 20%. Under $\tilde{H}_0 : \beta_{1,t_0}^{(1)} = 0$, from equation (3.17) the true parameter value of $\beta_{1,t_0}^{(0)}$ is obtained as 1.61, 1.40, 1.18 and 0.98 at $t_0 = 0, 1, 2$ and 3. The grid search algorithm described in the previous section was used with initial value of (1.6, 0) and ranges $a = b = 5$ to find the minimizer of the estimating equation (3.12). With sample size of 200, 1000 simulations were performed. Table 5 presents the result that the mean (median) values of the estimates of parameters are close to their true values for earlier time points, but the bias and SE tend to increase at later time points. This was expected due to loss of information as time progresses in terms of the number of type 1 events. Next, we examine the type I error probabilities and power for testing the null hypothesis $\tilde{H}_0 : \beta_{1,t_0}^{(1)} = 0$. In Table 6, when the true value of $\beta_{1,t_0}^{(1)}$ is 0, one can observe that the type I error probabilities tend to be conservative at the nominal level of 0.05. This is similar to the results presented in Ying et al.(1995) [32], and Jung et al.(2009) [16]. Table 5 also summarizes the probabilities power of rejecting the null hypothesis when the true parameter values are $\beta_{1,t_0}^{(1)} = 0.18, 0.69, \text{ and } 1.03$, respectively. Those values correspond to the differences in median residual lifetime of type 1 events between two

groups being 1, 5, and 9 at $t_0 = 0$. As expected, power increases with larger $\beta_{1,t_0}^{(1)}$ values and decreases with higher censoring proportions.

Table 6: Mean (Median) and standard error (SE) of empirical estimates of the true regression parameters $\beta_{1,t_0}^{(0)} = 1.61, 1.40, 1.18, 0.98$ at $t_0 = 0, 1, 2, 3$ with $\beta_{1,t_0}^{(1)} = 0$ and the total number of observation (n) is 200

t_0	$c\%$	$\beta_{1,t_0}^{(0)}$	SE	$\beta_{1,t_0}^{(1)}$	SE
0	0	1.640(1.602)	0.295	-0.041(0.006)	0.418
	10	1.661(1.616)	0.265	-0.075(-0.014)	0.382
	20	1.675(1.624)	0.279	-0.092(-0.035)	0.400
1	0	1.386(1.375)	0.259	0.032(0.033)	0.402
	10	1.426(1.398)	0.254	-0.044(-0.010)	0.366
	20	1.437(1.396)	0.272	-0.063(-0.023)	0.404
2	0	1.139(1.147)	0.315	0.058(0.0334)	0.475
	10	1.176(1.168)	0.384	-0.021(-0.010)	0.515
	20	1.187(1.174)	0.451	-0.042(-0.024)	0.598
3	0	0.874(0.919)	0.792	0.114(0.063)	1.025
	10	0.866(0.945)	1.054	0.082(0.010)	1.233
	20	0.838(0.961)	1.267	0.096(-0.002)	1.487

Table 7: Type 1 error probabilities and power for testing the null hypothesis $H_0 : \beta_{1,t_0}^{(1)} = 0$ ($t_0 = 0, 1, 2$) where the true values are $\beta_{1,0}^{(1)} = 0$ (type I error), 0.18, 0.67, 1.03 (power) and the total sample size (n) is 200

		$\beta_{1,t_0}^{(1)}$	0	0.18	0.69	1.03
$t_0 = 0$	$c\% = 0$	0	0.032	0.12	0.90	0.98
		10	0.026	0.07	0.54	0.83
		20	0.022	0.04	0.46	0.83
1		0	0.022	0.10	0.89	0.99
		10	0.023	0.08	0.64	0.78
		20	0.022	0.05	0.53	0.74
2		0	0.034	0.10	0.84	0.99
		10	0.025	0.07	0.73	0.71
		20	0.021	0.05	0.60	0.61

3.5 EXAMPLE

The B-04 study performed by National Surgical Adjuvant Breast and Bowel Project (NS-ABP) was a phase III randomized clinical trial on breast cancer to compare the effect of traditional radical mastectomy and less aggressive total mastectomy on patient's survival with or without additional radiation therapy. In this study, a total of 1079 women with clinically negative axillary nodes and 586 women with clinically positive axillary nodes were assigned to one of treatment groups. After long-term follow-up over 30 years (Fisher et al,2002) [8], about 90% of all patients were either followed or died and also about 30% among node-negative patients and about 20% among node-positive patients were censored. Death following breast cancer recurrence (type 1 events) and non-breast-cancer related death (type 2 events) were considered as competing events. In this section, we reanalyze the B-04 data to assess the effect of important prognostic factors on the quantile residual lifetime of the distribution of breast-cancer related deaths.

