STATISTICAL INFERENCE FOR COSTS AND INCREMENTAL COST-EFFECTIVENESS RATIOS WITH CENSORED DATA

A Thesis

by

SHUAI CHEN

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

May 2012

Major Subject: Statistics

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ABSTRACT

Statistical Inference for Costs and Incremental

Cost-Effectiveness Ratios with Censored Data. (May 2012)

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Dr. Lan Zhou

Cost-effectiveness analysis is widely conducted in the economic evaluation of new treatment options. In many clinical and observational studies of costs, data are often censored. Censoring brings challenges to both medical cost estimation and cost-effectiveness analysis. Although methods have been proposed for estimating the mean costs with censored data, they are often derived from theory and it is not always easy to understand how these methods work. We provide an alternative method for estimating the mean cost more efficiently based on a replace-from-the-right algorithm, and show that this estimator is equivalent to an existing estimator based on the inverse probability weighting principle and semiparametric efficiency theory. Therefore, we provide an intuitive explanation to a theoretically derived mean cost estimator.

In many applications, it is also important to estimate the survival function of costs. We propose a generalized redistribute-to-the right algorithm for estimating the survival function of costs with censored data, and show that it is equivalent to a simple weighted survival estimator of costs based on inverse probability weighting techniques. Motivated by this redistribute-to-the-right principle, we also develop a more efficient survival estimator for costs, which has the desirable property of being monotone, and more efficient, although not always consistent. We conduct simulation to compare

our method with some existing survival estimators for costs, and find the bias seems quite small. Thus, it may be considered as a candidate for survival estimator for costs in a real setting when the censoring is heavy and cost history information is available.

Finally, we consider one special situation in conducting cost-effectiveness analysis, when the terminating events for survival time and costs are different. Traditional methods for statistical inference cannot deal with such data. We propose a new method for deriving the confidence interval for the incremental cost-effectiveness ratio under this situation, based on counting process and the general theory for missing data process. The simulation studies show that our method performs very well for some practical settings. Our proposed method has a great potential of being applied to a real setting when different terminating events exist for survival time and costs.

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CHAPTER I

INTRODUCTION

Due to skyrocketing of health care costs and limited resource available, economic evaluation of new treatments has received more and more attention. To compare different treatments, cost-effectiveness analysis helps evaluate the economic impact of the new treatment and its effects on health care, in the hope of finding an effective treatment without causing too much a burden to the society.

The analysis of cost data involves some unique challenges that require advanced statistical methodologies, especially when costs are censored. For example, randomized clinical trials often enroll subjects over a broad time period, but the trial ends at a fixed time point. As a result, subjects are observed for differing amounts of time, and those who are still alive at the end of the study are considered censored. Thus, we cannot observe further costs after censored time for those patients. Besides, censoring poses a unique problem for cost estimation due to the "induced informative censoring" problem, first noted by Lin et al. (1997). Traditional survival analysis methods assume that the censoring time is independent of the survival time (conditional on some covariates). However, the costs at censoring time are no longer independent of the potential total costs. For example, a healthier patient will accumulate costs more slowly, and therefore will have less costs at the censoring time, and at the potential event time (Lin, 2003). Thus, many standard approaches for survival analysis (e.g., Kaplan-Meier estimator and Cox regression model) are not valid for the analysis of cost data.

Therefore, many researchers have proposed methods for estimating the mean med-

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This thesis follows the style of *Biometrics*.

ical costs, and most of them focus on the time-restricted medical costs, i.e., the costs accumulated within a time limit. Although many estimators for the mean costs have appeared in the literature, they are often based on theory, and it is not always easy for practitioners to understand why these methods work. To alleviate this situation, Zhao et al. (2011) established a mathematical equivalency between the BT estimator for the mean costs (Bang and Tsiatis, 2000), and a replace-from-the-right (RR) algorithm (Pfeifer and Bang, 2005). Thus, the BT estimator, which is based on the inverse probability weighting technique (Horvitz and Thompson, 1952), has a more intuitive explanation from the RR algorithm. Motivated by this idea, we will extend this work by proposing a modified RR algorithm, the RRimp method, which utilizes the cost history information and is therefore generally more efficient than the RR estimator. We will provide a proof of the mathematical equivalence between the RRimp method and an existing estimator for the mean costs, the ZT estimator (Zhao and Tian, 2001). Due to a lack of a theoretical background for understanding the BT and ZT estimators, some practitioners might be reluctant to use them. With the easy interpretation of the RR and RRimp estimators, and established equivalency between these estimators and the BT, ZT estimators, we believe these estimators will become more popular among practitioners.

Furthermore, since cost data are often highly skewed, it is more desirable to estimate the median and other quantiles of the costs. These quantities can be available if we can estimate the survival function of costs. Using the original redistribute-to-the right algorithm, we propose a RR^S (abbreviated as RR^S for survival estimator) survival estimator for costs, and show that it is equivalent to a simple weighted (SW) survival estimator for costs (Zhao and Tsiatis, 1997; Zhao et al., 2012). We extend this method and propose a RRimp^S survival estimator. Further simulation studies are conducted to compare this RRimp^S survival estimator with the RR^S survival estimator (or

equivalent SW estimator), and a more efficient ZT^S survival estimator (Zhao and Tsiatis, 1997; Zhao et al., 2012).

Moreover, in performing cost-effectiveness analysis with censored data, there have been several measures proposed to evaluate the treatments (Chaudhary and Sterns, 1996; Heitjan, 2000; Willan and Lin, 2001; Briggs et al., 2002; O'Brien and Briggs, 2002; Willan and Briggs, 2006). Among them the incremental cost-effectiveness ratio (ICER) is a widely used criterion. The ICER is defined as the costs incurred for saving an additional year of life. When one treatment has a significant effectiveness over another treatment but is more expensive, this measure is especially useful. Usually the effectiveness are defined as the survival time for patients, and therefore the endpoints for costs and effectiveness are the same. However, it is commonly encountered in clinical studies that we need to use different endpoints for costs and effectiveness estimation. For example, a new strategy might prevent the heart failure event. Hence, it may extend the heart-failure free survival time, but not overall survival time. However, we are still interested in the costs estimation up to death. In this situation, we are interested in estimating the ICER based on the heart-failure free survival time but costs accumulated until death. Although the construction for the confidence intervals (CI) of usual ICER with the same terminating points has been studied much, there are no theoretical results for research on this ICER and its CI which allow different terminating events. Thus, we propose a method to handle this problem.

The remainder of the thesis is organized as followed. In Chapter II, we will discuss the mean cost estimators with corresponding intuitive explanation, as well as the survival function estimators for cost. In Chapter III, we will concentrate on cost-effectiveness analysis, and show how to handle the problem of ICER with different terminating events. The Chapter IV is the Summary of this thesis, which summarizes the innovative methods we proposed in this thesis.

