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Finding the Cutpoint of a Continuous Covariate in a Parametric Survival Analysis Model

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FINDING THE CUTPOINT OF A CONTINUOUS COVARIATE IN A PARAMETRIC SURVIVAL ANALYSIS MODEL

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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ABSTRACT

FINDING THE CUTPOINT OF A CONTINUOUS COVARIATE IN A PARAMETRIC SURVIVAL ANALYSIS MODEL

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In many clinical studies, continuous variables such as age, blood pressure and cholesterol are measured and analyzed. Often clinicians prefer to categorize these continuous variables into different groups, such as low and high risk groups. The goal of this work is to find the cutpoint of a continuous variable where the transition occurs from low to high risk group. Different methods have been published in literature to find such a cutpoint. We extended the methods of Contal and O'Quigley (1999) which was based on

the log-rank test and the methods of Klein and Wu (2004) which was based on the Score test to find the cutpoint of a continuous covariate. Since the log-rank test is a nonparametric method and the Score test is a parametric method, we are interested to see if an extension of the parametric procedure performs better when the distribution of a population is known. We have developed a method that uses the parametric score residuals to find the cutpoint. The performance of the proposed method will be compared with the existing methods developed by Contal and O'Quigley and Klein and Wu by estimating the bias and mean square error of the estimated cutpoints for different scenarios in simulated data.

CHAPTER 1: INTRODUCTION

1.1 Introduction

In Survival analysis or time-to-event data analysis, different covariates are measured and analyzed in order to predict the time until the occurrence of an event of interest. In the medical research, the event of interest can be death of a patient, failure of an organ or remission of a disease. In engineering, the event can be failure of a mechanical engine or reduction on the performance of a device, and, in the meteorology, the event of interest can be onset of snowfall or rain.

Often in medical research, clinicians wish to categorize a continuous covariate into two different groups such as low and high risk. Although categorizing into more than two groups can occasionally be of interest for some variables, for example, blood pressure, cholesterol or Body-Mass-Index, the stated goal of the proposed methodology is to categorize the continuous variable into two groups.

The term “cutpoint” refers to the point that bifurcates the continuous covariate. There are different methods published in the literature regarding the estimation of a cutpoint, but none are recognized as a standard method. Some of the published methods determine a cutpoint by maximizing a test statistic. The different types of test statistics used in the published literature include the chi-square test statistic, two-sample test statistic, linear rank statistic (Log-rank or Wilcoxon) and score statistic. Most of these test

statistics are based on the non-parametric methods or semi-parametric methods. In 2004, Klein and Wu extended the non-parametric method of Contal and O'Quigley (1999) to both semi-parametric and parametric method. The ultimate goal of the work presented in the following chapters is to find a method that has similar or better performance than the methods developed by Contal and O'Quigley (1999) and Klein and Wu (2004).

In addition to the output oriented methods mentioned above, some graphical and descriptive methods are also available in the literature. Some of these graphical methods are based on residuals to determine a cutpoint. Since residuals are based on the difference(s) between observed and expected number of deaths, any obvious large difference(s) or pattern between observed and expected number of deaths can indicate the possibility of a cutpoint. Martingale residuals are one of the most popularly used residuals to determine the functional relationship between survival outcome and a continuous covariate.

Other commonly used residuals are Cox-Snell residuals, the Score residuals and the Schoenfeld residuals. The Martingale and Cox-Snell residuals are similar and are based on the differences in observed number of deaths vs expected number of deaths at each event time. The Score residuals and Schoenfeld residuals are based on the difference between the observed value of a covariate and the expected value of a covariate at each event time.

1.2 Prospectus

In Chapter 2, an overview of survival analysis will be presented. This chapter gives a short introduction on time-to-event data, censoring, survival functions, hazard functions,

and density functions. Chapter 2 also covers Kaplan-Meier survival curve estimation, Log-rank and Wilcoxon rank-statistics to test the equality of survival curves for two or more groups, the Cox Proportional hazard model, parametric models and the Accelerated Failure Time model. In Chapter 3, a literature review of the existing methods will be presented. In this chapter, methods developed by Miller and Siegmund (1982), Lausen and Schumacher (1992, 1996), Contal and O'Quigley (1999) and Klein and Wu (2004) will be described briefly. Chapter 4 presents the proposed method of finding a cutpoint. The first part of Chapter 4 provides the mathematical definition of the research question and the second part describes a method to compute the test statistics and determine a cutpoint. Chapter 5 presents a method to simulate data for different scenarios and application of the methods to the simulated data. The performance of the proposed method will be compared with the existing methods by computing bias, mean square error and 95^{th} percentile of the estimated cutpoint. Chapter 6 provides the application and result of the proposed method and existing methods to a real world dataset. Finally, Chapter 7 provides the conclusion and the future direction of the research. An appendix containing the results for individual tables for simulated data and SAS codes used for the cutpoint computation and the simulations is provided.

CHAPTER 2: BACKGROUND

2.1 Time-to-Event Data

In survival analysis, the response variable is typically defined as time to an event of interest. In biological or medical research, examples of an event of interest include death of a subject, failure of an organ or the remission of a disease. An important feature of survival data is that the response variable, time to the event of interest, is positive and, in general, the event of interest occurs toward the end of the study. In the case that the event was not observed by the end of the study the data are said to be right censored, which results in a right skewed or positively skewed distribution. Hence, the normal distribution assumption is not suitable for the outcomes in survival analysis. Thus, an important and unique feature of survival analysis is that it incorporates the information on censoring, which cannot be taken into account in simple linear regression or logistic regression.

2.2 Censoring

A subject is said to be censored if (i) they did not experience the event of interest by the end of the study (ii) they dropped out or were lost to follow up during the study period or (iii) experienced an event that prevented them from experiencing the event of interest (for example: if we are interested in the death of a patient from a lung cancer but

a patient died due to heart attack during the study). The last example of censoring is also called the competing risk. Three different types of censoring are: (i) Right censoring (ii) Left censoring and (iii) Interval censoring.

2.2.1 Right Censoring

Let T_i denotes the event time of the i^{th} individual in the study and let C_i be the censoring time of that subject. If T_i is less than C_i then exact lifetime of the individual will be observed and that individual will be known to have an event but if T_i is greater than C_i then the lifetime of that individual will be unobserved and is called the right censored observation. The right censored data can be represented by a pair of random variables (X_i, δ_i), where, $X_i = \min(T_i, C_i)$, X_i is also called the observed event time. The failure indicator variable δ_i is denoted by:

$$\delta_i = \begin{cases} 1 & \text{if } T_i \le C_i \\ 0 & \text{if } T_i > C_i \end{cases}$$

For example, if a study is observing the death from a lung cancer patients receiving chemotherapy, but some patients were still alive by the end of study, the patients who were still alive at the end of the study are said to be right censored individuals. The work presented in the following chapters will be focused on right censored data.

2.2.2 Left Censoring

Let a random variable T_i denotes the event time of the i^{th} subject in the study and let C_i be the censoring time of that subject. If T_i is less than C_i, then the event has already occurred for the individual before that person was observed at time C_i, but the exact event time is unknown. The data from this study can be represented by pairs of random variable (X_i, δ_i), where $X_i = \max(T_i, C_i)$, X_i is also called observed event time. The failure indicators δ_i are denoted as:

$$\delta_i = \begin{cases} 1 & \text{if } C_i \le T_i \\ 0 & \text{if } C_i > T_i \end{cases}$$

This type of study is called the left censoring. For example, suppose a study is teaching some learning skills to children and if some children enrolled in the study already had learned the skills, in this case the individuals who had learned the skills before the enrollment are called left censored individuals. Note that the work in the following chapters will not consider left censoring.

2.2.3 Interval Censoring

In interval censoring, the event of interest occurs within some interval of time. For example, in a study of leukemia, some healthy participants with family history of leukemia were recruited and follow up was scheduled after 6 month. During the first 6 month follow up some previously healthy participants were found to develop the leukemia. In such cases, the investigator does not know the exact date of onset but knows that it occurred during the

previous 6 month period. Note that the work in the following chapters will not be focused on interval censoring.

2.3 The Mathematical Model for Survival Analysis

Let T represent a non-negative random variable representing the failure time of an individual from a homogeneous population. Associated with T is $f(t)$, the probability density function (p.d.f.) of T and $F(t)$ the cumulative distribution function of a random variable T. We know that $F(t) = \Pr(T < t) = \int_0^t f(u)du.$ We will define the survival function, $S(t)$, as the probability that the survival time is greater than or equal to t. That is, $S(t) = \Pr(T \geq t) = \int_t^\infty f(u)du = 1 - F(t).$ Note that since $f(t)$ is a p.d.f., we know that $S(0) = 1.$

Another important function is the hazard function, $h(t).$ The hazard function represents the probability that an individual dies at time $t,$ conditional upon survival to that point. Therefore the hazard function represents the instantaneous death rate for an individual surviving to time $t.$ If T is a continuous random variable, the hazard function can be written as:

$$h(t) = \lim_{\Delta t \to 0} \left\{ \frac{\Pr(t \leq T < t + \Delta t / T \geq t)}{\Delta t} \right\} = \lim_{\Delta t \to 0} \left\{ \frac{\Pr(t \leq T < \Delta t \text{ and } T \geq t}{\Pr(T \geq t)\Delta \text{ t}} \right\}$$

$$= \lim_{\Delta t \to 0} \left\{ \frac{\Pr(T \in [t, t + \Delta t]}{\Pr(T \geq t)\Delta t} \right\} = \lim_{\Delta t \to 0} \left\{ \frac{F(t + \Delta t) - F(t)}{S(t)\Delta t} \right\}$$

$$= \lim_{\Delta t \to 0} \left\{ \frac{F(t+\Delta t) - F(t)}{\Delta t} \right\} \frac{1}{S(t)} = \frac{f(t)}{S(t)}$$

Thus we see that $h(t) = \frac{f(t)}{S(t)} \Rightarrow h(t) = \frac{-\partial \log(S(t))}{\partial t}$. The cumulative hazard function $H(t)$ can be defined as follows:

$$H(t) = \int_0^t h(u)du = -\int_0^t \frac{\partial \log S(u)}{\partial u} du = -\log(S(u))\Big|_0^t$$

$$= -\log(S(t)) + \log(S(0)) = -\log(S(t)) \Rightarrow$$

$$\log(S(t)) = -\int_0^t h(u)du \Rightarrow S(t) = \exp\left(-\int_0^t h(u)du \right) \qquad (2.3.1)$$

Since survival time and hazard function are related with equation in (2.3.1), we can calculate the hazard function and convert it to survival function or vice versa.

2.4 Non Parametric Methods

Time-to-event for subjects in a study can be analyzed using non-parametric methods, semi-parametric methods or parametric methods. Non-parametric methods can be an important alternative to parametric and semi-parametric method, when the distribution of survival times is unknown.

2.4.1 Estimating the Survivor Function using Non Parametric Methods

Previously it was stated that:

$$S(t) = \Pr(T \geq t) = \int_t^\infty f(u)du = 1 - F(t) \qquad (2.4.1)$$

If T is a continuous random variable, then the survival function in equation (2.4.1) is defined as the probability of surviving for time t or greater than time t. If no individual is censored, the empirical survivor function may be written as:

$$\hat{S}(t) = \frac{\#\text{ of individuals with survival times} \geq t}{\#\text{ of individuals in the data set}}$$

In other words, the empirical survival function is the ratio of the total number of individuals alive at time t to the total number of individuals in the study. The empirical survival function $\hat{S}(t)$ is equal to one at the beginning of the study when all individuals are alive and is zero when the last observation experienced the event. It should be noted that the survival function is a step function, which decreases immediately after each observed failure time. However we cannot use the empirical survival function if the data contains any censored observations.

2.4.2 Non Parametric Methods that Incorporate Censoring

Two other non-parametric methods that do incorporate censoring include life-tables and Kaplan-Meier survival curve.

2.4.3 Life Table Estimate

The life-table estimate of the survival function divides time into a series of time intervals of interest. Life-tables estimates are possible even when actual failure times are unknown and the only information available is the number of failures in a series of consecutive intervals. When the failure times are observable, the Kaplan-Meier approach is preferred over life-table estimation.

2.4.4 Kaplan-Meier Estimator of the Survival Function

Let $t_1,...,t_n$ be *n* times until an event of interest in the dataset. Suppose there are r unique time-to-events such that $r \le n$. Let $t_{(1)} < ... < t_{(r)}$ be the r ordered failure times. Let n_j be the number of individuals still alive at time $t_{(j)}$ including those who are about to fail at time $t_{(j)}$ and d_j be the number of deaths at time $t_{(j)}$ for $j = 1, 2, ..., r$. The quantity $d_{(j)} / n_{(j)}$ is called the conditional probability of failure between $t_{(j-\delta)}$ and $t_{(j)}$, where δ is some infinitesimal time interval that includes at least one failure time. The estimator of survival function is also called product-limit estimator or the Kaplan-Meier estimator and it is calculated as:

$$\hat{S}(t) = \begin{cases} 1 & \text{if } t < t_{(1)} \\ \prod_{j=1}^{k} \left[1 - \frac{d_j}{n_j} \right] & \text{if } t_{(k)} \le t \le t_{(k+1)} \end{cases} \qquad (2.5.1)$$

where $k = 1, 2, ..., r$ ordered survival times. The Kaplan-Meier estimator is also a step function like the empirical function but the censored observations are taken into account when calculating the number of persons at risk. If a censored and failure event occurs at the same time $t_{(j)}$, it is assumed that the censored observation is censored immediately after the failure time $t_{(j)}$ and is included in number of risk n_j. The variance of the Kaplan-Meier estimator is given by Greenwood's formula:

$$\hat{V}\left[\hat{S}(t)\right] = \hat{S}(t)^2 \sum_{j=1}^{k} \frac{d_j}{n_j(n_j - d_j)} \qquad (2.5.2)$$

Using Greenwood's formula we can construct a confidence interval for the survival function $\hat{S}(t)$ given by:

$$\left[\hat{S}(t) - z_{1-\alpha/2}\hat{V}(t)^{1/2}, \hat{S}(t) + z_{1-\alpha/2}\hat{V}(t)^{1/2}\right] \qquad (2.5.3)$$

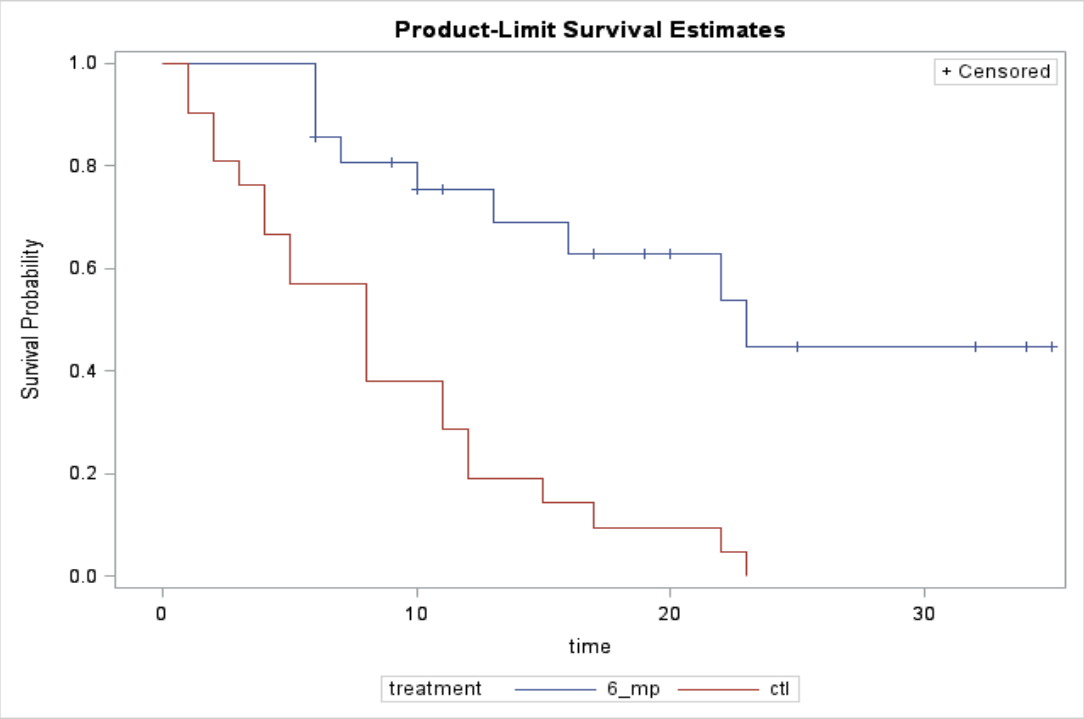
Example 2.1 – Leukemia data

6-MP (n=21): 6^+, 6, 6, 6, 7, 9^+, 10^+, 10, 11^+, 13, 16, 17^+, 19^+, 20^+, 22, 23, 25^+, 32^+, 32^+, 34^+,35^+

Control (n=21): 1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

The pluses (+) indicate that at the end of the study no reoccurrence of leukemia had taken place; these are censored observations.

Figure 2.1: Kaplan-Meier Survival curves for placebo and treatment group



In Figure 2.1 above, the treatment (6-MP) group appears to have better survival than the control group because the survival probabilities at different event times are higher for treatment group as compared to control group.

2.5 The Log-Rank Test

The log-rank test is a useful tool to compare the survival distribution between two or more groups in the presence of right censoring. As a nonparametric procedure, no assumption on the distribution of the outcome variable is required to make inferences on the population. Previously presented, the survival curves derived from the Kaplan-Meier (KM) estimator allows for a graphical comparison of the survival probabilities between two groups, but it does not provide a formal test of statistical significance. The log-rank

test and the associated Wilcoxon test allow for this formal statistical comparison of the curves.

The null hypothesis for the log-rank test is written as: $H_0 : S_1(t) = S_2(t)$ (no difference in the survival between two groups) versus $H_1 : S_1(t) \neq S_2(t)$ (there is a difference in the survival between the groups). The log-rank test for two groups is calculated as follows:

Let O_{1i} be the observed number of failures in group 1 at time of event *i* and let E_{1i} be the expected number of failures in group 1 at the same event time. Let the time of events be ordered such that $t_{(1)} < ... < t_{(r)}$ for r distinct event times. It can be shown that when number of deaths is not too small and number of subject n is large, the sum of the differences in observed and expected failures $\left(\sum_{i=1}^{r} (O_{1i} - E_{1i}) \right)$ follows a normal distribution. Combine the data from both groups. Then, find the number of distinct event times in the combined group. Let r be the number of distinct event time in the combined dataset. Construct a 2×2 table at each distinct failure time. For the event time $= i$, the 2×2 table is constructed as:

	# Failure(deaths)	#Survival	Number at risk
Group1	d_{1i}	$n_{1i} - d_{1i}$	n_{1i}
Group2	d_{2i}	$n_{2i} - d_{2i}$	n_{2i}
Total	d_i	$n_i - d_i$	n_i

In the above table, d_{1i} is the number of failures in group 1 at time point i, n_{1i} is the number of people at risk in group 1 at time point $i, n_i = n_{1i} + n_{2i} =$ number of people at risk in both groups at time point $i, d_i = d_{1i} + d_{2i} =$ number of failures in both groups at time point i.

If the marginal totals in above table are considered to be fixed, then all the other entries in the table can be obtained by d_{1i}. Here d_{1i} follows hypergeometric distribution, i.e.,

$$p\left(d_{1i}\right) = \frac{\binom{d_i}{d_{1i}}\binom{n_i - d_i}{n_{1i} - d_{1i}}}{\binom{n_i}{n_{1i}}}$$

with mean $e_{1i} = \frac{n_{1i} d_i}{n_i}$ and the variance of d_{1i} is given by:

$$V_{1i} = \frac{n_{1i} n_{2i} d_i (n_i - d_i)}{n_i^2 (n_i - 1)}.$$

Now, U_L = sum of differences in the observed and expected failure at each time point given by:

$$U_L = \sum_{i=1}^{r} \left(d_{1i} - e_{1i}\right) = \sum_{i=1}^{r} \left(d_{1i} - n_{1i} \frac{d_i}{n_i} \right).$$

The chi-square statistics is:

$$\chi^2 = \frac{{U_L}^2}{Var\left(U_L\right)} \sim \chi^2_{df},$$

if G is number of groups in the sample then degrees of freedom $= G - 1$.

Since the failure times are independent, the variance of U_L is the sum of the variance of d_{1i} given by:

$$Var(U_L) = \sum_{i=1}^{r} Var\left(d_{1i}\right) = \sum_{i=1}^{r} V_{1i} = V_L.$$

Here, U_L has approximately normal distribution when n is large, it implies:

$$\frac{U_L}{\sqrt{V_L}} \sim N(0,1).$$

Hence, $\frac{U_L^2}{V_L} \sim \chi_1^2$. The ratio $\frac{U_L^2}{V_L}$ is called the log-rank statistics.

While the log-rank test is a powerful tool, it does have some disadvantages. Some of the disadvantages of the log-rank test include:

1. The log-rank test detects the difference only in the case of constant differences across time and it may not show the difference if the survival curves are crossed at some point (Bland & Altman, 2004).
2. The log-rank test provides a test of significance but does not provide information on the size of the difference between the two groups. Also, it cannot provide a confidence interval on the difference (Bland & Altman, 2004).

2.6 The Wilcoxon Test

Wilcoxon test is a modification of the log-rank test that can also be used to test the difference in survival between two groups. The Wilcoxon test is based on the statistics

$U_w = \sum_{j=1}^{r}\left(n_j(d_{1j} - e_{1j})\right)$ and, as such, can be seen to be a weighted version of the log-rank test. The Wilcoxon test provides weight at each time point by multiplying the number of people at risk at each event time with the difference in observed and expected number of failures. The variance of the Wilcoxon statistic is given by $V_w = \sum_{j=1}^{r} n_j^2 v_{1j}$, where:

$$v_{1j} = \frac{n_{1j} n_{2j} \left(n_j - d_j\right)}{n_j^2 \left(n_j - 1\right)}$$

which is same as in the log-rank test. The Wilcoxon test statistics is given by:

$$W_w = \frac{U_w^2}{V_w} \sim \chi_1^2 .$$

2.7 The Cox-Proportional Hazards Model

In the previous section, we discussed the use of log-rank test to conduct a hypothesis test in two different groups without adjusting for any other covariates. When we have several covariates that we wish to include in the model, the Cox Proportional hazards model may be used. The Cox-proportional hazards model allows us to control for multiple variables. The Cox-proportional hazard model, developed by D.R. Cox in 1972, is a semi-parametric approach to estimating the survival function that makes no distributional assumptions on the baseline hazard function. While there are no distributional assumptions on the model, there is an assumption on the hazard function. The assumption states that the hazards in any groups are constant over time.

The proportional hazard model for two different individuals i and j with covariate vectors x_i and x_j can be written as:

$$h_i(t) = h_0(t)\exp(\beta' x_i)$$

$$h_j(t) = h_0(t)\exp\left(\beta' x_j\right)$$

$$\frac{h_i(t)}{h_j(t)} = \frac{h_0(t)\exp(\beta' x_i)}{h_0(t)\exp(\beta' x_j)}$$

$$\frac{h_i(t)}{h_j(t)} = \exp\left(\beta'(x_i - x_j)\right) \qquad (2.7.1)$$

The ratio of the hazard function in equation (2.7.1) does not depend on time, i.e. the hazard ratio is constant regardless of the time elapsed, hence Cox's model is also called the proportional-hazard (PH) model. The only difference between parametric proportional hazard regression and the Cox proportional hazard regression model is the shape of the baseline hazard function. The baseline hazard function $h_0(t)$ is specified in parametric proportional hazard regression but not in the Cox model, hence the Cox model is also called the semi-parametric model. For estimating the parameters in the model the partial likelihood functions in Cox-proportional hazard model are given by:

$$L(\beta) = \prod_{i=1}^{n}\left\{\frac{\exp\left(\beta^T z_i\right)}{\sum_{j\in R(t_i)}\exp\left(\beta^T z_j\right)}\right\}^{\delta_i} \qquad (2.7.2)$$

Where, n denotes the total number of observations, $R(t_i) = \{j : t_j \geq t_i\}$ denotes the risk set at time t_i, δ_i is censoring variable (1 if the event of interest occurs and 0 if observation is

censored), and, $\hat{\beta}$ is the maximum (partial) likelihood estimate of β obtained by maximizing the partial log-likelihood function $l(\beta) = \ln L(\beta)$. Taking the log on both sides of equation (2.8.2) yields:

$$\ln L(\beta) = \sum_{i=1}^{n} \delta_i \left(\beta^T z_i\right) - \sum_{i=1}^{n} \delta_i \ln \left\{ \sum_{j \in R(t_i)} \exp\left(\beta^T z_j\right) \right\} \qquad (2.7.3)$$

For Cox's model, the partial likelihood equation is valid only when there are no ties in the data, i.e., when no two individuals have an event of interest at the same time. When ties are present in the dataset, the Exact, Breslow or Efron's adjustment to the likelihood is commonly used.

2.7.1 Exact Method

The exact method for adjusting for ties is based on the idea that ties are due to the imprecision in measurements and that two events of interest cannot occur at the exact same time. The method assumes different ordering for the events that occurred at the same time. For illustrating the exact method consider the example data from below:

Example data:

Patient	Time-to-event	event (1=death,0=censored)	Covariate
1	t_1	1	Z_1
2	t_2	0	Z_2
3	t_3	1	Z_3
4	t_3	1	Z_4
5	t_4	1	Z_5

Here, the first patient died at time t_1 and second patient is censored at time t_2, the third and fourth patient died exactly same time, let us say t_3. And 5th patient died at time t_4.

The partial likelihood function for patient 1 (L_1) and patient 5 (L_5) can be written as:

$$L_1 = \frac{e^{\beta z_1}}{e^{\beta z_1} + e^{\beta z_2} + e^{\beta z_3} + e^{\beta z_4} + e^{\beta z_5}} \quad \text{and} \quad L_5 = \frac{e^{\beta z_5}}{e^{\beta z_5}} = 1$$

For patient 3 and 4 the likelihood function can be written as:

$$L_3(\beta) = P(\text{observe two deaths at time } t_3) = P(A_3 \cup A_4) = P(A_3) + P(A_4)$$

$$P(A_3) = \frac{e^{\beta Z_3}}{e^{\beta Z_3} + e^{\beta Z_4} + e^{\beta Z_5}} \times \frac{e^{\beta Z_4}}{e^{\beta Z_4} + e^{\beta Z_5}}$$

$$P(A_4) = \frac{e^{\beta Z_4}}{e^{\beta Z_4} + e^{\beta Z_3} + e^{\beta Z_5}} \times \frac{e^{\beta Z_3}}{e^{\beta Z_3} + e^{\beta Z_5}}$$

$$L_3(\beta) = \frac{e^{\beta Z_3}}{e^{\beta Z_3} + e^{\beta Z_4} + e^{\beta Z_5}} \times \frac{e^{\beta Z_4}}{e^{\beta Z_4} + e^{\beta Z_5}} + \frac{e^{\beta Z_4}}{e^{\beta Z_4} + e^{\beta Z_3} + e^{\beta Z_5}} \times \frac{e^{\beta Z_3}}{e^{\beta Z_3} + e^{\beta Z_5}}$$

$$L_3(\beta) = \frac{e^{\beta Z_3}\, e^{\beta Z_4}}{\left(e^{\beta Z_4} + e^{\beta Z_5}\right)\left(e^{\beta Z_3} + e^{\beta Z_4} + e^{\beta Z_5}\right)} + \frac{e^{\beta Z_4}\, e^{\beta Z_3}}{\left(e^{\beta Z_3} + e^{\beta Z_5}\right)\left(e^{\beta Z_4} + e^{\beta Z_3} + e^{\beta Z_5}\right)}$$

$$\text{Let, } A = e^{\beta Z_3} + e^{\beta Z_4} + e^{\beta Z_5}, B = e^{\beta Z_3}, C = e^{\beta Z_4}$$

$$\text{Then, } e^{\beta Z_4} + e^{\beta Z_5} = A - B$$

$$e^{\beta Z_3} + e^{\beta Z_5} = A - C$$

$$L_3(\beta) = \frac{B}{A} \times \frac{C}{(A-B)} + \frac{C}{A} \times \frac{B}{(A-C)}$$

$$L_3(\beta)=\frac{BC}{A(A-B)}+\frac{BC}{A(A-C)}$$

$$L(\beta)=\prod_{i=1}^{n}L_i(\beta)=L_1(\beta)L_2(\beta)L_3(\beta)$$

$$L(\beta)=\frac{e^{\beta Z_1}}{e^{\beta Z_1}+e^{\beta Z_2}+e^{\beta Z_3}+e^{\beta Z_4}+e^{\beta Z_5}}\times$$

$$\left(\frac{e^{\beta Z_3}\,e^{\beta Z_4}}{\left(e^{\beta Z_4}+e^{\beta Z_5}\right)\left(e^{\beta Z_3}+e^{\beta Z_4}+e^{\beta Z_5}\right)}+\frac{e^{\beta Z_4}\,e^{\beta Z_3}}{\left(e^{\beta Z_3}+e^{\beta Z_5}\right)\left(e^{\beta Z_4}+e^{\beta Z_3}+e^{\beta Z_5}\right)}\right)\times\frac{e^{\beta Z_5}}{e^{\beta Z_5}}$$

After the likelihood $L(\beta)$ is constructed the estimation of β can be done in the same manner as in the method with no ties.

2.7.2 Breslow's and Efron's approximation to the Log Likelihood

The Breslow's approximation is based on the approximation of likelihood functions. For the example data above, the approximation can be written as:

$$\frac{e^{\beta Z_4}}{e^{\beta Z_4}+e^{\beta Z_5}}\approx\frac{e^{\beta Z_4}}{e^{\beta Z_3}+e^{\beta Z_4}+e^{\beta Z_5}}$$

$$\frac{e^{\beta Z_3}}{e^{\beta Z_3}+e^{\beta Z_5}}\approx\frac{e^{\beta Z_3}}{e^{\beta Z_3}+e^{\beta Z_4}+e^{\beta Z_5}}$$

$$P(A_3)\approx\frac{e^{\beta Z_3}}{\left(e^{\beta Z_3}+e^{\beta Z_4}+e^{\beta Z_5}\right)}\times\frac{e^{\beta Z_4}}{\left(e^{\beta Z_3}+e^{\beta Z_4}+e^{\beta Z_5}\right)}$$

$$P(A_4)\approx\frac{e^{\beta Z_4}}{\left(e^{\beta Z_3}+e^{\beta Z_4}+e^{\beta Z_5}\right)}\times\frac{e^{\beta Z_3}}{\left(e^{\beta Z_3}+e^{\beta Z_4}+e^{\beta Z_5}\right)}$$

Here, $P(A_3)$ and $P(A_4)$ are equal hence,

$$L_3(\beta) \approx \frac{e^{\beta Z_3}}{\left(e^{\beta Z_3} + e^{\beta Z_4} + e^{\beta Z_5}\right)} \times \frac{e^{\beta Z_4}}{\left(e^{\beta Z_3} + e^{\beta Z_4} + e^{\beta Z_5}\right)}$$

$$L_3(\beta) \approx \frac{e^{\beta(Z_3+Z_4)}}{\left(e^{\beta Z_3} + e^{\beta Z_4} + e^{\beta Z_5}\right)^2}$$

If there are d_j tied event times at the j^{th} distinct event time, then $L_j(\beta)$ is approximated by:

$$L_j(\beta) \approx \frac{e^{\beta \sum_{l \in D_j} Z_l}}{\left(\sum_{l \in R(j)} e^{\beta Z_l}\right)^{d_j}}$$

where $R(j)$ is the risk set at the j^{th} survival time and D_j is the event set at the j^{th} distinct failure time. So, the overall likelihood can be written as:

$$L(\beta) = \prod_{j=1}^{r} L_j(\beta) \approx \prod_{j=1}^{r} \frac{e^{\beta \sum_{l \in D_j} z_l}}{\left(\sum_{l \in R(j)} e^{\beta z_l}\right)^{d_j}}$$

Here, r is the number of total distinct events and d_j is number of events at each distinct failure time j. Breslow's approximation is preferred when the number of events d_j is small and number of person at risk n_j is large. Thus, if ties are relatively small Breslow's approximation works well, otherwise, the next approximation called Efron's approximation is better.

From the example in the Exact test:

$$L_3(\beta) = \frac{BC}{A(A-B)} + \frac{BC}{A(A-C)}$$

which can be approximated by:

$$L_3(\beta) \approx \frac{2BC}{A(A-(B+C)/2)}.$$

Based on the above equation, Efron's approximation can be written as:

$$L_3(\beta) = \frac{e^{\beta \sum_{l \in D_3} z_l}}{\prod_{j=1}^{d_3} \left(\sum_{l \in R_1} e^{\beta z_l} - \frac{j-1}{d_3} \sum_{l \in D_3} e^{\beta z_l} \right)}$$

2.7.3 Hypothesis Testing in Cox-Proportional Hazards Model:

There are three main global tests for hypotheses about the regression parameters β, where β is a *p*-dimensional column vector of regression parameters. For testing the null hypothesis $H_0 : \beta = \beta_0$, first define $\hat{\beta} = (\hat{\beta}_1, ..., \hat{\beta}_p)$ as partial maximum likelihood estimate of β. Let $I(\beta)$ be the $p \times p$ information matrix calculated by taking the second derivative of the log likelihood function of β, it can be written as:

$$I(\beta) = -E\left(\frac{\partial^2 \ln L(\beta)}{\partial \beta^2} \right)$$

2.7.3.1 Wald Test for Multiple Parameters:

For large samples the Wald test is based on the asymptotic distribution of $\hat{\beta}$, i.e., $\hat{\beta}$ follows *p*-variate normal distribution with mean $E(\hat{\beta}) = \beta$ and $Var\left(\hat{\beta}\right) = I^{-1}\left(\beta\right)$. For testing $H_0 : \beta = \beta_0$, the Wald test statistics may be written as:

$$\chi_W^2 = \left(\hat{\beta} - \beta_0\right)^T I\left(\hat{\beta}\right)\left(\hat{\beta} - \beta_0\right)$$

where $\hat{\beta}$ is the maximum likelihood estimate (MLE) and $I\left(\hat{\beta}\right)$ is expected Fisher information evaluated at the MLE $\hat{\beta}$, χ_w^2 follows an asymptotic χ^2 distribution with p degrees of freedom under H_0.

2.7.3.2 Likelihood Ratio Test for Multiple Parameters:

For testing $H_0 : \beta = \beta_0$, the likelihood ratio test is given by:

$$\chi_{LR}^2 = 2\left(\text{LogL}(\hat{\beta}) - \text{LogL}(\beta_0)\right)$$

where $\text{LogL}\left(\hat{\beta}\right)$ is the log likelihood of β evaluated at the MLE $\hat{\beta}$, and $\text{LogL}\left(\beta_0\right)$ is log likelihood of β evaluated at the null value β_0. χ_{LR}^2 follows an asymptotic chi-square distribution with *p* degrees of freedom under H_0.