First, we consider a simple regression model with only one covariate of nodal status, x_{node} coded as 0 or 1 for node-negative and node-positive. Figure 7 shows the estimated cause-specific residual cumulative incidence for breast cancer related death at different time points. It is clear from the plots that the most estimates does not exceed 0.5, so that we regress on lower quantiles ($\tau = 0.1, 0.2, 0.3$) rather than the median. Parameters $\beta_{1,t_0|\tau}^{(intercept)}$ and $\beta_{1,t_0|\tau}^{(node)}$ are estimated at different time points, $t_0 = 0, 2, 4, 6, 8$. Based on those estimates, the τ -percentile residual lifetime for node-negative and node-positive were obtained from $\hat{Q}_{1,t_0}^{(\ominus)}(\tau) = \exp(\hat{\beta}_{1,t_0|\tau}^{(intercept)})$ and $\hat{Q}_{1,t_0}^{(\oplus)}(\tau) = \exp(\hat{\beta}_{1,t_0|\tau}^{(intercept)} + \hat{\beta}_{1,t_0|\tau}^{(node)})$. Those values were illustrated graphically denoting the smallest value at which the estimated residual cumulative incidence for breast cancer related death crosses τ as shown in Figure 8 when $\tau = 0.3$ and $t_0 = 0$. To confirm that our parameter estimates are reasonable, we compared ours with the estimates from Jeong and Fine (2009) [13] that were evaluated separately for node-negative and node-positive patients. Table 7 summarizes the parameter estimates, which indicates that our regression estimates are comparable to ones from Jeong and Fine (2009).

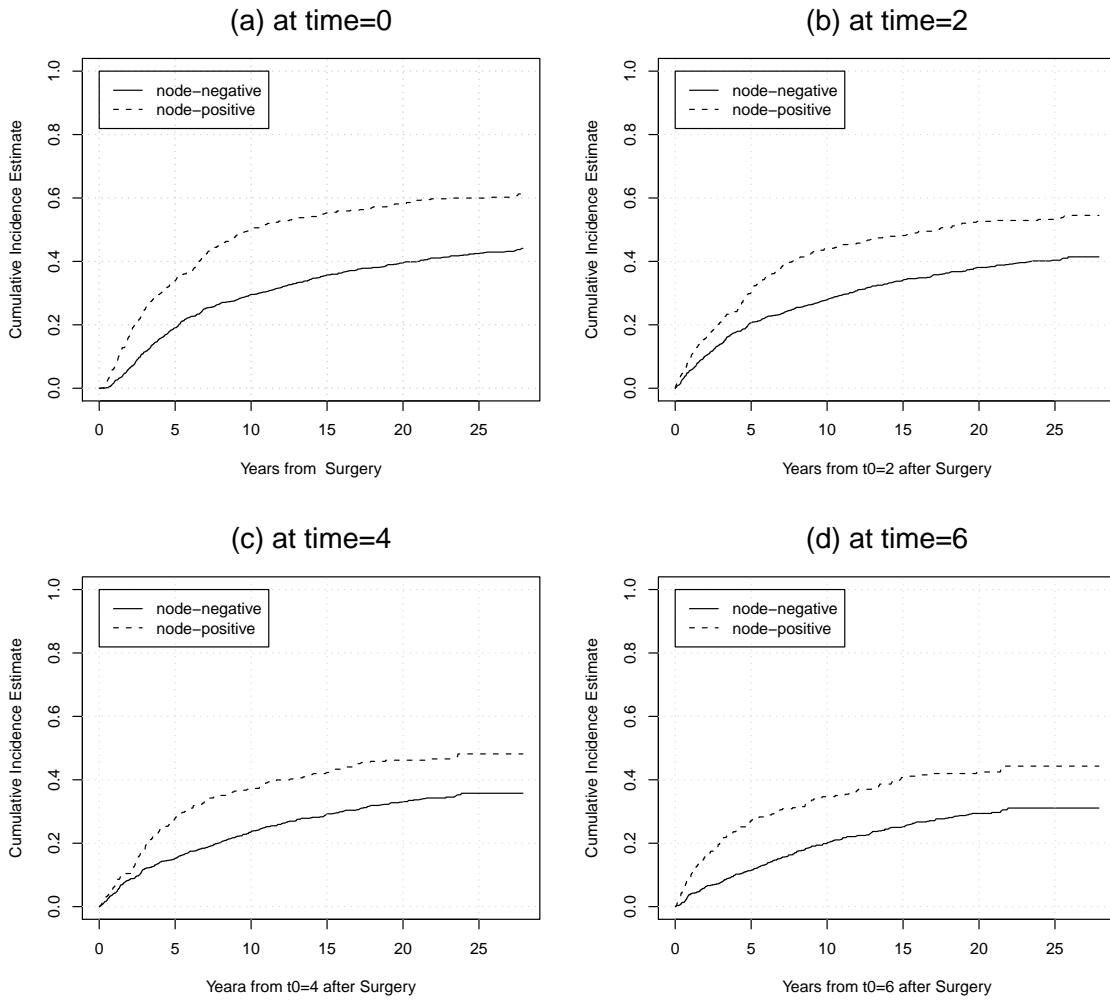
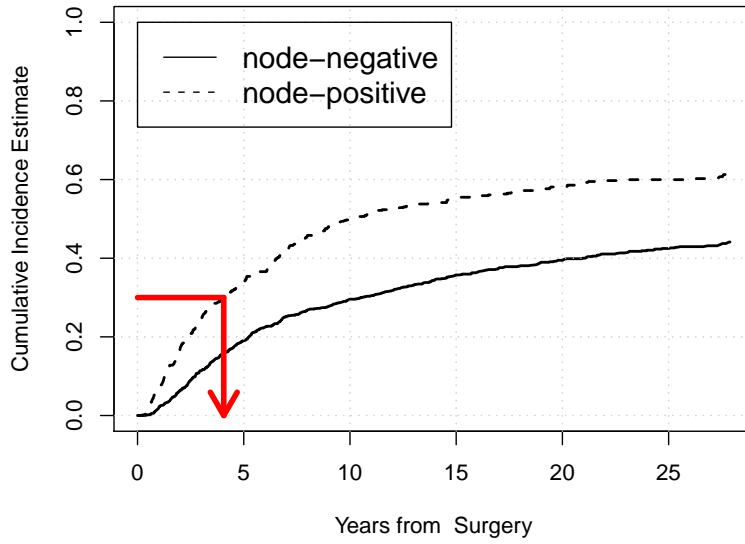