CHAPTER II

ESTIMATING THE MEAN COST AND SURVIVAL FUNCTIONS FOR COSTS

1. Introduction

Economic evaluation of new treatments has received more and more attention, due to skyrocketing of health care costs and limited resource available. Cost-effectiveness study is often carried out to evaluate new treatments in the hope of finding an effective treatment without causing too much a burden to the society. In clinical trials and in observational studies, survival time and health costs are often censored for administrative reasons, since not all patients can be observed until they experience some events, such as death, or disease relapse. Censoring poses a unique problem for cost estimation due to the "induced informative censoring" problem, first noted by Lin et al. (1997). Traditional survival analysis methods assume that the censoring time is independent of the survival time (conditional on some covariates). However, the costs at censoring time are no longer independent of the total uncensored costs. For example, a healthier patient will accumulate costs more slowly, and therefore will have less costs at the censoring time, and at the potential event time (Lin, 2003). Thus, many standard approaches for survival analysis, such as the Kaplan-Meier estimator (Kaplan and Meier, 1958), or the Cox regression model (Cox, 1972), are not valid for the analysis of cost data. Many researchers have proposed methods for estimating the mean medical costs, and most of them focus on the restricted medical costs, i.e., the costs accumulated within a time limit. Among them, Lin et al. (1997) proposed estimators via survival probability weighting using partitioned time intervals; Bang and Tsiatis (2000) proposed consistent estimators using the inverse probability weighting

technique; Zhao and Tian (2001) proposed a more efficient estimator. Later, Zhao et al. (2007) discovered some conditions under which the estimators without using cost history, and estimators using cost history become identical within each class.

Although many estimators for the mean costs have appeared in the literature, they are often based on theory, and it is not always easy for practitioners to understand why these methods work. To alleviate this situation, Zhao et al. (2011) established a mathematical equivalency between the BT estimator for the mean costs (Bang and Tsiatis, 2000), and a replace-from-the-right (RR) algorithm (Pfeifer and Bang, 2005). Thus, the BT estimator, which is based on the inverse probability weighting technique (Horvitz and Thompson, 1952), has a more intuitive explanation from the RR algorithm. Motivated by this idea, we will propose a modified RR algorithm, the RRimp method, which utilizes the cost history information and is therefore generally more efficient than the RR estimator. We will provide a proof of the mathematical equivalence between the RRimp method and an existing estimator for the mean costs, the ZT estimator (Zhao and Tian, 2001). The ZT estimator was derived from complicated theory. Therefore, the RRimp algorithm will provide an insight on how the ZT estimator works and will eventually help promote its application in practice.

Since cost data are often highly skewed, with most people incur little costs, but a few people accumulate huge costs, it is often desirable to estimate the median and other quantiles of the costs. These quantities can be readily available if we can estimate the survival function of costs. Using the original redistribute-to-the right algorithm, we propose a RR^S (abbreviated as RR^S for survival estimator) survival estimator for costs, and show that it is equivalent to a simple weighted (SW) survival estimator for costs (Zhao and Tsiatis, 1997; Zhao et al., 2012). We extend this method and propose a RRimp^S survival estimator. We conduct simulation studies to compare this RRimp^S survival estimator with the RR^S survival estimator (or equivalent SW

estimator), and a more efficient ZT^S survival estimator (Zhao and Tsiatis, 1997; Zhao et al., 2012). We will discuss our findings in the Conclusion section.

2. Notation and Assumptions

For the ith individual in the study, $i = 1, 2, \ldots, n$, we define T_i as the survival time from the beginning of the study until the occurrence of some event, e.g. death, or disease relapse. The censoring time for the ith individual is denoted as C_i. We can observe either the survival time or the censoring time, whichever is smaller, i.e. we observe the follow-up time $X_i = \min(T_i, C_i)$ and the indicator variable $\Delta_i = I(T_i \leq C_i)$. We define $M_i(t)$ as the accumulated cost of patient i from time 0 to t. For some real applications, we only observe the total cost $M_i = M_i(X_i)$. However, in other studies, we may know the entire cost history, $M_i(t), 0 < t < X_i$.

We assume that the censoring variable is independent of the survival time and cost accumulation process, which is often satisfied in well-conducted clinical trials and some observational studies where censoring is caused mainly by administrative reasons. Due to the presence of censoring, the marginal distribution of cost may be nowhere identifiable without making some parametric assumptions (Huang, 2002). Hence we adopt an approach that focuses on the accumulated cost by a time limit L, where L is chosen such that a reasonable amount of information is still available at that time. A consequence of using such a restriction is that a survival time larger than L can be considered equivalently as having an event at time L, i.e. $T_i^L = \min(T_i, L)$ (we still use T_i for notational convenience).

We consider the problem of estimating the mean cost, $\mu = E\{M_i(T_i)\}$, and the survival function of cost, $S(x) = \Pr\{M_i(T_i) > x\}$, for costs accumulated to a time L. For reasons that will become clear later, we also need to define the survival function

for the event time as $S^T(t) = \Pr(T_i > t)$, and the survival function for the censoring time as $K(t) = \Pr(C_i > t)$.

3. Estimating the Mean Cost

3.1. Without Using Cost History: The BT Estimator and Its Equivalent RR Estimator

For estimation of mean cost accumulated over time L with censoring data, a consistent estimator was proposed by Bang and Tsiatis (2000) based on the inverse probability weighting technique:

$$\hat{\mu}_{BT} = \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i M_i}{\hat{K}(T_i)}, \tag{2.1}$$

where M_i is the total observed cost for the ith individual, and $\hat{K}(T_i)$ is the Kaplan-Meier estimator for the survival function of the censoring time, $K(t) = Pr(C_i > t)$. $K(T_i)$ represents the probability that a subject is uncensored at T_i. The basic idea of the BT estimator is that each complete observation represents potential $1/\hat{K}(T_i)$ observations who might be censored.