2.7.3.3 Score Test for Multiple Parameters:

The score test is based on the vector of efficient scores $U(\beta)$, where $U(\beta)=\left(U_1(\beta),\mathrm{U}_2(\beta),...,U_p(\beta)\right)$. The scores are calculated by taking the first derivative of the log likelihood function of β.

$$U(\beta)=\frac{d\ln L(\beta)}{d\beta}$$

In Cox-partial log likelihood the scores are given by:

$$U(\beta)=\frac{d\left(\sum_{i=1}^{n}\delta_i\left(\beta^T z_i\right)-\sum_{i=1}^{n}\delta_i\ln\left\{\sum_{j\in R(t_i)}\exp\left(\beta^T z_j\right)\right\}\right)}{d\beta}$$

$$=\sum_{i=1}^{n}\delta_i z_i-\sum_{i=1}^{n}\delta_i\frac{\sum_{j\in R(t_i)}\exp\left(\beta^T z_j\right)z_j}{\sum_{j\in R(t_i)}\exp\left(\beta^T z_j\right)}$$

where $i=1,...,n$ is number of subjects in the study and $j\in R(t_i)$ is number of people at risk at time t_i.

$$U_k(\beta)=\frac{d\ln L(\beta)}{d\beta_k}\text{ for }k=1,...,p$$

For large samples, $U(\beta)$ is asymptotically distributed *p*-variate normal with mean 0 and covariance $I(\beta)$. For testing $H_0:\beta=\beta_0$ the score test statistic is given by $\chi^2_{SC}=U(\beta_0)^T I^{-1}(\beta_0)U(\beta_0)$, which follows χ^2 distribution with p degrees of freedom under the null hypothesis.

For testing a hypothesis about a subset of the $\beta's$, the null hypothesis is $H_0 : \beta_1 = 0$ where β is partitioned as $\beta = (\beta_1, \beta_2)$. There are three types of local tests named the Likelihood Ratio, Wald and Score tests.

2.7.3.4 Likelihood Ratio Test for Subset of Parameters:

The likelihood ratio test statistics for $H_0 : \beta_1 = 0$ is given by:

$$\chi^2_{LR} = 2\text{LogL}\left(\hat{\beta}\right) - 2\text{LogL}\left(\hat{\beta}_0\right)$$

where, $\hat{\beta}_0 = \left(0^T, \hat{\beta}_2^T(0)\right)^T$, 0 is $q \times 1$ dimensional vector and $\hat{\beta}_2(0)$ is the $(p-q)\times 1$ dimensional vector. For this case, $\hat{\beta}_2(0)$ is also called restricted partial maximum likelihood estimate for β_2, since it can be obtained by substituting the null hypothesis value $\beta_1 = 0$ in the partial log-likelihood function. The asymptotic distribution of the likelihood ratio test statistics is chi-square with *q* degrees of freedom $\left(\chi^2_q\right)$ under null hypothesis. This can be written as:

$$\chi^2_{LR} = 2\left[\text{LogL}\left(\hat{\beta}_{(p\times 1)}\right) - \text{LogL}\left(0_{(q\times 1)}, \hat{\beta}_{2((p-q)\times 1)}(0)\right)\right] \sim \chi^2_q.$$

p-values may be calculated by $P\left(\chi^2_q > \chi^2_{LR}\right)$.

2.7.3.5 Wald Test for Subset of Parameters:

Let $\hat{\beta} = \left(\hat{\beta}_1^T, \hat{\beta}_2^T\right)^T$ be the maximum partial likelihood estimate of the full parameter vector $\beta = \left(\beta_1^T, \beta_2^T\right)^T$. The variance of β is the inverse of the observed

information evaluated at $\hat{\beta}$, i.e., $Var(\hat{\beta}) = I\left(\hat{\beta}\right)^{-1}$. The observed information matrix $I(\beta)$ is given by the negative of the second derivative of log-likelihood function or:

$$I(\beta) = -\frac{d^2 l}{d\beta^2}$$

$$= -\frac{d^2\left(\sum_{i=1}^{n}\delta_i\left(\beta^T z_i\right) - \sum_{i=1}^{n}\delta_i \ln\left\{\sum_{j\in R(t_i)}\exp\left(\beta^T z_j\right)\right\}\right)}{d\beta^2}$$

Next, the variance of β (inverse of information matrix $I(\beta)$) is partitioned into:

$$I^{-1}(\beta) = \begin{pmatrix} I^{11}(\beta) & I^{12}(\beta) \\ I^{21}(\beta) & I^{22}(\beta) \end{pmatrix}$$

where, $I^{11}(\beta)$ is $q \times q$ submatrix of $I^{-1}(\beta)$ and $I^{22}(\beta)$ is $(p-q)\times(p-q)$ submatrix of $I^{-1}(\beta)$. Finally, the Wald test statistics for $H_0 : \beta_1 = 0$ is given by:

$$\chi_W^2 = \left(\hat{\beta}_1 - 0\right)^T \left[I^{11}(\hat{\beta})\right]^{-1}\left(\hat{\beta} - 0\right).$$

Under the null hypothesis, the Wald statistics is distributed as an asymptotic chi-square with *q* degrees of freedom $\left(\chi_q^2\right)$.

2.7.3.6 Score Test for Subset of Parameters:

Let $U_1(\beta)$ denote the first $q \times 1$ vector of score function $U(\beta)$, where $U(\beta)$ is defined as the first derivative of log likelihood function $l(\beta)$ and can be written as:

$$U(\beta) = \frac{dl}{d\beta}$$

The score test statistics for $H_0 : \beta_1 = 0$ is given by:

$$\chi^2_{SC} = U_1\left(0, \hat{\beta}_2(0)\right)^T I^{11}\left(0, \hat{\beta}_2(0)\right) U_1\left(0, \hat{\beta}_2(0)\right).$$

Here, $U_1\left[0, \hat{\beta}_2(0)\right]$ is the $q \times 1$ vector of scores for β_1 evaluated at $\beta_1 = 0$ and the restricted partial MLE $\hat{\beta}_2$. Here, $I^{11}\left(0, \hat{\beta}_2(0)\right)$ is the upper $q \times q$ submatrix of $I(\beta_0)^{-1}$ evaluated at $\beta_1 = 0$ and restricted partial MLE $\hat{\beta}_2$. The large sample distribution of the score test statistics under the null hypothesis is χ^2_q.

2.8 Parametric Models

We have reviewed non-parametric estimation of the survival function (empirical survival function, Kaplan-Meier estimation) and semi-parametric methods of estimating the survival function (the Cox proportional Hazards model). If the assumption of a particular probability distribution for the data is valid, inferences based on such assumption will be stronger. Models in which a specific probability distribution is assumed for the observed survival times are known as parametric models.

The two most commonly used parametric models are the Weibull distribution and the exponential distribution, which is a special case of the Weibull distribution. Other common parametric distributions used are the log-normal distribution, the log-logistic distribution, the gamma distribution and the generalized gamma distribution.

2.8.1 The Exponential Distribution:

The Exponential distribution assumes that the hazard is constant over time. That is, the hazard of failure at any time after the beginning of the study is same regardless of how much time has elapsed.

The hazard function for exponential distribution is given by:

$$h(t) = \lambda \text{ for } 0 \le t < \infty$$

where λ is a positive constant. Thus, we get:

$$S(t) = \exp(-H(t)) = \exp(-\int_0^t h(u)du) = \exp(-\int_0^t \lambda du) = \exp(-\lambda t) = e^{-\lambda t}.$$

Using the previously described relationship between the p.d.f., survival function and hazard function, the p.d.f. is:

$$f(t) = h(t)S(t) = \lambda e^{-\lambda t} \text{ for } 0 \le t < \infty.$$

For the exponential model, the mean lifetime may be written as:

$$E(T) = \int_0^\infty uf(u)du = \int_0^\infty S(\mathrm{u})du = \int_0^\infty e^{-\lambda u}du = \frac{e^{-\lambda u}}{-\lambda}|_0^\infty = \frac{1}{\lambda}(e^{-0} - e^{-\infty}) = \frac{1}{\lambda}(1-0) = \frac{1}{\lambda}.$$

This gives the mean of the exponential distribution as: $\frac{1}{\lambda}$

The *p*th quantile of the distribution of *T* is the smallest value of t $\left(\text{denoted by } t_p\right)$ is such that $S\left(t_p\right) \le 1 - p.$ It may also be written as: $t_p = \inf\left\{t : S(t) \le 1 - p\right\}$. The *p*th percentile of the exponential survival distribution is given by:

$$t_p = \inf\left\{t : e^{-\lambda t} \le 1-p\right\} = \inf\left\{t : -\lambda t \le \log(1-p)\right\}$$

$$= \inf\left\{t : \lambda t \ge \log(\frac{1}{1-p})\right\} = \inf\left\{t : t \ge \frac{1}{\lambda}\log\left(\frac{1}{1-p}\right)\right\}.$$

Hence, the *p*th percentile of the exponential survival distribution for *p*=0.5 (median) is:

$$t(p) = \frac{1}{\lambda}\log\left(\frac{1}{1-p}\right)$$

$$t_{0.5} = \frac{1}{\lambda}\log\left(\frac{1}{0.5}\right) = \frac{1}{\lambda}\log(2) = \frac{1}{\lambda} * 0.693.$$

2.8.2 The Weibull Distribution

The hazard function of the Weibull distribution is given by $h(t) = \lambda\gamma t^{\gamma-1}$ for $0 \le t < \infty$. This hazard function depends on the shape parameter γ and scale parameter λ. Note that when γ = 1, the hazard function for the Weibull distribution reduces to the constant hazard function for the exponential distribution. The survival function for Weibull distribution is given by:

$$S(t) = \exp\left(-\int_0^t \lambda\gamma u^{\gamma-1} du\right) = \exp\left(-\lambda\int_0^t \gamma u^{\gamma-1} du\right)$$

$$= \exp\left(-\lambda\gamma \frac{u^{\gamma-1+1}}{\gamma-1+1}\Big|_0^t\right) = \exp\left(-\lambda u^{\gamma}\Big|_0^t\right) = \exp\left(-\lambda t^{\gamma}\right).$$

The density function of random variable *T* that has Weibull distribution is given by:

$$f(t) = h(t)S(t) = \lambda\gamma t^{\gamma-1} e^{-\lambda t^{\gamma}} \quad \text{for } 0 \le t < \infty.$$

Without proving the result, we note that the mean of random variable *T* that has a Weibull distribution is given by:

$$E(T) = \lambda^{\frac{-1}{\gamma}} \Gamma(\gamma^{-1} + 1).$$

The p^{th} percentile of Weibull distribution is given by:

$$t(p) = \left\{ \frac{1}{\lambda} \log\left(\frac{1}{1-p} \right) \right\}^{\frac{1}{\gamma}}$$

Other parametric models are the log-normal distribution, the log-logistic distribution and the gamma distribution. All these distributions can be used to find the hazard rate or survival rate when the population is homogeneous. If we want to calculate the survival rate in heterogeneous population, we need to account for the different covariates such as age, weight, blood pressure, gender, race, treatment group etc. The simplest parametric model using a classical linear regression approach is the accelerated failure time model or AFT.

2.9 The Accelerated Failure Time Model (AFT)

Survival models that can be linearized by taking logs of the survival time *T* are called accelerated failure time models. The reason this terminology is used is that the effect of the covariate is multiplicative on the time scale whereas in the PH model the effect of covariates is multiplicative on the hazard function.

Let, $Y = \log(T)$, then the linear model for Y is given by: $Y = \beta' Z + \sigma W$, where W is a random error distribution. If the error distribution is normal the resulting model is the log-normal regression model. If we assume the error distribution is the extreme value distribution it will yield either the exponential or Weibull regression model.

As stated previously, the Weibull regression model is the most commonly used parametric distribution. Let $Z = \left(Z_1, ..., Z_p\right)'$ is a matrix of *p* explanatory variables. Assuming an intercept for every individual, if $Z_1 = 1 \Rightarrow \beta = \left(\mu, \beta_1, \beta_2, ..., \beta_{p-1}\right)$ is a *p*-dimensional vector of regression parameters. When there are no covariates in the model, $\log(T)$ is given by:

$$\log(T) = \mu + \sigma W$$

$$T = \exp\left(\mu + \sigma W\right)$$

If there are covariates in the model, the survival function can be written as:

$$\Pr(T \geq t / Z) = \Pr\left(\log(T) \geq \log(t) / Z\right)$$

$$S(t / Z) = \Pr\left(Y \geq \log(t) / Z\right)$$

$$S(t / Z) = \Pr(\mu + \beta' Z + \sigma W \geq \log(t) / Z)$$

$$S(t / Z) = \Pr\left(\mu + \sigma W \geq \log(t) - \beta' Z / Z\right)$$

$$S(t / Z) = \Pr(\exp(\mu + \sigma W) \geq \exp(\log(t) - \beta' Z) / Z)$$

$$S\left(t / Z\right) = \Pr\left(\exp(\mu + \sigma W) \geq t \exp(-\beta' Z) / Z\right) \qquad (2.9.1)$$

For no covariate in the model survival function is given by:

$$\Pr\left(T \geq t\right) = \Pr\left(\log T \geq \log t\right)$$

$$= \Pr\left(\mu + \sigma W \geq \log t\right)$$

$$= \Pr\left(\exp\left(\mu + \sigma W\right) \geq t\right)$$

$$\Pr\left(T \geq t\right) = S_0\left(t\right) \qquad (2.9.2)$$

From equations (2.9.1) and (2.9.2) we can write:

$$S(t / \mathrm{Z}) = S_0\left(t \exp\left(-\beta' \mathrm{Z}\right)\right)$$

As stated previously, since the original time scale is multiplied by the acceleration factor $\exp(-\beta' Z),$ this model is also called the Accelerated Failure Time model or AFT. Depending upon the sign of $\beta' \mathrm{Z}$ the time is either accelerated by a constant factor or de-accelerated by a constant factor. This model can also be written in terms of hazard function as:

$$H_0\left(t \exp(-\beta' \mathrm{Z}\right) = -\log\left(S_0(t \exp(-\beta' \mathrm{Z}))\right)$$

$$\frac{\partial H_0\left(t \exp(-\beta' \mathrm{Z})\right)}{\partial t} = \frac{\partial H_0\left(t \exp(-\beta' \mathrm{Z})\right)}{\partial (t \exp(-\beta' Z))} \frac{\partial t \exp(-\beta' Z)}{\partial t}$$

$$= h_0(t \exp(-\beta' Z)) \exp(-\beta' Z). \qquad (2.9.3)$$

This is the relationship of an individual with a covariate vector Z to the baseline hazard rate. It should be noted that in the Cox-Proportional hazards model, the impact of covariate is multiplicative on the hazard while in the AFT model the impact of covariate is multiplicative on time.

2.10 Residuals in Survival Analysis

As in regression analysis, we need some diagnostic tools for our models in survival analysis. The four main reasons for diagnostic tests are:

1) Testing goodness of fit of the model;
2) Testing if the assumptions of the model are valid;

3) Testing the functional form of the covariate, such as if the covariates need any kind of transformation. For example: log, square root , or if the covariate needs to be categorized; and
4) Testing for presence of outliers.

Although residuals for survival are not as simple as linear regression because of the censoring involved, there are some commonly recognized residuals used for diagnostic purposes. The residuals used for diagnostic purposes differ depending on if we are using the proportional hazard (PH) or AFT model. For the PH model, the commonly used residuals include:

1) Cox-Snell residuals;
2) Martingale residuals;
3) Deviance residuals; and
4) Score residual

2.10.1 Cox-Snell Residuals for the Cox Proportional Hazards Model

Cox-Snell residuals are useful for finding the goodness of fit of the model. The hazard rate for Cox proportional hazard is given by:

$$h_i(t) = h_0(t)\exp(\beta X)$$

Integrating on both sides

$$\int_0^t h_i(u)du = \int_0^t h_0(u)\exp(\beta X)du$$

$$\int_0^t h_i(u)du = \exp(\beta X)\int_0^t h_0(u)du$$

$$H_i(t) = H_0(t)\exp(\beta' X)$$

The estimated cumulative hazard function is given by:

$$\hat{H}_i(t) = \hat{H}_0(t)\exp(\hat{\beta}' X)$$

$$r_{c_i} = \hat{H}_0(t)\exp(\hat{\beta} X) \qquad (2.10.1)$$

Based on equation (2.10.1), the Cox-Snell residual given by r_{c_i} is the estimated cumulative hazard. If the model fits appropriately, the Cox-Snell residual are the censored sample from a unit exponential distribution. The relationship is illustrated below:

The survival function for a Cox proportional hazard model is given by:

$$\Pr(T \geq t) = S(t) = \exp(-H(t))$$

$$S(t) = \exp\left(-\int_0^t h_0(u)\exp(\beta X)du\right)$$

If the baseline hazard is given by an exponential parameter λ then the survival function is:

$$S(t) = \exp(-\lambda \exp(\beta X)t)$$

If U is uniformly distributed on $(0,1)$ then $(1-U)$ is also uniformly distributed on $(0,1)$.

The cumulative distribution function (c.d.f.) for a random variable T is given by:

$$F(T < t) = F(t).$$

From the Probability integral transformation theorem (Casella and Berger, 2002),

$F_T(t) = U$ if U is uniformly distributed on $(0,1)$. Also,

$$F_T(t) = (1-U)$$

$$S(t) = U$$

$$\exp\left(-\lambda \exp\left(\beta X\right)t\right) = U$$

$$-\log\left(U\right) = \lambda \exp\left(\beta X\right)t\,.$$

If we consider, after replacing λ and β by the estimates $\hat{\lambda}$ and $\hat{\beta}$, the random variable U still follows uniform distribution on $(0,1)$ for a large sample, then we can write:

$$-\log(U) = \hat{\lambda} \exp\left(\hat{\beta} X\right)$$

$$-\log\left(U\right) = r_{c_i}$$

Let $y = -\log(U)$

$$U = \exp(-\mathrm{y})$$

$$f(y) = f(U)\left|\frac{dU}{dy}\right| = 1.\left|\frac{d\exp(-y)}{dy}\right| = e^{-y}\,.$$

This is the p.d.f. of the unit exponential distribution. Because of the exponential distribution, Cox-Snell residuals are not symmetrically distributed about zero. The value of the Cox-Snell residuals range from 0 to ∞.

2.10.2 Martingale Residuals for the Cox Proportional Hazards Model:

Consider the counting process $N_i(t)$ as the number of observed events for the ith subject over time t. The intensity function for $N_i(t)$ is given by:

$$Y_i(t)\,d\Lambda\{t, Z_i(t)\} = Y_i(t)e^{\beta' Z_i(t)}d\Lambda_0(t)$$

where $Y_i(t) = \begin{cases} 1 & \text{if the } i\text{th subject is still at risk at time } t \\ 0 & \text{if the event has already occured} \end{cases}$, $\beta =$ vector of regression coefficients, $Z_i(t) = p$ dimensional vector of covariate processes, and $\Lambda_0 =$ Baseline cumulative hazard function.

Let $M_i(.)$ be a subject specific martingale defined as the difference between the counting process and the integrated intensity function (Therneau et al., 1990):

$$M_i(t) = N_i(t) - \int_0^t Y_i(s)\exp(\beta' Z_i(\mathrm{s}))d\Lambda_0(s) \quad (i = 1,...,\mathrm{n})$$

Let $\hat{\beta}$ be the maximum partial likelihood estimate of β and $\hat{\Lambda}_0$ is the Breslow estimate of the baseline cumulative hazard Λ_0 defined by:

$$\hat{\Lambda}_0(t) = \int_0^t \frac{\sum dN_i(s)}{\sum Y_j(s)e^{\hat{\beta}' Z_j(s)}}$$

Then the martingale residual are given by:

$$\hat{M}_i(t) = N_i(t) - \int_0^t Y_i(s)\exp(\hat{\beta}' Z_i(s)d\hat{\Lambda}_0(s).$$

The martingale residual at each time t is the excess number of events or deaths, defined as the difference in the number of observed events minus the expected number of events. The properties of martingale residual are as follows:

1. The sum of martingale residual is 0, i.e. $\sum_{i=1}^{n} \hat{M}_i(t) = 0, \text{for any t.}$;

2. The martingale residual for each individual is independent; that is:

$$\text{cov}(\hat{M}_i, \hat{M}_j) = 0, \text{ for each } i \neq j, \text{ where } \hat{M}_i = \hat{M}_i(\infty)$$

3. For a PH model the martingale residual is given by:

$$\hat{M}_i = \delta_i - \hat{\Lambda}_0(\tau_i)\exp\left(\hat{\beta}' Z_i(s)\right),$$

where $\delta_i = \begin{cases} 1 & \text{if event occurs} \\ 0 & \text{otherwise} \end{cases}$.

We know from the previous section that the Cox-Snell residual are given by:

$$r_{c_i} = \hat{\Lambda}_0(\tau_i)\exp\left(\hat{\beta} Z_i(s)\right)$$

$$\hat{M}_i = \delta_i - r_{c_i} \qquad (2.10.2)$$

From equation (2.10.2), it can be seen that the martingale residual is simply a linear transformation of Cox-Snell residual. The maximum value of the martingale residual can be +1 and minimum value can be $-\infty$. Similar to the Cox-Snell residuals, the martingale residuals have skewed distribution.

2.10.3 Score Residuals for the Cox Proportional Hazards Model:

The Score residuals are the first derivative with respect to the coefficient β_j for the partial log-likelihood of Cox-proportional hazard. That is,

$$\left[\frac{d \log L_p}{d\beta_j}\right]_{\beta=\hat{\beta}} = \sum_{i=1}^{n}\int_0^{\infty}\left\{Z_{ij}(s) - \bar{Z}_j(\hat{\beta}, s)\right\}dN_i(s)$$

$$= \sum_{i=1}^{n}\int_0^{\infty}\left\{Z_{ij}(s) - \bar{Z}_j(\hat{\beta}, s)\right\}d\hat{M}_i(s)$$

$$= \sum_{i=1}^{n} S_{ij}(\hat{\beta}, \infty)$$

$$\text{where} \quad \bar{Z}_j\left(\hat{\beta}, s\right) = \frac{\sum_{i=1}^{n}\left\{Y_i(s)e^{\hat{\beta}' Z_i(s)}Z_{ij}(s)\right\}}{\sum_{i=1}^{n}Y_i(s)e^{\hat{\beta}' Z_i(s)}} \quad \text{for } j = 1,..., p$$

Here, $\bar{Z}_j\left(\hat{\beta}, s\right)$ is a weighted mean of the covariates over the risk set at time s. According to Klein and Moeschberger (2003), $U_j(\hat{\beta}, t) = \sum_{i=1}^{n} S_{ij}\left(\hat{\beta}, t\right)$ is the score process for the jth covariate and $S_{ij}\left(\hat{\beta}, \infty\right) = \int_0^{\infty}\left\{Z_{ij}(\mathrm{s}) - \bar{Z}_j(\hat{\beta}, s)\right\}d\hat{M}_i(s)$ is the score residual for the ith subject and the jth covariate (Therneau et al., 1990). The score residual can be useful in finding each subject's leverage on parameter estimates $\hat{\beta}$. These residuals are also useful in the assessment of the proportional hazard model assumption. The score residuals sum to zero. By the definition of $\hat{\beta}$, $U_j(\hat{\beta}, 0) = U_j(\hat{\beta}, \infty) = 0.$

2.10.4 Deviance Residuals for the Cox Proportional Hazards Model:

To overcome the skewness in the martingale residuals, the deviance residuals allow some transformation to get the symmetrical distribution. The deviance residuals are based on the deviance statistics given by:

$$D = -2\left\{\log\hat{\mathrm{L}}_c - \log\hat{\mathrm{L}}_f\right\}$$

where $\hat{L}_c$ is the maximized partial likelihood under the current model and $\hat{L}_f$ is the maximized partial likelihood under the full model. If model fits appropriately, the deviance would be smaller. The deviance residual are defined as:

$$D_i = \text{sign}\left(\hat{M}_i\right)\left[-2\left\{\hat{M}_i + \delta_i \log\left(\delta_i - \hat{M}_i\right)\right\}\right]^{\frac{1}{2}} \qquad (2.10.4)$$

where $\hat{M}_i$ is the martingale residual defined earlier in chapter $2.10.2$ and the $\text{sign}(\ )$ is the sign function; that is:

$$\text{sign}(x) = \begin{cases} +1 \text{ if } x \geq 0 \\ -1 \text{ if } x < 0 \end{cases}$$

The deviance residual has value 0 when martingale residual is zero. The deviance residuals provide the more symmetrical values in comparison to the martingale residuals.

2.11 Residuals in Accelerated Failure Time (AFT) Model

For the AFT model, some commonly used residuals are:

1. Standardized residuals
2. Cox-Snell residuals
3. Score residuals

2.11.1 Standardized Residuals:

If T_i is a random variable associated with the survival time for the ith subject and $x_{1i},...,x_{pi}$ are observed values of p-covariates $X_{1i}, X_{2i},..., X_{pi}$, then the AFT model for T_i is given by:

$$\log(T_i) = \mu + \alpha_1 x_{1i} + ... + \alpha_p x_{pi} + \sigma W_i$$

where W_i is a random variable and also called the error distribution. The distribution of W_i depends on the distribution of survival time T_i. For example, if T_i is distributed as Weibull distribution then W_i will have a standard extreme value distribution. Here, μ and σ are

intercept and scale parameter, respectively and $\alpha_1,...,\alpha_p$ are the unknown coefficients of the values of p explanatory variables. If $\hat{\mu},\hat{\alpha}_1,...,\hat{\alpha}_p$ and $\hat{\sigma}$ are the maximum likelihood estimates for the unknown parameters then the standardized residual is defined by:

$$r_{s_i} = \left(\frac{\log(t_i) - \hat{\mu} - \hat{\alpha}_1 x_{1i} - ... - \hat{\alpha}_p x_{pi}}{\hat{\sigma}} \right)$$

Although the standardized residuals are the simplest and most closely related with the residuals in the linear regression by same relation as in the 'observed-fitted values of outcome variable' these residuals are not adjusted for censoring. Standardized residuals will have the same distribution as that of the error distribution W_i, if the model were correct.

2.11.2 Cox-Snell Residuals in Parametric Model

The Cox-Snell residuals in the Cox-proportional hazard were given by the estimated values of the cumulative hazard, which can be written as:

$$r_{c_i} = -\log \hat{S}_i(t_i) \qquad (2.11.2)$$

where, t_i is the event time for the ith individual. The estimated survival function for the ith individual in the AFT model is given by:

$$\hat{S}_i(t_i) = p(T_i \geq t_i)$$

$$\hat{S}_i(t_i) = p\left(\log(T_i) \geq \log(t_i)\right)$$

$$\hat{S}_i(t_i) = p\left(\hat{\mu} + \hat{\alpha}_1 x_{1i} + ... + \hat{\alpha}_p x_{pi} + \hat{\sigma} W_i \geq \log(t_i)\right)$$

$$\hat{S}_i(t_i) = p\left(W_i \geq \left(\frac{\log(t_i) - \hat{\mu} - \hat{\alpha}_1 x_{1i} - ... - \hat{\alpha}_p x_{pi}}{\hat{\sigma}} \right) \right) = p\left(W_i \geq r_{S_i} \right)$$

$$\hat{S}_i(t_i) = S_{W_i}\left(r_{s_i} \right). \qquad (2.11.3)$$

From equations $(2.11.2)$ and $(2.11.3)$:

$$r_{C_i} = -\log \hat{S}_i(t_i) = -\log S_{W_i}(r_{S_i}) .$$

The Cox-Snell residual for AFT can also be used to assess the goodness of fit of the model. As previously proved in the Cox-Snell residual for Cox proportional hazard, if the model is correct the Cox-Snell residual will be distributed as unit exponential distribution.

2.11.3 Score Residuals for Parametric Model

The score residuals in parametric model are similar to the score residual for the PH model. These residuals are calculated by taking the partial derivative of the log-likelihood function. The likelihood function for the random variable W_i is given by:

$$L(\alpha, \mu, \sigma) = \prod_{i=1}^{n} \left((\sigma t_i)^{-\delta_i} \left\{ f_{W_i}(z_i) \right\}^{\delta_i} \left\{ S_{W_i}(z_i) \right\}^{1-\delta_i} \right)$$

$$\log L(\alpha, \mu, \sigma) = \sum_{i=1}^{n} -\delta_i \log(\sigma t_i) + \delta_i \log\left(f_{W_i}(z_i) \right) + (1-\delta_i) \log S_{W_i}(z_i)$$

where $z_i = \left(\log t_i - \mu - \alpha_1 x_{1i} - ... - \alpha_p x_{pi} \right) / \sigma$, $f_{W_i}(z_i)$ and $S_{W_i}(z_i)$ are the density and survival functions of W_i, and δ_i is the event indicator for the ith observation, given by:

$$\delta_i = \begin{cases} 1 \text{ if event} \\ 0 \text{ otherwise} \end{cases} .$$

If the survival times are assumed to have a Weibull distribution, then the log-likelihood function is given by:

$$\log L(\alpha,\mu,\sigma)=\sum_{i=1}^{n}\left\{\begin{array}{l}\delta_i\log\left(\exp\left(z_i-\exp\left(z_i\right)\right)\right)+\\(1-\delta_i)\log\left(\exp\left(-\exp\left(z_i\right)\right)\right)-\delta_i\log\left(\sigma t_i\right)\end{array}\right\}$$

$$=\sum_{i=1}^{n}\delta_i\left(z_i-\exp\left(z_i\right)\right)+(1-\delta_i)\left(-\exp\left(z_i\right)\right)-\delta_i\log\left(\sigma t_i\right)$$

$$=\sum_{i=1}^{n}\delta_i z_i-\exp\left(z_i\right)-\delta_i\log\left(\sigma t_i\right).$$

Differentiating with respect to α,μ and σ:

$$\frac{\partial\log L}{\partial\mu}=\sum_{i=1}^{n}\delta_i\left(\frac{-1}{\sigma}\right)+\frac{1}{\sigma}\exp\left(z_i\right)$$

$$=\sum_{i=1}^{n}\frac{1}{\sigma}\left\{\exp\left(z_i\right)-\delta_i\right\} \qquad (2.11.4)$$

$$\frac{\partial\log L}{\partial\sigma}=\sum_{i=1}^{n}\left\{\delta_i z_i\left(\frac{-1}{\sigma}\right)-\exp\left(z_i\right)z_i\left(\frac{-1}{\sigma}\right)-\frac{\delta_i}{\sigma}\right\}$$

$$=\sum_{i=1}^{n}\left\{z_i\left(\frac{-1}{\sigma}\right)\left(\delta_i-\exp\left(z_i\right)\right)-\frac{\delta_i}{\sigma}\right\}$$

$$=\sum_{i=1}^{n}\frac{1}{\sigma}\left\{\left(\exp\left(z_i\right)-\delta_i\right)z_i-\delta_i\right\} \qquad (2.11.5)$$

$$\frac{\partial\log L}{\partial\alpha_j}=\sum_{i=1}^{n}\delta_i\frac{(-x_{1i})}{\sigma}-\exp\left(z_i\right)\left(\frac{-x_{1i}}{\sigma}\right)\ \text{for}\ j=1,\ldots,p$$

$$=\sum_{i=1}^{n}\frac{x_{1i}}{\sigma}\left(\exp\left(z_i\right)-\delta_i\right) \qquad (2.11.6)$$

The *i*th component of each derivative, evaluated at the maximum likelihood estimates of the unknown parameters, is then called the score residual for the corresponding parameter.

We discussed the residuals in both the PH model and AFT model. Residuals in the model were used for finding the functional form, model validity, leverage, and fit of individual subjects by Therneu et al. (1990). The main goal of presenting these residuals in this Chapter is to describe the methods to compute different residuals, since the method proposed in the following chapters will be based on the residuals.

CHAPTER 3: REVIEW OF EXISTING LITERATURE

3.1 Motivation

In clinical or medical settings when the relationship between covariates and outcome is not known or if the relationship is non-linear, categorizing a continuous variable into different groups can assist in the interpretation of the result. Although a continuous variable can be categorized into many groups depending on the nature of the study and types of covariates, dichotomizing the continuous covariate into high and low risk group is a common practice in the clinical literature. In these instances, the question arises as to the appropriate cutpoint to bifurcate the continuous covariate.

3.2 Use of Categorization in Clinical Studies

In spite of the fact that dichotomizing a continuous covariate is controversial ostensibly due to statistical reasons such as loss of information or existence of linear relationship, categorization is commonly done in the medical literature. For example, blood pressure, body mass index and cholesterol are some of the variables where patients are categorized into different groups depending on the value of these variables below the cutoff point or higher than the cutoff point. To reduce the controversy among statisticians, graphical strategies have been proposed examining the relationships between the outcome and independent variable to inform decisions whether or not to categorize. If the graphical display between outcome and independent variables shows a linear relationship then

categorization may not be required; however if the graphical display shows a clear non-linear relationship then categorization may be appropriate and effective for interpretation of the relationship.

3.3 Review of Existing Methods

Current methods for the dichotomization of a continuous covariate in the literature vary. However, the methods generally coalesces around four basic approaches; 1) graphical selection of a cutpoint; 2) use of prior information to select a cutpoint; 3) data-oriented methods; or 4) output oriented methods.

3.3.1 Graphical Methods

The use of different forms of the residuals, such as martingale and score residuals, from semiparametric proportional hazard model were used to describe the functional form of a covariate vector by Therneau et al. (1990).

3.3.1.1 Example of Graphical Methods on a Simulated Data:

In Chapter 5, a dataset with four variables was simulated. The four variables were ID, censor, age and time, where id indicates unique ID for each participant, $\text{censor} = 0$ if the event of interest occurred, 1 if censored (event of interest did not occur or was not observed). Age was simulated uniformly in the interval 0 to 90 using the "ranuni" function in SAS. The survival time t was simulated using the formula $t = \left(\frac{-\log(u)}{\lambda \exp(\beta_1 x)} \right)^{\frac{1}{\gamma}}$

if $\text{age} \le 25$ and $t = \left(\frac{-\log(u)}{\lambda \exp(\beta_2 x)} \right)^{\frac{1}{\gamma}}$ if $\text{age} > 25$, where u was a uniformly distributed random variable in $(0,1)$, and λ was scale parameter, γ was the shape parameter, β_1 and β_2 were parameters of covariate age. Mean age was 41.02, minimum age was 1 and maximum age was 88 in the dataset. No censoring was applied and considered that all participants experienced the event of interest before the end of study. The value of β_1 was 0 which indicates the risk ratio was constant per unit increase in age before age 25, and the value of β_2 was 0.09531, after age 25, which indicates the risk ratio increases by $\exp(0.09531) = 1.10$ units i.e. 10% per unit increase in age.

To illustrate the use of plots, Martingale residuals for covariate age were calculated using Cox proportional hazards model. A plot of martingale residual versus covariate vector age is shown below in Figure 3.1. For this plot LOESS smoothing parameter of 0.30 was chosen after looking at different smoothing parameter since the results can vary based on different values of the smoothing parameter.