Figure 7: Residual cumulative incidence estimates for breast cancer related death at different time points ($t_0 = 0, 2, 4, 6$) in B-04

(a) $Q(0.3)$ estimate for node positive at time=0



(b) $Q(0.3)$ estimate for node negative at time=0

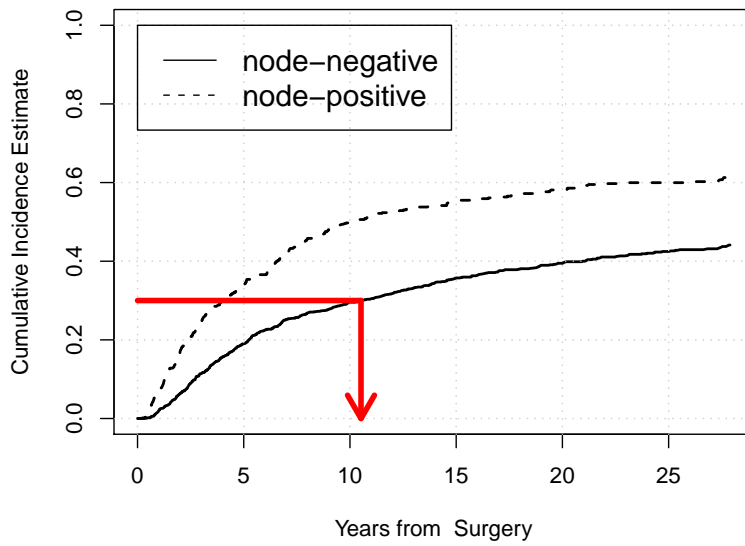


Figure 8: Graphical demonstration of residual Life for (a) node-positive and (b) node-negative with $\tau=0.3$ at $t_0 = 0$

Table 8: Simple regression model; regression parameter estimates and various quantile residual life estimates (0.1, 0.2, 0.3) at different time points ($t_0 = 0, 2, 4, 6, 8$) with a single covariate (nodal status)

τ	t_0	Estimates via Regression				Jeong & Fine	
		$\hat{\beta}_{1,t_0 \tau}^{(intercept)}$	$\hat{\beta}_{1,t_0 \tau}^{(node)}$	$\hat{Q}_{1,t_0}^{(\ominus)}(\tau)$	$\hat{Q}_{1,t_0}^{(\oplus)}(\tau)$	$\hat{Q}_{1,t_0}^{(\ominus)}(\tau)$	$\hat{Q}_{1,t_0}^{(\oplus)}(\tau)$
0.1	0	0.98	-0.70	2.66	1.32	2.72	1.28
	2	0.65	-0.58	1.91	1.07	1.95	1.04
	4	0.98	-0.53	2.65	1.57	2.63	1.73
	6	1.37	-1.31	3.92	1.06	3.96	1.04
	8	1.56	-0.84	4.77	2.05	4.92	2.17
0.2	0	1.66	-0.80	5.24	2.36	5.26	2.36
	2	1.57	-0.55	4.81	2.77	4.81	2.76
	4	2.05	-0.90	7.75	3.17	7.87	3.16
	6	2.29	-1.20	9.83	2.96	9.99	2.98
	8	2.45	-0.56	11.60	6.60	11.80	6.57
0.3	0	2.35	-0.96	10.53	4.04	10.53	4.07
	2	2.45	-0.84	11.57	4.99	11.45	4.98
	4	2.79	-0.09	16.31	5.49	16.03	5.63
	6	3.19	-1.19	24.24	7.39	21.41	6.77