Even though the BT estimator is easy to obtain mathematically, it is not very intuitive for people to understand why it works. The replace-from-the-right (RR) estimator proposed by Pfeifer and Bang (2005), on the other hand, is a more intuitive estimator. To explain the main idea of the RR method, first we note that without censoring, a mean cost estimator is simply the average of costs from all observations. When a subject is censored, we only know that this subject lives longer than his censoring time, but we do not have information on his total cost. In the RR algorithm, we replace this subject's cost by an average of costs from those individuals who survived longer than this subject. Specifically, a RR estimator for the mean costs can be obtained by first arranging all the subjects from the smallest observed time to the

largest observed time (if there is a tie, put the events a little before the censored). We then move from the right (the largest observation time) to the left (the smallest observation time). When we encounter the largest censored observation, say, at time C_i, we replace its costs by the average of costs from all the observations to its right,

$$M_i^{RR} = \frac{\sum_{j=1}^{n} I(X_j > C_i) M_j}{\sum_{j=1}^{n} I(X_j > C_i)}. \tag{2.2}$$

We move to the left and repeat this process of replacing all the censored costs with the average of all upstream costs (some of these are real costs and some are replaced costs). The RR mean cost estimator is simply an average of all the costs from both complete observations and censored observations (replaced costs), i.e.

$$\hat{\mu}_{RR} = \frac{1}{n} \sum_{i=1}^{n} \{\Delta_i M_i + (1 - \Delta_i) M_i^{RR}\}. \tag{2.3}$$

Although the BT estimator (2.1) and the RR method (2.3) look quite different – the former is based on a well-known theory, and the latter makes intuitive sense, it is quite amazing that the two estimators are actually mathematically equivalent. The detailed proof was provided in Zhao et al. (2011).

3.2. Using the Cost History: The ZT Estimator and Its Equivalent RRimp Estimator

The BT estimator and its equivalent RR algorithm use only the total cost information from uncensored subjects. Hence, they are not very efficient. An improved estimator was proposed by Zhao and Tian (2001), which utilizes cost history information from both censored and uncensored observations. Therefore the ZT estimator is often more efficient. The ZT estimator has the following simplified form (Pfeifer and Bang, 2005):

$$\hat{\mu}_{ZT} = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i M_i}{\hat{K}(T_i)} + \frac{1}{n} \sum_{i=1}^{n} \frac{(1 - \Delta_i)[M_i(C_i) - \overline{M(C_i)}]}{\hat{K}(C_i)}, \tag{2.4}$$

where $\overline{M(C_i)} = \sum_{j=1}^{n} I(X_j \geq C_i) M_j(C_i) / \sum_{j=1}^{n} I(X_j \geq C_i)$, which is the average accumulative cost at time C_i of those subjects who are alive at C_i.

The ZT estimator consists of two terms. The first term is the BT estimator. The second term is constructed using cost history information, which can be viewed as an adjustment term. The ZT estimator gains more efficiency by adjusting the BT estimator based on the difference of censored costs and the average accumulated costs at the same time point. Zhao and Tian (2001) established the large sample property for this estimator. Furthermore, Zhao et al. (2007) described the conditions under which this estimator is equivalent to the partitioned Bang and Tsiatis (2000) estimator, as well as the two estimators of medical costs proposed by Lin et al. (1997).

Since the BT estimator has an intuitive explanation through the RR algorithm, it is natural to wonder whether the ZT estimator has a similar intuitive explanation. As a result, we propose a RRimp algorithm, which makes intuitive sense, and later we show that it is equivalent to the ZT estimator. In contrast to the simple RR method, which depends only on the total costs from complete observations, the RRimp algorithm uses the cost history information. Intuitively, for a censored subject, we already know his accumulated cost before censoring. Hence, the only thing we need to estimate is his cost after the censoring time point. We can achieve that by the average of additional costs accumulated by those subjects who survive longer. The detailed RRimp estimator can be described as follows. First arrange all the subjects from the smallest observed time to the largest observed time. If there is a tie, we assume events happen shortly before censoring times. Since we focus on time-restricted costs estimation, we assume that the individual with the largest observed time is uncensored. Starting from the right (the largest observed time) we move to the left. We first find the largest censoring time, denoted as C_i. We replace the cost for this observation by a summation of his observed cost and the average additional accumulated costs from

all subjects who have a larger survival time, i.e.

$$M_i^{RRimp} = M_i(C_i) + \frac{\sum_{j=1}^{n} I(X_j > C_i)\{M_j - M_j(C_i)\}}{\sum_{j=1}^{n} I(X_j > C_i)}. \tag{2.5}$$

We then move to the second largest censoring time and perform the same replacement procedure, where we use the replaced cost for the largest censoring time in calculating the average. We move to the left and repeat this process until we replace all the censored costs. The RRimp estimator is then obtained by an average of costs from all complete observations (real costs) and the censored observations (replaced costs), i.e.

$$\hat{\mu}_{RRimp} = \frac{1}{n}\sum_{i=1}^{n}\{\Delta_i M_i + (1-\Delta_i)M_i^{RRimp}\}. \tag{2.6}$$

We illustrate this algorithm using a simple example in Figure 1. Suppose we observe the following data: $X = \{1, 2, 3, 4, 5\}$, $\Delta = \{1, 0, 1, 0, 1\}$, and their accumulated costs $M_i(\cdot)$ are shown in the figure below. Here the 2nd and 4th subjects are censored. In Step 1, we try to obtain the replacement cost for subject 4. Since subject 5 is the only one surviving longer than subject 4. the replacement cost for subject 4 is equal to the summation of the censored cost of subject 4 (=60) and the additional accumulated cost of subject 5 from time X_4 to X_5 ($= 40 - 30$), which is 70. Similarly, in Step 2 we try to obtain the replacement cost for subject 2 by adding the observed cost of subject 2 (=50) and the average of additional costs after time X_2 for subject 3 (=100-60, real costs), subject 4 (=70-20, replaced costs) and subject 5 (=40-10, real costs), which is equal to 90. Therefore, the mean cost estimated from the RRimp method gives an estimate of 62, as shown in the graph below.

$X_i =$	1	2	3	4	5
	x	o	x	o	x
$M_1(\cdot) =$	10				
$M_2(\cdot) =$	20	50			
$M_3(\cdot) =$	30	60	100		
$M_4(\cdot) =$	10	20	40	60	
$M_5(\cdot) =$	5	10	20	30	40
Step 1: (M_4^{RRimp})				$70\{= 60 + (40 - 30)\}$	
Step 2: (M_2^{RRimp})	$90\{= 50 + [(100 - 60) + (70 - 20) + (40 - 10)]/3\}$				

$\hat{\mu}_{RRimp} = (10 + 90 + 100 + 70 + 40)/5 = 62.$

Figure 1. An example for the RRimp mean cost estimator.