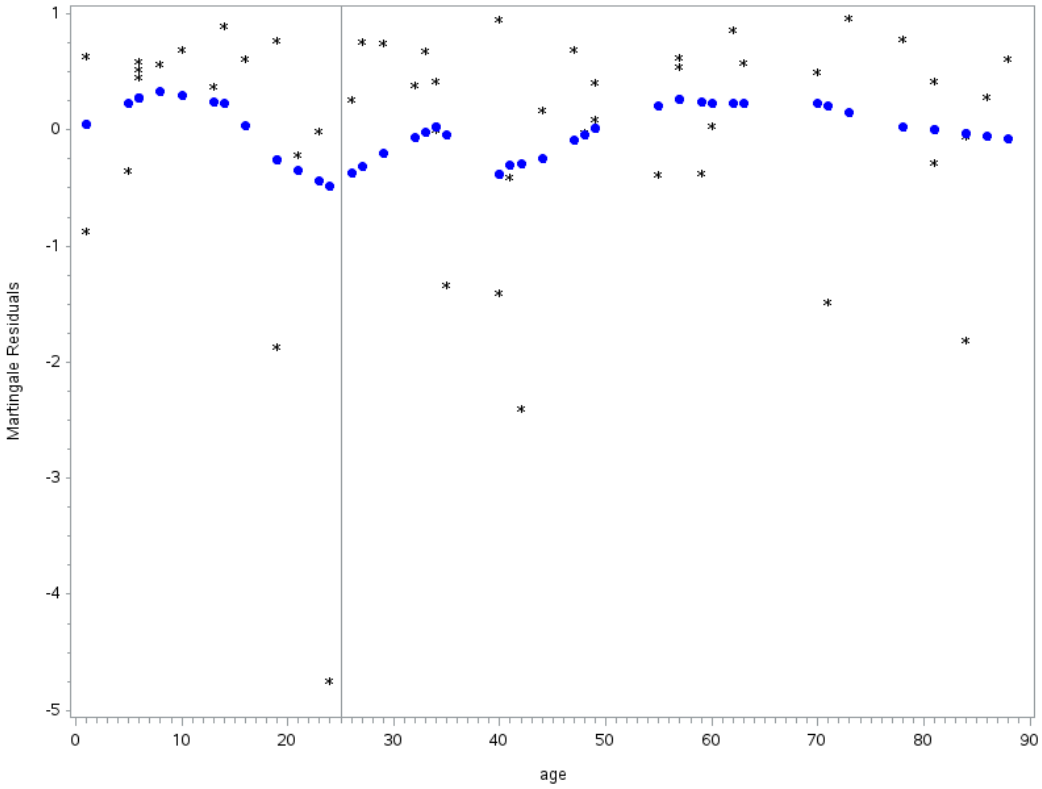


Figure 3.1 Plot of martingale residual versus age in simulated data

Looking at the plot in Figure 3.1, there apprears to be a downward peak at 25 and 40, also an upward peak at age 10. Since we are only interested in dichotomizing a covariate but not interested in finding the multiple cutpoints, we will apply some estimation methods to find a cutpoint.

3.3.2 Prior information

In his dissertation, Kuo (1997) discussed the use of existing or published sources in determining a cutpoint for a continuous variable. This method is also referred as the prior information method. The disadvantage of the prior information method is that the information on the cutpoint value may not be available for all of the variables being

studied. Also, if the population in the study is different than the general population then the prior information method may not be suitable. For example, the cutpoint for infants and adolescents may be different than the cutpoint for adults. While this method is an option, it has limited applicability especially when examining potentially new covariates.

3.3.3 Data-oriented Method

A common method of determining cutpoints is based on using the descriptive statistics such the mean, median, quantile or percentile to categorize a continuous covariate. The disadvantage with utilizing a data-oriented method is that the cutpoint determined for one study very well may differ from another study. Another disadvantage is that even within the same study the cutpoint may be different based on the type of statistic (mean or median or quantile) being used to determine the cutpoint. Again, while using a data-oriented method is possible, it is certainly not optimal.

3.3.4 Output oriented Method

Output oriented methods are the most popular categorization methods in the survival analysis literature. Output oriented methods are based on the maximized value of some statistic. Four different output oriented methods proposed by Miller and Siegmund (1982), Lausen and Schumacher (1992, 1996), Contal and O'Quigley (1999) and Klein and Wu (2004) will be discussed here.

3.4 Miller and Siegmund (1982)

In 1982, Miller and Siegmund developed the "maximizing the chi-square" approach for finding a cutpoint of the continuous covariate with a binary outcome. This approach consists of a series of 2×2 tables (high/low group vs event/no event) at each value of the covariate and calculating the chi-square statistics for all respective tables. The point with the largest value of the standard chi-square statistic would then be determined to be the optimal cutpoint for that continuous covariate. The standard chi-square statistic would be defined as:

$$\chi^2 = \frac{N\left(ad-bc\right)^2}{\left(a+b\right)\left(c+d\right)\left(a+c\right)\left(b+d\right)} \qquad (3.4.1)$$

where $a=$ number of individual in low risk group with event, $b=$ number of individual in high risk group with event, $c=$ number of individual in low risk group with no event, $d=$ number of individual in high risk group with no event, and $N=a+b+c+d=$ total number of participants in all group.

The alternative of the chi-square statistic was the standardized log odds ratio given by:

$$\frac{\left|\log\left(ad/bc\right)\right|}{\left(a^{-1}+b^{-1}+c^{-1}+d^{-1}\right)^{\frac{1}{2}}} \qquad (3.4.2)$$

The theory developed by Miller and Siegmund (1982) was directly applicable to find the limiting distribution of the statistic in $(3.4.2)$. For a large sample, the chi-square statistic

in $(3.4.1)$ can be further modified and presented as the square root of the chi-square statistic given by:

$$\left(\chi^2\right)^{\frac{1}{2}} = \frac{\left|\hat{F}_1(x) - \hat{F}_2(x)\right|}{\left[\hat{F}(x)\left\{1-\hat{F}(x)\right\}\left(\frac{1}{n_1}+\frac{1}{n_2}\right)\right]^{\frac{1}{2}}} \qquad (3.4.3)$$

where $\hat{F}_1(x) = \Pr\left(X_1 \le x\right) = \frac{a}{a+b}$ = estimated probability of being in low risk and having the event, $\hat{F}_2(x) = \Pr\left(X_2 \le x\right) = \frac{c}{c+d} =$ estimated probability of being in low risk and not having the event, $\hat{F}\left(x\right) = \Pr\left(X \le x\right) = \frac{a+c}{N} =$ estimated probability of being in low risk group for both event and no group, $n_1 = \left(a+b\right) =$ total number of participants with the event, and $n_2 = \left(c+d\right) =$ total number of participants with no event.

The null hypothesis for the empirical distribution functions $\hat{F}_1, \hat{F}_2$ and $\hat{F}$ is given by:

$$H_0 : F_1 = F_2 = F$$

(i.e., probability of being in low risk group for participants with event is same as the probability of being in low risk group for participants with no event). Assuming F is continuous and $n_1, n_2 \to \infty$, the statistic in equation $(3.4.3)$ converges weakly under H_0 to:

$$\frac{|W_0(t)|}{\{t(1-t\}^{\frac{1}{2}}} \qquad (3.4.4)$$

where $W_0(t)$ is a tied-down Wiener process with expectation 0 and variance $t(1-t)$ on $[0,1]$ with $t = F(x)$. The distribution of supremum of equation $(3.4.3)$ over values of covariate $x \in \left[F^{-1}(\varepsilon), F^{-1}(1-\varepsilon)\right]$ is asymptotically equal to the distribution of supremum of equation $(3.4.4)$ over values of $F(x) = \mathrm{t} \in [\varepsilon, 1-\varepsilon], 0 < \varepsilon < 1$. Since the variance at the beginning or end can take the value 0 on $[0,1]$, the supremum needs to be searched in $[\varepsilon, 1-\varepsilon]$ rather than over $[0,1]$. The $p-$value for the supremum of statistic in $(3.4.4)$ as for large w i.e. as $w \to \infty$ is given by:

$$\Pr\left[\sup_{t_1 \le t \le t_2} \frac{|W_0(t)|}{\{t(1-t\}^{\frac{1}{2}}} \ge w\right] = \frac{4\phi(w)}{w} + \phi(w)\left(w - \frac{1}{w}\right)\log\left(\tau_2 / \tau_1\right) + o\left\{w^{-1}\phi(w)\right\} \qquad (3.4.5)$$

for $0 < t_1 < t_2 < 1$ where $\tau_j = t_j / (1-t_j)$ and $\phi(w)$ is the standard normal density given by:

$$\phi(w) = (2\pi)^{-\frac{1}{2}} \exp\left(-\frac{1}{2}w^2\right).$$

The significance of the chi-square statistics were calculated using equation (3.4.5) to determine the validity of the cutpoint. Concerns were raised regarding the use of the significance criteria because a large sample size usually detects small differences and vice versa. To overcome this concern it was suggested that one should always be aware about the magnitude of odds ratio or relative risk in two groups that could be considered clinically significant. Miller and Siegmund (1982) also suggested that the cutpoint should

be searched in the defined percentile interval rather than on all possible values of cutpoints. Although Miller and Siegmund's method did not address continuous outcomes, such as time to an event, this method was the basis for other methods such as Lausen and Schumacher, who developed the maximally selected rank statistics in 1992.

3.5 Lausen and Schumacher (1992, 1996)

In 1992, Lausen and Schumacher developed a method called "Maximally Selected Rank Statistics". Let $(X_1, Y_1), ..., (X_n, Y_n)$ be n bivariate observations where X_i denotes the value of a continuous covariate for the ith observation and Y_i denotes the value of the dependent variable for the ith observation. Consider all distinct given values of a covariate as potential cutpoints. At each potential cutpoint, divide participants into two groups depending upon if the covariate value is higher or lower than the given cutpoint. Let $R_{1n}, ..., R_{nn}$ denote the ranks for the ordered dependent variable $Y_{(1)}, ..., Y_{(n)}$ and $a_n(1), ..., a_n(n)$ denote the associated score. If observation has tied or censored values then associated scores will be given by the mid-scores or log-rank scores. The two sample rank statistic for fixed μ is given by:

$$S_{n\mu} = \sum_{i=1}^{n} I_{(X_i \le \mu)} a_n(i) \qquad (3.5.1)$$

where $I_{(X_i \le \mu)} = 1$ for $\{X_i \le \mu\}$ and 0 otherwise. If the scores are set as rank i.e. $a_n(i) = i$ then the rank statistic $S_{n\mu}$ is called Wilcoxon two-sample rank statistic. For the estimation and test of the significance of the cutpoint, the null hypothesis is defined as:

$H_0 : \Pr(Y \le y / X \le \mu) = \Pr(Y \le y / X > \mu)$ for all $y, \mu \in \mathbb{R}$. i.e. no difference in the distribution of Y for all μ. An approximation to the location shift model can be written as:

$$\Pr(Y \le y / X \le \mu) = \Pr(Y - \nu \le y / X > \mu) \text{ for all } \nu, \mu, y \in \mathbb{R} \qquad (3.5.2)$$

From equation $(3.5.2)$, the probability density function (p.d.f.) of a random variable Y can be written as a two-group mixture model in cluster analysis:

$$f_Y(y) = \Pr(X \le \mu)\, f_{Y/X>\mu}(y) + \Pr(X > \mu)\, f_{Y/X>\mu}(y - \nu) \qquad (3.5.3)$$

Under the null hypothesis the conditional expectation and conditional variance of the rank score $S_{n\mu}$ in $(3.5.1)$ is given by:

$$E(S_{n\mu} / a, X) = nF_{nX}(\mu)\bar{a}_n$$

$$V(S_{n\mu} / a, X) = A_n^2 nF_{nX}(\mu)(1 - F_{nX}(\mu)) \qquad (3.5.4)$$

where $A_n^2 = \frac{1}{n-1}\sum_{i=1}^{n}(a_{in} - \bar{a}_n)^2$, with $a_{in} = a_n(i), \bar{a}_n = (1/n)\sum_{i=1}^{n} a_{in}$ and

$F_{nX}(\mu) = (1/n)\sum_{i=1}^{n} I_{\{X_i \le \mu\}}$ is the empirical distribution function of a covariate X. The standardized test statistic $T_{n\mu}$ for $S_{n\mu}$ is computed using the expectation and variance given above, i.e.:

$$T_{n\mu} = \frac{S_{n\mu} - E(S_{n\mu} / a, X)}{\left(Var(S_{n\mu} / a, X)\right)^{1/2}}$$

and the maximally selected rank statistic is:

$$M_n(\varepsilon_1, \varepsilon_2) = \max_{\mu \in [x_1, x_2]} |T_{n\mu}| \qquad (3.5.5)$$

where $x_1 = F_{nX}^{-1}(\varepsilon_1), x_2 = F_{nX}^{-1}(\varepsilon_2)$ and $0 < \varepsilon_1 < \varepsilon_2 < 1.$

The cutpoint is searched in the interval bound given by sample quantiles i.e.: $\mu \in \left[F_{nX}^{-1}(\varepsilon_1), F_{nX}^{-1}(\varepsilon_2) \right]$ where $0 < \varepsilon_1 < \varepsilon_2 < 1$ and $F_{nX}^{-1}(t) = \min\{x : F_{nX}(x) \geq t\}$, since there may be very few number of participants at the both end to assume the asymptotic distribution.

As an alternative to rank statistic above the two-sample statistic was suggested. The two-sample t statistic $T_{n\mu}^{t}$ is given by:

$$T_{n\mu}^{t} = \left(\frac{n_{1\mu} n_{2\mu}}{n} \right)^{\frac{1}{2}} \left(\frac{\bar{Y}_{1\mu} - \bar{Y}_{2\mu}}{s_\mu} \right)$$

where $s_\mu^2 = \frac{1}{(n-2)} \left(\sum_{\{i:X_i \leq \mu\}} \left(Y_i - \bar{Y}_{1\mu} \right)^2 + \sum_{\{i:X_i > \mu\}} \left(Y - \bar{Y}_{2\mu} \right)^2 \right)$, $n_{1\mu} = nF_{nX}(\mu)$,

$n_{2\mu} = n(1 - F_{nX}(\mu))$, $\bar{Y}_{1\mu} = (1/n_{1\mu}) \sum_{\{i:X_i \leq \mu\}} Y_i$, and $\bar{Y}_{2\mu} = (1/n_{2\mu}) \sum_{\{i:X_i > \mu\}} Y_i$.

A Gaussian statistic can be obtained if variance σ^2 is known.

In 1996, Lausen and Schumacher developed a cutpoint model and test procedure for a location shift model. The location shift model with unknown cutpoint $\mu \in \mathbb{R}$ and unknown location shift or effect $\nu \in \mathbb{R}$ is given by:

$$\Pr(Y \leq y / X \leq \mu) = \Pr(Y - \nu / X > \mu), \quad \forall y \in \mathbb{R} \qquad (3.5.6)$$

where Y is a dependent variable and X is a continuous covariate. The null hypothesis for the location shift model can be written as: $H_0 : \nu = 0.$ The difference between two groups separated by unknown cutpoint μ can be obtained from the absolute value of a

standardized two-sample statistic with normal distribution $\left(N(0,1)\right)$ after dividing the subjects into two groups using an arbitrarily chosen but fixed hypothetical cutpoint $\rho \in \mathbb{R}$.. The two-sample statistic can be calculated for all possible values of cutpoint between ε and $\left(1-\varepsilon\right)$ sample quantile of covariate X, where $0<\varepsilon<0.5.$ The maximally selected test statistic is given by:

$$M\left(\varepsilon\right)=\max_{\rho\in\left[x_n(\varepsilon),x_n(1-\varepsilon)\right]}\left|T_{np}\right| \tag{3.5.7}$$

where $x_n(.)$ is the sample quantile and T_{np} is the standardized two sample statistics. In this method, the standardized rank statistic with the minimum *p*-value was considered the optimal cutpoint.

For a large sample, the *p*-value given by Miller and Siegmund (1982) was:

$$P_{cor}\approx P_{cor}^{(1)}=\varphi(\mathrm{z})\left(z-1/z\right)\log\left((1-\varepsilon)^2/\varepsilon^2\right)+4\varphi(z)/z \tag{3.5.8}$$

where $z=\Phi^{-1}\left(1-P_{\min}/2\right),$ φ is standard normal p.d.f. and Φ is the standard normal distribution function.

For small sample size, Lausen and Schumacher (1996) suggested a *p*-value based on Bonferroni inequality:

$$P_{cor}\approx P_{cor}^{(2)}=P_{\min}+\sum_{i=1}^{k-1}D\left(l_i,l_{i+1}\right), \tag{3.5.9}$$

where l_i denote the size of the k subgroups with values in X less or equal to the cutpoint c_i, $l_k = n - \sum_{i=1}^{k-1} l_i$, $D(i,j) = (2/\pi)^{0.5} \phi(z)\left(t_{ij} - \left(z^2/4 - 1\right)(t_{ij})^3/6\right)$, $z = \Phi^{-1}(1 - P_{\min}/2)$ and $t_{ij} = \left(1 - i(n-j)/((n-i)j)\right)^{0.5}$.

Since the *p*-values given by (3.5.8) and (3.5.9) can be conservative, the minimum of the (3.5.8) and (3.5.9) was suggested by Lausen and Schumacher, i.e.:

$$P_{cor} \approx \min\left(P_{cor}^{(1)}, P_{cor}^{(2)}\right).$$

This approach allows the correction of *p*-value for a given interval.

3.6 Contal and O'Quigley (1999)

Let $(Z_1, X_1), ..., (Z_n, X_n)$ be n bivariate observation where Z_i denotes a continuous covariate value for the ith observation and X_i denotes the dependent variable for the ith observation. Contal and O'Quigley (1999) aimed to find the estimation of the cutpoint as well as the associated inference regarding the cutpoint. Looking back to the Miller and Siegmund (1982) and Lausen and Schumacher (1992) both have used the variance $t(1-t)$ of the Brownian bridge process $W_0(t)$ to globally standardize the test statistic. Since the variance $t(1-t)$ implies the estimation and testing of the cutpoint in the restricted interval $(0,1)$, Contal and O'Quigley focused to find the alternative method to not restrict the estimation in this interval. According to Billingsley (1968), if $\alpha_1, ..., \alpha_n$ are

exchangeable random variables (that is joint distribution of $\alpha_1,...,\alpha_n$ is permutation invariant for each n) and if the α_i satisfies the following three condition as $n \to \infty$:

1. $\sum_{i=1}^{n} \alpha_i \xrightarrow{P} 0$ (i.e., the sum of the random variable converges in probability to zero).
2. $\sum_{i=1}^{n} \alpha^2 \xrightarrow{P} 1$ (i.e., the sum of square of the random variable converges in probability to 1).
3. $\max_{1 \le i \le n} |\alpha_i| \xrightarrow{P} 0$

then the process defined by:

$$S_n(t) = \sum_{i=1}^{[nt]} \alpha_i \text{ with } t \in [0,1],$$

and

$$S_n(t) = 0 \text{ for } 0 \le t < 1/n$$

where $[nt]$ is the smallest integer greater than $(nt-1),$ converges in distribution to the Brownian bridge. According to the Brownian bridge property (Billingley, 1968), if $W_0(t)$ is Brownian bridge Gaussian stochastic process in $[0,1],$ with mean $E(W^0(t)) = 0,$ and covariance $Cov(W_0(s), W_0(t)) = s(1-t)$, for $s < t$, the supremum of the absolute value of the Brownian bridge is given by:

$$\Pr\left(\sup_{t \in [0;1]} |W^0(t)| > b \right) = 2\sum_{j=1}^{\infty} (-1)^{j+1} \exp\left(-2j^2 b^2\right) \qquad (3.6.1)$$

for $b > 0.$ Contal and O'Quigley(1999) proposed a process that looked like the Brownian bridge. According to Contal and O'Quigley (1999), let $Z_1,...,Z_n$ represent the increasing ordered covariates so that $Z_1 < ... < Z_n$. Let the scores of the outcomes $X_1,...,X_n$ are $a_1,...,a_n$ for n participants.

For the tied or censored observation the scores are same as the log-rank score. The scores are random variables and the expectation and variance of the score is given by: $\bar{a} = \frac{1}{n}\sum_{j=1}^{n} a_j$ and $\text{var}(a) = \frac{1}{(n-1)}\sum_{j=1}^{n}\left(a_j - \bar{a}\right)^2$ respectively. Using this expectation and variance the standardized form of the score is given by:

$$\alpha_i = \frac{1}{\sqrt{n-1}} \frac{a_i - \bar{a}}{\sqrt{\text{Var}(a)}}$$

Let X_i denotes the survival time of the ith individual and δ_i denotes the censoring indicator for the ith individual. If $\left(X_1, \delta_1\right),...,\left(X_n, \delta_n\right)$ are independent and identically distributed, then the scores given by log-rank statistic are exchangeable random variables. The three condition of the Brownian bridge given above can be satisfied by these exchangeable score in the following way:

1. $$\sum_{j=1}^{n} \alpha_j = \sum_{j=1}^{n} \frac{1}{\sqrt{n-1}} \frac{\left(a_j - \bar{a}\right)}{\sqrt{\text{Var}(a)}} = \frac{1}{\sqrt{n-1}} \frac{\sum_{j=1}^{n}\left(a_j - n\bar{a}\right)}{\sqrt{\text{Var}(a)}} = 0$$

2. $$\sum_{j=1}^{n} \alpha_j^2 = \sum_{j=1}^{n} \left\{ \frac{1}{\sqrt{n-1}} \frac{\left(a_j - \bar{a}\right)}{\sqrt{\text{Var}(a)}} \right\} = \frac{1}{\text{Var}(a)} \frac{\sum_{j=1}^{n}\left(a_j - \bar{a}\right)^2}{n-1} = 1$$

3. Assuming the third condition is verified for classical rank scores (log-rank, Wilcoxon, median...)

The process defined by $S_n(t) = \sum_{i=1}^{[nt]} \alpha_i$ converges in distribution, under H_0 to the Brownian bridge. Applying equation (3.6.1), the limiting distribution of $\max|S_n(t)|$ is given by:

$$p = \Pr\left(\sup_{t\in[0;1]} |S_n(t)| > b \right) = 2\sum_{j=1}^{\infty} (-1)^{j+1} \exp\left(-2j^2b^2\right)$$

For $b > 1$ the formula can be written as:

$$p \approx 2\exp\left(-2b^2\right)$$

Application in Survival analysis:

Let $x_{(1)} < ... < x_{(k)}$ be k number of distinct observed death times. Let $Z \le \mu$ as low risk group and $Z > \mu$ as high risk group for some fixed cutpoint μ. Constructing $k(2\times 2)$ table for the each potential cutpoint μ in Z, a log-rank statistic for a fixed μ can be written as:

$$U = \sum_{i=1}^{k} \left(d_i^+ - d_i \frac{r_i^+}{r_i} \right)$$

where d_i is the number of deaths at time $x_{(i)}$, d_i^+ is the number of deaths in the high risk group, r_i^+ as the number of patients at risk in high risk group and r_i is number of patients at risk in both groups. In such case,

$$S_n(t) = \frac{1}{\sigma\sqrt{k-1}} \sum_{i=1}^{k} \left(d_i^+ - d_i \frac{r_i^+}{r_i} \right)$$

where $\sigma^2 = \frac{1}{(k-1)}\sum_{j=1}^{k} a_j^2,$ has the asymptotic distribution as the Brownian bridge under random censoring model. The cutpoint μ associated with the maximum value of the Brownian process $S_n(t)$ would be selected as the optimal cutpoint.

Contal and O'Quigley (1999) presented a method similar to Lausen and Schumacher (1992, 1996). The test statistic was developed based on the asymptotic null distribution of a process based on re-scaled rank statistics is same as the distribution of the Brownian bridge. The test statistic was applied to the survival analysis with censored data.

3.6.1 Method presented by Contal and O'Quigley (1999)

Let Z_i be a prognostic factor and X_i be an outcome for i^{th} subject; then a null hypothesis of no difference in the outcome when the variable Z lies below the cutpoint μ to the outcome when the variable Z lies above the cutpoint μ is given by:

$$H_0 : \Pr(X \le t / Z \le \mu) = \Pr(X \le t / Z > \mu) \text{ for all } t, \mu \in \mathbb{R}$$

And the alternative hypothesis that there is a location shift in the outcome by the amount v when the variable Z lie above the cutpoint μ is given by:

$$H_1 : \Pr(\mathrm{X} \le \mathrm{t} / \mathrm{Z} \le \mu) = \Pr(\mathrm{X} - \nu \le \mathrm{t} / \mathrm{Z} > \mu) \text{ for all } \mathrm{t} \in \mathbb{R}$$

This result also can be shown by using non-nested proportional hazards regression model (Cox, 1972), in which it is given by:

$$\lambda(t; Z) = \lambda_0(t) \exp(\beta' Z) \qquad (3.6.1)$$

Here, $\lambda(t;Z)$ is the hazard rate, $\lambda_0(t)$ is the baseline hazard function, β is a vector of parameters and Z is a design matrix for covariates, and t is the time to the event of interest.

The proportional hazard rate in (3.6.1) is based on the assumption of proportional hazards, meaning that the risk of the hazard is constant throughout time. If we specify $Z > \mu$ as 1 and $Z \leq \mu$ as 0, we can write the relation in (3.6.1) as following:

$$\lambda(t / Z > \mu) = \exp(\beta)\lambda(t / \mathrm{Z} \leq \mu) \qquad (3.6.2)$$

Where, $\nu = \exp(\beta)$ is the ratio of risk when the factor Z is above the cutpoint μ to the risk when factor Z is below the cutpoint μ.

Lausen and Schumacher (1992) discussed that to standardize the test statistics, it should be divided by $\{t(1-t)\}^{-1}$, which restrict the subinterval within (0, 1), for $0 \leq t \leq 1$. However, there are some cases when not restricting the estimation and hypothesis testing is preferred and Contal and O'Quigley (1999) focused on the approach of not restricting the interval to (0, 1).

3.6.2 Test procedure of Contal and O'Quigley (1999)

Let a Brownian bridge, also called a Gaussian stochastic process, $W^0(t)$ on [0, 1], where t is the time of event. The mean of $W^0(t)$ is given by $E(W^0(t)) = 0$ and its variance is given by $Cov(W^0(s), W^0(t)) = s(1-\mathrm{t})$, for s is the time of event, which is less than t, at the boundary $W^o(0) = \mathrm{W}^0(1) = 0$ with probability 1.

The probability of the supremum of the absolute value of the Brownian Bridge is greater than some positive quantity b is given by:

$$\Pr\left(\sup_{t\in[0;1]} |W^0(t)| > b \right) = 2\sum_{j=1}^{\infty} (-1)^{j+1} \exp(-2j^2b^2) \qquad for\ \ b>0$$

Let $Z_1,...,Z_n$ be the values of a covariate and let $Z_1 < ... < Z_n$ be arranged such that they are in the increasing order. Let $a_1,...,a_n$ be the ranked score of the outcomes $X_1,...,X_n$ associated with the ranked variables. The scores are calculated by using the log-rank statistic in the case of censored observations. The expectation and variance of a_i are given by:

$$E(a_i) = \bar{a} = \frac{1}{n}\sum_{j=1}^{n} a_i$$

$$Var(a_i) = \frac{1}{(n-1)}\sum_{j=1}^{n} (a_j - \bar{a})^2$$

By subtracting the mean and dividing by the square root of variance, we can obtain the standardized score α_i given by:

$$\alpha_i = \frac{1}{\sqrt{(n-1)}} \frac{a_i - \bar{a}}{\sqrt{Var(a_i)}}.$$

Under the assumption that outcome X and covariate Z are independent and α_i converges, we are interested in the maximization of absolute value of sum $S_n(t)$. The limiting distribution of $\max|S_n(t)|$ is given by:

$$p = \Pr\left(\sup_{t\in[0;1]} |S_n(t)| > b \right) = 2\sum_{j=1}^{\infty} (-1)^{j+1} \exp(-2j^2b^2).$$

For values of b greater than 1, a value slightly less than the 33rd percentile is a good approximation to the above formula obtained by simply taking the first terms i.e.:

$$p \approx 2\exp(-2b^2).$$

3.7 Klein and Wu (2004)

In 2004, Klein and Wu extended the method of Contal and O'Quigley to the parametric model. The test statistics for this method is based on the score residual for the parametric model. The log-likelihood of the accelerated failure time model with a Weibull distributed time-to-event is given by:

$$\log L(\mu, \beta_1, \sigma) = \sum_{i=1}^{n}\left[-\delta_i \log(\sigma t_i) + \delta_i\left(\frac{\log(T_i) - \mu - \beta_1 Z_i}{\sigma}\right) - \exp\left(\frac{\log(T_i) - \mu - \beta_1 Z_i}{\sigma}\right)\right]$$

Differentiating with respect to parameter β_1

$$\frac{d\log L(\mu, \beta_1, \sigma)}{d\beta_1} = \sum_{i=1}^{n}\left[\frac{Z_i}{\sigma}\left(\exp\left(\frac{\log(T_i) - \mu - \beta_1 Z_i}{\sigma}\right) - \delta_i\right)\right] \qquad (3.7)$$

For the null hypothesis $H_0 : \beta_1 = 0$ the above equation can be written as:

$$\frac{d\log L(\mu = \hat{\mu}, \beta_1 = 0, \sigma = \hat{\sigma})}{d\beta_1} = \sum_{i=1}^{n}\left[\frac{Z_i}{\hat{\sigma}}\left(\exp\left(\frac{\log(T_i) - \hat{\mu} - (\beta_1 = 0)Z_i}{\hat{\sigma}}\right) - \delta_i\right)\right]$$

The test statistics for Klein and Wu (2004) is given by:

$$S(c_j) = \frac{U_\beta^\gamma(\hat{\mu}, \beta_1 = 0, \hat{\sigma})}{\sqrt{(vn)}} \qquad (3.7.2)$$

where c_j = jth cutpoint, j=1,...,N, and N=number of distinct covariate values.

$$U_{\beta}^{\gamma}\left(\hat{\mu},\beta_1=0,\hat{\sigma}\right)=\sum_{i=1}^{n}\left[\frac{1}{\hat{\sigma}}\left(\exp\left(\frac{\log(\mathrm{T}_i)-\hat{\mu}-(\beta_1=0)\times\mathrm{Z}_i}{\hat{\sigma}}\right)-\delta_i\right)\right] \qquad (3.7.3)$$

$$=\sum_{i=1}^{n}I\left[X_i\le\gamma\right]\psi_i$$

The variance in equation (3.7.2) can be estimated consistently by weight ψ^2, where ψ^2 is given by:

$$\psi^2=\sum_{i=1}^{n}\left[\frac{Z_i}{\hat{\sigma}}\left(\exp\left(\frac{\log(\mathrm{T}_i)-\hat{\mu}}{\hat{\sigma}}\right)-\delta_i\right)\right]^2\frac{1}{n} \qquad (3.7.4)$$

According to Klein and Wu, the cutpoint which provides the maximum value of the absolute test statistics denoted by $\left|S\left(c_j\right)\right|$ will be selected as the optimal cutpoint estimate.

Klein and Wu (2004) also showed that the partial sum of the ergodic process:

$$S\left(p\right)=\frac{U_{\beta}^{\gamma}(p)}{v\sqrt{n}} \qquad (3.7.1)$$

which converges weakly to the Brownian motion process $\left(W\right)$ on the unit interval, when $v=E\left[\psi_i^2\right]^{1/2}$. According to Wu(2001), for a different parametric model such as Weibull, log logistic and log normal models, the ψ_i's have mean zero and the variance v can be consistently estimated by $\sum\psi_i^2/n$. Substituting the estimated variance in (3.7.1),

$$S(p)=\frac{\sum_{i=1}^{\lceil np\rceil}\psi_i}{\sqrt{\sum_{i=1}^{n}\psi_i^2}}$$

converges to Brownian bridge and cutpoint associated with the maximum value of $S(p)$ can be selected as the optimal cutpoint. The p-value for the cutpoint can be estimated by the equation given by:

$$P\left(\underset{0\le p\le 1}{Sup}\left|W^{0}(p)\right| \ge k \right) = 2\left(\sum_{j=1}^{\infty}(-1)^{j+1} \exp\left(-2j^{2}k^{2}\right) \right) \qquad (3.7.2)$$

In addition to parametric method, Klein and Wu (2004) also provided the test statistics for Cox-proportional hazard model. The method developed for Cox-proportional hazard regression model is an extension of Contal and O'Quigley (1999), Jespersen (1986) and Lausen and Schumacher (1992, 1996), which will not be discussed here.

The Contal and O'Quigley (1999) and Klein and Wu (2004) are similar in terms of calculating the $p-$value and finding the statistic that converge to Brownian bridge without restriction to the interval $[0,1]$. In chapter 4, we will discuss the proposed method of estimating a cutpoint. The proposed method focuses on estimating the cutpoint rather than the inference based on *p*-value.

CHAPTER 4: PROPOSED METHOD

4.1 Introduction

The most widely used methods of estimating cutpoints are based on the maximization of the test statistic. Although a martingale residual plot with the LOESS smoothing may indicate a presence of a cutpoint, it may not provide the exact value of a cutpoint. Thus, the maximization of a test statistic approach allows the selection of a cutpoint that yields the largest difference between two groups. In an attempt to address the controversy about the loss of information due to categorization of the continuous covariate of interest, both a continuous covariate and a categorical version of the covariate will be utilized in the model.

The proposed method will use the derivative of the log-likelihood function with respect to unknown parameter θ, with θ evaluated at null θ_0 in the result from the parametric model with both the continuous and categorical covariate.

4.2 Mathematical Formulation of the Proposed Method

The proposed method of determining a cutoff of a covariate of interest is accomplished by searching across the range of the covariate for a significant difference in the survival between two groups defined by the cutpoint γ. Thus, the null hypothesis would be:

$$H_0 : S(t / Z \le \gamma) = S(\text{t}/\ \text{Z} > \gamma) \qquad (4.1)$$

In case of a Cox proportional hazards model, we can rephrase the null hypothesis in (4.1) as follows:

$$H_0 : h(t / Z \le \gamma) = h(t / Z > \gamma) \Rightarrow$$

$$H_0 : h_0(t)\exp(\beta_\gamma I[Z \le \gamma]) = h_0(t)\exp(\beta_\gamma I[Z > \gamma]) \Rightarrow$$

$$H_0 : \exp\left(\beta_\gamma I[Z \le \gamma]\right) = \exp(\beta_\gamma I[Z > \gamma]) \qquad (4.2)$$

In equation (4.2), $I[\text{Z} \le \gamma]$ is an indicator variable for subjects with covariate value less than or equal to the cutoff point.

Similarly, for the accelerated failure time (AFT) model we can rephrase the null hypothesis in (4.1) as follows:

$$H_0 : \ln\left(T / Z \le \gamma\right) = \ln\left(T / Z > \gamma\right) \Rightarrow$$

$$H_0 : \mu + \beta_\gamma I[Z \le \gamma] + \sigma W = \mu + \beta_\gamma I[Z > \gamma] + \sigma W \qquad (4.3)$$

In equation (4.3), $\ln(T)$ denotes the log of the survival time T, μ is the coefficient for intercept and β_γ is the coefficient for an indicator variable indicating either the covariate value is greater than or equal to some cutpoint γ or less than the cutpoint γ, σ is the scale parameter, and W is the error term. There are many possible distributions for W, but the most commonly used are the extreme value distribution, the normal distribution and the logistic distribution.