Secondly, we fit the proposed model to adjust for additional important covariates such as age at diagnosis of breast cancer and pathological tumor size along with the node-status to predict percentile residual lifetimes for breast-cancer-related death at any follow-up time point. A multiple regression model was constructed with $Z = (1, X_{node}, X_{age}, X_{tsize})$ where X_{age} and X_{tsize} were included as continuous covariates after rescaled by multiplying by 0.01 just for computational convenience. Table 8 shows the estimated regression parameters and corresponding p -values. At the bottom of Table 8, for a comparison we also present p -values from the subdistribution hazard regression model ([7]), which compares the average subdistribution hazards under the proportionality assumption. As expected, nodal status and tumor size had negative effect on the quantile residual lifetimes for breast-cancer-related death, at all time points considered. This implies that patients with positive nodes and larger tumor size at the diagnosis tend to live shorter than ones with the opposite characteristics, no matter what follow-up time point they were evaluated. Interestingly, however, age at diagnosis of breast cancer shows positive effects at earlier time points, but the effects become negative in later time points, while the Fine & Gray model indicates the average negative effect of age in subdistribution hazard rate. This might imply that breast cancers developed in younger patients (possibly genetic effect) are known to be more aggressive, so that they tend to die earlier due to breast cancer, but patients who have overcome the “high-risk” period (about 2 years) would have longer life expectancy than ones whose diseases were developed at older ages (possibly age effect).

To verify the tendency of age effect over time on breast cancer related death, we re-analyzed NSABP B-14 data with age at diagnosis of breast cancer and pathological tumor size as covariates. This data have relatively lower cumulative incidence rate with higher censoring proportion (58%) shown in Figure 9, thus only lower percentile of $\tau = 0.1, 0.2$ were considered. Table 9 summarized the estimated regression parameters and corresponding p -values along with the results from subdistribution hazard regression model (Fine & Gray, 1999) for comparison. We confirm the coherent tendency of age effect on breast cancer related death in that it has positive effects at earlier time points but become negative at time=6 when $\tau = 0.2$.

Table 9: Multiple regression model; regression parameter estimates for different quantiles (0.1, 0.2, and 0.3) at different time points ($t_0 = 0, 2, 4, 6, 8$) with multiple covariates (nodal status, age, tumor size) and associated p -values with B-04

τ	t_0	$\hat{\beta}_{1,t_0 \tau}^{(intercept)}$	p -value	$\hat{\beta}_{1,t_0 \tau}^{(node)}$	p -value	$\hat{\beta}_{1,t_0 \tau}^{(age)}$	p -value	$\hat{\beta}_{1,t_0 \tau}^{(tsize)}$	p -value
0.1	0	1.11	<0.0001	-0.67	<0.0001	0.78	0.010	-1.56	<0.0001
	2	0.20	0.286	-0.41	0.296	1.85	0.067	-1.89	0.008
	4	0.93	0.145	-0.44	0.103	0.79	0.554	-1.49	0.147
	6	1.80	<0.0001	-1.27	<0.0001	0.10	0.748	-1.51	0.063
	8	2.61	0.005	-0.93	0.001	-1.51	0.289	-0.42	0.374
0.2	0	1.02	<0.0001	-0.56	<0.0001	2.14	0.003	-1.63	<0.0001
	2	0.74	0.004	-0.44	0.004	2.49	0.007	-1.63	0.0003
	4	3.77	<0.0001	-0.71	<0.0001	-1.89	0.838	-2.04	0.026
	6	3.54	<0.0001	-1.20	<0.0001	-1.08	0.075	-1.64	0.002
	8	6.76	<0.0001	-1.07	0.005	-5.70	0.005	-2.24	0.019
0.3	0	1.97	<0.0001	-0.77	<0.0001	1.75	0.0009	-1.81	<0.0001
	2	3.18	<0.0001	-0.79	<0.0001	-0.02	0.048	-2.11	<0.0001
	4	4.09	<0.0001	-1.09	<0.0001	-0.92	0.189	-1.92	<0.0001
Fine and Gray model				0.54	<0.0001	-1.04	0.0008	0.78	<0.0001