Meanwhile, the ZT estimator of the mean cost obtained from the same data set is:

$$\begin{aligned}
\hat{\mu}_{ZT} &= \frac{1}{5}\sum_{i=1}^{5}\frac{\Delta_i M_i}{\hat{K}(T_i)} + \frac{1}{5}\sum_{i=1}^{5}\frac{(1-\Delta_i)[M_i(C_i) - \overline{M(C_i)}]}{\hat{K}(C_i)} \\
&= \frac{1}{5}(\frac{10}{1} + \frac{100}{3/4} + \frac{40}{3/8}) + \frac{1}{5}(\frac{50-35}{3/4} + \frac{60-45}{3/8}) \\
&= \frac{1}{5}(10 + 400/3 + 320/3) + \frac{1}{5}(20 + 40) \\
&= 50 + 12 = 62,
\end{aligned}$$

where the Kaplan-Meier estimates for $K(t) = \Pr(C_i > t)$ are $\hat{K}(X_i)$=(1, 3/4, 3/4, 3/8, 3/8), at $X_i = \{1, 2, 3, 4, 5\}$, and $\overline{M(C_i)} = \{35, 45\}$, at $C_i = \{2, 4\}$, respectively. Hence, We obtain exactly the same estimate for the mean cost using the ZT estimator and the RRimp method using this data set. Actually they are always the same no matter what data sets we use. A mathematical proof of the equivalence of these two estimators is provided in Appendix A.

In summary, the RRimp method works as follows. Due to censoring, we use the upstream complete costs to infer the censored cost. When we have cost history infor-

mation for both censored and uncensored observations, we can replace the censored cost by supplementing what we have observed with the additional accumulated costs from upstream observations. This RRimp method is mathematically equivalent to the ZT estimator, and as demonstrated by simulations and examples in Zhao and Tian (2001), they are generally more efficient than the BT estimator and its equivalent RR method.

4. Estimating Survival Functions for Costs

In additional to estimating the mean costs, it is often desirable to estimate the survival function of costs in practice, since the the survival function can provide more information about the costs, such as the medians, and quartiles, which are more robust to outliers. Motivated by the idea of the RR algorithm for estimating the mean costs, we investigate how to use the RR principle to develop survival estimators for the costs. We show that a naive way of deriving the survival estimator based on the RR algorithm for the mean cost estimator will result in a biased estimator. Instead we propose a new redistribute-to-the-right (RR^S) algorithm for an estimator of the survival function of costs (we add "S" to indicate it is a survival estimator), based on the original idea from Efron (1967) who discovered the algorithm for the survival time. We will show that it is equivalent to a simple weighted (SW) survival estimator of costs, whose form was described in the context of estimating the quality adjusted lifetime by Zhao and Tsiatis (1997). We also attempt to derive a survival estimator based on the redistribute-to-the-right algorithm that uses cost history information. We will discuss the advantage and disadvantage of such an estimator.

4.1. The SW Estimator and Its Equivalent RR^S Estimator

Following the idea of Zhao and Tsiatis (1997), a SW estimator for the survival function of costs can be obtained by

$$\hat{S}_{SW}(x) = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} I(M_i > x). \tag{2.7}$$

The large sample property of this estimator, such as its consistency and asymptotic normality can be established similarly, which is omitted here.

To construct an equivalent RR survival estimator, one is tempted to use the replacement costs at each censored points, and estimate the survival function for costs using the following formula:

$$\hat{S}_{naive}(x) = \frac{1}{n}\sum_{i=1}^{n} \{\Delta_i I(M_i > x) + (1-\Delta_i) I(M_i^{RR} > x)\}. \tag{2.8}$$

Unfortunately, if we use the empirical distribution function shown above to estimate the survival function for costs, treating the replaced costs as if they were the real costs, the estimated curve will be biased, although the area under the curve, i.e., the estimated mean costs, is unbiased. This will be demonstrated in subsequent simulation studies.

In order to find an equivalent RR^S estimator, we rely on the original idea of redistribution-to-the-right proposed by Efron (1967), which was used to explain the Kaplan-Meier estimator for survival time. For each censored subject, since we do not know the actual costs, we will find the contributions from observations that are larger than this subject. Specifically, we first sort all subjects according to their observation times from the smallest (left) to the largest (right). For any tied observations, we assume the death time occurs a little earlier than the censored time. Consider a censored observation i whose initial weight is set to be 1. We distribute its weight evenly

to all the time points to its right. For example, if there are n_i such observations, then each one gets a weight of $1/n_i$. Next we find the smallest censored observation to its right, and redistribute its weight again evenly to all the observations to its right. Repeat this process until we have redistributed the weight of the largest censoring time. Note that after redistribution the weights are non-zero only at those complete observations larger than the censored observation i. Denoting the final weight at the jth complete event time as $W_j^{(i)}$, it represents the contribution of a complete subject j to the censored subject i.

Due to censoring we often cannot evaluate the mark $I(M_i > x)$, instead we use the weighted sum

$$I(M_i > x)^{RR} = \sum_{j=1}^{n} \Delta_j I(T_j > X_i) W_j^{(i)} I(M_j > x) \tag{2.9}$$

as the replacement mark. As a result, the RR^S estimator for the survival function of costs is

$$\hat{S}_{RR}(x) = \frac{1}{n} \sum_{i=1}^{n} \{\Delta_i I(M_i > x) + (1 - \Delta_i) I(M_i > x)^{RR}\}. \tag{2.10}$$

We illustrate this idea using a simple example. Assume we have data $[X = \{1, 2, 3, 4, 5\}, \Delta = \{1, 0, 1, 0, 1\}, M = \{10, 20, 40, 30, 50\}]$. As shown in Figure 2, we first find the weight $W_j^{(2)}$, i.e. the contribution of complete observations to the censored observation 2. In Step 0, the censored observation 2 gets the weight of 1. In Step 1, we distribute its weight of 1 to all the 3 observations to its right, so that each of them gets a weight of 1/3. Moving to the next censoring time, observation 4, we distribute its weight of 1/3 to the one observation to its right, making the weight at time 5 to be 2/3. Hence we have $W_3^{(2)} = 1/3$, and $W_5^{(2)} = 2/3$.

It is easy to obtain the contributions of complete observations to the censoring

$X_j =$	1	2	3	4	5
	x	o	x	o	x
Step 0:	0	1	0	0	0
Step 1:	0	0	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$
Step 2:	0	0	$\frac{1}{3}$	0	$\frac{2}{3}(=\frac{1}{3}+\frac{1}{3})$
$W_j^{(2)}$:			$\frac{1}{3}$		$\frac{2}{3}$

Figure 2. An example for weight $W_j^{(2)}$.

observation 4, in this case, $W_5^{(4)}$=1. Hence the RR^S estimator is

$$\begin{aligned}
\hat{S}_{RR}(x) &= \frac{1}{5}\sum_{i=1}^{5}[\Delta_i I(M_i > x) + (1-\Delta_i) I(M_i > x)^{RR}] \\
&= \frac{1}{5}\{I(M_1 > x) + I(M_3 > x) + I(M_5 > x) + I(M_2 > x)^{RR} + I(M_4 > x)^{RR}\} \\
&= \frac{1}{5}\{I(M_1 > x) + I(M_3 > x) + I(M_5 > x) \\
&\quad + \frac{1}{3} I(M_3 > x) + \frac{2}{3} I(M_5 > x) + I(M_5 > x)\} \\
&= \frac{1}{5}\{I(M_1 > x) + \frac{4}{3} I(M_3 > x) + \frac{8}{3} I(M_5 > x)\}.
\end{aligned}$$

The simple weighted estimator for this example is

$$\begin{aligned}
\hat{S}_{SW}(x) &= \frac{1}{5}\sum_{i=1}^{5}[\frac{\Delta_i I(M_i > x)}{\hat{K}(T_i)}] \\
&= \frac{1}{5}\{\frac{I(M_1 > x)}{1} + \frac{I(M_3 > x)}{3/4} + \frac{I(M_5 > x)}{3/8}\} \\
&= \frac{1}{5}\{I(M_1 > x) + \frac{4}{3} I(M_3 > x) + \frac{8}{3} I(M_5 > x)\}.
\end{aligned}$$

It is clear that the RR^S estimator is equivalent to the SW survival estimator for costs in this example.