Equation (4.2) and (4.3) do not adjust for multiple covariates. If we want to adjust for multiple covariates in the model the equations (4.2) and (4.3) can be modified, respectively, as:

$$h(t / X, Z) = h_0(t) \exp\left\{\beta X + \beta_\gamma I\left[\leq \gamma\right]\right\} \quad (4.4)$$

$$\ln(T) = \mu + \beta X + \beta_\gamma I[Z \leq \lambda] + \sigma W \quad (4.5)$$

4.3 Proposed method for determining a cutpoint

The proposed method is based on the parametric model and is the extension of both the Contal and O'Quigley (1999) and Klein and Wu (2004) methods for determining a cutpoint. This proposed method is based on the information that the log-rank statistic is approximately equal to the score statistic. Thus the score statistic for a parametric Weibull model with the continuous covariate of interest will be fit. In addition to the continuous covariate of interest, a categorized version of the continuous covariate will also be included in the model. Each distinct value of the continuous variable will be considered as a candidate cutpoint. For each candidate cutpoint this model will calculate the score statistic of the continuous covariate.

The accelerated failure time (AFT) model for the i^{th} subject with time to an event T_i can be written as:

$$\log(T_i) = \mu + \beta_1 Z_i + \beta_2 X_i + \sigma W_i \quad (4.6)$$

In equation (4.6), $\log(T_i)$ is the logarithm of the time-to-event for the i^{th} subject in the study, μ is the parameter for the intercept, β_1 is the parameter for a categorical variable, β_2 is the parameter for a continuous covariate, X_i is the value of a continuous covariate for the i^{th} subject, Z_i is the value of an indicator variable given by $Z_i = 1$ if $X_i > \gamma$ and 0 otherwise, γ is a proposed cutpoint, σ is a scale parameter, and W_i is a random variable also known as random error. The distribution of random error W_i will be dependent upon the distribution assumed for time to event T_i. For example, if T_i has a Weibull distribution then W_i has an extreme value distribution also known as the Gumbel distribution (Collette, 2003).

Before going into detail about the proposed method, some properties of the score function will be discussed. Let $L(\theta)$ be the likelihood function for the parameter θ and let $l(\theta)$ be the log-likelihood function for a univariate parameter θ and data x. The score function $U(\theta)$ is defined as the first derivative of the log-likelihood with respect to θ and is given by:

$$U(\theta) = \frac{\partial}{\partial \theta} \log\left[L(\theta)\right]$$

Thus, the mean of the score function is $E\left[U(\theta)\right]=0$ and $Var\left[U(\theta)\right]=I(\theta),$ where $I(\theta)$ is negative of the second derivative of the log-likelihood function with respect to $\theta,$ also known as the Fisher information given by:

$$I(\theta)=-E\left[\frac{\partial^2 \log\left[L(\theta)\right]}{\partial\theta^2}\right]$$

For the null hypothesis $H_0:\theta=\theta_0$, if H_0 is true then the variance of the score function is:

$$Var\left[U(\theta_0)\right]=I(\theta_0).$$

The score function as a random variable converges to a normal distribution asymptotically when H_0 is true. Considering these properties of the score function, the score function $U(\beta_2)$ may be calculated for the continuous covariate X_i in the model and may be written as

$$U(\beta_2)=\frac{\partial}{\partial\beta_2}\log\left[L(\beta_2)\right].$$

For the Weibull distributed time to event, the Score function with respect to β_2 may be shown to be:

$$U(\beta_2)=\sum_{i=1}^{n}X_i\left[\left(\exp\left(\frac{\log(T_i)-\mu-\beta_1 Z_i-\beta_2 X_i}{\sigma}\right)-\delta_i\right)\right]\frac{1}{\sigma},$$

where $i = 1,...,n$ is number of subjects in the study, T_i is the survival time of the i^{th} subject, μ is the parameter for intercept, σ is the parameter for scale, β_1 is the parameter for indicator variable Z_i, β_2 is the parameter for the continuous covariate X_i, and δ_i is the censoring indicator for the i^{th} individual denoting $\delta_i = 1$ if event, and 0 otherwise. For the null hypothesis $H_0 : \beta_2 = 0$ and assuming H_0 is true, the score function with respect to β_2 may be written as:

$$U(\beta_2 = 0) = \sum_{i=1}^{n} X_i \left[\left(\exp\left(\frac{\log(T_i) - \hat{\mu}_0 - \hat{\beta}_{10} Z_i}{\hat{\sigma}_0} \right) - \delta_i \right) \right] \frac{1}{\hat{\sigma}_0} \qquad (4.7)$$

where $\hat{\mu}_0, \hat{\beta}_{10}, \hat{\sigma}_0$ are the maximum likelihood estimates for the restricted model. From the properties of score function provided earlier in the chapter, $E\left[U(\beta_2)\right] = 0.$ Also, let the inside quantity $\frac{1}{\hat{\sigma}_0} \left(\exp\left(\frac{\log(T_i) - \hat{\mu}_0 - \hat{\beta}_{10} Z_i}{\hat{\sigma}_0} \right) - \delta_i \right) = \psi_i$. Also, it should be noted that $\left(\exp\left(\frac{\log(T_i) - \hat{\mu}_0 - \hat{\beta}_{10} Z_i}{\hat{\sigma}_0} \right) - \delta_i \right)$ is the negative of the martingale residual and can take any values between -1 to ∞. The equation in (4.7) can be written as:

$$U(\beta_2 = 0) = \sum_{i=1}^{n} X_i \psi_i .$$

Since the interest is in computing the difference regardless of positive or negative values, the test statistic using the absolute value of the i^{th} score function of the continuous covariate is calculated for each proposed cutpoint. The cutpoint which provides the maximum value of the test statistic is considered as the best (optimal) cutpoint. The test statistic for the proposed model is given by:

$$U\left(\beta_2 = 0\right)_{c_k} = \sum_{i=1}^{n} \left| \frac{X_i}{\hat{\sigma}_0} \left(\exp\left(\frac{\log\left(T_i\right) - \hat{\mu}_0 - \hat{\beta}_{10} Z_i - (\beta_2 = 0) X_i}{\hat{\sigma}_0} \right) - \delta_i \right) \right| \qquad (4.8)$$

Here, $c_k, \mathrm{k} = 1,...,m$ denotes the m distinct values of proposed cutpoints obtained by using m distinct values of the continuous covariate. Notice that the proposed test statistic is based on the maximum value of the sum of the absolute i^{th} score function, whereas the Klein and Wu (2004) method is based on the maximum value of the ratio, where ratio = $\frac{U\left(\theta_0\right)}{\sqrt{\mathrm{v}}}$ and v is the variance of $U\left(\theta_0\right)$.

We have discussed the proposed method for estimating the cutpoint in chapter 4. In the following chapter, we will compare the performance of proposed method with other two methods existing methods, for different scenarios of simulated data.

CHAPTER 5: SIMULATION SET UP AND RESULTS

5.1 Simulation Set-Up

Based on the mathematical definition provided in Chapter 4 for the problem at hand, the simulations were constructed in such a way that before a specified value for a continuous covariate, say τ_1, one hazard function is in effect and after τ_1 a different hazard function is in effect. Thus, the goal is to identify τ_1.

For the simulation study, the Weibull and exponential parametric distribution were considered for time-to-event T_i to simulate the data. The SAS function *ranuni*, with a seed of 0, was used to simulate a covariate for a uniformly distributed age between 0 and 90 years. Using a seed of 0 provided a random seed based on the running time of the computer. The inverse transformation method was used to generate the Weibull and exponential distributed data from uniform (0, 1) variables. The different scenarios used in these simulations were as follows:

Scenario 1:

Before τ_1, the hazard ratio (HR) was 1.00 indicating 0 percent increase (i.e., no increase or decrease) in hazard rate per unit increase in the continuous covariate. After τ_1, the hazard ratio (HR) was 1.01 indicating that 1 percent increase in hazard rate per unit increase in a continuous covariate.

Scenario 2:

Before τ_1, the hazard ratio (HR) was 1.01 indicating 1 percent increase in hazard rate per unit increase in the continuous covariate. After τ_1, the hazard ratio (HR) was 1.03 indicating that 3 percent increase in hazard rate per unit increase in a continuous covariate.

Scenario 3:

Before τ_1, the hazard ratio (HR) was 1.01 indicating 1 percent increase in hazard rate per unit increase in the continuous covariate. After τ_1, the hazard ratio (HR) was 1.06 indicating that 6 percent increase in hazard rate per unit increase in a continuous covariate.

Scenario 4:

Before τ_1, the hazard ratio (HR) was 1.01 indicating 1 percent increase in hazard rate per unit increase in the continuous covariate. After τ_1, the hazard ratio (HR) was 1.10 indicating that 10 percent increase in hazard rate per unit increase in a continuous covariate.

Sample size:

Four different sample sizes were used in the simulations for each of the scenarios above: 50, 100, 500 and 1000.

Cutpoint:

Three different cutpoint were used in the simulations for each of the scenarios above: τ_1=25, τ_1=50 and τ_1=75.

Replication:

For all combinations of the above scenarios and sample sizes 1,000 simulated datasets were created.

Censoring:

Two different scenarios were used for censoring. First, it was assumed that all observations experienced an event, hence $\text{censor} = 0$ was assigned for all individuals. Second, it was assumed that 25% of all individuals were censored. For creating the censoring variable, the SAS function ranuni with a seed of 0 was used to simulate a uniformly distributed random variable between 0 and 1. If the value of the simulated random variable was less than or equal to 0.25, then that observation was assigned as censored, otherwise the observations were assigned as non-censored (i.e., had an event).

5.2 Description of the Inverse transformation method

Let U follow a uniform distribution on the (0,1) interval. Let T be a random variable that follows the Weibull distribution. The inverse transformation states that the cumulative distribution function (c.d.f.) $F_T(t)$ of a random variable T should be equal to U, given that U has a uniform distribution on (0,1). The c.d.f. of T can be written as $P(T \le t) = F(t)$. Also, if $U \sim u(0,1)$ then $(1-U) \sim u(0,1)$. According to inverse transformation, if F_T is strictly increasing then F_T^{-1} is well defined by:

$$F_T(T) = U$$

$$F_T^{-1}(U) = T$$

Recall that the hazard rate written in terms of proportional hazard model can be written as:

$$h(t) = h_0(t)\exp(X\beta) \tag{5.1}$$

In equation (5.1), $h(t)$ is the hazard function at time t, $h_0(t)$ is a baseline hazard, X is a vector of covariates, β is a vector of unknown coefficients. Assuming time to event T has Weibull distribution, the baseline hazard is given by:

$$h_0(t) = \lambda\gamma t^{\gamma-1} \tag{5.2}$$

where λ is the scale parameter and γ is the shape parameter. Substituting the baseline hazard from (5.2) in equation (5.1), hazard function is:

$$h(t) = \lambda\gamma t^{\gamma-1}\exp(X\beta) \tag{5.3}$$

The accelerated failure time model can be written as:

$$\log(T) = \mu + \alpha x + \sigma W \tag{5.4}$$

If event time T in equation (5.4) has a Weibull distribution then W has the standard extreme value distribution. Comparing equation (5.3) and (5.4) the parameters are $\lambda = \exp(-\mu/\sigma)$, $\gamma = 1/\sigma$ and $\beta_j = -\alpha_j/\sigma$ where $j = 1, \ldots, p$.

The survival function for a random variable T with a Weibull distribution is given by:

$$S(t)=\exp\left(-\int_0^t h(u)\,du\right)=\exp\left(-\int_0^t \lambda\gamma u^{\gamma-1}\exp(X\beta)\,du\right)$$

$$=\exp\left(-\lambda\gamma\exp(X\beta)\int_0^t u^{\gamma-1}du\right)=\exp\left(-\lambda\gamma\exp(X\beta)\frac{t^{\gamma}}{\gamma}\right)$$

$$=\exp\left(-\lambda\exp(X\beta)t^{\gamma}\right) \tag{5.5}$$

$$S(t)=1-F(t)\Rightarrow S(t)=U \tag{5.6}$$

From equation (5.5) and (5.6),

$$U=\exp\left(-\lambda\exp(X\beta)t^{\gamma}\right)$$

$$\lambda\exp(X\beta)t^{\gamma}=-\log(U)$$

$$t^{\gamma}=\frac{-\log(U)}{\lambda\exp(X\beta)}$$

$$t=\left[\frac{-\log(U)}{\lambda\exp(X\beta)}\right]^{\frac{1}{\gamma}} \tag{5.7}$$

For simulation purposes a scale parameter of $\lambda=0.00011$ was provided. The shape parameter γ was 0.78137. If the shape parameter γ equals to 1, then the Weibull distribution reduces into the exponential distribution. Because of the baseline hazard $h_0(t)=\lambda\gamma t^{(\gamma-1)}$, if $\gamma<1$, baseline hazard decreases as time increases and if $\gamma>1$ then the baseline hazard increases as time increases. A figure to illustrate the effect of different values of the shape parameter on the probability density function (p.d.f.) is provided below:

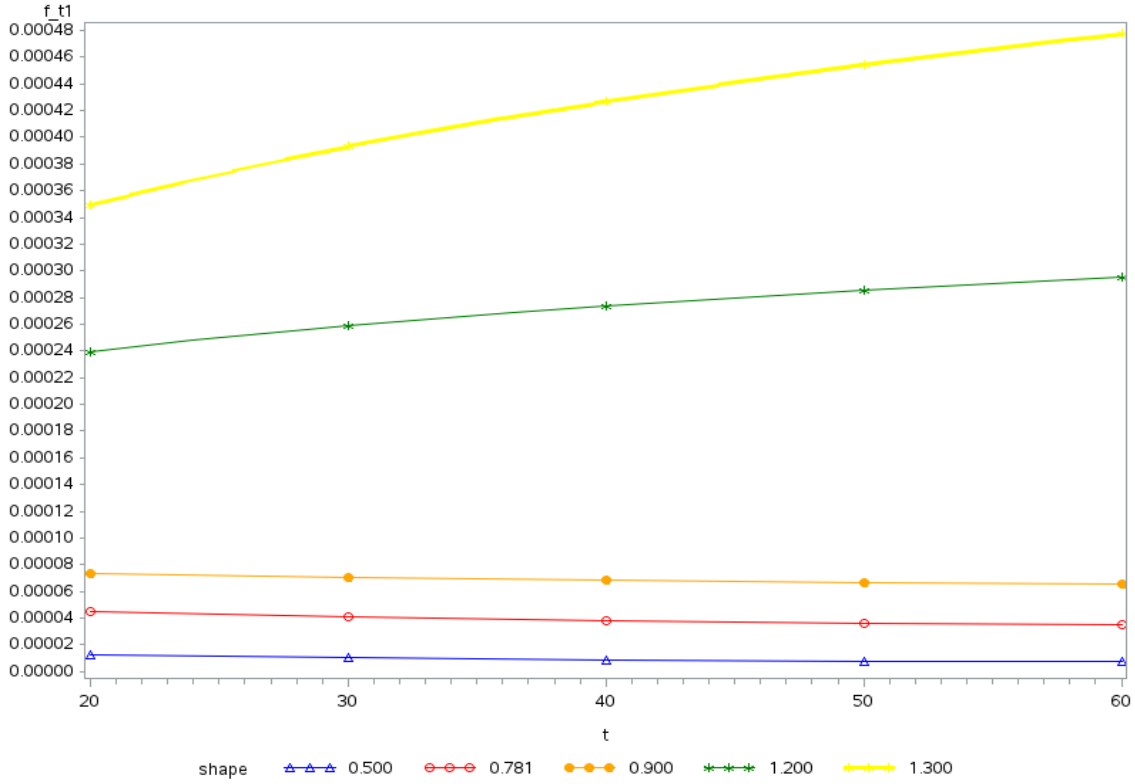


Figure 5.0 Probability density functions for different values of the shape parameter

5.3 Evaluation Criteria for the Estimated Cutpoints

For evaluating the performance of the cutpoint estimation the statistical indicators of bias, mean squared error (MSE), and the 95th percentile intervals were calculated.

5.3.1 Bias

Bias is the difference between the true value of the parameter and the estimated value of the parameter. The bias can be written as:

$$Bias = \frac{1}{n}\sum_{j=1}^{n}\left(\hat{\theta}_j - \theta_{true}\right) = \frac{1}{n}\sum_{j=1}^{n}\hat{\theta}_j - \theta_{true} = \bar{\theta} - \theta_{true}$$

where n is the number of replicates, and $\hat{\theta}_j$ is an estimate of the parameter θ from the j^{th} replicate and $\bar{\theta}$ is the average of estimated cutpoint and is given by:

$$\bar{\theta} = \frac{1}{n}\sum_{j=1}^{n}\hat{\theta}_j .$$

5.3.2 Mean Squared Error:

Mean squared error (MSE) is the average squared difference between the estimator and the true value of the cutpoint and is defined as:

$$MSE = \frac{1}{n}\sum_{j=1}^{n}\left(\hat{\theta}_j - \theta_{true}\right)^2 .$$

5.3.3 95th Percentile Interval

A percentile indicates that the percentage of time the data points are below the resulting value. To calculate the 95th percentile interval, the lower 2.5th and upper 97.5th percentile will be calculated from the estimated cutpoints. The obtained values of 95th percentile interval will indicate that 95% of the time the estimated values of the cutpoints are within that interval.

5.4.1 Cutpoint of 25, Weibull distribution

The first set of results examine an estimator for $\tau_1 = 25$. The results from the proposed score method will be followed by the results from the existing methods.

Table 5.4.1 Simulation Results from the Weibull distributed data, Overall Comparison of three Methods at $\tau_1 = 25$ no censoring

		Proposed Score Method				Klein and Wu Method .				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p 2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	11.37	180.92	25.00	51.00	5.80	58.53	24.00	43.00	9.50	135.40	25.00	48.00
50	2	11.48	268.60	16.00	60.00	9.67	177.95	19.00	53.00	11.74	220.29	21.00	55.00
50	3	10.99	193.83	23.00	53.00	7.24	92.06	23.00	46.00	9.91	150.58	24.00	50.00
50	4	11.57	187.78	25.00	52.00	5.97	61.56	24.00	42.00	9.50	135.20	25.00	48.00
100	1	10.73	150.81	25.00	48.00	4.83	38.96	25.00	39.00	8.19	94.31	25.00	44.00
100	2	10.77	204.15	21.00	55.00	9.28	141.41	22.00	50.00	11.11	181.06	23.50	51.00
100	3	10.08	150.81	25.00	50.00	5.97	58.23	24.00	41.00	8.42	101.85	25.00	45.00
100	4	10.56	147.12	25.00	47.50	4.75	37.11	25.00	38.00	8.05	90.91	25.00	44.00
500	1	10.96	134.30	29.00	43.00	3.80	20.61	25.00	34.00	7.24	61.41	27.00	38.00
500	2	11.67	177.41	25.00	49.00	9.06	104.95	25.00	44.00	10.54	134.67	27.00	45.00
500	3	10.40	130.41	27.00	45.00	5.49	40.20	25.00	37.00	8.01	76.17	26.00	40.00
500	4	11.02	135.81	28.00	43.00	3.78	19.99	25.00	34.00	7.26	62.94	26.00	39.00
1000	1	11.13	133.37	30.00	42.00	3.63	16.80	25.00	32.50	7.10	55.82	27.00	36.00
1000	2	11.96	171.91	27.00	48.00	9.04	96.03	27.00	41.00	10.61	127.63	28.00	43.00
1000	3	10.46	124.41	28.00	43.00	5.43	36.02	26.00	35.50	7.97	71.32	27.00	38.00
1000	4	11.30	137.41	30.00	42.00	3.66	17.12	25.00	32.00	7.09	56.24	27.00	37.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5^{th} percentile and p97.5 refers to upper 97.5^{th} percentile

For the cutpoint of 25, all three methods overestimate the cutpoint. In particular the proposed score method has larger bias and MSE than the other two existing methods. The bias for the proposed score method at sample size 1000 and risk ratio 1.00-1.01 is

11.13 and whereas the bias for the Klein and Wu and the Contal and O'Quigley methods at the same scenario is 3.63 and 7.10 respectively. The sample size 1000 and risk ratio 1.00-1.01 was chosen because it has the smallest bias and MSE for the Klein and Wu method. For all three methods, the risk ratio of 1.01-1.03 had highest MSE and bias at each different sample sizes. Also, the 95th percentile interval is wider at sample size of 50 and risk ratio of 1.01-1.03 for all three methods.

Table 5.4.2 Simulation Results from the Weibull distributed data, Overall Comparison of three methods for 25% censoring and $\tau_1 = 25$

		Proposed Score Method				Klein and Wu Method .				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	12.44	213.88	25.00	54.00	7.46	99.36	24.00	49.00	9.32	130.84	25.00	49.00
50	2	13.25	336.14	16.00	65.00	11.12	232.97	19.00	58.00	11.79	228.99	21.00	57.00
50	3	12.36	237.50	23.00	57.00	8.68	140.20	22.00	52.50	9.97	151.03	23.50	50.00
50	4	12.40	210.63	25.00	52.00	7.28	98.32	24.00	48.50	9.24	131.63	25.00	49.50
100	1	11.98	179.89	26.00	48.00	5.91	60.87	24.00	42.00	8.06	94.99	25.00	45.50
100	2	11.73	231.55	21.00	57.00	9.85	164.67	20.00	52.00	10.06	152.01	23.00	51.00
100	3	11.39	184.02	25.00	51.00	7.32	90.63	24.00	46.00	8.83	111.63	25.00	46.00
100	4	12.14	187.20	26.00	49.00	6.04	63.98	25.00	44.00	7.99	91.61	25.00	44.00
500	1	12.03	160.75	29.00	44.00	4.30	27.87	25.00	36.00	7.08	59.89	26.00	38.00
500	2	11.93	182.29	25.00	49.00	9.09	110.37	25.00	46.00	10.33	129.13	27.00	45.00
500	3	11.38	152.42	27.00	45.00	5.76	48.11	25.00	39.00	7.81	72.98	26.00	40.00
500	4	11.91	157.11	29.00	44.00	4.16	27.10	25.00	36.00	7.20	60.83	26.00	38.00
1000	1	12.47	165.19	31.00	43.00	4.02	22.61	25.00	34.00	7.19	57.71	28.00	37.00
1000	2	12.12	177.03	26.50	47.00	9.04	99.00	26.00	42.00	10.49	124.21	28.00	42.00
1000	3	11.97	159.23	29.00	44.50	5.47	39.06	25.00	37.00	8.06	72.84	28.00	38.00
1000	4	12.45	165.64	31.00	44.00	4.07	23.98	25.00	35.00	7.11	56.59	27.00	37.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5th percentile and p97.5 refers to upper 97.5th percentile

Looking at Table 5.4.2 above, all three methods overestimated the cutpoint, the largest bias for the proposed score method was 13.25 and the smallest bias was 11.38. The largest bias for the Klein and Wu method was 11.12 and the smallest bias was 4.07. The largest bias for the Contal and O'Quigley method was 11.79 and the smallest bias was 7.11. These results are similar to situation with no censoring.

5.4.2 Cutpoint of 50, Weibull distribution

The first set of results examine an estimator for $\tau_1 = 50$. The results from the proposed score method will be followed by the results from the existing methods.

Table 5.4.3 Simulation Results from the Weibull distributed data, Overall Comparison of Three Methods at $\tau_1 = 50$ no censoring

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	1.93	9.41	50.00	58.50	0.27	7.95	42.50	55.00	-1.48	22.50	37.00	55.00
50	2	-1.12	108.40	17.50	65.00	-4.35	80.33	24.50	56.00	-3.50	65.63	28.00	57.50
50	3	2.12	16.33	46.00	60.50	-1.10	20.73	37.00	55.00	-1.87	30.16	34.00	55.00
50	4	1.87	9.63	50.00	58.00	0.40	8.19	44.00	56.00	-1.51	24.90	36.50	55.00
100	1	1.04	3.65	50.00	55.50	0.05	2.34	46.00	53.00	-0.99	8.16	42.00	52.00
100	2	0.21	29.40	36.50	61.00	-2.99	33.28	34.00	53.00	-2.67	30.12	35.00	53.00
100	3	1.08	4.83	48.00	56.00	-0.63	5.24	44.00	52.00	-1.17	9.05	42.00	52.00
100	4	0.89	3.03	50.00	55.00	0.05	1.80	47.00	52.00	-0.88	6.73	42.00	52.00
500	1	0.15	0.26	50.00	52.00	-0.02	0.03	50.00	50.00	-0.17	0.27	48.00	50.00
500	2	0.49	2.21	49.00	55.00	-0.83	3.49	44.00	51.00	-0.77	3.09	45.00	51.00
500	3	0.27	0.59	50.00	53.00	-0.15	0.24	48.00	50.00	-0.25	0.49	48.00	50.00
500	4	0.15	0.25	50.00	51.00	-0.02	0.03	50.00	50.00	-0.18	0.37	48.00	50.00
1000	1	0.06	0.07	50.00	51.00	-0.00	0.00	50.00	50.00	-0.04	0.04	49.00	50.00
1000	2	0.34	0.94	49.00	53.00	-0.43	1.04	47.00	50.00	-0.39	0.84	47.00	50.00
1000	3	0.11	0.16	50.00	51.00	-0.04	0.05	49.00	50.00	-0.08	0.11	49.00	50.00
1000	4	0.08	0.11	50.00	51.00	-0.01	0.01	50.00	50.00	-0.05	0.02	49.00	50.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5^{th} percentile and p97.5 refers to upper 97.5^{th} percentile

Looking at the Table 5.4.3, bias and MSE are large at sample size 50 and risk ratio 1.01-1.03. Also, the 95^{th} percentile interval is wider for all three methods at the same scenario. The bias and MSE are smaller for a sample size of 500 and 1000. All three methods performed well at a sample size 500 and 1000 for the cutpoint of 50.

Table 5.4.4 Simulation Results from the Weibull distributed data, overall Comparison of three methods at $\tau_1 = 50$ with 25% censoring

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**bias**	**MSE**	**p2.5**	**p97.5**	**bias**	**MSE**	**p2.5**	**p97.5**	**bias**	**MSE**	**p2.5**	**p97.5**
50	1	2.18	11.80	50.00	60.00	0.02	17.32	40.00	58.00	-1.56	23.52	36.00	55.00
50	2	-0.25	96.82	24.00	69.00	-4.47	98.11	24.00	60.00	-3.53	67.39	27.00	57.00
50	3	1.97	14.75	46.00	60.00	-1.41	35.13	33.00	58.00	-1.84	27.50	34.50	55.00
50	4	2.11	11.26	50.00	59.00	0.12	16.07	40.00	58.00	-1.47	23.97	36.00	55.00
100	1	1.20	4.59	50.00	56.00	-0.06	5.01	44.00	54.00	-0.99	8.36	41.00	52.00
100	2	0.39	32.38	38.00	61.50	-3.01	43.37	32.00	55.00	-2.90	33.72	34.00	54.00
100	3	1.23	5.78	48.00	57.00	-1.02	13.82	39.00	54.00	-1.23	10.49	40.00	52.50
100	4	1.14	4.00	50.00	56.00	-0.13	4.52	44.00	54.00	-0.79	5.96	43.00	53.00
500	1	0.18	0.30	50.00	52.00	-0.05	0.15	49.00	50.50	-0.17	0.32	48.00	50.00
500	2	0.65	2.67	49.00	55.00	-1.02	5.39	43.00	52.00	-0.77	3.05	45.00	51.00
500	3	0.30	0.68	50.00	53.00	-0.29	0.87	47.00	51.00	-0.20	0.34	48.00	50.00
500	4	0.22	0.43	50.00	52.00	-0.10	0.23	49.00	50.00	-0.19	0.38	48.00	50.00
1000	1	0.09	0.14	50.00	51.00	-0.02	0.03	50.00	50.00	-0.05	0.06	49.00	50.00
1000	2	0.35	0.93	49.00	53.00	-0.60	2.03	46.00	51.00	-0.40	0.99	47.00	50.00
1000	3	0.12	0.16	50.00	51.00	-0.08	0.12	49.00	50.00	-0.06	0.07	49.00	50.00
1000	4	0.08	0.10	50.00	51.00	-0.02	0.02	50.00	50.00	-0.04	0.04	49.00	50.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5^{th} percentile and p97.5 refers to upper 97.5^{th} percentile

From Table 5.4.4, the Klein and Wu and Contal and O'Quigley methods underestimated the cutpoint 50 whereas the proposed score method overestimated the cutpoint. But the absolute bias is small for the large sample sizes for all three methods. The largest bias for the proposed score method is 2.18, the largest absolute bias for the Klein and Wu method is 4.47 and largest absolute bias for the Contal and O'Quigley method is 3.53. The largest MSE for the proposed score method is 96.82, for the Klein and Wu method is 98.11 and for Contal and O'Quigley method it is 67.39. At the sample

size 1000, all three methods have small bias and MSE. The proposed score method tends to have the lowest bias and MSE.

5.4.3 Cutpoint of 75, Weibull distribution

The first set of results examine an estimator for $\tau_1 = 75$. The results from the proposed score method will be followed by the results from the existing methods.

Table 5.4.5 Simulation Results from Weibull distributed data Overall Comparison of Three Methods at $\tau_1 = 75$ no censoring

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**bias**	**MSE**	**p2.5**	**p97.5**	**bias**	**MSE**	**p2.5**	**p97.5**	**bias**	**MSE**	**p2.5**	**p97.5**
50	1	1.16	11.00	74.00	81.00	-14.27	399.94	28.00	78.00	-22.12	735.00	23.00	76.00
50	2	-20.86	847.94	12.00	79.00	-25.30	889.24	17.00	75.00	-24.75	854.01	19.00	75.00
50	3	-2.47	115.81	34.00	80.00	-20.42	657.82	23.00	76.00	-23.15	781.81	21.00	76.00
50	4	0.93	10.58	74.00	81.00	-13.59	363.79	29.00	77.00	-21.23	664.61	22.00	76.00
100	1	0.45	0.97	75.00	78.00	-12.01	266.17	38.00	76.00	-21.05	614.71	28.00	75.00
100	2	-17.36	614.79	16.00	78.00	-23.71	742.81	25.00	74.00	-23.60	613.11	25.00	74.00
100	3	-0.13	8.27	69.00	78.00	-16.49	433.80	30.00	75.00	-20.72	602.90	26.50	75.00
100	4	0.48	0.97	75.00	78.00	-13.22	316.15	34.00	76.00	-21.70	645.71	27.00	75.00
500	1	0.01	0.01	75.00	75.00	-8.12	120.13	49.00	75.00	-18.80	436.66	38.00	73.00
500	2	-10.64	263.42	36.00	75.00	-21.53	544.95	36.00	71.00	-22.12	571.53	35.00	71.00
500	3	-0.01	0.01	75.00	75.00	-13.53	262.88	43.00	75.00	-18.77	440.92	37.50	74.00
500	4	0.00	0.01	75.00	75.00	-7.84	113.80	49.50	75.00	-18.44	423.47	38.00	73.50
1000	1	0.00	0.00	75.00	75.00	-6.30	73.55	55.00	75.00	-18.23	385.80	43.00	71.50
1000	2	-8.83	202.40	42.00	75.00	-21.00	495.79	39.00	69.00	-21.53	521.10	39.00	69.00
1000	3	0.00	0.00	75.00	75.00	-12.65	211.45	48.00	75.00	-18.58	402.12	41.50	70.00
1000	4	0.00	0.00	75.00	75.00	-6.39	75.07	54.00	75.00	-18.61	139.07	41.00	70.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5^{th} percentile and p97.5 refers to upper 97.5^{th} percentile

For the cutpoint of 75, the Klein and Wu and Contal and O'Quigley methods underestimated the cutpoint at all scenarios. The proposed score method has accurate

result except at the risk ratio of 1.01-1.03. The cutpoints estimated at that risk ratio has high bias and MSE for every sample size. In the proposed score method with sample size 50 and risk ratio 1.01-1.03, the 95th percentile interval range from 12 to 79 giving highly variable estimates at the lower end. Similarly, Klein and Wu has (17, 75) and Contal and O'Quigley has (19, 75) 95th percentile interval at that risk ratio. Overall, for the cutpoint 75 the proposed score method has lower bias and MSE regardless of the sample size in comparison to other two methods.

Table 5.4.6 Simulation Results from the Weibull distributed data, Overall Comparison of three methods, 25% censoring, $\tau_1 = 75$

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	1.09	12.74	75.00	81.00	-16.34	486.37	24.50	78.00	-21.94	705.86	21.00	76.00
50	2	-15.72	632.62	13.00	80.50	-25.45	924.74	19.00	76.00	-24.78	861.77	19.00	76.00
50	3	-0.76	66.98	46.00	81.00	-20.36	676.75	20.00	77.00	-22.80	763.44	20.00	76.50
50	4	1.00	18.90	75.00	81.00	-15.89	484.72	23.50	77.50	-22.15	719.37	22.00	76.00
100	1	0.47	0.99	75.00	78.00	-14.53	386.74	29.50	76.00	-21.09	616.81	28.00	75.00
100	2	-11.91	417.09	20.00	78.00	-24.21	802.12	22.00	75.00	-24.13	770.38	22.50	75.00
100	3	0.11	8.00	72.00	78.00	-18.26	528.74	26.00	75.00	-21.43	645.02	24.00	75.00
100	4	0.47	0.90	75.00	78.00	-13.87	351.62	31.00	76.00	-21.45	644.71	24.50	75.00
500	1	0.00	0.00	75.00	75.00	-8.77	144.12	47.00	75.00	-18.48	427.71	37.00	73.50
500	2	-3.28	66.04	47.50	75.00	-21.23	547.93	36.00	72.50	-22.02	567.62	36.00	71.00
500	3	-0.00	0.01	75.00	75.00	-14.15	290.90	40.50	75.00	-19.29	458.18	37.00	73.00
500	4	0.00	0.00	75.00	75.00	-8.81	143.62	47.00	75.00	-18.51	429.14	37.00	74.00
1000	1	0.00	0.00	75.00	75.00	-7.53	101.53	52.00	75.00	-18.28	389.66	43.00	72.00
1000	2	-0.99	14.96	62.00	75.00	-21.11	516.11	37.00	71.00	-21.94	536.43	39.00	67.00
1000	3	0.00	0.00	75.00	75.00	-12.99	235.30	45.00	75.00	-18.18	392.01	41.00	72.00
1000	4	0.00	0.00	75.00	75.00	-7.34	98.97	52.00	75.00	-18.03	381.22	43.00	71.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5th percentile and p97.5 refers to upper 97.5th percentile

Looking at the Table 5.4.6, the proposed score method has better performance overall. For sample size 50 and relative risk 1.01-1.03, the absolute bias is 15.72 and MSE is 632.62. The 95^{th} percentile interval at sample size 50 and relative risk of 1.01-1.03 for the proposed score method is (13.0, 80.5), the 95^{th} percentile interval for the Klein and Wu for that scenario is (19.0, 76.0), similarly the 95^{th} percentile interval for the Contal and O'Quigley method for the same scenario is (19.0, 76.0). Since the proposed score method has wider percentile interval at sample size 50 and relative risk of 1.01-1.03 in comparison to other existing methods, but narrower percentile intervals at larger sample size, the performance of score method depends upon the relative risk estimates as well as sample size. The result is similar to that with no censoring.