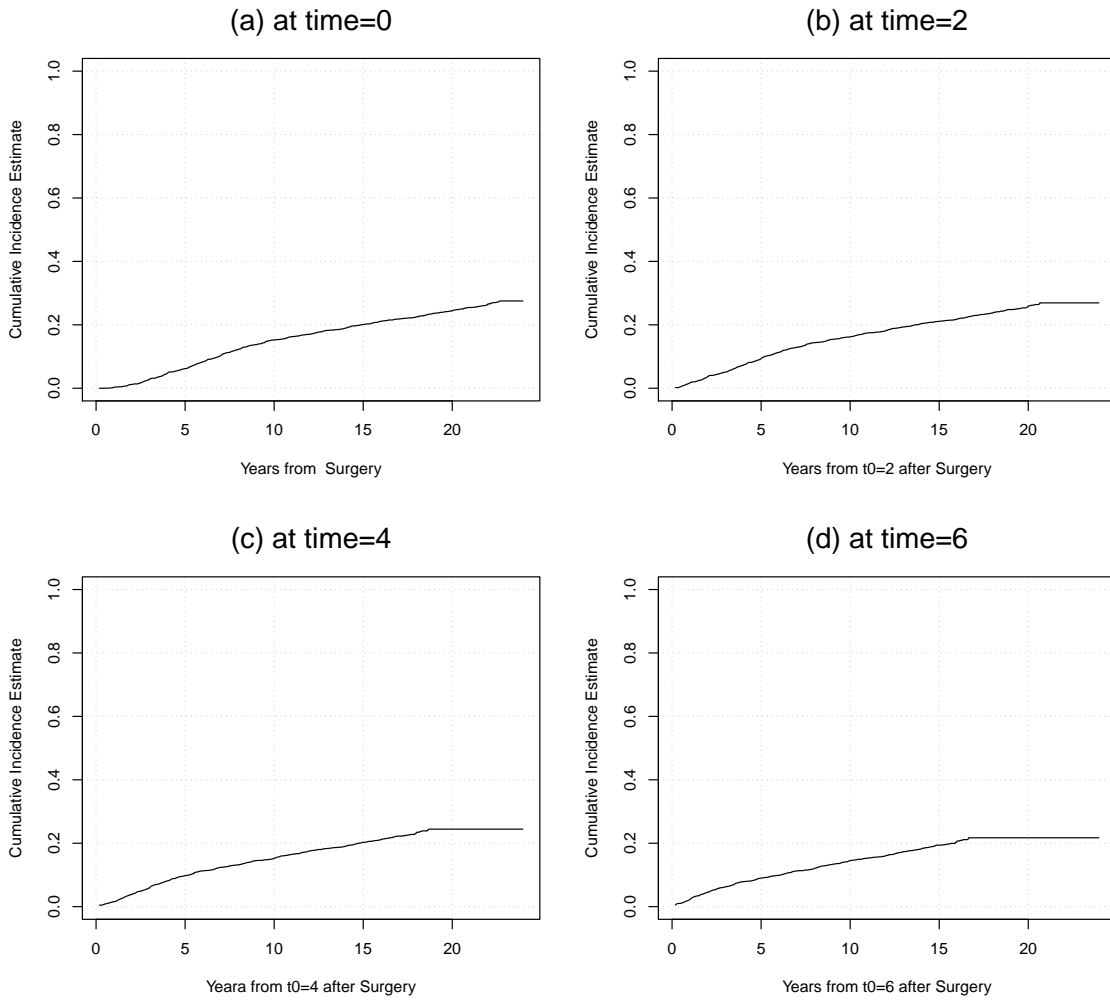


Figure 9: Residual cumulative incidence estimates for breast cancer related death at different time points ($t_0 = 0, 2, 4, 6$) in B-14

Table 10: Multiple regression model; regression parameter estimates for different quantiles (0.1, 0.2) at different time points ($t_0 = 0, 2, 4, 6, 8$) with multiple covariates (age, tumor size) and associated p -values with B-14

τ	t_0	$\hat{\beta}_{1,t_0 \tau}^{(intercept)}$	p -value	$\hat{\beta}_{1,t_0 \tau}^{(age)}$	p -value	$\hat{\beta}_{1,t_0 \tau}^{(tsize)}$	p -value
0.1	0	1.51	0.02	1.80	0.02	-2.51	<0.0001
	2	1.81	0.14	1.34	0.14	-3.75	<0.0001
	4	1.25	0.09	1.92	0.08	-2.70	<0.0001
	6	1.69	0.38	1.32	0.42	-2.94	0.0004
	8	1.95	0.59	1.03	0.59	-2.35	0.03
0.2	0	3.14	0.05	0.49	0.06	-3.11	<0.0001
	2	3.12	0.04	0.89	0.17	-4.52	0.0008
	4	3.27	0.37	0.25	0.79	-3.02	0.09
	6	5.08	0.67	-1.51	0.51	-4.87	0.38
Fine and Gray model				-0.73	0.084	1.89	<0.0001

3.6 SUMMARY

Competing risks is often encountered in medical research with multiple failure types. We proposed a regression model to associate the quantile residual lifetime with important covariates at a given time point under a competing risks setting. A vector of covariates was regressed on the conditional cause-specific quantile residual life function, which can be obtained by inverting the cause-specific residual cumulative incidence function. We constructed the estimating equation for the regression coefficients and a test statistic to evaluate the covariate effects. Asymptotic distributions of the regression parameter estimator and test statistic have been derived. Simulation studies show that the proposed test procedure has reasonable finite sample properties in type I error probabilities and powers. A real dataset from the NSABP B-04 study was reanalyzed for the quantiles of $\tau = 0.1, 0.2, 0.3$ at given follow-up years. The grid search method was used for optimization in our simulation studies and real data example. The proposed model can be a useful alternative to the subdistribution proportional hazard model by providing more detailed and clinically more relevant information of covariate effects on the life expectancy.