Remarks

1. It is not difficult to find that the weight $W_j^{(i)}$ is related to the estimated conditional probability of an event occurring at X_j given that the subject is alive at X_i (discrete case). Thus, $W_j^{(i)}$ can be easily obtained from Kaplan-Meier estimator:

$$W_j^{(i)} = \frac{1}{n\hat{S}^T(C_i)\hat{K}(T_j)}, \tag{2.11}$$

where $\hat{S}^T(x)$ is the Kaplan-Meier estimator for $\Pr(T > x)$, $\hat{K}(x)$ is the Kaplan-Meier estimator for $\Pr(C > x)$.

2. The weights $W_j^{(i)}$ are exactly the weights needed for obtaining the replaced costs for a censored observation i, in estimating the mean costs, i.e.

$$M_i^{RR} = \sum_{j=1}^{n} \Delta_j I(X_j > X_i) W_j^{(i)} M_j. \tag{2.12}$$

3. We can show that this RR^S estimator (2.10) for the survival function of costs is mathematically equivalent to the SW estimator based on the similar results for mean cost estimators.

4.2. RR Improved Survival Estimator for the Survival Function of Costs

As in the case of estimating the mean costs, the SW and its equivalent RR^S estimator for the survival function of costs are not efficient, since they utilize only the costs from complete observations. Based on the principles of constructing the RR^S survival estimator and the RRimp estimator for mean costs, we propose an improved RR survival (RRimp^S) estimator, as shown below:

$$\hat{S}_{RRimp}(x) = \frac{1}{n}\sum_{i=1}^{n}[\Delta_i I(M_i > x) + (1-\Delta_i) I(M_i > x)^{RRimp}], \tag{2.13}$$

where

$$I(M_i > x)^{RRimp} = \sum_j [\Delta_j I(T_j > X_i) W_j^{(i)} I(M_j^{(i)} > x)], \tag{2.14}$$

is the new replacement mark, and $M_j^{(i)} = M_i(C_i) + M_j - M_j(C_i)$ is the cost combining information from censored and complete data.

This RRimp^S estimator is always monotone, which is a desirable property for a survival estimator. In contrast, an improved survival function estimator of costs developed similar to Zhao and Tsiatis (1997), which we will call the ZT^S survival estimator, cannot be guaranteed to be monotone (Huang and Louis, 1998). The RRimp^S estimator is also more efficient than the SW estimator and the ZT^S estimator, for many realistic situations. However, unlike the SW and the ZT^S estimators, this RRimp^S estimator is not consistent anymore. In the next section, we will conduct simulation experiments to examine the properties of these survival estimators.

5. Simulation Studies

We conduct simulation studies under several different scenarios to evaluate the survival function estimators for costs. We generate survival times using an exponential distribution $T \sim exp(10)$, and a uniform distribution $T \sim Unif(0, 15)$. The survival time is truncated at L=10. We generate also censoring times using a uniform distribution, $C \sim Unif(0, 22)$, for light (25%-30%), and $Unif(0, 15)$, for heavy censoring (37%-44%). The sample size is set to be 100, and the number of simulations is 1000.

We consider U-shaped sample paths for the cost distribution, similar to the simulation settings of Bang and Tsiatis (2002) and Zhao et al. (2012). We partition the entire time period of 10 years into 10 equal intervals. Each individual's costs consist of initial diagnostic costs incurred at time 0, terminal costs incurred during the last year before the failure time, fixed annual costs, and random annual costs (which vary

from year to year). The diagnostic costs, fixed annual costs, random annual costs, and terminal costs are generated using a log normal distribution with parameters $(10, 0.245^2)$, $(6, 0.245^2)$, $(4, 0.245^2)$, $(9, 0.632^2)$, respectively. We estimate the survival function of costs using the SW estimator, the ZT^S estimator from Zhao and Tsiatis (1997), and our RRimp^S estimator, under the four different simulation scenarios. We also examined the naive survival estimator of (2.8) for one of the settings.

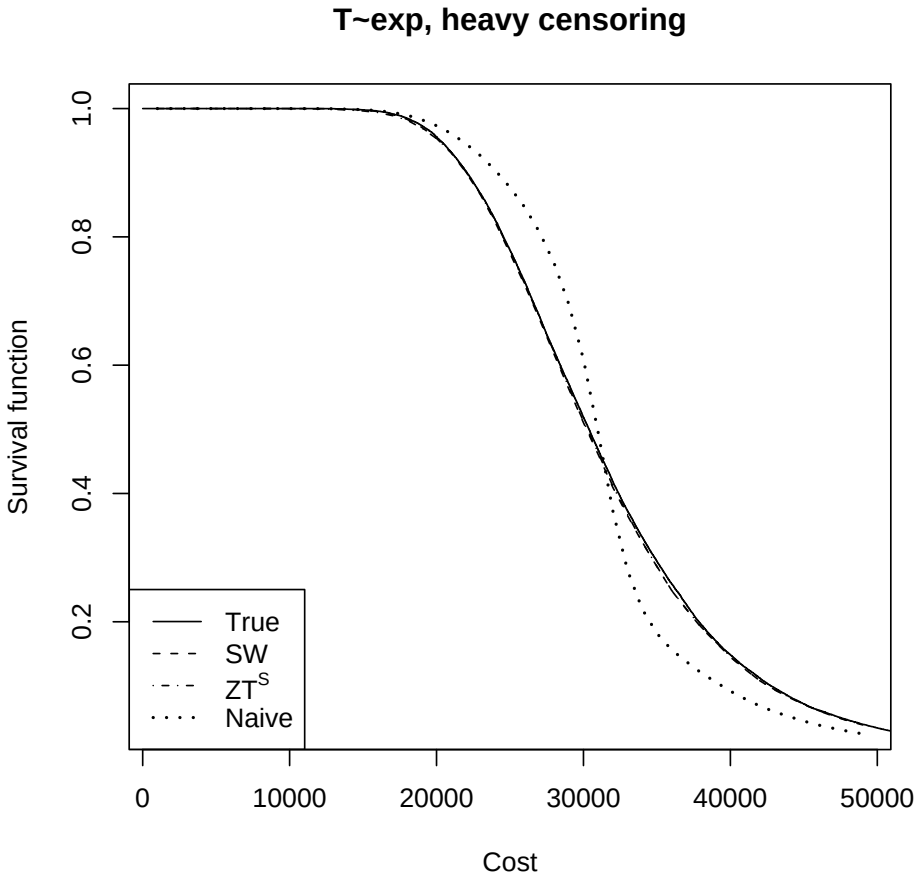

Figure 3. The mean of estimated survival functions for costs from 1000 replications with naive method.