In the section above the proposed score method was compared with the Klein and Wu and the Contal and O'Quigley methods for the Weibull distributed data. In the section below, performance from the proposed score method will be compared with the Klein and Wu and the Contal and O'Quigley methods with data obtained from an exponential distribution.

5.5.1 Cutpoint of 25, Exponential Distribution

The result from the proposed method will be compared with the existing methods Klein and Wu (2004) and Contal and O'Quigley (1999) for the true cutpoint of 25.

Table 5.5.1 Overall Comparisons, Exponential distribution, no censoring, $\tau_1 = 25$

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	-3.77	94.08	10.00	49.50	0.64	9.44	19.00	31.00	8.81	120.99	25.00	49.00
50	2	15.71	1006.49	2.50	86.50	7.50	135.95	17.00	51.50	11.90	231.80	21.00	57.50
50	3	-3.79	318.60	5.00	79.00	2.14	26.57	19.00	38.50	10.02	154.09	24.00	51.00
50	4	-3.82	90.63	11.00	47.50	0.56	8.88	18.00	31.00	9.74	140.44	25.00	49.50
100	1	-6.35	65.06	13.00	31.50	0.12	3.12	21.00	29.00	8.23	96.21	25	42.0
100	2	14.33	1007.60	3.00	88.00	7.10	103.79	20.00	48.00	11.40	189.63	25	50.0
100	3	-9.22	254.02	5.00	68.50	1.27	10.08	21.00	33.00	8.75	109.65	25	44.0
100	4	-6.36	60.80	13.00	27.00	0.08	2.19	21.50	28.00	8.20	94.74	25	42.0
500	1	-7.41	57.11	15.00	20.00	-0.03	0.08	24.00	25.00	7.24	62.77	26.00	38.00
500	2	-2.27	619.03	4.00	88.00	6.43	59.96	25.00	40.50	10.38	129.66	27.00	45.00
500	3	-12.97	171.79	9.00	16.00	0.61	1.70	24.00	29.00	7.84	73.24	26.00	40.00
500	4	-7.49	57.82	15.00	20.00	-0.04	0.07	24.00	25.00	7.03	59.73	26.00	39.00
1000	1	-7.54	58.46	16.00	19.00	0.02	0.40	25.00	25.00	7.19	57.12	27.50	37.00
1000	2	-10.48	377.14	5.00	86.50	6.35	54.01	25.00	39.00	10.73	131.65	28.00	43.00
1000	3	-13.20	176.28	9.00	15.00	0.41	0.84	25.00	28.00	7.92	70.78	27.50	38.00
1000	4	-7.57	58.25	16.00	19.00	-0.00	0.00	25.00	25.00	7.12	56.34	27.00	37.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5^{th} percentile and p97.5 refers to upper 97.5^{th} percentile

For the cutpoint of 25, the proposed score method tends to underestimate the actual cutpoint, whereas the Contal and O'Quigley method tends to overestimate the actual cutpoint. In particular the proposed score method has larger bias and MSE than the two existing methods. The bias for the proposed score method at sample size 1000 and risk ratio 1.00-1.01 is 7.57 whereas the bias for the Klein and Wu and the Contal and

O'Quigley methods at the same scenario is 0 and 7.12 respectively. The sample size 1000 and risk ratio 1.00-1.01 was chosen because it has the smallest bias and MSE for the Klein and Wu method. At the sample size 50 and risk ratio of 1.01-1.03, the proposed score has largest bias of 15.71 whereas the Klein and Wu has bias of 7.50 and the Contal and O'Quigley has bias of 11.90 at the given scenario. For all three methods, the risk ratio of 1.01-1.03 had highest MSE and bias at each sample size. Also, the 95th percentile interval is wider at sample size 50 and risk ratio of 1.01-1.03 for all three methods.

Table 5.5.2 Overall Comparison, Exponential distribution, 25% censoring, $\tau_1 = 25$

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	5.55	284.71	14.00	72.00	1.12	15.42	18.00	35.00	9.44	131.36	25.00	49.00
50	2	19.93	1015.84	4.00	86.00	8.03	157.99	16.00	55.00	11.62	222.75	21.00	57.00
50	3	10.26	648.01	9.00	84.00	2.77	33.54	19.00	40.00	9.75	146.50	24.00	50.00
50	4	5.18	294.86	14.00	75.00	0.90	12.72	18.00	34.00	9.59	137.03	25.00	48.00
100	1	-0.37	131.72	15.00	59.00	0.43	3.52	21.00	29.00	8.03	90.63	25.00	44.00
100	2	19.44	1040.80	6.00	87.00	7.84	120.24	21.00	50.00	10.97	179.36	23.00	53.00
100	3	2.84	426.92	10.00	82.00	1.73	14.71	21.00	36.00	8.32	101.99	25.00	46.00
100	4	-0.35	131.28	15.00	58.50	0.36	3.45	21.00	29.00	8.33	96.90	25.00	44.00
500	1	-5.83	38.09	17.00	22.00	0.01	0.20	24.00	26.00	7.28	62.49	26.00	38.00
500	2	5.01	542.66	8.00	85.00	6.81	67.25	25.00	42.00	10.71	139.52	26.00	45.00
500	3	-9.21	97.86	12.00	20.00	0.78	2.49	24.00	29.00	8.12	78.37	26.00	41.00
500	4	-5.88	38.01	17.00	21.00	0.00	0.12	24.00	26.00	7.28	62.31	26.00	38.00
1000	1	-5.98	37.24	17.00	21.00	0.03	0.86	25.00	25.00	7.11	56.62	28.00	37.00
1000	2	-4.22	216.97	9.00	68.50	6.47	57.16	25.00	40.00	10.61	127.33	28.00	43.00
1000	3	-9.75	97.20	13.00	18.00	0.56	1.27	25.00	28.00	7.84	69.29	28.00	38.00
1000	4	-5.97	36.63	17.00	21.00	0.00	0.01	25.00	25.00	7.24	57.81	28.00	37.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5th percentile and p97.5 refers to upper 97.5th percentile

For the cutpoint of 25, the Contal and O'Quigley tends to overestimate the cutpoint, the proposed score method has mixed results with overestimation of the actual cutpoint at smaller sample sizes and underestimation of the actual cutpoint at larger sample sizes. The Klein and Wu method has estimates approximately equal to the true cutpoint. In particular the proposed score method has larger bias and MSE than the two existing methods. The bias for the proposed score method at sample size 1000 and risk ratio 1.00-1.01 is 5.97 and whereas the bias for the Klein and Wu and the Contal and O'Quigley methods at the same scenario is 0 and 7.24 respectively. The sample size 1000 and risk ratio 1.00-1.01 was chosen because it has the smallest bias and MSE for the Klein and Wu method. For all three methods, the risk ratio of 1.01-1.03 had highest MSE and bias at each different sample sizes. Also, the 95^{th} percentile interval is wider at sample size 50 and risk ratio of 1.01-1.03 for all three methods.

5.5.2 Cutpoint of 50, Exponential distribution

The result from the proposed method will be compared with the existing methods of Klein and Wu (2004) and Contal and O'Quigley (1999) for the true cutpoint of 50.

Table 5.5.3 Overall Comparison, Exponential distribution, no censoring, $\tau_1 = 50$

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	-4.62	31.66	37.00	49.00	-4.21	64.68	26.00	53.50	-1.49	22.21	36.00	54.00
50	2	-17.53	788.02	4.00	85.00	-6.09	105.31	24.00	55.00	-4.09	76.30	26.00	57.00
50	3	-12.53	199.78	24.00	47.00	-4.09	57.58	28.50	54.00	-1.81	26.33	35.00	54.00
50	4	-4.54	31.37	37.00	49.00	-4.09	61.67	28.50	54.00	-1.46	22.42	35.50	55.00
100	1	-4.17	22.56	41.00	49.00	-3.05	30.60	34.00	52.00	-1.49	22.21	36.00	54.00
100	2	-21.43	793.75	8.00	85.00	-4.13	50.06	31.00	52.50	-4.09	76.30	26.00	57.00
100	3	-12.19	172.46	28.00	46.00	-2.77	25.69	36.00	52.00	-1.81	26.33	35.00	54.00
100	4	-4.04	21.68	40.00	49.00	-2.87	28.07	35.00	52.00	-1.46	22.42	35.50	55.00
500	1	-3.78	15.53	44.00	48.00	-0.82	2.80	45.00	50.00	-0.20	0.36	48.00	50.00
500	2	-28.05	812.25	14.00	31.00	-1.41	6.66	42.00	50.00	-0.83	3.51	44.00	51.00
500	3	-12.40	159.48	33.00	42.00	-0.69	2.07	46.00	50.00	-0.23	0.45	48.00	50.00
500	4	-3.81	15.84	44.00	48.00	-0.72	2.18	46.00	50.00	-0.20	0.34	48.00	50.00
1000	1	-3.72	14.52	45.00	48.00	-0.30	0.56	48.00	50.00	-0.05	0.06	49.00	50.00
1000	2	-28.77	837.38	15.00	27.50	-0.83	2.84	45.00	50.00	-0.42	1.11	47.00	50.00
1000	3	-12.47	158.75	34.00	41.00	-0.34	0.72	47.00	50.00	-0.07	0.09	49.00	50.00
1000	4	-3.72	14.52	45.00	48.00	-0.29	0.53	48.00	50.00	-0.05	0.06	49.00	50.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5^{th} percentile and p97.5 refers to upper 97.5^{th} percentile

For the true cutpoint of 50, the proposed score method underestimates the true cutpoint but the Klein and Wu and the Contal and O'Quigley has estimates approximately equal to the true cutpoint. In particular the proposed score method has larger bias and MSE than the other two methods. The bias for the proposed score method at sample size 1000 and risk ratio 1.00-1.01 is 3.72, whereas the bias for the Klein and

Wu and the Contal and O'Quigley methods at the same scenario is 0.29 and 0.05 respectively. The sample size 1000 and risk ratio 1.00-1.01 was chosen because it has the smallest bias and MSE for the Klein and Wu method. For all three methods, the risk ratio of 1.01-1.03 had highest MSE and bias at each different sample sizes. Also, the 95th percentile interval is wider at sample size 50 and risk ratio of 1.01-1.03 for all three methods.

Table 5.5.4 Overall comparisons, Exponential distribution, 25% censoring, $\tau_1 = 50$

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	-4.04	26.15	38.00	49.00	-4.17	70.55	27.00	56.00	-1.35	21.30	37.00	55.00
50	2	-10.98	553.75	7.00	84.00	-5.51	117.45	22.00	58.00	-3.73	65.97	28.00	57.00
50	3	-9.73	142.37	26.00	49.00	-4.69	81.94	25.00	56.00	-1.71	25.30	35.00	55.00
50	4	-4.13	27.67	38.00	49.00	-4.00	68.55	27.00	56.00	-1.46	22.33	37.00	54.00
100	1	-3.37	15.06	42.00	49.00	-2.96	30.87	34.00	52.50	-0.93	6.66	43.00	52.00
100	2	-15.13	561.45	11.00	84.00	-4.48	65.53	28.00	54.50	-2.59	31.74	34.00	54.00
100	3	-9.50	111.14	30.00	48.00	-3.14	36.21	32.00	53.00	-1.20	9.90	40.00	52.00
100	4	-3.41	15.97	41.50	49.00	-2.69	28.02	35.00	52.50	-0.96	7.03	42.00	52.00
500	1	-3.05	10.31	45.00	49.00	-0.86	3.45	45.00	50.00	-0.17	0.26	48.00	50.00
500	2	-22.37	523.68	19.00	37.00	-1.55	8.76	41.50	51.00	-0.73	2.60	45.00	51.00
500	3	-9.55	96.57	35.50	44.00	-0.96	4.09	44.00	50.00	-0.25	0.46	48.00	50.00
500	4	-3.04	10.24	45.00	49.00	-0.83	2.96	45.00	50.00	-0.17	0.32	49.00	50.00
1000	1	-2.97	9.35	46.00	48.00	-0.35	0.74	47.00	50.00	-0.05	0.06	49.00	50.00
1000	2	-23.00	542.16	21.00	34.00	-0.82	3.06	44.00	50.00	-0.34	0.84	47.00	50.00
1000	3	-9.52	93.62	37.00	44.00	-0.40	0.85	47.00	50.00	-0.07	0.10	49.00	50.00
1000	4	-2.97	9.41	46.00	48.00	-0.41	0.93	47.00	50.00	-0.05	0.07	49.00	50.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5th percentile and p97.5 refers to upper 97.5th percentile

At the actual cutpoint of 50 and 25% censoring, the Contal and O'Quigley method has the smallest bias and MSE among three methods. For sample size 50 and risk ratio of

1.01-1.03, the 95th percentile for the proposed score method is (7, 84) which shows high variability in the estimate at that scenario. The 95th percentile interval for the Klein and Wu method at the same scenario is (22, 58) and the 95th percentile interval for the Contal and O'Quigley method is (28, 57). This indicates the Contal and O'Quigley is best performer for a cutpoint of 50 for exponentially distributed data.

5.5.3 Cutpoint of 75, Exponential distribution

The result from the proposed method will be compared with the existing methods of Klein and Wu (2004) and Contal and O'Quigley (1999) for the true cutpoint of 75.

Table 5.5.5 Overall comparison, Exponential distribution, no censoring, $\tau_1 = 75$

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	-4.84	70.78	50.00	74.00	-24.49	860.50	16.50	76.00	-22.07	732.16	21.50	76.00
50	2	-27.73	1045.27	12.00	74.00	-26.73	976.33	17.00	75.00	-24.07	818.14	19.00	75.00
50	3	-10.26	212.16	33.00	74.00	-25.80	925.29	17.00	75.00	-23.19	780.26	21.00	76.00
50	4	-4.62	64.24	50.50	74.00	-24.93	872.42	20.00	75.00	-22.01	705.03	23.00	75.50
100	1	-2.35	10.84	66.00	74.00	-23.07	718.20	23.00	75.00	-22.07	732.16	21.50	76.00
100	2	-27.64	952.06	20.00	71.00	-25.42	831.52	24.00	74.00	-24.07	818.14	19.00	75.00
100	3	-7.28	96.75	47.00	74.00	-23.94	771.37	23.00	74.00	-23.19	780.26	21.00	76.00
100	4	-2.36	11.15	67.00	74.00	-23.21	736.16	24.00	75.00	-22.01	705.03	23.00	75.50
500	1	-1.25	1.80	73.00	74.00	-21.94	567.77	34.50	71.50	-18.57	425.21	38.00	73.00
500	2	-28.81	889.47	32.00	61.00	-23.96	663.39	32.00	69.00	-21.52	546.40	35.00	71.00
500	3	-4.99	29.71	65.00	73.00	-21.82	563.54	35.00	72.00	-19.06	450.18	38.00	73.00
500	4	-1.22	1.71	73.00	74.00	-21.66	555.73	34.00	70.50	-18.70	432.33	38.00	73.00
1000	1	-1.09	1.28	73.00	74.00	-21.85	536.55	38.00	68.00	-18.44	402.04	41.00	73.00
1000	2	-29.20	891.24	35.00	58.00	-23.45	602.60	37.00	65.50	-21.88	531.67	39.00	67.00
1000	3	-4.71	24.56	67.00	73.00	-21.64	523.12	38.00	68.00	-18.73	405.21	42.00	71.00
1000	4	-1.10	1.31	73.00	74.00	-21.28	505.68	39.50	68.00	-18.10	380.27	43.00	71.00

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5^{th} percentile and p97.5 refers to upper 97.5^{th} percentile

For the cutpoint of 75 with no censoring, the proposed score method has lowest bias and MSE for all risk ratios except for 1.01-1.03. The 95^{th} percentile interval for the proposed score method at sample size 50 and risk ratio 1.01-1.03 is (12, 74), whereas the 95^{th} percentile interval for the Klein and Wu method at the same scenario is (17, 75) and for the Contal and O'Quigley method the 95^{th} percentile interval is (19, 75) for that

scenario. For all relative risks other than 1.01-1.03, proposed score method has less variability in terms of percentile intervals and MSE.

Table 5.5.6 Overall comparison, Exponential distribution, 25% censoring, $\tau_1 = 75$

		Proposed Score Method				Klein and Wu Method				Contal and O'Quigley Method			
N	**RR**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**	**Bias**	**MSE**	**p2.5**	**p97.5**
50	1	-5.22	89.57	45.00	74.00	-25.21	902.90	18.00	75.00	-22.38	741.67	22.00	76.00
50	2	-24.21	893.22	14.00	79.00	-28.07	1088.59	14.00	76.00	-25.38	903.41	17.00	76.00
50	3	-8.76	170.85	36.00	74.00	-25.66	943.99	15.50	76.00	-22.84	752.38	23.00	76.00
50	4	-5.66	102.62	43.00	74.00	-24.53	877.16	17.00	76.00	-21.97	722.32	21.00	76.00
100	1	-2.42	17.27	66.50	74.00	-24.19	780.76	22.00	74.50	-21.84	649.63	27.00	75.00
100	2	-23.32	745.48	21.00	73.00	-25.57	890.67	18.00	75.00	-23.98	758.73	23.00	75.00
100	3	-6.11	76.24	51.00	74.00	-24.02	783.16	23.00	75.00	-21.34	630.68	27.00	75.00
100	4	-2.35	13.00	67.00	74.00	-24.16	784.65	22.00	75.00	-21.17	628.32	28.00	75.00
500	1	-1.13	1.42	73.00	74.00	-21.74	565.77	35.00	71.50	-18.79	438.77	38.00	73.00
500	2	-22.33	575.26	34.00	67.00	-23.96	671.48	32.00	71.00	-22.26	576.13	35.00	71.00
500	3	-3.67	16.63	67.00	74.00	-21.91	580.77	33.00	71.00	-19.16	453.29	37.00	73.00
500	4	-1.15	1.50	73.00	74.00	-21.60	560.22	34.00	72.00	-18.79	435.17	38.00	72.50
1000	1	-1.03	1.09	73.00	74.00	-20.98	506.46	38.50	69.00	-17.99	378.51	43.50	71.00
1000	2	-22.56	559.24	38.50	65.00	-23.81	634.35	35.00	67.00	-21.82	533.62	39.00	67.00
1000	3	-3.46	13.55	69.00	73.00	-21.30	521.22	38.00	69.00	-18.76	411.38	41.00	71.00
1000	4	-1.03	1.10	73.00	74.00	-20.72	492.68	38.00	70.00	-18.23	390.80	42.00	71.50

Note: 1) RR represents the hazard ratio scenarios
2) p2.5 refers to lower 2.5^{th} percentile and p97.5 refers to upper 97.5^{th} percentile

For the actual cutpoint of 75, the proposed score method has better results than the two existing methods. For the relative risk 1.01-1.03, the proposed score method has larger bias and MSE than other relative risks. The bias and MSE decreases as the sample size increases. The results using a cutpoint of 75 with exponential distributed data are similar to the results from Weibull distributed data.

Looking at all the results from Weibull distributed data and exponentially distributed data, the results vary for each distribution. For Weibull distributed data, the proposed score method overestimated the cutpoint of 25, but for exponentially distributed data, the proposed score has both underestimation and overestimation for the cutpoint. The proposed score method has better result for Weibull distributed data for the cutpoint of 75. The Klein and Wu method performed better for the cutpoint of 25 for both Weibull and exponentially distributed data. At the actual cutpoint of 50, the Klein and Wu and the Contal and O'Quigley methods had similar results for both distribution.

In this chapter 5, we discussed the performance of proposed method versus the performance of other two existing methods, for different scenarios in simulated data. In Chapter 6, results from proposed method will be compared with the Klein and Wu (2004) and Contal and O'Quigley (1999) on real dataset to evaluate the performance of these methods.

CHAPTER 6: APPLICATION TO REAL DATA

6.1 Introduction

Data used for the application in the proposed method was also presented in the textbook "Survival Analysis: Techniques for Censored and Truncated Data" by Klein and Moeschberger (2003). The data set was obtained from a kidney transplant trial of 863 patients conducted during the period 1982 to 1992 from The Ohio State University, Columbus, Ohio. The maximum follow up time for this study was 9.47 years. Patients were censored because of loss of follow-up or were still alive at the end of the study in June 30, 1992.

Data from this study were composed of 432 white males, 92 black males, 280 white females and 59 black females in the study. The age of the patient ranged from 9.5 months to 74.5 years with mean age of 42.8 years. Seventy three out of 432 (16.9%) white males, 14 out of 92 (15.2%) black males, 39 out of 280 (13.9%) white females and 14 out of 59 (23.7%) black females died during the study. The goal of the following analysis is to categorize the patients into low or high risk groups based on their age at transplant.

6.2 Method

To control the effect of race and gender, separate analysis were conducted for each category. To demonstrate the result, a two-step approach consisting of visual plot

followed by estimated cutpoints obtained from proposed method and existing method will be presented below:

Visual plot*:* A graph of Martingale residual versus covariate age will be plotted for each category. If there is a pattern such as peaks or saddle in the expected vs observed martingale residuals in LOESS smoothed plot, a cutpoint would be required. If there is a linear pattern, then cutpoint may not be appropriate.

Estimation of a cutpoint: The proposed method will be applied to all four categories and result will be compared with the existing methods.

6.3 Results

For the 92 black males, the number of distinct ages at transplant was 43. The possible number of candidate cutpoints for black males were 43 and the number of distinct death times was 14. For the 432 white males, the number of distinct ages at transplant was 59, which gives the possible number of candidate cutpoints for white males as 59. There were 73 deaths but only 70 death times were distinct, since 3 death times overlapped.

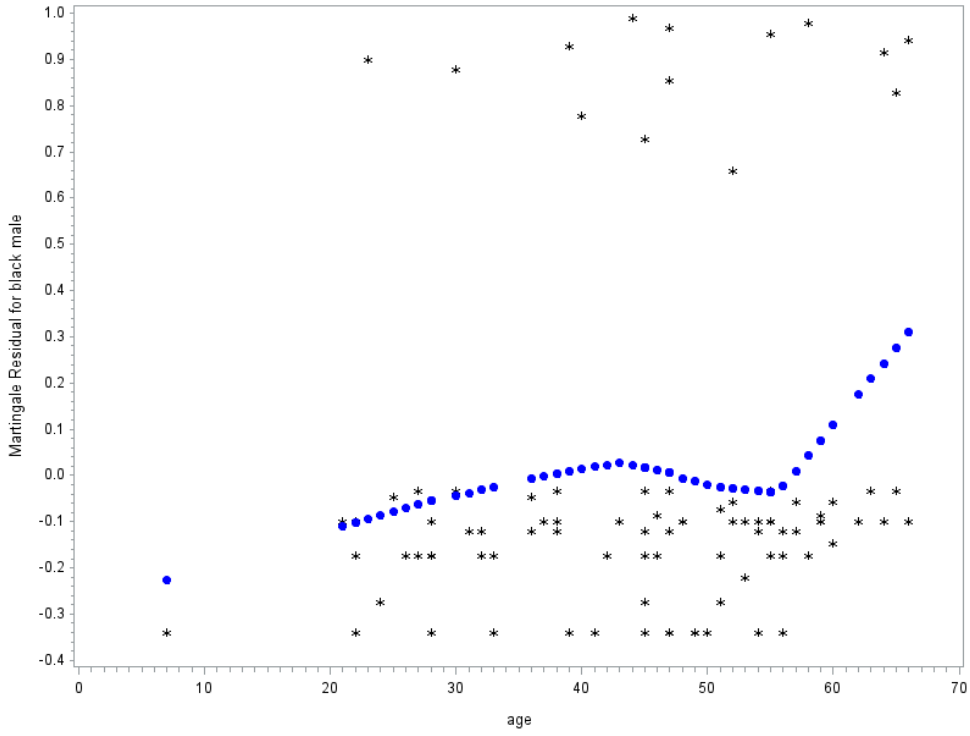
For the 59 black females, there were 32 distinct ages during the time of transplant; hence the number of possible candidate cutpoint for black female is 32 and there were 14 distinct death times. For the 280 white females, there were 59 distinct ages; hence the number of possible candidate cutpoint for white females was 59. Because there were 39 deaths with 1 death time overlapped, only 38 death times were distinct.

Table 6.1: Descriptive Statistics for Different Race/Gender

Group	N	Distinct Ages	Distinct Death Times	Min Age at transplant	Max Age at transplant	Mean Age at transplant
black males	92	43	14	7	66	43.0
white males	432	59	70	2	75	40.5
black females	59	32	38	13	66	42.2
white females	280	59	14	1	71	39.5

Using the proposed method, the estimation of cutpoint for black males was 57. This choice is illustrated in Figure 6.1.

Figure 6.1: Martingale residuals versus age in black males



In the Figure 6.1 above, the blue dotted line is predicted martingale residuals, which was obtained by using a LOESS smoothing parameter of 0.60. It appears

increasing upwards until age 41 then it starts decreasing and has a saddle point at age 57. With a saddle point of 57, it indicates possibility of a cutpoint at 57.

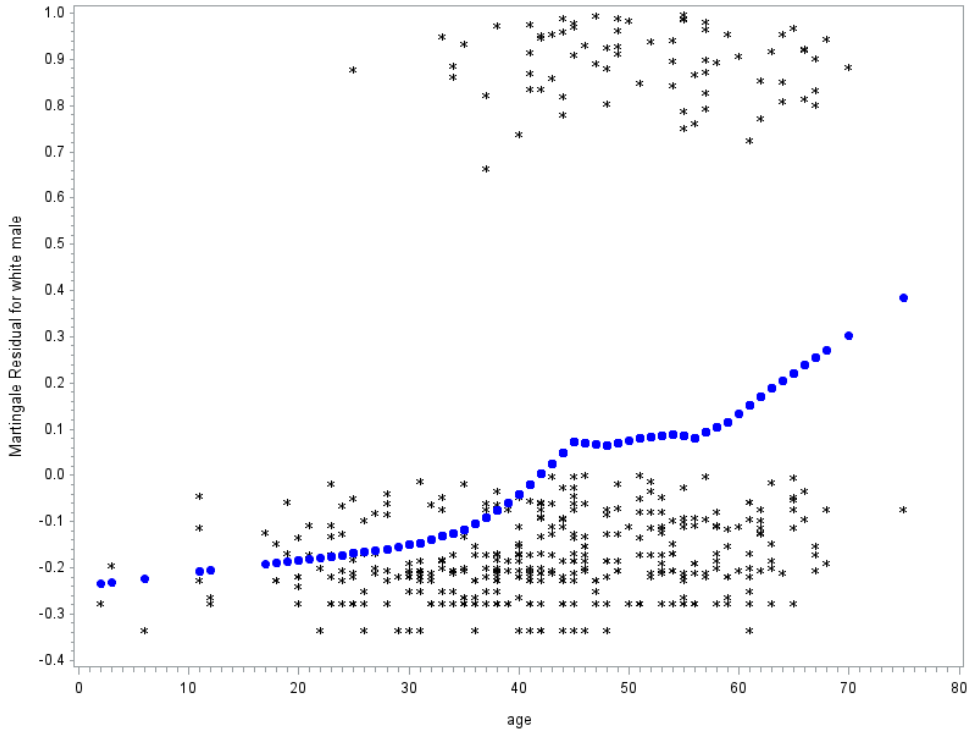
Table 6.2: Cutpoint obtained from three methods for black males

Group	Method	Optimal Cutpoint	Statistic	S^2	p-value
Black Males	Proposed method	57	931.1	NA	NA
	Klein and Wu	58	0.7120	0.8268	0.3300
	Contal and O'Quigley	58	0.8029	0.8268	0.3300

In the Table 6.2 above, cutpoints were obtained using three different methods. The proposed method provided the cutpoint of 57, whereas Contal and O'Quigley (1999) and Klein and Wu (2004) both provided the cutpoint of 58. All three methods had similar result. The visual plot also indicated the possible cutpoint of 57 in the Figure 6.1.

Using the proposed method, the estimation of cutpoint for white males was 41. This choice is illustrated in Figure 6.2.

Figure 6.2: Martingale residuals versus age in white males



In the Figure 6.2 above, the dotted blue line represents the predicted martingale residuals plot, obtained by using a LOESS smoothing parameter of 0.40. The predicted line has an increasing trend until age 44, then it has relatively constant trend and starts increasing again at age 58. The peak indicates a possible cutpoint at age 44.

Table 6.3: Cutpoint obtained from three methods for white males

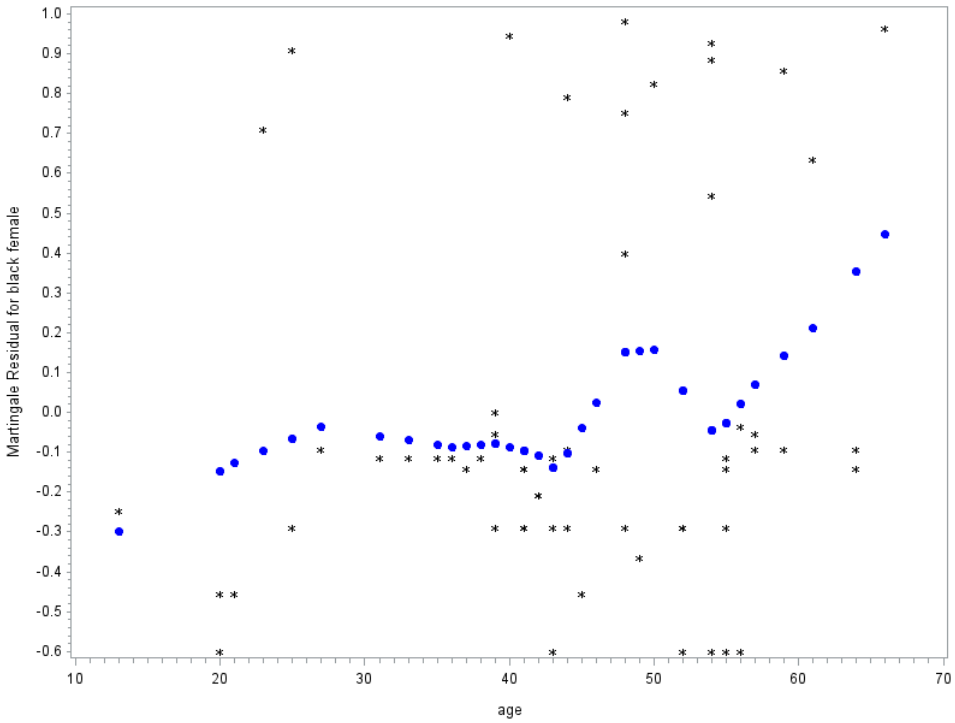
Group	Method	Optimal Cutpoint	Statistic	S^2	p-value
White Males	Proposed method	41	4204.4	NA	NA
	Klein and Wu	41	2.9814	0.9445	0.0000
	Contal and O'Quigley	41	3.1232	0.9445	0.0000

For white males the estimated cutpoint was 44 in the visual plot in the Figure 6.2, but using three different methods above the estimated cutpoint was obtained as age 41.

All three methods have similar results and Contal and O'Quigley (1999) has a significant *p*-value for the estimated cutpoint.

Using the proposed method, the estimation of cutpoint for black females was 64. This choice is illustrated in the Figure 6.3 below.

Figure 6.3: Martingale residual versus age for black females



In Figure 6.3, there are two saddles, one at age 43, and other at age 54. It is possible that there exists no unique cutpoint, i.e., there are more than one cutpoint. Alternatively, another reason for the multiple peaks in Figure 4.3 could have resulted from the relatively small sample size for black females, i.e. only 59. The small sample may not have been able to detect the actual difference. Also, from the Contal and O'Quigley *p*-value, estimated cutpoints for black males and black females were not

significant. Table 6.4 below provides the estimated cutpoint for black females using all three methods:

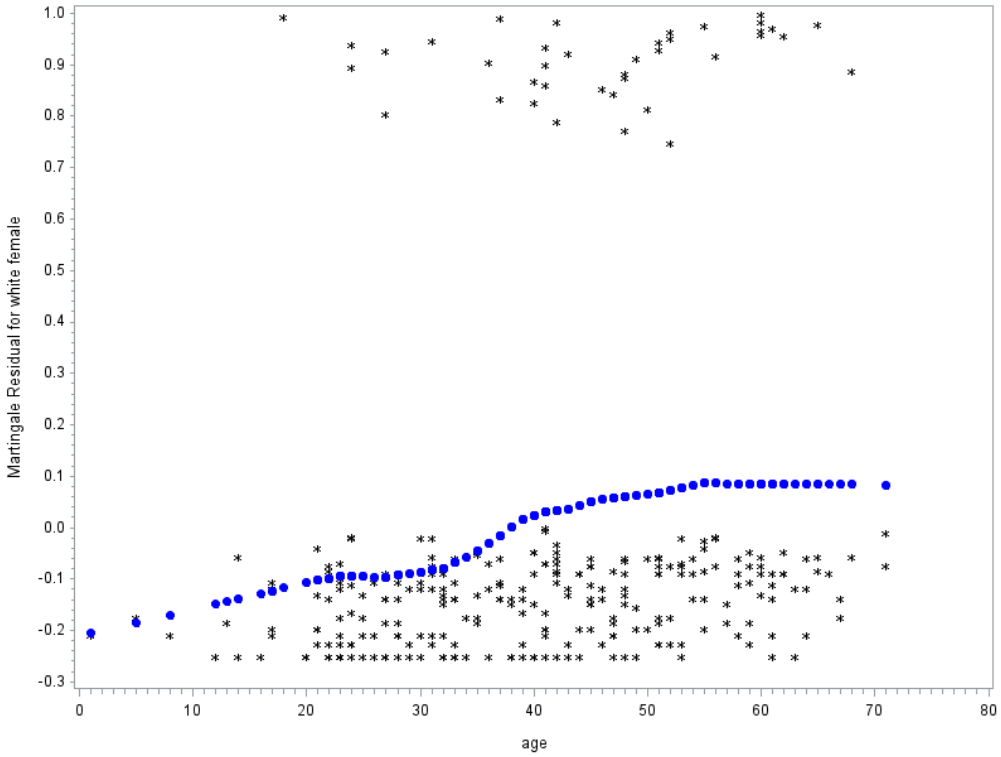
Table 6.4: Cutpoint obtained from three methods for black females

Group	Method	Optimal Cutpoint	Statistic	S^2	p-value
Black Females	Proposed method	64	909.5	NA	NA
	Klein and Wu	48	0.8777	0.8268	0.3300
	Contal and O'Quigley	48	0.9445	0.8268	0.3300

The estimated cutpoint for black females using the proposed method was 64, while the estimated cutpoint using Klein and Wu (2004) and Contal and O'Quigley (1999) was 48. As indicated in the Figure 6.3 above, there may not be a unique cutpoint for age in the black females group.

Using the proposed method, the estimation of cutpoint for white females was 40. This choice is illustrated in Figure 6.4.

Figure 6.4: Martingale residuals versus age for white females



In Figure 6.4 above, there appears a straight line with a slight decrease at age 23, after age 33 it starts increasing. It appears there is a constant upward linear trend after age 40, it is possible that the cutpoint exists at age 40.