4.0 DISCUSSION

In clinical research, patients/subjects could have more than one types of outcomes including the primary event of interest and other events, because in reality they are exposed to multiple risk factors that might possibly be correlated. The primary goal of this study was to extend existing methods for survival analysis to the competing risks settings.

First study was initially motivated from the need to relate the prognostic effect to dichotomized status of biomarker in cancer clinical trials where competing risks are often encounter. To determine the optimal cutpoint in competing risks setting, we simply modified the log-rank test using the notion of the improper random variable from Gray's test [12]. This enables us to modify the Contal and O'Quigely method to improve the accuracy of estimated optimal cutpoint and it's significance under competing risks. Simulation results indicated the adequacy of our method using the proposed statistics, which was illustrated with a real dataset from NSABP B-14 study to estimate an optimal cutpoint of age and estrogen receptor level.

Second study was to develop a residual life regression model for competing risks. This regression model associates the quantile residual life times with important covariates at a given time point under a competing risks setting. A vector of covariates was regressed on the conditional cause-specific quantile residual life function, which can be obtained by inverting the cause-specific residual cumulative incidence function. The proposed inference method for the effects of prognostic factors does not involve estimation of the improper probability density function of the cause-specific residual life distribution under competing risks. Simulation studies showed that the proposed estimation and test procedures have reasonable finite sample properties. A real dataset from the NSABP B-04 study was reanalyzed for different quantiles of $\tau = 0.1, 0.2, 0.3$. The model can be a useful alternative to the subdistribution

proportional hazards model by providing more detailed and clinically more relevant information of covariate effects on the life expectancy at a given time point. The grid search method used to minimize the estimating equation provided reasonable solutions in our simulation studies and real examples. However, computational time of this method tends to increase exponentially as more parameters are included in the model, proportional to increasing grid points. A more efficient method to speed up the optimization procedure and to reduce the computational cost might promote the practicability of our proposed method for the data with manifold covariates in the future.

APPENDIX A

CONSISTENCY OF $\hat{\beta}_{1,t_0|\tau}$

Assume that the covariate vector Z is uniformly bounded and suppose that the true value $\beta_{1,t_0|\tau}^0$ of $\beta_{1,t_0|\tau}$ is in the interior of a bounded convex region D . Define

$$\tilde{S}_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}) = \sum_{i=1}^n [F_1\{t_0 + \exp(\beta'_{1,t_0|\tau} Z_i) | Z_i\} - F_1(t_0 | Z_i) - \tau P(T_i \geq t_0 | Z_i)] Z_i,$$

which reduces to 0 when $\beta_{1,t_0|\tau} = \beta_{1,t_0|\tau}^0$. From Csörgö and Hovárth (1983) [6], for all $\epsilon > 0$,

$$\sup |\hat{G}(s) - G(s)| = o(n^{-1/2+\epsilon}), \quad a.s.,$$

which can be used to show that for $\beta_{1,t_0|\tau} \in D$,

$$\begin{aligned} S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}) - \tilde{S}_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}) &= \sum_{i=1}^n [G^{-1}(Y_i) [I\{Y_i \leq t_0 + \exp(\beta'_{1,t_0|\tau} Z_i)\} - I(Y_i \leq t_0)] I(\delta_i = 1) \\ &\quad - \Pr(Y_i \leq t_0 + \exp(\beta_{1,t_0|\tau} Z_i), \delta_i = 1 | Z_i) - \Pr(Y_i \leq t_0, \delta_i = 1 | Z_i)] \\ &\quad - \tau G^{-1}(t_0) \{I(Y_i \geq t_0) - \Pr(Y_i \geq t_0 | Z_i)\} Z_i + o(n^{1/2+\epsilon}), \quad a.s. \end{aligned}$$

Since

$$\begin{aligned} \sup_{\beta_{1,t_0|\tau} \in D} \left| \sum_{i=1}^n G^{-1}(Y_i) [I\{Y_i \leq t_0 + \exp(\beta'_{1,t_0|\tau} Z_i)\} - I(Y_i \leq t_0)] I(\delta_i = 1) \right. \\ \left. - \Pr(Y_i \leq t_0 + \exp(\beta'_{1,t_0|\tau} Z_i), \delta_i = 1 | Z_i) - \Pr(Y_i \leq t_0, \delta_i = 1 | Z_i) \right| = o(n^{1/2+\epsilon}) \end{aligned}$$

and

$$\sup_{\beta_{1,t_0|\tau} \in D} \left| \sum_{i=1}^n G^{-1}(t_0) \{I(Y_i \geq t_0) - P(Y_i \geq t_0 | Z_i)\} \right| = o(n^{1/2+\epsilon}),$$

then

$$\sup_{\beta_{1,t_0|\tau} \in D} ||n^{-1}S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}) - n^{-1}\tilde{S}_{1,t_0|\tau,n}(\beta_{1,t_0|\tau})|| = o(n^{-1/2+\epsilon}), \quad a.s. \quad (\text{A.1})$$