Figure 3 shows the true survival function for costs and the average of the survival curves from the 1000 simulations using different estimators, for the setting with heavy censoring and exponential survival time. As expected, the SW estimator and the ZT^S estimator are both unbiased since they overlap with the true survival curve. However, the naive method obtained by using the replacement costs as the true costs is severely biased. Similar biases for the naive method under other scenarios are also observed.

Figure 4 and Figure 5 display the mean and sample variance of different survival function estimators for costs based on 1000 replications, under four simulation scenarios. The SW and ZT^S estimators are consistent as in Figure 3, since they overlap with the true survival curve. Although from a theoretical point of view the new proposed RRimp^S estimator is not always consistent, its average survival curves follow the true survival curves very well, for all the settings considered here. This indicates that the bias of the RRimp^S survival estimator is relatively small. In the plots of the sample variances, we find that the ZT^S estimator is more efficient than the SW estimator. More importantly, our RRimp^S estimator outperforms both SW and ZT^S estimators under all these four scenarios, with more efficiency gain under a heavy censoring. The results show that the RRimp^S survival function has significant improvement in efficiency. More importantly, the improvement is achieved without sacrificing the monotonicity property, unlike the ZT^S estimator and other more efficient estimators (Huang and Louis, 1998).

Since the RRimp^S survival estimator performs worse when there is a high correlation between costs accumulated in different periods, we design an extreme case to examine how biased the RRimp^S estimator could be. We generate the fixed annual costs using a log normal distribution with parameters $(8, 0.245^2)$, while setting the diagnostic costs, random annual costs, and terminal costs to be 0. All other parameters stay the same. The mean survival curves and the Mean Squared Errors

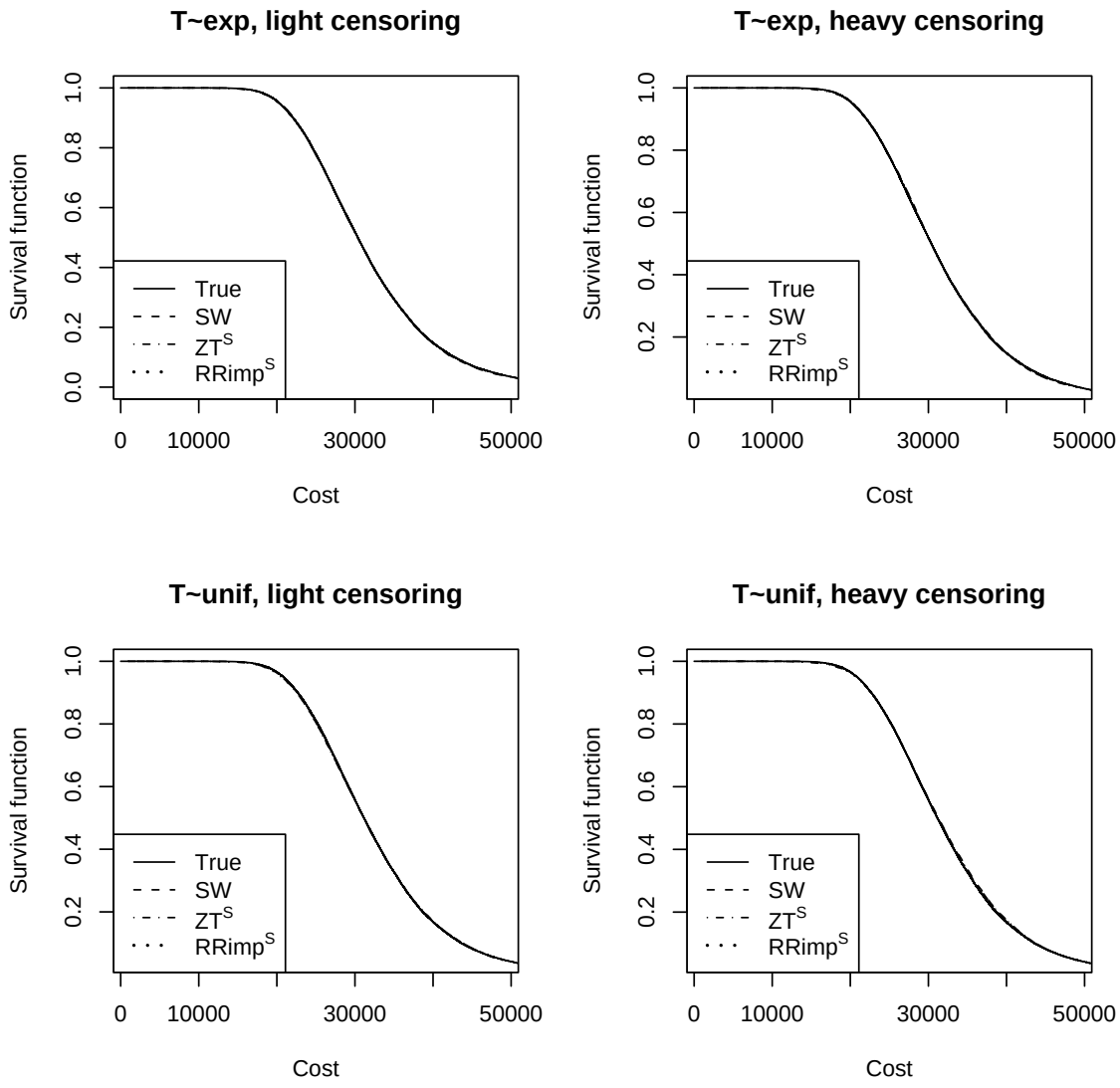

Figure 4. The mean of estimated survival functions for costs from 1000 replications.