Table 6.5: Cutpoint obtained from three methods for White Females

Group	Method	Optimal Cutpoint	Statistic	S^2	p-value
White Females	Proposed method	40	1780.6	NA	NA
	Klein and Wu	40	1.7829	0.9128	0.0035
	Contal and O'Quigley	36	1.9310	0.9128	0.0012

In the table 6.5 above, the estimated cutpoint using the proposed method and the Klein and Wu (2004) method is 40 while the estimated cutpoint using the Contal and O'Quigley (1999) method is 36.

6.4 Conclusion

All three methods have similar results except for black females. A larger sample size might be required to find the significant cutpoint if one truly exists. Although the martingale residual plot gives a visual idea about the cutpoint, the interpretation can be highly subjective and the results can vary depending on different smoothing parameters.

CHAPTER 7: CONCLUSION AND FUTURE WORK

7.1 Conclusion

In a clinical study it is may be desirable from a clinical standpoint to categorize the continuous covariates into different groups. Blood pressure, cholesterol, and BMI are some examples where categorization often used in a clinical setting over the continuous variable. When the statistical relationship between an outcome and a covariate is non-linear or if there is a sharp increase or decrease after a particular point then categorizing the continuous covariate into two groups may be useful. Before using any numerical method to estimate the cutpoint, it is better to use the existing graphical method, to see if there is any pattern of a cutpoint for the continuous covariate. If the graphical method supports the possibility of a cutpoint, one would then proceed to apply all of the existing methods, as well as the proposed method, to determine the value of the cutpoint. The choice of which method to favor can be determined based upon the results of the simulation studies in Chapter 5.

The proposed method uses the sum of the absolute value of the score residuals, whereas the Klein and Wu (2004) method is based on the sum of the score residuals divided by the square root of its variance. Hence, the test-statistic for Klein and Wu uses the ratio while the proposed method only utilizes the absolute difference in the score residuals. The Contal and O'Quigely method is based on non-parametric methods and does not utilize the information about the distribution of the failure time.

In the Chapter 5 it was shown through simulations that the proposed score method has better performance when the actual cutpoint occurs in the middle to the higher end of the continuous covariate under consideration for dichotomization. As the sample sizes increased the bias and MSE decreased, but this result also depended upon the size of the change in the risk ratio.

All three methods had less satisfactory performance for small to moderate sample sizes and hazard ratio difference of 1.01-1.03. For a cutpoint of 25, the Klein and Wu method had the best performance in terms of bias and MSE. For a cutpoint of 50, all three methods had similar performance when the data had a Weibull distribution. For a cutpoint of 50 and an exponential distribution, the Contal and O'Quigely method performed well. For a cutpoint of 75, the proposed score method had better performance for the large sample sizes and large risk ratios with both Weibull and exponential distributed data.

For the proposed method, MSE and bias are smaller for larger sample size for cutpoint of 50 and 75. For the proposed method and the cutpoint 25, there is not much change in the bias after increasing the sample size but MSE decreases as sample size increases. For the Klein and Wu and Contal and O'Quigley methods, bias and MSE decreases as sample size increases for all cutpoints. The largest bias and MSE were observed for relative risk of 1.01-1.03 in comparison to other relative risks regardless of method. Relative risks 1.00-1.01 and 1.01-1.10 had lowest bias and MSE for each method regardless of sample size. The reason for the higher bias and MSE at the relative risk of

1.01:1.03 can be a result of comparatively smaller changes in the relative risk before and after the cutpoint.

If a cutpoint is not expected to be in the lower end of the covariate, the proposed method can be used due to the smaller bias and MSE for cutpoints in the middle to high point of the range of the covariate. If there is some reason to believe that the cutpoint exist in the lower end of the covariate then Klein and Wu would have lowest bias and MSE among all three methods and would be the preferred method to use.

7.2 Limitation and Future direction

The proposed score method is extremely sensitive to the size of the risk ratio. If the size of risk ratio is large, the proposed score method performed well but if the size of relative risk is small, the proposed score method has higher bias and MSE. The proposed score method provides the estimation of the cutpoint, but it doesn't provide inference on the estimated value. Both Contal and O'Quigley (1999) and Klein and Wu (2004) have adopted the method of calculating the *p*-value using Jesperson's method for the estimated test statistic. One solution can be obtaining the confidence interval from the bootstrap samples for conducting the inference on the estimation. Future direction would be developing some scale to satisfy the assumption on the Brownian Bridge and to calculate the *p*-value.

Methods were compared on simulated data with no censoring and 25% censoring; varying %'s of censoring as well as censoring mechanisms to assess the impact would be an interest for the future research.

In conclusion, before estimating the cutpoint, it would be recommended to look at the martingale residual plot of the continuous covariate. If there appears a pattern in the LOWESS Smoothed curve of martingale residual, we can assume an existence of a cutpoint and estimate the cutpoint using all three methods. After estimating a cutpoint using all three methods, we can look for an agreement between the estimated cutpoint and the possible cutpoint based on graphical method. If a cutpoint looks reasonable based on the estimated methods and a graphical method, we can make a conclusion about the cutpoint. On the other hand, if there is no pattern in the LOWESS Smoothed curve, we can safely assume a linear relationship between a covariate and the response variable. In that case, an estimation of a cutpoint is not needed.

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APPENDIX A

Table A.5.4.1 Simulation Results from the Weibull distributed data using the Proposed Score Method with no censoring at $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	36.37	7.19	11.37	180.92	25.00	51.00
50	1.01-1.03	36.48	11.71	11.48	268.60	16.00	60.00
50	1.01-1.06	35.99	8.55	10.99	193.83	23.00	53.00
50	1.01-1.10	36.57	7.34	11.57	187.78	25.00	52.00
100	1.00-1.01	35.73	5.98	10.73	150.81	25.00	48.00
100	1.01-1.03	35.77	9.40	10.77	204.15	21.00	55.00
100	1.01-1.06	35.08	7.01	10.08	150.81	25.00	50.00
100	1.01-1.10	35.56	5.97	10.56	147.12	25.00	47.50
500	1.00-1.01	35.96	3.77	10.96	134.30	29.00	43.00
500	1.01-1.03	36.67	6.43	11.67	177.41	25.00	49.00
500	1.01-1.06	35.40	4.71	10.40	130.41	27.00	45.00
500	1.01-1.10	36.02	3.78	11.02	135.81	28.00	43.00
1000	1.00-1.01	36.13	3.08	11.13	133.37	30.00	42.00
1000	1.01-1.03	36.96	5.37	11.96	171.91	27.00	48.00
1000	1.01-1.06	35.46	3.89	10.46	124.41	28.00	43.00
1000	1.01-1.10	36.30	3.12	11.30	137.41	30.00	42.00

Looking at the Table A.5.4.1, the proposed score method seems to overestimate the cutpoint 25. The minimum bias was 10.08 at sample size 100 and the risk ratio of 1.01-1.06. Maximum bias of 11.96 was observed at sample size 1000 and risk ratio of 1.01-1.03. Bias didn't decrease for the increased sample size, The lowest MSE of 124.41 was observed at sample size 1000 and risk ratio 1.01-1.06. The largest MSE of 268.60 was

observed at sample size 50 and risk ratio 1.01-1.03. The lowest observed value for 2.5th percentile was 16.0 at the sample size 50 and risk ratio of 1.01-1.03, which indicates 2.5% of estimates for that scenario were below 16. The highest value observed for 97.5th percentile was 60 at sample size 50 and risk ratio of 1.01-1.03, which means 2.5% of estimates were even higher than the 60 at that scenario. Overall the distribution of cutpoint estimate seems wide for the true cutpoint of 25.

Table A.5.4.2 Simulation Results from the Weibull distributed data using the Proposed Score method and 25% censoring at $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	37.44	7.69	12.44	213.88	25.00	54.00
50	1.01-1.03	38.25	12.68	13.25	336.14	16.00	65.00
50	1.01-1.06	37.36	9.21	12.36	237.50	23.00	57.00
50	1.01-1.10	37.40	7.54	12.40	210.63	25.00	52.00
100	1.00-1.01	36.98	6.04	11.98	179.89	26.00	48.00
100	1.01-1.03	36.73	9.70	11.73	231.55	21.00	57.00
100	1.01-1.06	36.39	7.38	11.39	184.02	25.00	51.00
100	1.01-1.10	37.14	6.32	12.14	187.20	26.00	49.00
500	1.00-1.01	37.03	4.00	12.03	160.75	29.00	44.00
500	1.01-1.03	36.93	6.33	11.93	182.29	25.00	49.00
500	1.01-1.06	36.38	4.79	11.38	152.42	27.00	45.00
500	1.01-1.10	36.91	3.91	11.91	157.11	29.00	44.00
1000	1.00-1.01	37.47	3.13	12.47	165.19	31.00	43.00
1000	1.01-1.03	37.12	5.49	12.12	177.03	26.50	47.00
1000	1.01-1.06	36.97	4.00	11.97	159.23	29.00	44.50
1000	1.01-1.10	37.45	3.25	12.45	165.64	31.00	44.00

Looking at the Table A.5.4.2 above (Score method, 25% censoring), the proposed score method over-estimates the cutpoint at 25. The bias ranges from 11.38 at sample size 500 to 13.25 at sample size 50, and MSE ranges from 152.42 at sample size 500 and risk ratio of 1.01-1.06 to 336.14 at sample size 50 and risk ratio of 1.01-1.03. The result is similar to the case with no censoring. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (16, 65), denoting that 95% of sample estimate were between 16 and 65.

Table A.5.4.3 Simulation Results from the Weibull distributed data using the Klein and Wu Method with no censoring at $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	30.80	5.00	5.80	58.53	24.00	43.00
50	1.01-1.03	34.67	9.19	9.67	177.95	19.00	53.00
50	1.01-1.06	32.24	6.30	7.24	92.06	23.00	46.00
50	1.01-1.10	30.97	5.10	5.97	61.56	24.00	42.00
100	1.00-1.01	29.83	3.95	4.83	38.96	25.00	39.00
100	1.01-1.03	34.28	7.44	9.28	141.41	22.00	50.00
100	1.01-1.06	30.97	4.76	5.97	58.23	24.00	41.00
100	1.01-1.10	29.75	3.82	4.75	37.11	25.00	38.00
500	1.00-1.01	28.80	2.49	3.80	20.61	25.00	34.00
500	1.01-1.03	34.06	4.79	9.06	104.95	25.00	44.00
500	1.01-1.06	30.49	3.18	5.49	40.20	25.00	37.00
500	1.01-1.10	28.78	2.38	3.78	19.99	25.00	34.00
1000	1.00-1.01	28.63	1.90	3.63	16.80	25.00	32.50
1000	1.01-1.03	34.04	3.77	9.04	96.03	27.00	41.00
1000	1.01-1.06	30.44	2.55	5.43	36.02	26.00	35.50
1000	1.01-1.10	28.66	1.93	3.66	17.12	25.00	32.00

Looking at the Table A.5.4.3 (Klein and Wu method with no censoring, cutpoint=25), the cutpoint is again overestimated for the true cutpoint of 25. The smallest bias is 3.63 at sample size 1000 and risk ratio of 1.00-1.01. The largest bias 9.67 was observed at sample size 50 and risk ratio of 1.01-1.03. The smallest MSE was 16.80 at the sample size of 1000 and the risk ratio of 1.00-1.01. The largest MSE was 177.95 at the sample size of 50 and risk ratio of 1.01-1.03. The risk ratio 1.01-1.03 has larger bias and MSE in comparison to other risk ratios at each sample size. Overall, bias decreases as

sample size increases. The lowest observed value for lower 2.5th percentile was 19.0 at sample size 50 and risk ratio 1.01-1.03, which means at given scenario 2.5% of cutpoint estimates were lower than 19. The highest observed value for upper 97.5th percentile was 53 at sample size 50 and risk ratio of 1.01-1.03, which indicates 2.5% of cutpoint estimates were higher than 53. The percentile interval is narrower than the proposed score method.

Table A.5.4.4 Simulation Results from the Weibull distributed data using the Klein and Wu method and 25% censoring at $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	32.46	6.62	7.46	99.36	24.00	49.00
50	1.01-1.03	36.12	10.47	11.12	232.97	19.00	58.00
50	1.01-1.06	33.68	8.06	8.68	140.20	22.00	52.50
50	1.01-1.10	32.28	6.74	7.28	98.32	24.00	48.50
100	1.00-1.01	30.91	5.09	5.91	60.87	24.00	42.00
100	1.01-1.03	34.85	8.23	9.85	164.67	20.00	52.00
100	1.01-1.06	32.32	6.09	7.32	90.63	24.00	46.00
100	1.01-1.10	31.04	5.25	6.04	63.98	25.00	44.00
500	1.00-1.01	29.30	3.06	4.30	27.87	25.00	36.00
500	1.01-1.03	34.09	5.27	9.09	110.37	25.00	46.00
500	1.01-1.06	30.76	3.87	5.76	48.11	25.00	39.00
500	1.01-1.10	29.16	3.13	4.16	27.10	25.00	36.00
1000	1.00-1.01	29.02	2.54	4.02	22.61	25.00	34.00
1000	1.01-1.03	34.04	4.15	9.04	99.00	26.00	42.00
1000	1.01-1.06	30.47	3.03	5.47	39.06	25.00	37.00
1000	1.01-1.10	29.07	2.72	4.07	23.98	25.00	35.00

From the Table A.5.4.4 above, using Klein and Wu method with 25% censoring, cutpoint was overestimated. The result is similar to that with no censoring with slightly higher bias and MSE than no censoring case. The lowest bias and MSE were 4.02 and 22.61 respectively at sample size 1000 and risk ratio of 1.00-1.01. The highest bias and MSE were 11.11 and 232.96 respectively at sample size 50 and risk ratio 1.01-1.03. The widest 95th percentile interval was (19, 58) at sample size 50 and risk ratio of 1.01-1.03.

Table A.5.4.5 Simulation Results from the Weibull distributed data using Contal and O'Quigley Method with no censoring at $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	34.50	6.72	9.50	135.40	25.00	48.00
50	1.01-1.03	36.74	9.08	11.74	220.29	21.00	55.00
50	1.01-1.06	34.91	7.23	9.91	150.58	24.00	50.00
50	1.01-1.10	34.50	6.70	9.50	135.20	25.00	48.00
100	1.00-1.01	33.19	5.22	8.19	94.31	25.00	44.00
100	1.01-1.03	36.11	7.59	11.11	181.06	23.50	51.00
100	1.01-1.06	33.42	5.57	8.42	101.85	25.00	45.00
100	1.01-1.10	33.05	5.11	8.05	90.91	25.00	44.00
500	1.00-1.01	32.25	2.99	7.24	61.41	27.00	38.00
500	1.01-1.03	35.54	4.87	10.54	134.67	27.00	45.00
500	1.01-1.06	33.01	3.47	8.01	76.17	26.00	40.00
500	1.01-1.10	32.26	3.21	7.26	62.94	26.00	39.00
1000	1.00-1.01	32.10	2.33	7.10	55.82	27.00	36.00
1000	1.01-1.03	35.61	3.88	10.61	127.63	28.00	43.00
1000	1.01-1.06	32.97	2.81	7.97	71.32	27.00	38.00
1000	1.01-1.10	32.09	2.45	7.09	56.24	27.00	37.00

From the Table A.5.4.5 above (Contal and O'Quigley method and no censoring), the cutpoint is overestimated for the true cutpoint of 25. The lowest bias was 7.09 at sample size 1000 and risk ratio of 1.01-1.10. The highest bias was 11.74 at sample size 50 and risk ratio of 1.01-1.03. The lowest MSE was 55.82 at sample size 1000 and risk ratio 1.00-1.01. The highest MSE was 220.29 at sample size 50 and risk ratio of 1.01-1.03. The lowest observed value for 2.5th percentile was 21.0, which means 2.5% of the estimates

were below 21.0 years. The highest observed value of 97.5th percentile estimate was 55.0, which means 2.5% of estimates were above 55.

Table A.5.4.6 Simulation Results from the Weibull distributed data using Contal and O'Quigley method and 25% censoring at $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	34.32	6.63	9.32	130.84	25.00	49.00
50	1.01-1.03	36.79	9.50	11.79	228.99	21.00	57.00
50	1.01-1.06	34.97	7.19	9.97	151.03	23.50	50.00
50	1.01-1.10	34.24	6.80	9.24	131.63	25.00	49.50
100	1.00-1.01	33.06	5.49	8.06	94.99	25.00	45.50
100	1.01-1.03	35.06	7.13	10.06	152.01	23.00	51.00
100	1.01-1.06	33.83	5.80	8.83	111.63	25.00	46.00
100	1.01-1.10	32.99	5.27	7.99	91.61	25.00	44.00
500	1.00-1.01	32.08	3.12	7.08	59.89	26.00	38.00
500	1.01-1.03	35.33	4.74	10.33	129.13	27.00	45.00
500	1.01-1.06	32.81	3.46	7.81	72.98	26.00	40.00
500	1.01-1.10	32.20	3.00	7.20	60.83	26.00	38.00
1000	1.00-1.01	32.19	2.45	7.19	57.71	28.00	37.00
1000	1.01-1.03	35.49	3.75	10.49	124.21	28.00	42.00
1000	1.01-1.06	33.06	2.82	8.06	72.84	28.00	38.00
1000	1.01-1.10	32.11	2.45	7.11	56.59	27.00	37.00

Looking at the Table A.5.4.6 (Contal and O'Quigley, 25% censoring), the lowest bias of 7.08 was observed at sample size 500 and risk ratio of 1.00-1.01. The highest bias was 11.79 at sample size 50 and risk ratio of 1.01-1.03. Similarly, the lowest MSE of 56.59 was observed at sample size 1000 and risk ratio of 1.01-1.10. The highest bias was 228.99 at sample size 50 and risk ratio of 1.01-1.03. The results from 25% censoring and no censoring were similar.

Table A.5.4.7 Simulation Results from the Weibull distributed data using the Proposed Score Method with no censoring at $\tau_1 = 50$

N	scenario	Mean	Sd	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	51.93	2.38	1.93	9.41	50.00	58.50
50	1.01-1.03	48.88	10.36	-1.12	108.40	17.50	65.00
50	1.01-1.06	52.12	3.44	2.12	16.33	46.00	60.50
50	1.01-1.10	51.87	2.48	1.87	9.63	50.00	58.00
100	1.00-1.01	51.04	1.60	1.04	3.65	50.00	55.50
100	1.01-1.03	50.21	5.42	0.21	29.40	36.50	61.00
100	1.01-1.06	51.08	1.91	1.08	4.83	48.00	56.00
100	1.01-1.10	50.89	1.50	0.89	3.03	50.00	55.00
500	1.00-1.01	50.15	0.49	0.15	0.26	50.00	52.00
500	1.01-1.03	50.49	1.40	0.49	2.21	49.00	55.00
500	1.01-1.06	50.27	0.72	0.27	0.59	50.00	53.00
500	1.01-1.10	50.15	0.47	0.15	0.25	50.00	51.00
1000	1.00-1.01	50.06	0.25	0.06	0.07	50.00	51.00
1000	1.01-1.03	50.34	0.91	0.34	0.94	49.00	53.00
1000	1.01-1.06	50.11	0.38	0.11	0.16	50.00	51.00
1000	1.01-1.10	50.08	0.32	0.08	0.11	50.00	51.00

From Table A.5.4.7, the proposed score method estimates are approximately equal to the true cutpoint of 50 with smaller bias and MSE. The largest absolute bias was 2.12 at sample size 50 and risk ratio of 1.01-1.06. The smallest bias was 0.06 at sample size 1000 and risk ratio of 1.00-1.01. The largest MSE was 108.40 at sample size 50 and smallest MSE was 0.07 at sample size 1000. Increasing the sample size decreases both bias and MSE for the true cutpoint of 50. The 95th percentile interval for sample size 50 and risk ratio of 1.01-1.03 was (17.5, 65.0), which indicates 95% of the time estimated values were

in the range between 17.5 and 65, which is a wide range for a cutpoint of 50 but for sample size 1000, 95th percentile are narrow for all risk ratios.

Table A.5.4.8 Simulation Results from the Weibull distributed data using the Proposed Score method with 25% censoring at $\tau_1 = 50$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	52.18	2.66	2.18	11.80	50.00	60.00
50	1.01-1.03	49.75	9.84	-0.25	96.82	24.00	69.00
50	1.01-1.06	51.97	3.30	1.97	14.75	46.00	60.00
50	1.01-1.10	52.11	2.61	2.11	11.26	50.00	59.00
100	1.00-1.01	51.20	1.78	1.20	4.59	50.00	56.00
100	1.01-1.03	50.39	5.68	0.39	32.38	38.00	61.50
100	1.01-1.06	51.23	2.07	1.23	5.78	48.00	57.00
100	1.01-1.10	51.14	1.65	1.14	4.00	50.00	56.00
500	1.00-1.01	50.18	0.52	0.18	0.30	50.00	52.00
500	1.01-1.03	50.65	1.50	0.65	2.67	49.00	55.00
500	1.01-1.06	50.30	0.77	0.30	0.68	50.00	53.00
500	1.01-1.10	50.22	0.62	0.22	0.43	50.00	52.00
1000	1.00-1.01	50.09	0.36	0.09	0.14	50.00	51.00
1000	1.01-1.03	50.35	0.90	0.35	0.93	49.00	53.00
1000	1.01-1.06	50.12	0.39	0.12	0.16	50.00	51.00
1000	1.01-1.10	50.08	0.31	0.08	0.10	50.00	51.00

Looking at the Table A.5.4.8 (Score method, 25% censoring) for cutpoint 50, the estimated cutpoint was approximately equal to the true cutpoint. The lowest bias was 0.08 at sample size 1000 and risk ratio 1.01-1.10. The highest bias was 2.18 at sample size 50 and risk ratio of 1.00-1.01. The lowest MSE was 0.10 at sample size 1000 and risk ratio 1.01-1.10 and highest MSE was 96.82 at sample size 50 and risk ratio 1.01-1.03. The

results were similar to the previous result from no censoring for the proposed score method.

Table A.5.4.9 Simulation Results from the Weibull distributed data using the Klein and Wu Method with no censoring at $\tau_1 = 50$

N	scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	50.27	2.81	0.27	7.95	42.50	55.00
50	1.01-1.03	45.65	7.84	-4.35	80.33	24.50	56.00
50	1.01-1.06	48.90	4.42	-1.10	20.73	37.00	55.00
50	1.01-1.10	50.40	2.84	0.40	8.19	44.00	56.00
100	1.00-1.01	50.05	1.53	0.05	2.34	46.00	53.00
100	1.01-1.03	47.01	4.94	-2.99	33.28	34.00	53.00
100	1.01-1.06	49.37	2.20	-0.63	5.24	44.00	52.00
100	1.01-1.10	50.05	1.34	0.05	1.80	47.00	52.00
500	1.00-1.01	49.98	0.16	-0.02	0.03	50.00	50.00
500	1.01-1.03	49.17	1.67	-0.83	3.49	44.00	51.00
500	1.01-1.06	49.85	0.46	-0.15	0.24	48.00	50.00
500	1.01-1.10	49.98	0.18	-0.02	0.03	50.00	50.00
1000	1.00-1.01	50.00	0.04	-0.00	0.00	50.00	50.00
1000	1.01-1.03	49.57	0.92	-0.43	1.04	47.00	50.00
1000	1.01-1.06	49.96	0.22	-0.04	0.05	49.00	50.00
1000	1.01-1.10	49.99	0.08	-0.01	0.01	50.00	50.00

From the Table A.5.4.9 (Klein and Wu method, no censoring), the estimated cutpoint is approximately equal to the true cutpoint. The largest absolute bias was 4.35 at sample size 50 and relative risk of 1.01-1.03. The smallest absolute bias was 0.00 at sample size 1000 and risk ratio 1.01-1.01. The smallest MSE was 0.00 at sample size 1000 and risk ratio 1.00-1.01 and largest MSE was 80.33 at sample size 50 and risk ratio 1.01-1.03. Increasing the sample size decreases both bias and MSE for the true cutpoint of 50.

The 95th percentile interval at sample size 50 and risk ratio of 1.01-1.03 was (24.5, 56.0), which indicates 95% of the times the estimated cutpoint were between 24.5 and 56.0. The narrowest range for 95th percentile interval was (50, 50) at sample size 1000 and sample size 500 for risk ratio of 1.00-1.01 and 1.01-1.10, means the estimation was almost exact for the larger sample size and larger risk ratios.

Table A.5.4.10 Simulation Results from the Weibull distributed data using the Klein and Wu method with 25% censoring at $\tau_1 = 50$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	50.02	4.16	0.02	17.32	40.00	58.00
50	1.01-1.03	45.53	8.84	-4.47	98.11	24.00	60.00
50	1.01-1.06	48.59	5.76	-1.41	35.13	33.00	58.00
50	1.01-1.10	50.12	4.01	0.12	16.07	40.00	58.00
100	1.00-1.01	49.94	2.24	-0.06	5.01	44.00	54.00
100	1.01-1.03	46.99	5.86	-3.01	43.37	32.00	55.00
100	1.01-1.06	48.98	3.58	-1.02	13.82	39.00	54.00
100	1.01-1.10	49.87	2.12	-0.13	4.52	44.00	54.00
500	1.00-1.01	49.95	0.38	-0.05	0.15	49.00	50.50
500	1.01-1.03	48.98	2.08	-1.02	5.39	43.00	52.00
500	1.01-1.06	49.71	0.89	-0.29	0.87	47.00	51.00
500	1.01-1.10	49.90	0.47	-0.10	0.23	49.00	50.00
1000	1.00-1.01	49.98	0.16	-0.02	0.03	50.00	50.00
1000	1.01-1.03	49.40	1.29	-0.60	2.03	46.00	51.00
1000	1.01-1.06	49.92	0.34	-0.08	0.12	49.00	50.00
1000	1.01-1.10	49.98	0.15	-0.02	0.02	50.00	50.00

From the Table A.5.4.10 above (Klein and Wu, 25% censoring, $\tau_1 = 50$), the highest absolute bias and MSE were 4.47 and 98.11 respectively at sample size 50 and risk

ratio 1.01-1.03. The lowest absolute bias was 0.02 and lowest MSE was 0.02 at sample size 1000 and risk ratio of 1.01-1.10. The 95th percentile interval was (24.0, 60.0) at sample size 50 and risk ratio of 1.01-1.03, indicating that 95% of the times the estimated cutpoints were between 24 and 60. At sample size 1000, the 95th percentile was (50, 50), which indicates for larger sample the estimation was approximately close to the true cutpoint. The results from censoring are similar to the results with no censoring.

Table A.5.4.11 Simulation Results from the Weibull distributed data using Contal and O'Quigley Method with no censoring at $\tau_1 = 50$

N	scenario	Mean	Sd	Bias	MSE	Lower2.5th percentile	Upper97.5th percentile
50	1.00-1.01	48.52	4.51	-1.48	22.50	37.00	55.00
50	1.01-1.03	46.50	7.31	-3.50	65.63	28.00	57.50
50	1.01-1.06	48.13	5.17	-1.87	30.16	34.00	55.00
50	1.01-1.10	48.49	4.76	-1.51	24.90	36.50	55.00
100	1.00-1.01	49.01	2.68	-0.99	8.16	42.00	52.00
100	1.01-1.03	47.33	4.80	-2.67	30.12	35.00	53.00
100	1.01-1.06	48.83	2.77	-1.17	9.05	42.00	52.00
100	1.01-1.10	49.12	2.44	-0.88	6.73	42.00	52.00
500	1.00-1.01	49.83	0.49	-0.17	0.27	48.00	50.00
500	1.01-1.03	49.23	1.58	-0.77	3.09	45.00	51.00
500	1.01-1.06	49.75	0.65	-0.25	0.49	48.00	50.00
500	1.01-1.10	49.82	0.58	-0.18	0.37	48.00	50.00
1000	1.00-1.01	49.96	0.20	-0.04	0.04	49.00	50.00
1000	1.01-1.03	49.61	0.83	-0.39	0.84	47.00	50.00
1000	1.01-1.06	49.92	0.32	-0.08	0.11	49.00	50.00
1000	1.01-1.10	49.95	0.22	-0.05	0.02	49.00	50.00

The Contal and O'Quigley method consistently underestimates the cutpoint of 50. The largest absolute bias was 3.50 at sample size 50 and risk ratio of 1.01-1.03. The smallest absolute bias was 0.04 at sample size 1000 and risk ratio of 1.00-1.01. The smallest MSE was 0.02 for sample size 1000 and risk ratio of 1.01-1.10 and largest MSE was 65.63 for sample size 50. The 95th percentile interval was $(28.0, 57.5)$ at sample size 50 and risk ratio of 1.01-1.03, which means 95% of the times the estimates were between 28.0 and 57.5 at that scenario.

Table A.5.4.12 Simulation Result from the Weibull distributed data using Contal and O'Quigley method with 25% censoring at $\tau_1 = 50$

N	scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	48.44	4.60	-1.56	23.52	36.00	55.00
50	1.01-1.03	46.47	7.42	-3.53	67.39	27.00	57.00
50	1.01-1.06	48.16	4.91	-1.84	27.50	34.50	55.00
50	1.01-1.10	48.53	4.67	-1.47	23.97	36.00	55.00
100	1.00-1.01	49.01	2.72	-0.99	8.36	41.00	52.00
100	1.01-1.03	47.10	5.04	-2.90	33.72	34.00	54.00
100	1.01-1.06	48.77	3.00	-1.23	10.49	40.00	52.50
100	1.01-1.10	49.21	2.31	-0.79	5.96	43.00	53.00
500	1.00-1.01	49.83	0.54	-0.17	0.32	48.00	50.00
500	1.01-1.03	49.23	1.57	-0.77	3.05	45.00	51.00
500	1.01-1.06	49.80	0.55	-0.20	0.34	48.00	50.00
500	1.01-1.10	49.81	0.59	-0.19	0.38	48.00	50.00
1000	1.00-1.01	49.95	0.23	-0.05	0.06	49.00	50.00
1000	1.01-1.03	49.61	0.92	-0.40	0.99	47.00	50.00
1000	1.01-1.06	49.94	0.26	-0.06	0.07	49.00	50.00
1000	1.01-1.10	49.96	0.21	-0.04	0.04	49.00	50.00

From the Table A.5.4.12 above (Contal and O' Quigley method, 25% censoring), the estimated cutpoints were approximately equal to the true cutpoint 50. The highest absolute bias and MSE were 3.53 and 67.39 at sample size 50 and risk ratio 1.01-1.03. The lowest absolute bias and MSE were 0.04 and 0.04 at sample size 1000 and risk ratio of 1.01-1.10. The 95th percentile interval at sample size 50 and risk ratio 1.01-1.03 was (27.0, 57.0) and at sample size 1000 the 95th percentile interval was (49, 50) for all risk ratios except 1.01-1.03. Hence for the large sample the estimates were approximately equal to the true cutpoint with little or no variation.

Table A.5.4.13 Simulation Results from the Weibull distributed data using the Proposed Score Method with no censoring at $\tau_1 = 75$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	76.16	3.11	1.16	11.00	74.00	81.00
50	1.01-1.03	54.14	20.33	-20.86	847.94	12.00	79.00
50	1.01-1.06	72.53	10.48	-2.47	115.81	34.00	80.00
50	1.01-1.10	75.93	3.12	0.93	10.58	74.00	81.00
100	1.00-1.01	75.45	0.87	0.45	0.97	75.00	78.00
100	1.01-1.03	57.64	17.72	-17.36	614.79	16.00	78.00
100	1.01-1.06	74.87	2.87	-0.13	8.27	69.00	78.00
100	1.01-1.10	75.48	0.86	0.48	0.97	75.00	78.00
500	1.00-1.01	75.01	0.08	0.01	0.01	75.00	75.00
500	1.01-1.03	64.36	12.26	-10.64	263.42	36.00	75.00
500	1.01-1.06	74.99	0.11	-0.01	0.01	75.00	75.00
500	1.01-1.10	75.00	0.07	0.00	0.01	75.00	75.00
1000	1.00-1.01	75.00	0.00	0.00	0.00	75.00	75.00
1000	1.01-1.03	66.17	11.16	-8.83	202.40	42.00	75.00
1000	1.01-1.06	75.00	0.03	0.00	0.00	75.00	75.00
1000	1.01-1.10	75.00	0.00	0.00	0.00	75.00	75.00

Looking at the Table A.5.4.13, the proposed score method has estimated the values close to the true cutpoint. The smallest absolute bias was 0.00 for sample size 1000 for all risk ratios except the risk ratio of 1.01-1.03. The largest absolute bias was 20.86, which was observed at sample size 50 and risk ratio of 1.01-1.03. The 95^{th} percentile interval at sample size 50 and risk ratio 1.01-1.03 was $(12, 79)$ which seems to have high variability, and indicates that 95% of estimates were between 12 and 79. The smallest MSE of 0 was observed at sample size 1000 for all risk ratios except the 1.01-1.03. The largest MSE was 847.94 for sample size 50 and risk ratio of 1.01-1.03. For small sample size a smaller change such as 1.03 from 1.01 probably will not be detected with this method.

Table A.5.4.14: Simulation Results from the Weibull distributed data using the Proposed Score method and 25% censoring at $\tau_1 = 75$

N	scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	76.09	3.40	1.09	12.74	75.00	81.00
50	1.01-1.03	59.28	19.64	-15.72	632.62	13.00	80.50
50	1.01-1.06	74.24	8.15	-0.76	66.98	46.00	81.00
50	1.01-1.10	76.00	4.23	1.00	18.90	75.00	81.00
100	1.00-1.01	75.47	0.87	0.47	0.99	75.00	78.00
100	1.01-1.03	63.09	16.60	-11.91	417.09	20.00	78.00
100	1.01-1.06	75.11	2.83	0.11	8.00	72.00	78.00
100	1.01-1.10	75.48	0.82	0.47	0.90	75.00	78.00
500	1.00-1.01	75.00	0.06	0.00	0.00	75.00	75.00
500	1.01-1.03	71.72	7.44	-3.28	66.04	47.50	75.00
500	1.01-1.06	75.00	0.09	-0.00	0.01	75.00	75.00
500	1.01-1.10	75.00	0.06	0.00	0.00	75.00	75.00
1000	1.00-1.01	75.00	0.00	0.00	0.00	75.00	75.00
1000	1.01-1.03	74.01	3.74	-0.99	14.96	62.00	75.00
1000	1.01-1.06	75.00	0.04	0.00	0.00	75.00	75.00
1000	1.01-1.10	75.00	0.00	0.00	0.00	75.00	75.00

From the Table A.5.4.14 (the proposed method, 25% censoring, cutpoint 75), the estimated cutpoints were approximately equal except at the sample size 50, relative risk 1.01-1.03 and at sample size 100, relative risk 1.01-1.03. The largest absolute bias and MSE were 15.72 and 632.62 respectively at sample size 50 and relative risk 1.01-1.03. The 95th percentile interval was (13.0, 80.5) at sample size 50 and relative risk of 1.01-1.03. The smallest bias and MSE were observed for sample size 1000. The results were similar to the proposed method with no censoring.