Suppose that matrix $E [ZZ'f(0|Z)]$ is positive definite, where $f(\cdot|Z)$ denotes the conditional density of T given $Z = z$. By defining $A_n(\beta) = (1/n)(\partial/\partial\beta)\tilde{S}_{1,t_0|\tau,n}(\beta)$, $A_n(\beta_{1,t_0|\tau})$ is non-positive definite, and $A_n(\beta_{1,t_0|\tau}^0) \rightarrow -E [ZZ'f(0|Z)]$, with probability 1, which is negative definite. By Taylor series expansion around β^0 , we have

$$n^{-1}\{\tilde{S}_{1,t_0|\tau,n}(\hat{\beta}_{1,t_0|\tau}) - \tilde{S}_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}^0)\} \approx (\hat{\beta}_{1,t_0|\tau} - \beta_{1,t_0|\tau}^0)'A_n(\beta_{t_0}^*), \quad (\text{A.2})$$

where $\beta_{t_0}^*$ is some point between $\hat{\beta}_{1,t_0|\tau}$ and $\beta_{1,t_0|\tau}^0$. Because $n^{-1}S_{1,t_0|\tau,n}(\hat{\beta}_{1,t_0|\tau}) = 0$ by the definition of $\hat{\beta}_{1,t_0|\tau}$, from (A.1) $n^{-1}\tilde{S}_{1,t_0|\tau,n}(\hat{\beta}_{1,t_0|\tau}) \rightarrow 0$, a.s. as $n \rightarrow \infty$. This coupled with (A.2), implies that $\hat{\beta}_{1,t_0|\tau} \rightarrow \beta_{1,t_0|\tau}^0$, as $n \rightarrow \infty$.

APPENDIX B

ASYMPTOTIC NORMALITY OF $N^{-1/2}S_{1,T_0|\tau,N}(\beta_{1,t_0|\tau}^0)$

To show asymptotic normality, we approximate $n^{-1/2}S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}^0)$ by a sum of independent zero-mean random variables. By definition, $n^{-1/2}S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}^0)$ can be approximated by

$$\begin{aligned}
& n^{-1/2} \sum_{i=1}^n \left[\left\{ \frac{I\{Y_i \leq t_0 + \exp(\beta_{1,t_0|\tau}^{0'} Z_i)\} - I(Y_i \leq t_0)}{G(Y_i)} \right\} I(\delta_i = 1) - \tau \frac{I(Y_i \geq t_0)}{G(t_0)} \right] Z_i \\
& - n^{-1/2} \sum_{i=1}^n Z_i [I\{Y_i \leq t_0 + \exp(\beta_{1,t_0|\tau}^{0'} Z_i)\} - I(Y_i \leq t_0)] I(\delta_i = 1) \left[\frac{\hat{G}(Y_i) - G(Y_i)}{\hat{G}(Y_i)G(Y_i)} \right] \\
& + n^{-1/2} \tau \left\{ \frac{\hat{G}(Y_i) - G(Y_i)}{\hat{G}(Y_i)G(Y_i)} \right\} \sum_{i=1}^n Z_i I(Y_i \geq t_0) \tag{B.1}
\end{aligned}$$

Define

$$Q_1(s) = n^{-1} \sum_{i=1}^n Z_i [I(t_0 + \exp(\beta_{1,t_0|\tau}^{0'} Z_i)) \geq \min(s, Y_i) - I(t_0 \geq \min(s, Y_i))] I(\delta_i = 1),$$

then the second term in (B.1) is asymptotically equivalent to

$$- \int_{-\infty}^{\infty} \left[\frac{n^{1/2} \{\hat{G}(Y_i) - G(Y_i)\}}{G(s)^2} \right] dq_1(s),$$

where $q_1(\cdot) = \lim_{n \rightarrow \infty} Q_1(\cdot)$. Applying martingale integral representation, $-n^{1/2} \{\hat{G}(s) - G(s)\}/G(s)$ can be represented as

$$\int_{-\infty}^s \frac{n^{-1/2} \sum_{i=1}^n \{dI(Y_i \leq v, \delta_i = 0) - I(Y_i \geq v)d\Lambda_G(v)\}}{n^{-1} \sum_{i=1}^n I(Y_i \geq v)}, \tag{B.2}$$

where $\Lambda_G(\cdot)$ is the cumulative hazard function for the censoring variable. Then (B.2) is asymptotically equal to

$$\int_{-\infty}^s h^{-1}(v) n^{-1/2} \sum_{i=1}^n \{dI(Y_i \leq v, \delta_i = 0) - I(Y_i \geq v)d\Lambda_G(v)\}$$

where $h(v) = \lim_{n \rightarrow \infty} \sum_{i=1}^n I(Y_i \geq v)/n$. Therefore the second term of (B.1) is asymptotically equal to

$$\int_{-\infty}^{\infty} G^{-1}(s) \int_{-\infty}^s h^{-1}(v) n^{-1/2} \sum_{i=1}^n \{dI(Y_i \leq v, \delta_i = 0) - I(Y_i \geq v)\Lambda_G(v)\} dq_1(s).$$