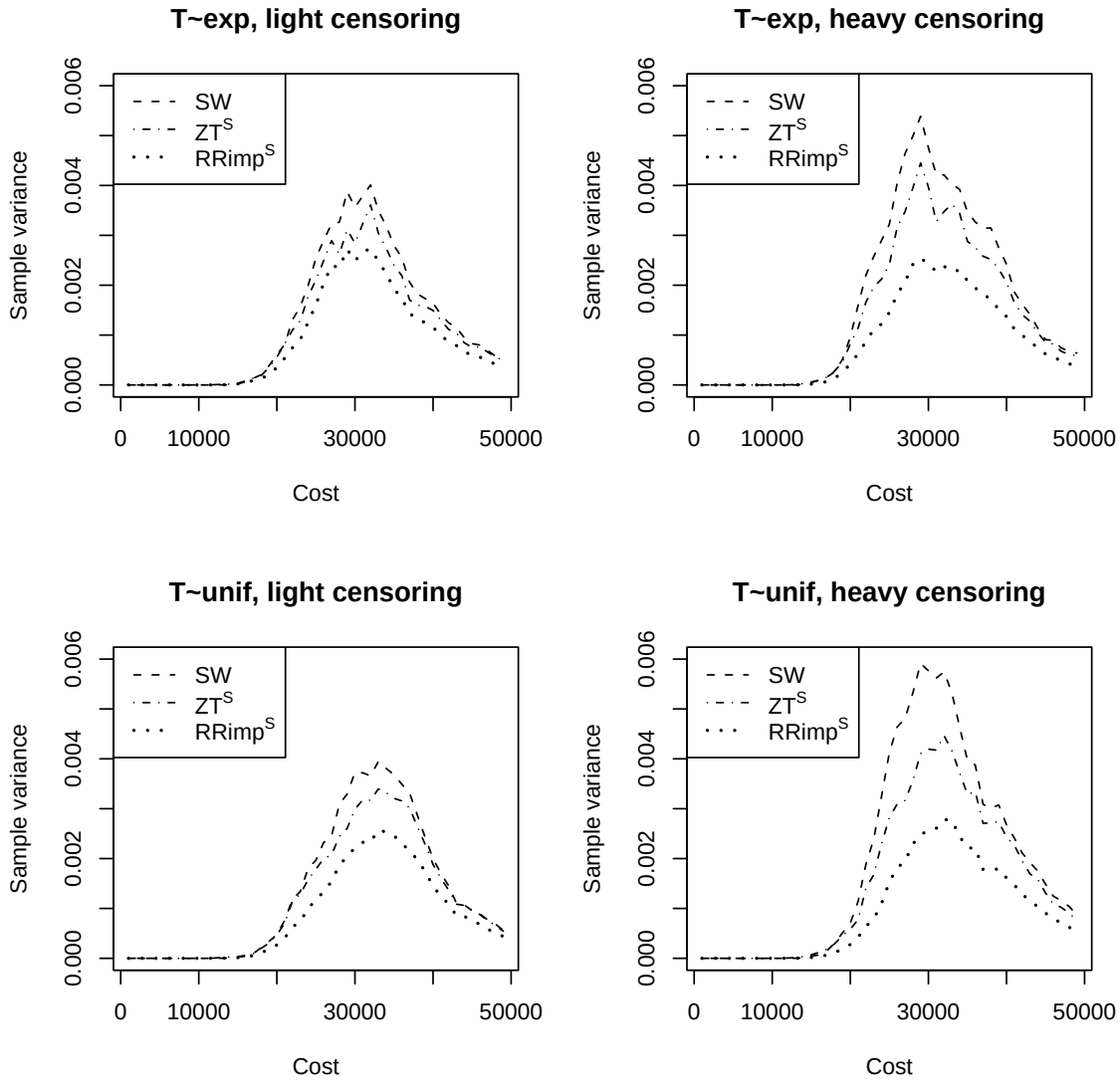

Figure 5. The sample variance of estimated survival functions for costs from 1000 replications.