Table A.5.4.15 Simulation Results from the Weibull distributed data using the Klein and Wu Method with no censoring at $\tau_1 = 75$

N	scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	60.73	14.01	-14.27	399.94	28.00	78.00
50	1.01-1.03	49.70	15.80	-25.30	889.24	17.00	75.00
50	1.01-1.06	54.58	15.53	-20.42	657.82	23.00	76.00
50	1.01-1.10	61.41	13.39	-13.59	363.79	29.00	77.00
100	1.00-1.01	63.00	11.05	-12.01	266.17	38.00	76.00
100	1.01-1.03	51.29	13.45	-23.71	742.81	25.00	74.00
100	1.01-1.06	58.51	12.73	-16.49	433.80	30.00	75.00
100	1.01-1.10	61.78	11.90	-13.22	316.15	34.00	76.00
500	1.00-1.01	66.88	7.36	-8.12	120.13	49.00	75.00
500	1.01-1.03	53.47	9.04	-21.53	544.95	36.00	71.00
500	1.01-1.06	61.47	8.94	-13.53	262.88	43.00	75.00
500	1.01-1.10	67.16	7.24	-7.84	113.80	49.50	75.00
1000	1.00-1.01	68.70	5.82	-6.30	73.55	55.00	75.00
1000	1.01-1.03	54.00	7.41	-21.00	495.79	39.00	69.00
1000	1.01-1.06	62.35	7.17	-12.65	211.45	48.00	75.00
1000	1.01-1.10	68.61	5.85	-6.39	75.07	54.00	75.00

From Table A.5.4.15 (Klein and Wu method), the true cutpoint of 75 was consistently underestimated for all different scenarios. The largest absolute bias was 25.3 for sample size 50 and risk ratio of 1.01-1.03. The smallest absolute bias was 6.30 at sample size 1000 and risk ratio 1.00-1.01. The largest MSE was 889.24 for sample size 50 and risk ratio of 1.01-1.03 and smallest MSE was 73.55 for sample size 1000 and risk ratio 1.00-1.01. The 95^{th} percentile interval was $(17, 75)$ for sample size 50 and risk ratio of 1.01-1.03. The percentile interval is wider at sample size 50 and risk ratio of 1.01-1.03,

which suggests larger variability in the estimates for the cutpoint of 75 at that scenario. But, for sample size 1000, the 95th percentile is relatively narrow with (55, 75) at risk ratio of 1.00-1.01.

Table A.5.4.16 Simulation Result from the Weibull distributed data using Klein and Wu method, 25 % censoring at $\tau_1 = 75$

N	scenario	Mean	SD	bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	58.66	14.82	-16.34	486.37	24.50	78.00
50	1.01-1.03	49.55	16.66	-25.45	924.74	19.00	76.00
50	1.01-1.06	54.64	16.20	-20.36	676.75	20.00	77.00
50	1.01-1.10	59.11	15.24	-15.89	484.72	23.50	77.50
100	1.00-1.01	60.48	13.26	-14.53	386.74	29.50	76.00
100	1.01-1.03	50.79	14.70	-24.21	802.12	22.00	75.00
100	1.01-1.06	56.74	13.99	-18.26	528.74	26.00	75.00
100	1.01-1.10	61.13	12.63	-13.87	351.62	31.00	76.00
500	1.00-1.01	66.23	8.20	-8.77	144.12	47.00	75.00
500	1.01-1.03	53.77	9.87	-21.23	547.93	36.00	72.50
500	1.01-1.06	60.85	9.53	-14.15	290.90	40.50	75.00
500	1.01-1.10	66.19	8.13	-8.81	143.62	47.00	75.00
1000	1.00-1.01	67.47	6.70	-7.53	101.53	52.00	75.00
1000	1.01-1.03	53.89	8.40	-21.11	516.11	37.00	71.00
1000	1.01-1.06	62.01	8.16	-12.99	235.30	45.00	75.00
1000	1.01-1.10	67.66	6.72	-7.34	98.97	52.00	75.00

From the Table A.5.4.16 (Klein and Wu method, 25% censoring), the true cutpoint of 75 was consistently underestimated. The highest absolute bias was 25.45 and highest MSE was 924.74 at sample size 50 and risk ratio 1.01-1.03. The lowest absolute bias was 7.34 and lowest MSE was 98.97 at sample size 1000 and relative risk 1.01-1.10. The 95th percentile interval at sample size 50 and relative risk 1.01-1.03 was (19, 76), indicating

2.5% of estimates were below 19 and 2.5% of estimates were higher than 76. For a sample size of 1000 and relative risk of 1.01-1.10 the 95th percentile interval was (52, 75), which is relatively narrower.

Table A.5.4.17 Simulation Results from the Weibull distributed data using the Contal and O'Quigley Method with no censoring at $\tau_1 = 75$

N	scenario	Mean	SD	bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	52.89	15.69	-22.12	735.00	23.00	76.00
50	1.01-1.03	50.25	15.54	-24.75	854.01	19.00	75.00
50	1.01-1.06	51.85	15.68	-23.15	781.81	21.00	76.00
50	1.01-1.10	53.77	14.64	-21.23	664.61	22.00	76.00
100	1.00-1.01	53.95	13.11	-21.05	614.71	28.00	75.00
100	1.01-1.03	51.40	13.45	-23.60	613.11	25.00	74.00
100	1.01-1.06	54.28	13.18	-20.72	602.90	26.50	75.00
100	1.01-1.10	53.30	13.23	-21.70	645.71	27.00	75.00
500	1.00-1.01	56.20	9.14	-18.80	436.66	38.00	73.00
500	1.01-1.03	52.88	9.08	-22.12	571.53	35.00	71.00
500	1.01-1.06	56.23	9.42	-18.77	440.92	37.50	74.00
500	1.01-1.10	56.56	9.14	-18.44	423.47	38.00	73.50
1000	1.00-1.01	56.77	7.31	-18.23	385.80	43.00	71.50
1000	1.01-1.03	53.47	7.58	-21.53	521.10	39.00	69.00
1000	1.01-1.06	56.42	7.55	-18.58	402.12	41.50	70.00
1000	1.01-1.10	56.39	7.16	-18.61	139.07	41.00	70.00

From the Table A.5.4.17 above, the Contal and O'Quigley method consistently underestimated cutpoints at all scenarios for true cutpoint of 75. The smallest absolute bias was 18.23 for sample size 1000 and risk ratio 1.00-1.01 and largest absolute bias was 24.75 at sample size 50 and risk ratio 1.01-1.03. The smallest MSE was 139.07 at sample size 1000 and risk ratio 1.01-1.10 and largest MSE was 854.01 at sample size 50 and risk ratio

1.01-1.03. Unlike proposed method and Klein and Wu method, for the large sample size and larger difference in risk ratio, this method still underestimates the cutpoint. The 95^{th} percentile interval was $(19, 75)$ for the sample size 50 and risk ratio of 1.01-1.03, which indicates 95% of estimates were between 19 and 75. This indicates the high variability in the estimates when the sample size and the difference in risk ratio both are small. For a sample size of 1000 and risk ratio of 1.00-1.01 the 95^{th} percentile was (43.0, 71.5), which is narrower than the 95^{th} percentile at sample size 50.

Table A.5.4.18 Simulation Results from the Weibull distributed data using the Contal and O'Quigley method, 25% censoring at $\tau_1 = 75$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	53.07	15.00	-21.94	705.86	21.00	76.00
50	1.01-1.03	50.22	15.75	-24.78	861.77	19.00	76.00
50	1.01-1.06	52.20	15.62	-22.80	763.44	20.00	76.50
50	1.01-1.10	52.85	15.14	-22.15	719.37	22.00	76.00
100	1.00-1.01	53.91	13.12	-21.09	616.81	28.00	75.00
100	1.01-1.03	50.87	13.72	-24.13	770.38	22.50	75.00
100	1.01-1.06	53.57	13.64	-21.43	645.02	24.00	75.00
100	1.01-1.10	53.56	13.60	-21.45	644.71	24.50	75.00
500	1.00-1.01	56.52	9.29	-18.48	427.71	37.00	73.50
500	1.01-1.03	52.98	9.09	-22.02	567.62	36.00	71.00
500	1.01-1.06	55.71	9.28	-19.29	458.18	37.00	73.00
500	1.01-1.10	56.49	9.30	-18.51	429.14	37.00	74.00
1000	1.00-1.01	56.72	7.44	-18.28	389.66	43.00	72.00
1000	1.01-1.03	53.07	7.44	-21.94	536.43	39.00	67.00
1000	1.01-1.06	56.82	7.84	-18.18	392.01	41.00	72.00
1000	1.01-1.10	56.97	7.49	-18.03	381.22	43.00	71.00

From the Table 5.4.18, the Contal and O'Quigley method with 25% censoring consistently underestimates the true cutpoint of 75. The largest absolute bias and MSE were 24.78 and 861.77 respectively at sample size 50 and relative risk 1.01-1.03. The smallest bias was 18.03 and smallest MSE was 381.22 at sample size 1000 and relative risk 1.01-1.10. The 95th percentile interval for sample size 50 and relative risk 1.01-1.03 is given by (19, 76), indicating the large variability in the estimate for smaller sample size.

Table A.5.5.1 Simulation Results from the Exponential distribution using the Proposed Score method, with no censoring, at $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	21.23	8.94	-3.77	94.08	10.00	49.50
50	1.01-1.03	40.71	27.58	15.71	1006.49	2.50	86.50
50	1.01-1.06	21.21	17.45	-3.79	318.60	5.00	79.00
50	1.01-1.10	21.19	8.73	-3.82	90.63	11.00	47.50
100	1.00-1.01	18.65	4.98	-6.35	65.06	13.00	31.50
100	1.01-1.03	39.33	28.34	14.33	1007.60	3.00	88.00
100	1.01-1.06	15.78	13.01	-9.22	254.02	5.00	68.50
100	1.01-1.10	18.64	4.51	-6.36	60.80	13.00	27.00
500	1.00-1.01	17.59	1.49	-7.41	57.11	15.00	20.00
500	1.01-1.03	22.74	24.79	-2.27	619.03	4.00	88.00
500	1.01-1.06	12.03	1.88	-12.97	171.79	9.00	16.00
500	1.01-1.10	17.51	1.33	-7.49	57.82	15.00	20.00
1000	1.00-1.01	17.46	1.27	-7.54	58.46	16.00	19.00
1000	1.01-1.03	14.52	16.36	-10.48	377.14	5.00	86.50
1000	1.01-1.06	11.80	1.41	-13.20	176.28	9.00	15.00
1000	1.01-1.10	17.43	0.99	-7.57	58.25	16.00	19.00

Looking at the Table A.5.5.1 above (Score method, no censoring), the proposed score method under-estimates the cutpoint at 25, except at sample size 50 and sample size 100 and risk ratio of 1.01-1.03. The absolute bias ranges from 2.27 at sample size 500 to 15.71 at sample size 50 and risk ratio of 1.01-1.03, and MSE ranges from 60.80 at sample size 100 and risk ratio of 1.01-1.10 to 1007.60 at sample size 100 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (2.50, 86.50), denoting that 95% of the times the estimates were between 2.50 and 86.50, which indicates very large variability for the cutpoint estimate of 25.

Table A.5.5.2 Simulation Results from the exponential distribution using the Proposed Score method, 25% censoring, $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	30.55	15.94	5.55	284.71	14.00	72.00
50	1.01-1.03	44.93	24.88	19.93	1015.84	4.00	86.00
50	1.01-1.06	35.26	23.31	10.26	648.01	9.00	84.00
50	1.01-1.10	30.18	16.38	5.18	294.86	14.00	75.00
100	1.00-1.01	24.63	11.48	-0.37	131.72	15.00	59.00
100	1.01-1.03	44.44	25.76	19.44	1040.80	6.00	87.00
100	1.01-1.06	27.84	20.48	2.84	426.92	10.00	82.00
100	1.01-1.10	24.65	11.46	-0.35	131.28	15.00	58.50
500	1.00-1.01	19.17	2.03	-5.83	38.09	17.00	22.00
500	1.01-1.03	30.01	22.76	5.01	542.66	8.00	85.00
500	1.01-1.06	15.79	3.60	-9.21	97.86	12.00	20.00
500	1.01-1.10	19.12	1.87	-5.88	38.01	17.00	21.00
1000	1.00-1.01	19.02	1.20	-5.98	37.24	17.00	21.00
1000	1.01-1.03	20.79	14.12	-4.22	216.97	9.00	68.50
1000	1.01-1.06	15.25	1.47	-9.75	97.20	13.00	18.00
1000	1.01-1.10	19.03	1.00	-5.97	36.63	17.00	21.00

From the Table A.5.5.2 above (proposed score method, 25% censoring), the proposed score method both over and under-estimates the cutpoint at 25. The absolute bias ranges from 0.35 at sample size 100, risk ratio 1.01-1.10 to 19.93 at sample size 50 and risk ratio 1.01-1.03, and MSE ranges from 36.63 at sample size 1000 and risk ratio of 1.01-1.10 to 1015.84 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (4.0, 86.0), denoting that 95% of the times the estimates were between 4.0 and 86.0, which indicates very large variability for the cutpoint estimate of 25. MSE decreases as the sample size increases.

Table A.5.5.3 Simulation Results from the exponential distribution using the Klein and Wu method, no censoring, $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	25.64	3.01	0.64	9.44	19.00	31.00
50	1.01-1.03	32.50	8.94	7.50	135.95	17.00	51.50
50	1.01-1.06	27.14	4.69	2.14	26.57	19.00	38.50
50	1.01-1.10	25.56	2.93	0.56	8.88	18.00	31.00
100	1.00-1.01	25.12	1.76	0.12	3.12	21.00	29.00
100	1.01-1.03	32.10	7.31	7.10	103.79	20.00	48.00
100	1.01-1.06	26.27	2.91	1.27	10.08	21.00	33.00
100	1.01-1.10	25.08	1.48	0.08	2.19	21.50	28.00
500	1.00-1.01	24.97	0.28	-0.03	0.08	24.00	25.00
500	1.01-1.03	31.43	4.32	6.43	59.96	25.00	40.50
500	1.01-1.06	25.62	1.15	0.61	1.70	24.00	29.00
500	1.01-1.10	24.96	0.25	-0.04	0.07	24.00	25.00
1000	1.00-1.01	25.02	0.63	0.02	0.40	25.00	25.00
1000	1.01-1.03	31.35	3.70	6.35	54.01	25.00	39.00
1000	1.01-1.06	25.41	0.82	0.41	0.84	25.00	28.00
1000	1.01-1.10	25.00	0.04	-0.00	0.00	25.00	25.00

Looking at the Table A.5.5.3 above (Klein and Wu method, no censoring), the Klein and Wu method provides estimates approximately equal to the true cutpoint, except at the sample size 50 and sample size 100 and risk ratio of 1.01-1.03. The absolute bias ranges from 0.0 at sample size 1000, risk ratio 1.01-1.10 to 7.50 at sample size 50 and risk ratio of 1.01-1.03, and MSE ranges from 0 at sample size 1000 and risk ratio of 1.01-1.10 to 135.95 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (17.0, 51.5), denoting that 95% of the times the

estimates were between 17.0 and 51.5, indicating small variability in comparison to the proposed score method. The MSE decreases as the sample size increases.

Table A.5.5.4 Simulation Results from the Exponential distribution using the Klein and Wu method, 25% censoring, $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	26.12	3.77	1.12	15.42	18.00	35.00
50	1.01-1.03	33.03	9.68	8.03	157.99	16.00	55.00
50	1.01-1.06	27.77	5.09	2.77	33.54	19.00	40.00
50	1.01-1.10	25.90	3.45	0.90	12.72	18.00	34.00
100	1.00-1.01	25.43	1.83	0.43	3.52	21.00	29.00
100	1.01-1.03	32.84	7.67	7.84	120.24	21.00	50.00
100	1.01-1.06	26.73	3.42	1.73	14.71	21.00	36.00
100	1.01-1.10	25.36	1.82	0.36	3.45	21.00	29.00
500	1.00-1.01	25.01	0.45	0.01	0.20	24.00	26.00
500	1.01-1.03	31.81	4.57	6.81	67.25	25.00	42.00
500	1.01-1.06	25.78	1.37	0.78	2.49	24.00	29.00
500	1.01-1.10	25.01	0.35	0.00	0.12	24.00	26.00
1000	1.00-1.01	25.03	0.93	0.03	0.86	25.00	25.00
1000	1.01-1.03	31.47	3.92	6.47	57.16	25.00	40.00
1000	1.01-1.06	25.56	0.98	0.56	1.27	25.00	28.00
1000	1.01-1.10	25.00	0.10	0.00	0.01	25.00	25.00

For 25% censoring and cutpoint 25, the Klein and Wu method estimates are approximately equal to the true cutpoint 25, except for the relative risk 1.01-1.03. At relative risk of 1.01-1.03, the Klein and Wu method overestimated the cutpoint. MSE and bias both decreases for the large sample size. The largest bias is 8.03 and largest MSE is 157.99 at sample size 50 and relative risk 1.01-1.03. The smallest bias is 0 at sample size

500 and sample size 1000 for the risk ratio of 1.01-1.10. The smallest MSE is 0.01 for the sample size 1000 and risk ratio of 1.01-1.10. The 95th percentile interval at sample size 50 and relative risk 1.01-1.03 is (16, 55), which is the wideset interval among all other scenarios.

Table A.5.5.5 Simulation Results from the Exponential distribution using the Contal and O'Quigley method, no censoring, $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	33.81	6.59	8.81	120.99	25.00	49.00
50	1.01-1.03	36.90	9.50	11.90	231.80	21.00	57.50
50	1.01-1.06	35.02	7.33	10.02	154.09	24.00	51.00
50	1.01-1.10	34.74	6.76	9.74	140.44	25.00	49.50
100	1.00-1.01	33.23	5.33	8.23	96.21	25.00	42.0
100	1.01-1.03	36.40	7.74	11.40	189.63	25.00	50.0
100	1.01-1.06	33.75	5.75	8.75	109.65	25.00	44.0
100	1.01-1.10	33.20	5.24	8.20	94.74	25.00	42.0
500	1.00-1.01	32.24	3.22	7.24	62.77	26.00	38.00
500	1.01-1.03	35.38	4.68	10.38	129.66	27.00	45.00
500	1.01-1.06	32.84	3.43	7.84	73.24	26.00	40.00
500	1.01-1.10	32.03	3.21	7.03	59.73	26.00	39.00
1000	1.00-1.01	32.19	2.34	7.19	57.12	27.50	37.00
1000	1.01-1.03	35.73	4.08	10.73	131.65	28.00	43.00
1000	1.01-1.06	32.92	2.84	7.92	70.78	27.50	38.00
1000	1.01-1.10	32.12	2.37	7.12	56.34	27.00	37.00

Looking at the Table A.5.5.5 above (Contal and O'Quigley, no censoring), the Contal and O'Quigley method overestimates the true cutpoint. The absolute bias ranges from 7.03 at sample size 500, risk ratio 1.01-1.10 to 11.90 at sample size 50 and risk ratio of 1.01-1.03, and MSE ranges from 56.34 at sample size 1000 and risk ratio of 1.01-1.10 to

231.80 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (21.0, 57.5), denoting that 95% of the times the estimates were between 21.0 and 57.5, indicating small variability in comparison to the proposed score method. MSE decreases as the sample size increases.

Table A.5.5.6 Simulation Results from the Exponential distribution using the Contal and O'Quigley method, 25% censoring, $\tau_1 = 25$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	34.44	6.51	9.44	131.36	25.00	49.00
50	1.01-1.03	36.62	9.37	11.62	222.75	21.00	57.00
50	1.01-1.06	34.75	7.18	9.75	146.50	24.00	50.00
50	1.01-1.10	34.59	6.72	9.59	137.03	25.00	48.00
100	1.00-1.01	33.03	5.12	8.03	90.63	25.00	44.00
100	1.01-1.03	35.97	7.69	10.97	179.36	23.00	53.00
100	1.01-1.06	33.32	5.73	8.32	101.99	25.00	46.00
100	1.01-1.10	33.33	5.25	8.33	96.90	25.00	44.00
500	1.00-1.01	32.28	3.08	7.28	62.49	26.00	38.00
500	1.01-1.03	35.71	4.99	10.71	139.52	26.00	45.00
500	1.01-1.06	33.12	3.53	8.12	78.37	26.00	41.00
500	1.01-1.10	32.28	3.05	7.28	62.31	26.00	38.00
1000	1.00-1.01	32.11	2.47	7.11	56.62	28.00	37.00
1000	1.01-1.03	35.61	3.84	10.61	127.33	28.00	43.00
1000	1.01-1.06	32.84	2.81	7.84	69.29	28.00	38.00
1000	1.01-1.10	32.24	2.32	7.24	57.81	28.00	37.00

Looking at the Table A.5.5.6 above (Contal and O'Quigley, 25% censoring), the Contal and O'Quigley method overestimates the true cutpoint. The absolute bias ranges from 7.11 at sample size 1000, risk ratio 1.00-1.01 to 11.62 at sample size 50 and risk ratio of 1.01-1.03, and MSE ranges from 56.62 at sample size 1000 and risk ratio of 1.00-1.01 to

222.75 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (21.0, 57.0), denoting that 95% of the times the estimates were between 21.0 and 57.0, indicating small variability in comparison to the proposed score method. MSE decreases as the sample size increases.

Looking at all three methods, at the lower cutpoint ($\tau_1 = 25$), the proposed score method underestimated the cutpoint (downward bias) for non-censored data, and it both under and over estimates for censored data. The Klein and Wu method has estimates close the true cutpoint and the Contal and O'Quigley overestimated the true cutpoint. Of the three methods, the Klein and Wu is best performer in terms of Bias, MSE and 95th percentile intervals.

Table A.5.5.7 Simulation Results from the Exponential distribution using the proposed Score method, with no censoring, at $\tau_1 = 50$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	45.38	3.21	-4.62	31.66	37.00	49.00
50	1.01-1.03	32.47	21.94	-17.53	788.02	4.00	85.00
50	1.01-1.06	37.47	6.54	-12.53	199.78	24.00	47.00
50	1.01-1.10	45.46	3.28	-4.54	31.37	37.00	49.00
100	1.00-1.01	45.83	2.27	-4.17	22.56	41.00	49.00
100	1.01-1.03	28.57	18.30	-21.43	793.75	8.00	85.00
100	1.01-1.06	37.81	4.88	-12.19	172.46	28.00	46.00
100	1.01-1.10	45.96	2.32	-4.04	21.68	40.00	49.00
500	1.00-1.01	46.22	1.12	-3.78	15.53	44.00	48.00
500	1.01-1.03	21.95	5.06	-28.05	812.25	14.00	31.00
500	1.01-1.06	37.60	2.38	-12.40	159.48	33.00	42.00
500	1.01-1.10	46.19	1.14	-3.81	15.84	44.00	48.00
1000	1.00-1.01	46.28	0.84	-3.72	14.52	45.00	48.00
1000	1.01-1.03	21.23	3.12	-28.77	837.38	15.00	27.50
1000	1.01-1.06	37.53	1.80	-12.47	158.75	34.00	41.00
1000	1.01-1.10	46.28	0.84	-3.72	14.52	45.00	48.00

Looking at the Table A.5.5.7 above (Score method, no censoring), the proposed score method under-estimates the cutpoint at 50. The absolute bias ranges from 3.72 at sample size 1000 and risk ratio of 1.01-1.10 to 28.77 at sample size 1000 and risk ratio of 1.01-1.03, and MSE ranges from 14.52 at sample size 1000(relative risk 1.01-1.10) to 837.38 at sample size 1000 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 1000 and risk ratio 1.01-1.03 is (15.0, 27.5), denoting that 95% of sample

estimate were between 15 and 27.5, which indicates that for cutpoint 50, score method underestimates the cutpoint even for large sample size.

The absolute bias and MSE both are large regardless of the sample size. It can be concluded that if risk ratio is small, then the proposed score method may not be the best method to obtain a cutpoint.

Table A.5.5.8 Simulation Results from the Exponential distribution using the proposed Score method, 25% censoring, $\tau_1 = 50$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	45.96	3.14	-4.04	26.15	38.00	49.00
50	1.01-1.03	39.02	20.82	-10.98	553.75	7.00	84.00
50	1.01-1.06	40.27	6.91	-9.73	142.37	26.00	49.00
50	1.01-1.10	45.87	3.26	-4.13	27.67	38.00	49.00
100	1.00-1.01	46.63	1.92	-3.37	15.06	42.00	49.00
100	1.01-1.03	34.87	18.24	-15.13	561.45	11.00	84.00
100	1.01-1.06	40.50	4.57	-9.50	111.14	30.00	48.00
100	1.01-1.10	46.59	2.08	-3.41	15.97	41.50	49.00
500	1.00-1.01	46.95	1.01	-3.05	10.31	45.00	49.00
500	1.01-1.03	27.63	4.84	-22.37	523.68	19.00	37.00
500	1.01-1.06	40.45	2.30	-9.55	96.57	35.50	44.00
500	1.01-1.10	46.96	0.99	-3.04	10.24	45.00	49.00
1000	1.00-1.01	47.04	0.75	-2.97	9.35	46.00	48.00
1000	1.01-1.03	27.00	3.65	-23.00	542.16	21.00	34.00
1000	1.01-1.06	40.48	1.71	-9.52	93.62	37.00	44.00
1000	1.01-1.10	47.03	0.75	-2.97	9.41	46.00	48.00

Looking at the Table A.5.5.8 above (Score method, 25% censoring), the proposed score method under-estimates the cutpoint at 50. The absolute bias ranges from 2.97 at

sample size 1000 (relative risk 1.01-1.10) to 23 at sample size 1000(relative risk 1.01-1.03), and MSE ranges from 9.35 at sample size 1000 (relative risk 1.01-1.10) to 542.16 at sample size 1000 and risk ratio of 1.01-1.03. The 95^{th} percentile interval for sample size 1000 and risk ratio 1.01-1.03 is (21, 34), denoting that 95% of the times the sample estimates were between 21 and 34. With censoring the result from the proposed score method is better than with no censoring. It still has underestimation at relative risk 1.01-1.03 but the estimation for all other relative risk looks better.

Table A.5.5.9 Simulation Results from the Exponential distribution using the Klein and Wu method,, no censoring, $\tau_1 = 50$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	45.79	6.85	-4.21	64.68	26.00	53.50
50	1.01-1.03	43.91	8.27	-6.09	105.31	24.00	55.00
50	1.01-1.06	45.91	6.39	-4.09	57.58	28.50	54.00
50	1.01-1.10	45.91	6.71	-4.09	61.67	28.50	54.00
100	1.00-1.01	46.95	4.62	-3.05	30.60	34.00	52.00
100	1.01-1.03	45.87	5.75	-4.13	50.06	31.00	52.50
100	1.01-1.06	47.24	4.25	-2.77	25.69	36.00	52.00
100	1.01-1.10	47.13	4.46	-2.87	28.07	35.00	52.00
500	1.00-1.01	49.18	1.46	-0.82	2.80	45.00	50.00
500	1.01-1.03	48.59	2.16	-1.41	6.66	42.00	50.00
500	1.01-1.06	49.31	1.26	-0.69	2.07	46.00	50.00
500	1.01-1.10	49.28	1.29	-0.72	2.18	46.00	50.00
1000	1.00-1.01	49.70	0.68	-0.30	0.56	48.00	50.00
1000	1.01-1.03	49.17	1.47	-0.83	2.84	45.00	50.00
1000	1.01-1.06	49.66	0.78	-0.34	0.72	47.00	50.00
1000	1.01-1.10	49.71	0.67	-0.29	0.53	48.00	50.00

Looking at the Table A.5.5.9 above (Klein and Wu method, no censoring), the Klein and Wu method under-estimates the cutpoint at 50 but the absolute bias is very small. The absolute bias ranges from 0.29 at sample size 1000(relative risk 1.01-1.10) to 6.09 at sample size 50 (relative risk 1.01-1.03), and MSE ranges from 0.53 at sample size 1000 (relative risk 1.01-1.10) to 105.31 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (24, 55), denoting that 95% of sample estimate were between 24 and 55. For cutpoint 50 and no censoring, the Klein and Wu method has very small bias and MSE for large sample size. It also has small

bias for small sample size 50 and 100 but MSE is relatively large in comparison to sample size 500 and 1000.

Table A.5.5.10 Simulation Results from the Exponential distribution using the Klein and Wu method, 25% censoring, $\tau_1 = 50$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	45.83	7.29	-4.17	70.55	27.00	56.00
50	1.01-1.03	44.49	9.34	-5.51	117.45	22.00	58.00
50	1.01-1.06	45.31	7.74	-4.69	81.94	25.00	56.00
50	1.01-1.10	46.00	7.25	-4.00	68.55	27.00	56.00
100	1.00-1.01	47.04	4.71	-2.96	30.87	34.00	52.50
100	1.01-1.03	45.53	6.75	-4.48	65.53	28.00	54.50
100	1.01-1.06	46.86	5.14	-3.14	36.21	32.00	53.00
100	1.01-1.10	47.31	4.56	-2.69	28.02	35.00	52.50
500	1.00-1.01	49.14	1.65	-0.86	3.45	45.00	50.00
500	1.01-1.03	48.45	2.52	-1.55	8.76	41.50	51.00
500	1.01-1.06	49.04	1.78	-0.96	4.09	44.00	50.00
500	1.01-1.10	49.17	1.51	-0.83	2.96	45.00	50.00
1000	1.00-1.01	49.65	0.79	-0.35	0.74	47.00	50.00
1000	1.01-1.03	49.18	1.55	-0.82	3.06	44.00	50.00
1000	1.01-1.06	49.60	0.83	-0.40	0.85	47.00	50.00
1000	1.01-1.10	49.59	0.88	-0.41	0.93	47.00	50.00

Looking at the Table A.5.5.10 above, the Klein and Wu method estimates values approximately equal to the actual cutpoint at 50. The absolute bias ranges from 0.35 at sample size 1000 (relative risk 1.00-1.01) to 5.51 at sample size 50 (relative risk 1.01-1.03), and MSE ranges from 0.74 at sample size 1000 (relative risk 1.00-1.01) to 117.45 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50

and risk ratio 1.01-1.03 is (28, 58), denoting that 95% of the times the sample estimates were between 28 and 58.For sample size 500 and 1000 bias and MSE are smaller. Also the 95^{th} percentile interval is narrower for the large sample size.

Table A.5.5.11 Simulation Results from the Exponential distribution using the Contal and O'Quigley method, no censoring, $\tau_1 = 50$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5^{th} percentile	Upper 97.5^{th} percentile
50	1.00-1.01	48.51	4.47	-1.49	22.21	36.00	54.00
50	1.01-1.03	45.92	7.72	-4.09	76.30	26.00	57.00
50	1.01-1.06	48.19	4.80	-1.81	26.33	35.00	54.00
50	1.01-1.10	48.54	4.51	-1.46	22.42	35.50	55.00
100	1.00-1.01	48.51	4.47	-1.49	22.21	36.00	54.00
100	1.01-1.03	45.92	7.72	-4.09	76.30	26.00	57.00
100	1.01-1.06	48.19	4.80	-1.81	26.33	35.00	54.00
100	1.01-1.10	48.54	4.51	-1.46	22.42	35.50	55.00
500	1.00-1.01	49.81	0.57	-0.20	0.36	48.00	50.00
500	1.01-1.03	49.17	1.68	-0.83	3.51	44.00	51.00
500	1.01-1.06	49.77	0.63	-0.23	0.45	48.00	50.00
500	1.01-1.10	49.81	0.55	-0.20	0.34	48.00	50.00
1000	1.00-1.01	49.95	0.23	-0.05	0.06	49.00	50.00
1000	1.01-1.03	49.58	0.97	-0.42	1.11	47.00	50.00
1000	1.01-1.06	49.93	0.30	-0.07	0.09	49.00	50.00
1000	1.01-1.10	49.95	0.24	-0.05	0.06	49.00	50.00

Looking at the Table A.5.5.11 above (Contal and O'Quigley method, no censoring), the Contal and O'Quigley method has estimated values approximately equal to the true cutpoint of 50. The absolute bias ranges from 0.05 at sample size 1000(risk ratio 1.01-1.10) to 4.09 at sample size 50(risk ratio 1.01-1.03), and MSE ranges from 0.06 at

sample size 1000 (relative risk 1.01-1.10) to 76.30 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (26, 57), denoting that 95% of the times the sample estimates were between 26 and 57.

Table A.5.5.12 Simulation Results from the Exponential distribution using the Contal and O'Quigley method, 25% censoring, $\tau_1 = 50$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	48.65	4.42	-1.35	21.30	37.00	55.00
50	1.01-1.03	46.28	7.22	-3.73	65.97	28.00	57.00
50	1.01-1.06	48.29	4.73	-1.71	25.30	35.00	55.00
50	1.01-1.10	48.54	4.50	-1.46	22.33	37.00	54.00
100	1.00-1.01	49.07	2.41	-0.93	6.66	43.00	52.00
100	1.01-1.03	47.41	5.01	-2.59	31.74	34.00	54.00
100	1.01-1.06	48.80	2.91	-1.20	9.90	40.00	52.00
100	1.01-1.10	49.04	2.47	-0.96	7.03	42.00	52.00
500	1.00-1.01	49.83	0.48	-0.17	0.26	48.00	50.00
500	1.01-1.03	49.28	1.44	-0.73	2.60	45.00	51.00
500	1.01-1.06	49.75	0.63	-0.25	0.46	48.00	50.00
500	1.01-1.10	49.83	0.54	-0.17	0.32	49.00	50.00
1000	1.00-1.01	49.95	0.24	-0.05	0.06	49.00	50.00
1000	1.01-1.03	49.66	0.85	-0.34	0.84	47.00	50.00
1000	1.01-1.06	49.93	0.30	-0.07	0.10	49.00	50.00
1000	1.01-1.10	49.95	0.26	-0.05	0.07	49.00	50.00

Looking at the Table A.5.5.12 above (Contal and O'Quigley method, 25% censoring), the Contal and O'Quigley method has results approximately equal to the true cutpoint of 50. The absolute bias ranges from 0.05 at sample size 1000(risk ratio 1.01-1.10) to 3.73 at sample size 50(risk ratio 1.01-1.03), and MSE ranges from 0.06 at sample

size 1000 (relative risk 1.01-1.10) to 65.97 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (28, 57), denoting that 95% of the times the sample estimates were between 28 and 57. The results of censoring were similar with the result from non-censoring. Bias and MSE decreases with increasing sample size.

Looking at all three methods, at the middle cutpoint ($\tau_1 = 50$), the existing methods provide better estimates than the proposed score method. Of the three methods, the Klein and Wu is best performer in terms of Bias, MSE and 95th percentile intervals.