The third term of (B.1) also can be represented in a similar way as

$$q_2(t_0) n^{1/2} \left\{ \frac{\hat{G}(t_0) - G(t_0)}{G(t_0)} \right\} = -q_2(t_0) \int_{-\infty}^{t_0} h^{-1}(v) n^{-1/2} \sum_{i=1}^n \{dI(Y_i \leq v, \delta_i = 0) - I(Y_i \geq v)d\Lambda_G(v)\},$$

where $q_2(t_0) = \lim_{n \rightarrow \infty} Q_2(t_0)$, and $Q_2(t_0) = (\tau/n)G(t_0)^{-1} \sum_{i=1}^n I(Y_i \geq t_0)Z_i$. Finally (B.1) is asymptotically equivalent to $n^{-1/2} \sum_{i=1}^n \xi_{1,t_0|\tau,i}$ where

$$\begin{aligned} \xi_{1,t_0|\tau,i} &= \left[\frac{\{I(Y_i \leq t_0 + \exp(\hat{\beta}_{1,t_0|\tau} Z_i)) - I(Y_i \leq t_0)\} I(\delta_i = 1)}{G(Y_i)} - \tau \frac{I(Y_i \geq t_0)}{G(t_0)} \right] Z_i \\ &+ \int_{-\infty}^{\infty} G^{-1}(s) \int_{-\infty}^s h^{-1}(v) \{dI(Y_i \leq v, \delta_i = 0) - I(Y_i \geq v)d\Lambda_G(v)\} dq_1(s) \\ &- q_2(t_0) \int_{-\infty}^{t_0} h^{-1}(s) \{dI(Y_i \leq s, \delta_i = 0) - I(Y_i \geq s)d\Lambda_G(s)\} \end{aligned}$$

Since $\xi_{1,t_0|\tau,i}, i = 1, \dots, n$, are independent random vectors with mean 0, the distribution of $n^{-1/2} S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}^0)$ is asymptotically normal with mean 0 and variance-covariance matrix $\Gamma_{1,t_0|\tau} = n^{-1} \sum_{i=1}^n \xi_{1,t_0|\tau,i} \xi_{1,t_0|\tau,i}'$ by Multivariate Central Limit Theorem. A consistent estimate $\hat{\Gamma}_{1,t_0|\tau}$ for the limiting covariance matrix of $n^{-1/2} S_{1,t_0|\tau,n}(\beta_{1,t_0|\tau}^0)$ can be obtained by substituting $\beta_{1,t_0|\tau}^0, G, h(s), q_1(s), q_2(t_0)$, and $d\Lambda_G(s)$ for $\hat{\beta}_{1,t_0|\tau}, \hat{G}, \sum_{i=1}^n I(Y_i \geq s)/n, Q_1(s), Q_2(t_0)$, and $\{\sum_{i=1}^n I(Y_i \geq s)\}^{-1} d\{\sum_{i=1}^n I(Y_i \leq s, \delta_i = 0)\}$, respectively. That is,

$$\hat{\Gamma}_{1,t_0|\tau} = n^{-1} \sum_{i=1}^n \hat{\xi}_{1,t_0|\tau,i} \hat{\xi}_{1,t_0|\tau,i}'$$

where

$$\begin{aligned}
\hat{\xi}_{1,t_0|\tau,i} &= \left[\frac{[I\{Y_i \leq t_0 + \exp(\hat{\beta}_{1,t_0|\tau} Z_i)\} - I(Y_i \leq t_0)] I(\delta_i = 1)}{\hat{G}(Y_i)} - \tau \frac{I(Y_i \geq t_0)}{\hat{G}(t_0)} \right] Z_i \\
&\quad + \sum_{l=1}^n \left[Z_l \frac{[I\{Y_l \leq t_0 + \exp(\hat{\beta}_{1,t_0|\tau} Z_l)\} - I(Y_l \leq t_0)] I(\delta_l = 1)}{\hat{G}(Y_l)} \right] \\
&\quad \left[\frac{I(\delta_i = 0) I\{Y_i \leq t_0 + \exp(\hat{\beta}_{1,t_0|\tau} Z_i)\}}{\sum_{m=1}^n I(Y_m \geq Y_i)} - \sum_{j=1}^n \frac{I(\delta_j = 0) I[Y_j \leq \min\{t_0 + \exp(\hat{\beta}_{1,t_0|\tau} Z_l), Y_j\}]}{\sum_{m=1}^n I(Y_m \geq Y_j)^2} \right] \\
&\quad - \sum_{l=1}^n \left\{ Z_l \frac{\tau I(Y_l \geq t_0)}{n \hat{G}(t_0)} \right\} \left[\frac{I(\delta_i = 0) I(Y_i \leq t_0)}{\sum_{m=1}^n I(Y_m \geq Y_i)} - \sum_{j=1}^n \frac{I(\delta_j = 0) I\{Y_j \leq \min(t_0, Y_i)\}}{\sum_{m=1}^n I(Y_m \geq Y_j)^2} \right].
\end{aligned}$$

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