Table A.5.5.13 Simulation Results from the Exponential distribution using the proposed Score Method, no censoring, $\tau_1 = 75$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	70.16	6.88	-4.84	70.78	50.00	74.00
50	1.01-1.03	47.28	16.64	-27.73	1045.27	12.00	74.00
50	1.01-1.06	64.74	10.35	-10.26	212.16	33.00	74.00
50	1.01-1.10	70.38	6.55	-4.62	64.24	50.50	74.00
100	1.00-1.01	72.65	2.31	-2.35	10.84	66.00	74.00
100	1.01-1.03	47.36	13.72	-27.64	952.06	20.00	71.00
100	1.01-1.06	67.72	6.62	-7.28	96.75	47.00	74.00
100	1.01-1.10	72.64	2.37	-2.36	11.15	67.00	74.00
500	1.00-1.01	73.75	0.49	-1.25	1.80	73.00	74.00
500	1.01-1.03	46.19	7.71	-28.81	889.47	32.00	61.00
500	1.01-1.06	70.01	2.20	-4.99	29.71	65.00	73.00
500	1.01-1.10	73.78	0.47	-1.22	1.71	73.00	74.00
1000	1.00-1.01	73.91	0.30	-1.09	1.28	73.00	74.00
1000	1.01-1.03	45.80	6.22	-29.20	891.24	35.00	58.00
1000	1.01-1.06	70.29	1.55	-4.71	24.56	67.00	73.00
1000	1.01-1.10	73.90	0.31	-1.10	1.31	73.00	74.00

Looking at the Table A.5.5.13 above (Score method, no censoring), the proposed score method provides the estimate approximately equal to the true cutpoint of 75, except at the relative risk of 1.01-1.03. The bias ranges from 1.10 at sample size 1000 (relative risk 1.01-1.10) to 27.73 at sample size 50 (relative risk 1.01-1.03), and MSE ranges from 1.31 at sample size 1000 (relative risk 1.01-1.10) to 1045.27 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (12, 74), denoting the high variability at sample size 50 and relative risk 1.01-1.03.

Table A.5.5.14 Simulation Results from the Exponential distribution using the proposed Score method, 25% censoring, $\tau_1 = 75$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	69.78	7.90	-5.22	89.57	45.00	74.00
50	1.01-1.03	50.79	17.54	-24.21	893.22	14.00	79.00
50	1.01-1.06	66.24	9.71	-8.76	170.85	36.00	74.00
50	1.01-1.10	69.34	8.40	-5.66	102.62	43.00	74.00
100	1.00-1.01	72.58	3.38	-2.42	17.27	66.50	74.00
100	1.01-1.03	51.68	14.21	-23.32	745.48	21.00	73.00
100	1.01-1.06	68.89	6.24	-6.11	76.24	51.00	74.00
100	1.01-1.10	72.65	2.74	-2.35	13.00	67.00	74.00
500	1.00-1.01	73.87	0.36	-1.13	1.42	73.00	74.00
500	1.01-1.03	52.67	8.77	-22.33	575.26	34.00	67.00
500	1.01-1.06	71.33	1.77	-3.67	16.63	67.00	74.00
500	1.01-1.10	73.85	0.41	-1.15	1.50	73.00	74.00
1000	1.00-1.01	73.97	0.17	-1.03	1.09	73.00	74.00
1000	1.01-1.03	52.44	7.10	-22.56	559.24	38.50	65.00
1000	1.01-1.06	71.54	1.26	-3.46	13.55	69.00	73.00
1000	1.01-1.10	73.97	0.18	-1.03	1.10	73.00	74.00

Looking at the Table A.5.5.14 above (Score method, 25% censoring), the proposed score method provides the estimate approximately equal to the true cutpoint of 75, except at the relative risk of 1.01-1.03. The bias ranges from 1.03 at sample size 1000 (relative risk 1.01-1.10) to 24.21 at sample size 50 (relative risk 1.01-1.03), and MSE ranges from 1.10 at sample size 1000 (relative risk 1.01-1.10) to 893.22 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for sample size 50 and risk ratio 1.01-1.03 is (14,

79), denoting the high variability at sample size 50 and relative risk 1.01-1.03. The result from censoring is similar with the result from non-censoring.

Table A.5.5.15 Simulation Results from the Exponential distribution using the Klein and Wu method, no censoring, $\tau_1 = 75$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	50.51	16.16	-24.49	860.50	16.50	76.00
50	1.01-1.03	48.27	16.19	-26.73	976.33	17.00	75.00
50	1.01-1.06	49.20	16.12	-25.80	925.29	17.00	75.00
50	1.01-1.10	50.07	15.85	-24.93	872.42	20.00	75.00
100	1.00-1.01	51.93	13.65	-23.07	718.20	23.00	75.00
100	1.01-1.03	49.58	13.62	-25.42	831.52	24.00	74.00
100	1.01-1.06	51.06	14.09	-23.94	771.37	23.00	74.00
100	1.01-1.10	51.79	14.06	-23.21	736.16	24.00	75.00
500	1.00-1.01	53.06	9.30	-21.94	567.77	34.50	71.50
500	1.01-1.03	51.04	9.46	-23.96	663.39	32.00	69.00
500	1.01-1.06	53.18	9.36	-21.82	563.54	35.00	72.00
500	1.01-1.10	53.34	9.31	-21.66	555.73	34.00	70.50
1000	1.00-1.01	53.15	7.68	-21.85	536.55	38.00	68.00
1000	1.01-1.03	51.55	7.27	-23.45	602.60	37.00	65.50
1000	1.01-1.06	53.36	7.42	-21.64	523.12	38.00	68.00
1000	1.01-1.10	53.72	7.27	-21.28	505.68	39.50	68.00

Looking at the Table A.5.5.15 above (Klein and Wu method, no censoring), the Klein and Wu method consistently under-estimates the true cutpoint of 75. The bias ranges from 21.28 at sample size 1000 (relative risk 1.01-1.10) to 26.73 at sample size 50 (relative risk 1.01-1.03), and MSE ranges from 505.68 at sample size 1000 (relative risk 1.01-1.10) to 976.33 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for

sample size 50 and risk ratio 1.01-1.03 is (17, 75), denoting the high variability at sample size 50 and relative risk 1.01-1.03.

Table A.5.5.16 Simulation Results from the Exponential distribution using the Klein and Wu method, 25% censoring, $\tau_1 = 75$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	49.79	16.36	-25.21	902.90	18.00	75.00
50	1.01-1.03	46.93	17.35	-28.07	1088.59	14.00	76.00
50	1.01-1.06	49.34	16.91	-25.66	943.99	15.50	76.00
50	1.01-1.10	50.47	16.61	-24.53	877.16	17.00	76.00
100	1.00-1.01	50.81	13.99	-24.19	780.76	22.00	74.50
100	1.01-1.03	49.43	15.39	-25.57	890.67	18.00	75.00
100	1.01-1.06	50.98	14.37	-24.02	783.16	23.00	75.00
100	1.01-1.10	50.84	14.18	-24.16	784.65	22.00	75.00
500	1.00-1.01	53.26	9.65	-21.74	565.77	35.00	71.50
500	1.01-1.03	51.04	9.88	-23.96	671.48	32.00	71.00
500	1.01-1.06	53.10	10.05	-21.91	580.77	33.00	71.00
500	1.01-1.10	53.40	9.67	-21.60	560.22	34.00	72.00
1000	1.00-1.01	54.02	8.15	-20.98	506.46	38.50	69.00
1000	1.01-1.03	51.19	8.21	-23.81	634.35	35.00	67.00
1000	1.01-1.06	53.70	8.23	-21.30	521.22	38.00	69.00
1000	1.01-1.10	54.29	7.98	-20.72	492.68	38.00	70.00

Looking at the Table A.5.5.16 above (Klein and Wu method, 25% censoring), the Klein and Wu method consistently under-estimates the true cutpoint of 75. The bias ranges from 20.72 at sample size 1000 (relative risk 1.01-1.10) to 28.07 at sample size 50 (relative risk 1.01-1.03), and MSE ranges from 492.68 at sample size 1000 (relative risk 1.01-1.10) to 1088.59 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for

sample size 50 and risk ratio 1.01-1.03 is (14, 76), denoting the high variability at sample size 50 and relative risk 1.01-1.03. The result from censoring is similar to result from non-censoring.

Table A.5.5.17 Simulation Results from the Exponential distribution using the Contal and O'Quigley method, no censoring, $\tau_1 = 75$

N	Scenario	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	52.93	15.66	-22.07	732.16	21.50	76.00
50	1.01-1.03	50.93	15.45	-24.07	818.14	19.00	75.00
50	1.01-1.06	51.81	15.58	-23.19	780.26	21.00	76.00
50	1.01-1.10	53.00	14.87	-22.01	705.03	23.00	75.50
100	1.00-1.01	52.93	15.66	-22.07	732.16	21.50	76.00
100	1.01-1.03	50.93	15.45	-24.07	818.14	19.00	75.00
100	1.01-1.06	51.81	15.58	-23.19	780.26	21.00	76.00
100	1.01-1.10	53.00	14.87	-22.01	705.03	23.00	75.50
500	1.00-1.01	56.43	8.98	-18.57	425.21	38.00	73.00
500	1.01-1.03	53.48	9.13	-21.52	546.40	35.00	71.00
500	1.01-1.06	55.94	9.33	-19.06	450.18	38.00	73.00
500	1.01-1.10	56.30	9.10	-18.70	432.33	38.00	73.00
1000	1.00-1.01	56.57	7.89	-18.44	402.04	41.00	73.00
1000	1.01-1.03	53.12	7.27	-21.88	531.67	39.00	67.00
1000	1.01-1.06	56.27	7.38	-18.73	405.21	42.00	71.00
1000	1.01-1.10	56.90	7.26	-18.10	380.27	43.00	71.00

Looking at the Table 5.5.17 above (Contal and O'Quigley, no censoring), the Contal and O'Quigley method consistently under-estimates the true cutpoint of 75. The bias ranges from 18.10 at sample size 1000 (relative risk 1.01-1.10) to 24.07 at sample size 50 (relative risk 1.01-1.03), and MSE ranges from 380.27 at sample size 1000 (relative risk 1.01-1.10) to 818.14 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile

interval for sample size 50 and risk ratio 1.01-1.03 is (19, 75), denoting the high variability at sample size 50 and relative risk 1.01-1.03.

Table A.5.5.18 Simulation Results from the Exponential distribution using the Contal and O'Quigley method, 25% censoring, $\tau_1 = 75$

N	Scenario	Cut	Mean	SD	Bias	MSE	Lower 2.5th percentile	Upper 97.5th percentile
50	1.00-1.01	75	52.62	15.52	-22.38	741.67	22.00	76.00
50	1.01-1.03	75	49.62	16.12	-25.38	903.41	17.00	76.00
50	1.01-1.06	75	52.16	15.20	-22.84	752.38	23.00	76.00
50	1.01-1.10	75	53.04	15.50	-21.97	722.32	21.00	76.00
100	1.00-1.01	75	53.17	13.15	-21.84	649.63	27.00	75.00
100	1.01-1.03	75	51.02	13.55	-23.98	758.73	23.00	75.00
100	1.01-1.06	75	53.66	13.25	-21.34	630.68	27.00	75.00
100	1.01-1.10	75	53.84	13.44	-21.17	628.32	28.00	75.00
500	1.00-1.01	75	56.21	9.26	-18.79	438.77	38.00	73.00
500	1.01-1.03	75	52.74	8.98	-22.26	576.13	35.00	71.00
500	1.01-1.06	75	55.84	9.29	-19.16	453.29	37.00	73.00
500	1.01-1.10	75	56.21	9.07	-18.79	435.17	38.00	72.50
1000	1.00-1.01	75	57.01	7.41	-17.99	378.51	43.50	71.00
1000	1.01-1.03	75	53.18	7.59	-21.82	533.62	39.00	67.00
1000	1.01-1.06	75	56.24	7.72	-18.76	411.38	41.00	71.00
1000	1.01-1.10	75	56.77	7.64	-18.23	390.80	42.00	71.50

Looking at the Table A.5.5.18 above (Contal and O'Quigley, 25% censoring), the Contal and O'Quigley method under-estimates the true cutpoint of 75. The bias ranges from 18.23 at sample size 1000 (relative risk 1.01-1.10) to 25.38 at sample size 50 (relative risk 1.01-1.03), and MSE ranges from 390.80 at sample size 1000 (relative risk 1.01-1.10) to 903.41 at sample size 50 and risk ratio of 1.01-1.03. The 95th percentile interval for

sample size 50 and risk ratio 1.01-1.03 is (17, 76), denoting the high variability at sample size 50 and relative risk 1.01-1.03. The result from censoring is similar to the result from non-censoring.

Looking at all three methods, at the upper cutpoint ($\tau_1 = 75$), the existing methods tend to under-estimate the cutpoint (downward bias). Of the three methods, the proposed score method has smaller bias and MSE than the existing methods and the proposed score method is best performer in terms of Bias, MSE and 95^{th} percentile intervals for the cutpoint of 75.

APPENDIX B

SAS Code

1. Code for simulation of data.

```
/*****************************************************************/
/* Simulation of data ********************************************/
/** Set I **/
%Let numsim=1000;
%Let lambda=0.00011;  /* Baseline Hazard Function */
%Let gamma =0.78137;
%Let nobs  =50;      /* How many subjects to simulate
*/
%Let beta1 =0.0; /* Beta coefficient for Age HR=1.00 */
%Let beta2 =0.00995; /* Beta coefficient for Age HR=1.01 */
libname kabita50 'C:\for survival\simulated data';

%Macro Sim1;
data survival1_50&i;
      do id=1 to &nobs;
        sigma=1/&gamma;
        mu   =-log(&lambda)/&gamma;
        alpha1=-&beta1/&gamma;
        alpha2=-&beta2/&gamma;
        censor=0;/*censor=0 is event*/
        u=ranuni(0);                              /* Seed=0 allows me to
get the different random numbers for U[0,1] values everytime   */
        age=round(0+(90)*ranuni(0));              /* Seed=0 allows me to
get the different random numbers for U[25,90] values everytime */
        if (age lt 50) then t=exp(mu+alpha1*age)*(-log(u))**sigma;
                       else t=exp(mu+alpha2*age)*(-log(u))**sigma;
        output;
      end;
run;

data kabita50.sampledata1_50&i;
      set survival1_50&i;
      keep id censor age t;
run;

%Mend Sim1;
/*****************************************************************
****************/
/** Set II **/
%Macro Sim2;
%Let beta1 =0.00995; /* Beta coefficient for Age HR=1.01 */
%Let beta2 =0.029559; /* Beta coefficient for Age HR=1.03 */

data survival2_50&i;
```

```
      do id=1 to &nobs;
        sigma=1/&gamma;
        mu   =-log(&lambda)/&gamma;
        alpha1=-&beta1/&gamma;
        alpha2=-&beta2/&gamma;
        censor=0;
        u=ranuni(0);                              /* Seed=0 allows
different random numbers at U[0,1] values everytime   */
        age=round(0+(90)*ranuni(0));              /* Seed=0 allows me to
get different random numbers at U[25,90] values everytime */
        if (age lt 50) then t=exp(mu+alpha1*age)*(-log(u))**sigma;
                       else t=exp(mu+alpha2*age)*(-log(u))**sigma;
        output;
      end;
run;

data kabita50.sampledata2_50&i;
      set survival2_50&i;
      keep id censor age t;
run;

%Mend Sim2;
/*************************************************************************
************/
/** Set III
*************************************************************************
******/
%Macro Sim3;
%Let beta1 =0.009950; /* Beta coefficient for Age HR=1.01 */
%Let beta2 =0.058269; /* Beta coefficient for Age HR=1.06 */

data survival3_50&i;
      do id=1 to &nobs;
        sigma=1/&gamma;
        mu   =-log(&lambda)/&gamma;
        alpha1=-&beta1/&gamma;
        alpha2=-&beta2/&gamma;
        censor=0;
        u=ranuni(0);                              /* Seed=148 allows me to
get the same U[0,1] values everytime   */
        age=round(0+(90)*ranuni(0));              /* Seed= 89 allows me to
get the same U[25,90] values everytime */
        if (age lt 50) then t=exp(mu+alpha1*age)*(-log(u))**sigma;
                       else t=exp(mu+alpha2*age)*(-log(u))**sigma;
        output;
      end;
run;

data kabita50.sampledata3_50&i;
      set survival3_50&i;
      keep id censor age t;
run;
```

```
%Mend Sim3;
/*************************************************************************
*****************/
/** Set IV **********************/
%Macro Sim4;
%Let beta1 =0.009950; /* Beta coefficient for Age HR=1.01 */
%Let beta2 =0.09531; /* Beta coefficient for Age HR=1.10 */

data survival4_50&i;
      do id=1 to &nobs;
        sigma=1/&gamma;
        mu   =-log(&lambda)/&gamma;
        alpha1=-&beta1/&gamma;
        alpha2=-&beta2/&gamma;
        censor=0;
        u=ranuni(0);                              /* Seed=0 allows me to
get the different U[0,1] values everytime   */
        age=round(0+(90)*ranuni(0));              /* Seed=0 allows me to
get the different U[25,90] values everytime */
        if (age lt 50) then t=exp(mu+alpha1*age)*(-log(u))**sigma;
                       else t=exp(mu+alpha2*age)*(-log(u))**sigma;
        output;
      end;
run;

data kabita50.sampledata4_50&i;
      set survival4_50&i;
      keep id censor age t;
run;
%Mend Sim4;
/*****************************************/

%Macro RunSim;

%do i=1 %to &NumSim;

%Sim1;
%Sim2;
%Sim3;
%Sim4;

%end;

%Mend RunSim;

%RunSim;


/*******************************************************/
```

2. Code for Proposed Method

```
/** SAS Code for Proposed Method**/
filename junk dummy;
proc printto log=junk;
run;
options ls=80;
/** 25% Censoring** Score Method ** ss=50** Weibull distribution**/
*libname test1 'C:\for survival\simulated data\samplesize1000\simsample';
*libname test2 'C:\for survival\simulated data\samplesize1000\testnov4';
libname test1 '/home/joshik2/simulateddata/ss1000/wsample_dec27';
libname test2 '/home/joshik2/simulateddata/ss1000/wsc_dec27';
title1 'Data for experiment ';
%macro ages;

%do i=1 %to &max;

data time&i;
      set ages;
if (_n_ eq &i);
      cutpoint=age;
      keep cutpoint;
run;

data all&i;
      set chemo;
if (_n_ eq 1) then set time&i;
      if (age ge cutpoint) then high=1;
                           else high=0;

run;

ods listing close;

proc lifereg data=all&i outest=parms&i(keep=_scale_) noprint;
      model time*censor1(1)=high/dist=weibull;
      output out=lf&i sres=rsi cres=rci;
run;

ods listing;

data lf&i;
      set lf&i;
if (_n_ eq 1) then set parms&i;
rs2i=abs((age*(exp(rsi)-status))/_scale_);
      *keep rs2i cutpoint;
run;

proc means data=lf&i sum noprint;
```

```
var rs2i;
output out=sum_score&i sum=sum_score;
run;

data timenew&i;
 set time&i;
 if _n_=1 then set sum_score&i;
 keep sum_score cutpoint;
 run;

proc append base=lrsummary&j data=timenew&i force;
run;

%end;
%Mend Ages;

%macro getlr(m=,ss=,newc=);
%do j=1 %to 1000;

data t2;
              set test1.sampledata&m&j._n&ss._cut&newc;
              time=t;
              if censor1=0 then status=1;
              else status=0;
      run;


      data t1;
              set test1.sampledata&m&j._n&ss._cut&newc;
              time=t;
              if censor1=0 then status=1;
              else status=0;
      run;

      data chemo;
            set t1;
      run;
************************************************
      * Get distinct failure time *
************************************************;
data times;
      set chemo;
if (censor eq 0); *Censor=0 is for who had death at the time of study;
run;

************************************************
* Remove any duplicate time from the times data *
************************************************;

proc sort data=times out=times nodupkey; by time; *If any of the time is
repeated delete the replicated time;
run;
```

```
*********************************************************
* Just keep the time variable in the times data*
*********************************************************;

data times;
      set times;
      keep time;
run;

*************************************************************
* Count the number of distinct times in the times data*
*************************************************************;

proc means data=times noprint;
      var time;
      output out=numtime n=k;
run;

*****************************************************************
* Assign the macro variable from the data *
*****************************************************************;
data numtime;
      set numtime;
      call symput('k', trim(k));
run;

proc sort data=chemo out=ages nodupkey; by age;
run;

*********************************************************
* Find out the minimum age and the maximum age and delete it from the
data *
*****************************************************************;
proc means data=ages noprint;
      var age;
      output out=minage min=minage max=maxage;
run;
*****************************************************************
* Delete the minimum age and maximum age*
*****************************************************************
****;
data ages;
      set ages;
if (_n_ eq 1) then set minage;
if (age eq minage) then delete;
if (age eq maxage) then delete;
      keep age;
run;
*****************************************************************
* Count the number of observations in ages data *
*****************************************************************;
```

```
proc means data=ages noprint;
      var age;
      output out=max n=max;
run;
*************************************************************************
***
* It will create the variable max for the macro *
*************************************************************************
;
data max;
      set max;
      call symput('max', trim(max));
run;

%ages;

data lrsummary&j;
      set lrsummary&j;
      z=abs(sum_score);
run;




proc means data=lrsummary&j noprint;
      var z;
      output out=maxz&j max=maxz;
run;

data cutpoint&j;
      set lrsummary&j;
if (_n_ eq 1) then set maxz&j;
if (z eq maxz);
id=&j;
rr=&m;
cut=&newc;
n=&ss;
run;



proc append base=test2.cut&m._cut&newc._n&ss data=cutpoint&j force;
run;




proc means data=test2.cut&m._cut&newc._n&ss noprint ;
var cutpoint;
output out=test2.mean&m._n&ss._cut&newc mean=mean std=std;
run;
```

```
data test2.cut&m._cut&newc._n&ss;
set test2.cut&m._cut&newc._n&ss;
diff=cutpoint-&newc;
diff_sq=diff**2;
run;

proc means data=test2.cut&m._cut&newc._n&ss noprint ;
var diff_sq;
output out=test2.sum&m._n&ss._cut&newc sum=sum;
run;

proc datasets;
save t2;
run;
quit;


%end;
%mend getlr;



%getlr(m=1,ss=1000,newc=75);
%getlr(m=2,ss=1000,newc=75);
%getlr(m=3,ss=1000,newc=75);
%getlr(m=4,ss=1000,newc=75);
```

3. Code for Klein and Wu method

```
/*  Code for Klein and Wu Method **/

filename junk dummy;
proc printto log=junk;
run;
options ls=80;

libname test1 '/home/joshik2/simulateddata/ss1000/expsample_dec21';
libname test2 '/home/joshik2/simulateddata/ss1000/wkw_jan19_exp';
title1 'Data for experiment ';
%macro ages;

%do i=1 %to &max;

data time&i;
      set ages;
if (_n_ eq &i);
      cutpoint=age;
      keep cutpoint;
run;
```

```
data all&i;
      set chemo;
if (_n_ eq 1) then set time&i;
      if (age ge cutpoint) then high=1;
                           else high=0;

run;


/*************************************************************************
***/
ods listing close;

proc lifereg data=all&i outest=parms&i(keep=_scale_) noprint;
      model time*censor1(1)=/dist=weibull;
      output out=lf&i sres=rsi cres=rci;
run;

ods listing;

data lf&i;
      set lf&i;
if (_n_ eq 1) then set parms&i;
rs2i_up=((high*(exp(rsi)-status))/_scale_);
rs2i_down=((exp(rsi)-status)/_scale_)**2;
      *keep rs2i cutpoint;
run;

proc means data=lf&i sum noprint;
var rs2i_up rs2i_down;
output out=sum_score&i sum=sum_up sum_down;
run;

data timescore&i;
 set time&i;
 if _n_=1 then set sum_score&i;
 snp=(sum_up/sqrt(sum_down));
 keep snp cutpoint;
 run;

proc append base=kwsummary&j data=timescore&i force;
run;

%end;
%Mend Ages;

%macro getlr(m=,ss=,newc=);
%do j=1 %to 1000;

      data t2;
              *set test1.sampledata&m&j._n&ss._cut&newc;
```

```
                set test1.sampledata&m&j._n&ss._cut&newc;
                time=t;
        run;

        data t1;
                *set test1.sampledata&m&j._n&ss._cut&newc;
                set test1.sampledata&m&j._n&ss._cut&newc;
                time=t;
                if censor1=0 then status=1;
                else status=0;
        run;

        data chemo;
              set t1;
        run;
************************************************
        * Get distinct failure time *
************************************************;
data times;
        set chemo;
if (censor eq 0); *Censor=0 is for who had death at the time of study;
run;

************************************************
* Remove any duplicate time from the times data *
************************************************;

proc sort data=times out=times nodupkey; by time; *If any of the time is
repeated delete the replicated time;
run;

********************************************************
* Just keep the time variable in the times data*
********************************************************;

data times;
        set times;
        keep time;
run;

************************************************************
* Count the number of distinct times in the times data*
************************************************************;

proc means data=times noprint;
        var time;
        output out=numtime n=k;
run;

*****************************************************************
* Assign the macro variable from the data *
*****************************************************************;
```

```
data numtime;
      set numtime;
      call symput('k', trim(k));
run;

proc sort data=chemo out=ages nodupkey; by age;
run;

*******************************************************
* Find out the minimum age and the maximum age and delete it from the
data *
*****************************************************************;
proc means data=ages noprint;
      var age;
      output out=minage min=minage max=maxage;
run;
*******************************************************************
* Delete the minimum age and maximum age*
*******************************************************************
****;
data ages;
      set ages;
if (_n_ eq 1) then set minage;
if (age eq minage) then delete;
if (age eq maxage) then delete;
      keep age;
run;
*******************************************************************
* Count the number of observations in ages data *
*******************************************************************;
proc means data=ages noprint;
      var age;
      output out=max n=max;
run;
*******************************************************************
***
* It will create the variable max for the macro *
*******************************************************************
;
data max;
      set max;
      call symput('max', trim(max));
run;

%ages;

data kwsummary&j;
      set kwsummary&j;
      z=abs(snp);
run;
```

```
proc means data=kwsummary&j noprint;
      var z;
      output out=maxz&j max=maxz;
run;

data cutpoint&j;
      set kwsummary&j;
if (_n_ eq 1) then set maxz&j;
if (z eq maxz);
id=&j;
rr=&m;
cut=&newc;
n=&ss;
run;




data test2.cutkw&m._cut&newc._n&ss;
set cutpoint&j;
diff=cutpoint-&newc;
diff_sq=diff**2;
run;

proc means data=test2.cutkw&m._cut&newc._n&ss noprint ;
var cutpoint;
output out=test2.outkw&m._n&ss._cut&newc mean=mean std=std;
run;

proc datasets;
save t2;
run;
quit;


%end;

%mend getlr;

%getlr(m=1,ss=1000,newc=25);
%getlr(m=2,ss=1000,newc=25);
%getlr(m=3,ss=1000,newc=25);
%getlr(m=4,ss=1000,newc=25);

%getlr(m=1,ss=1000,newc=50);
%getlr(m=2,ss=1000,newc=50);
%getlr(m=3,ss=1000,newc=50);
%getlr(m=4,ss=1000,newc=50);
```

```
%getlr(m=1,ss=1000,newc=75);
%getlr(m=2,ss=1000,newc=75);
%getlr(m=3,ss=1000,newc=75);
%getlr(m=4,ss=1000,newc=75);
```

4. Code for Contal and O'Quigley Method

```
/** Code for Contal and O'Quigley method **/
filename junk dummy;
proc printto log=junk;
run;

options ls=80;
*libname test1 'C:\for survival\simulated data\samplesize50\simsample';
*libname test2 'C:\for survival\simulated data\samplesize50\testnov4';
libname test1 '/home/joshik2/simulateddata/ss50/esample_dec27';
libname test2 '/home/joshik2/simulateddata/ss50/qqexp_dec27';
title1 'Data for experiment ';
%macro ages;

%do i=1 %to &max;

data time&i;
      set ages;
if (_n_ eq &i);
      cutpoint=age;
      keep cutpoint;
run;

data all&i;
      set chemo;
if (_n_ eq 1) then set time&i;
      if (age ge cutpoint) then high=1;
                           else high=0;

run;

ods listing close;


proc lifetest data=all&i method=km;
      time time*censor(1);
      strata high / test=logrank;
      ods output homstats=lr&i;
run;


ods listing;
```

```
data lr&i;
      set lr&i;
if (_n_ eq 1) then set time&i;
      keep logrank cutpoint;
run;

data lr&i;
      set lr&i;
if (_n_ eq 1);
run;

proc append base=logrank&j data=lr&i force;
run;


%end;
%Mend Ages;

%macro getlr(m=,ss=,newc=);
%do j=1 %to 1000;

      data t2;
              set test1.sampledata&m&j._n&ss._cut&newc;
              time=t;
      run;

      data t1;
              set test1.sampledata&m&j._n&ss._cut&newc;
              time=t;
      run;

      data chemo;
            set t1;
      run;
************************************************
      * Get distinct failure time *
************************************************;
data times;
      set chemo;
if (censor eq 0); *Censor=0 is for who had death at the time of study;
run;

************************************************
* Remove any duplicate time from the times data *
************************************************;

proc sort data=times out=times nodupkey; by time; *If any of the time is
repeated delete the replicated time;
run;

**********************************************************
* Just keep the time variable in the times data*
```

```
*********************************************************;

data times;
      set times;
      keep time;
run;

*************************************************************
* Count the number of distinct times in the times data*
*************************************************************;

proc means data=times noprint;
      var time;
      output out=numtime n=k;
run;

*****************************************************************
* Assign the macro variable from the data *
*****************************************************************;
data numtime;
      set numtime;
      call symput('k', trim(k));
run;

proc sort data=chemo out=ages nodupkey; by age;
run;

*********************************************************
* Find out the minimum age and the maximum age and delete it from the
data *
*****************************************************************;
proc means data=ages noprint;
      var age;
      output out=minage min=minage max=maxage;
run;
*****************************************************************
* Delete the minimum age and maximum age*
*****************************************************************
****;
data ages;
      set ages;
if (_n_ eq 1) then set minage;
if (age eq minage) then delete;
if (age eq maxage) then delete;
      keep age;
run;
*****************************************************************
* Count the number of observations in ages data *
*****************************************************************;
proc means data=ages noprint;
      var age;
      output out=max n=max;
```

```
run;
*************************************************************************
***
* It will create the variable max for the macro *
*************************************************************************
;
data max;
      set max;
      call symput('max', trim(max));
run;

%ages;

data logrank&j;
      set logrank&j;
      z=abs(logrank);
run;


proc means data=logrank&j noprint;
      var z;
      output out=maxlz&j max=maxz;
run;

data cutlr&j;
      set logrank&j;
if (_n_ eq 1) then set maxlz&j;
if (z eq maxz);
id=&j;
rr=&m;
cut=&newc;
run;


proc append base=test2.cutlr&m._cut&newc data=cutlr&j force;
run;

data test2.cutlr&m._cut&newc;
set test2.cutlr&m._cut&newc;
diff=cutpoint-&newc;
diff_sq=diff**2;
run;

proc means data=test2.cutlr&m._cut&newc noprint ;
var cutpoint;
output out=test2.outlr&m._n&ss._cut&newc mean=mean std=std;
run;

proc datasets;
save t2;
run;
quit;
```

```
%end;

%mend getlr;


%getlr(m=1,ss=50,newc=25);
%getlr(m=2,ss=50,newc=25);
%getlr(m=3,ss=50,newc=25);
%getlr(m=4,ss=50,newc=25);
```

5. Code for compilation of result:

```
libname lib "C:\for survival\simulateddata\samplesize50\wsc_dec27_25per";
libname test
"C:\forsurvival\simulateddata\samplesize50\wsc_25censoring_result";

%macro compile(rr=,cut=,n=);
data res&rr&cut&n;
set lib.cut&rr._cut&cut._n&n;
run;


/** find the mean value of cutpoint from 1000 estimated cutpoints*/
proc means data=res&rr&cut&n;
var cutpoint;
output out=out1&rr&cut&n mean=mean std=std p5=p5 p95=p95;
run;
/*mean=30.7950000*/
/* Find the bias by subtracting the true cutpoint from mean value of
estimated cutpoint*/
data out1&rr&cut&n;
set out1&rr&cut&n;
bias=mean-&cut;
sq_bias=bias**2;
run;

/*Find MSE by taking the sum of the diff_sq and dividing the sum by n*/
proc means data=res&rr&cut&n sum;
var diff_sq;
output out=out2&rr&cut&n sum=sum;
run;

/* MSE=Sum(diff_sq)/n**/
data out2&rr&cut&n;
set out2&rr&cut&n;
MSE=sum/1000;
run;
```

```
/*MSE=58.533*/
data outscore&rr&cut&n;
merge out2&rr&cut&n out1&rr&cut&n;
ss=&n;
rr=&rr;
cut=&cut;
run;

proc append base=test.outscore&n data=outscore&rr&cut&n force;
run;

%mend compile;
/*Sample size=50*/
%compile(rr=1,cut=25,n=50);
%compile(rr=2,cut=25,n=50);
%compile(rr=3,cut=25,n=50);
%compile(rr=4,cut=25,n=50);
/***********************************/
/** Sample size=100**/
%compile(rr=1,cut=25,n=100);
%compile(rr=2,cut=25,n=100);
%compile(rr=3,cut=25,n=100);
%compile(rr=4,cut=25,n=100);
/***********************************/
/** Sample size=500**/
%compile(rr=1,cut=25,n=500);
%compile(rr=2,cut=25,n=500);
%compile(rr=3,cut=25,n=500);
%compile(rr=4,cut=25,n=500);
/** Sample size=1000**/
%compile(rr=1,cut=25,n=1000);
%compile(rr=2,cut=25,n=1000);
%compile(rr=3,cut=25,n=1000);
%compile(rr=4,cut=25,n=1000);
```

VITA

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Education:

- PhD in Biostatistics, Virginia Commonwealth University: 2010-2016
- Master's in public Health, Major Biostatistics, Georgia Southern University, Statesboro, GA: 2008-2010
- Master's in Statistics, Tribhuvan University Nepal: 2002-2004
- Bachelor of Science in Statistics: Tribhuvan University, Nepal: 1998-2002

Work Experience:

- Teaching Assistant for ANOVA course (BIOS 554), VCU, Richmond, VA: Jan 2015-Aug 2015
- Teaching Assistant for Linear regression course (BIOS 553), VCU, Richmond, VA: Aug 2014 - Dec 2014
- Research Assistant for Twin data, VCU, Richmond, VA: May 2014 - Jul 2014
- Research Assistant for American Cancer Society grant, VCU, Richmond, VA: May 2013 - Apr 2014
- Teaching Assistant for Mathematical Statistics (BIOS 513/514), VCU, Richmond, VA: Aug 2012 - May 2013
- Teaching Assistant for Biostatistics Introductory course for clinicians (BIOS 543/544), VCU, Richmond, VA: Aug 2010-Jul 2012
- Graduate Assistant for Biostatistics Introductory course, Georgia Southern University, Statesboro, GA: Aug 2009- May 2010

Skills:

- SAS
- R
- JMP
- SPSS
- Microsoft Word, Excel, PowerPoint, Access

Poster Presentation:

- **Joshi, K**., Thacker, L.R., Elswick, R.K. 31st Annual Daniel T. Watts Research Symposium: Virginia Commonwealth University, Richmond, VA: October 2014. Topic: "Finding a Cutpoint of a Continuous Covariate in Survival Analysis"
- **Joshi, K.** and Gennings, C. The Society of Toxicology (SOT) 52nd Annual Meeting, San Antonio, TX: March 2013. Topic: "Use of Human Environmental Chemical Concentration Patterns: Preliminary Steps in a Whole Mixture Strategy for Risk Evaluation"