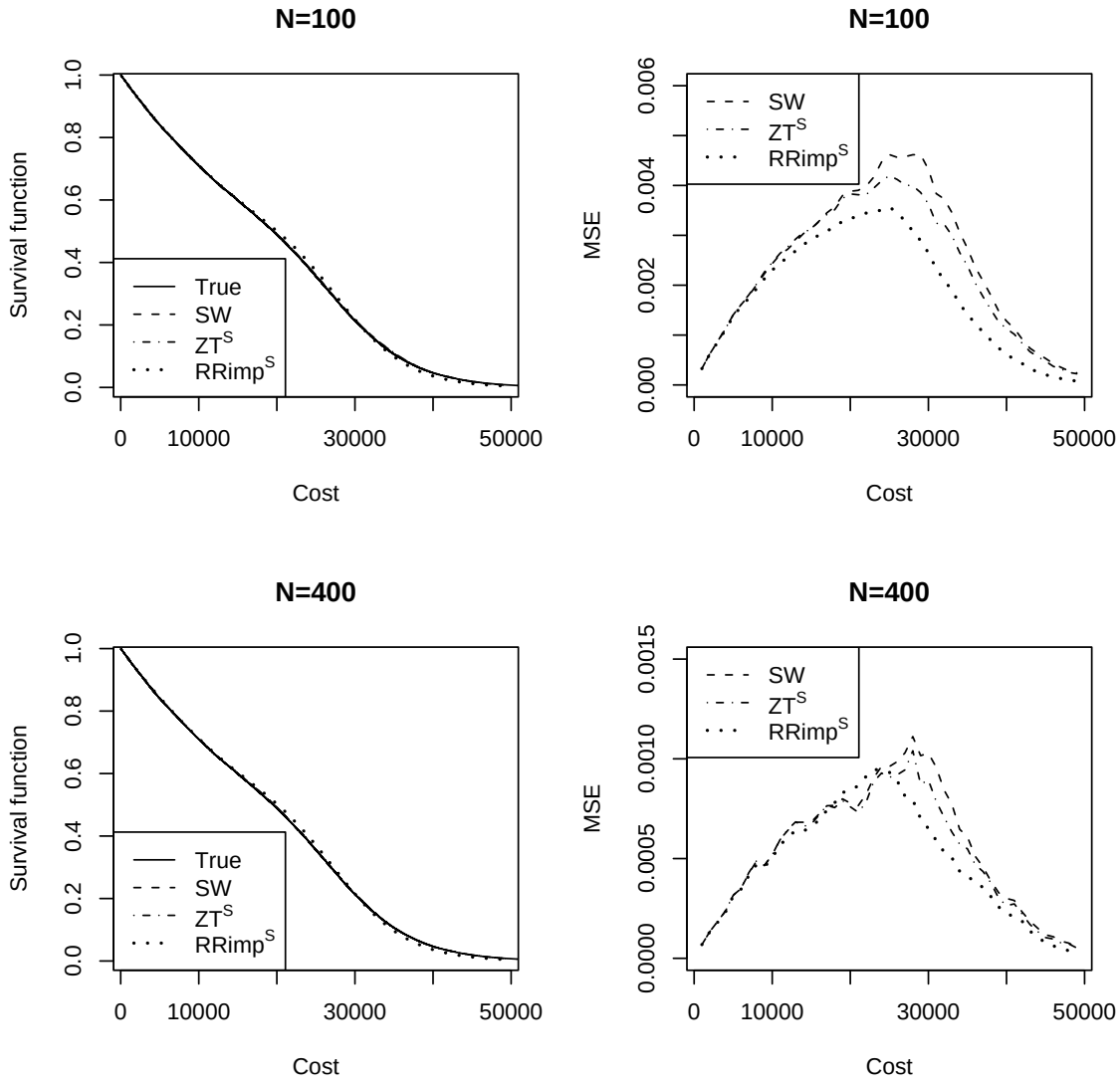

Figure 6. The mean and MSE of estimated survival functions for costs under the extreme case from 1000 replications.

(MSE=variance+bias^2), for the case with exponential survival time and heavy censoring, and for different sample sizes (n=100, 400), are displayed in Figure 6. We observe similar trends for other simulation settings. Figure 6 shows that the bias for the RRimp^S estimator is noticeable now, albeit very small. The MSE for the RRimp^S estimator is still mostly the smallest among the three methods available, even when the sample size is as large as 400. In general, as the sample size gets larger, the variance becomes smaller but the bias stays the same, we expect the gain in terms of MSE for the RRimp^S estimator will decrease with increasing sample sizes.

6. Conclusion

In this chapter we extend the research conducted by Zhao et al. (2011) who provided a link between a theoretically justified mean cost estimator which is based on the inverse probability weighting techniques, the BT estimator, and an intuitive RR estimator. We propose a modified replace-from-the-right algorithm, the RRimp estimator, which utilizes the cost history process and therefore is generally more efficient than the RR estimator. We establish a mathematical equivalency between the RRimp estimator and an improved mean cost estimator, the ZT estimator. Thus, we are able to provide an intuitive explanation on how the ZT estimator works. We believe our effort enables a better understanding of the theoretically derived mean cost estimators, the BT and ZT estimators, and meanwhile provides justification for the simple, intuition based RR and RRimp estimators. Due to a lack of a theoretical background for understanding the BT and ZT estimators, some practitioners might be reluctant to use them. With the easy interpretation of the RR and RRimp estimators, and established equivalency between these estimators and the BT, ZT estimators, we believe these estimators will become more popular among practitioners.

It proves to be a more challenging problem deriving an intuitive estimator for the survival function of costs. We show that a naive method using the replaced cost as the true costs in an empirical survival function gives rise to a biased estimator. Resorting to the original idea of redistribute-to-the right algorithm (Efron, 1967) for explaining the Kaplan-Meier estimator, we construct a RR^S survival estimator, which can be shown to be equivalent to the SW survival estimator for costs. We also propose a RRimp^S survival estimator which has the desirable property of being monotone, and more efficient than the RR^S survival estimator, but unfortunately, this estimator is not always consistent. Since the bias seems to be quite small from many simulations we conduct, it may be considered as an alternative survival estimator for costs in a real setting when the sample size is not very large and cost history information is available. Further research needs to be conducted in order to find a survival estimator for costs which is monotone, consistent and efficient.

CHAPTER III

ESTIMATING ICER AND CI WITH DIFFERENT TERMINATING EVENTS FOR SURVIVAL TIME AND COSTS

1. Introduction

Due to skyrocketing costs of health care and limited resources available, economic studies of different treatment options are becoming increasingly popular in evaluating new treatment strategies. The U.S. Preventive Services Task Force and the Panel of Cost-Effectiveness in Health and Medicine have urged consideration of both cost and clinical effectiveness when directing health care investments. They have also issued a comprehensive set of guidelines to aid practitioners of Cost-effectiveness Analysis (CEA) (Gold et al., 1996; Walker, 2001; American College Physicians, 2008). It is clear that if two competing programs do not differ in their health benefits, then the one with the lower cost would be preferred. On the other hand, if the costs of two programs are judged equivalent, the intervention with the greater health benefit would be preferred. However, when a program has both higher cost and greater benefit than its competitor, a decision must be made as to which of the two programs should be adopted. The incremental cost-effectiveness ratio (ICER) is designed to measure the trade-off between the costs and health benefits of medical interventions. It is defined as the costs incurred for saving an additional year of life. This measure has been the most popular tool used for CEA (e.g., Zwanziger et al., 2006; Wailoo et al., 2008; McIntosh et al., 2009; Edlin et al., 2010; Huang et al., 2010; Maud et al., 2010; Shiroiwa et al., 2010; Linde et al., 2011).

The analysis of cost data involves some unique challenges that require advanced statistical methodologies, especially when costs are censored. For example, randomized

clinical trials often enroll subjects over a broad time period, but the trial ends at a fixed time point. As a result, subjects are observed for differing amounts of time, and those who are still alive at the end of the study are considered censored. It has been just over a decade since it was recognized that caution should be exercised regarding the non-standard survivorship bias inherent in censored cost data, as described in a landmark paper by Lin et al. (1997). The authors pointed out that censored cost data can be problematic when analyzed using most standard tools, including sample mean and variance, t-test, ordinary least squares, Kaplan-Meier estimator, Log-rank test, and Cox proportional hazards regression. The problem arises from the induced informative censoring problem. Even when the survival time and the censoring time are independent, which is true for end-of-study or administrative censoring in clinical trials, the corresponding costs are generally not independent. Major efforts have been made to provide consistent and efficient estimation of mean medical costs (Bang and Tsiatis, 2000; Zhao and Tian, 2001; Bang, 2005; Zhao et al., 2007, among others).

Since ICER is a ratio statistics, the distribution of ICER is quite skewed. Thus, instead of providing the standard errors of the ICER, it is often desirable to construct a confidence interval (CI) for the ICER in order to estimate its variability. Various methods have been proposed on finding CIs for the ICER. Non parametric bootstrapping methods include Efron and Tibshirani (1986); Efron and Tibshirani (1993); Cook and Heyse (2000); Jiang and Zhou (2004); Dinh and Zhou (2006); Wang and Zhao (2008), and parametric methods include Fieller (1954); O'Brien et al. (1994); Laska et al. (1997); Gardiner et al. (2001). Although most researchers believe that the bootstrap method provides better coverage, since the Fieller method is based on the large sample normal assumption, Hwang (1995) and Jiang et al. (2000) showed that both of them are equivalent since they are both first order accurate.

To estimate ICER and calculate its confidence intervals by Fieller's theorem, we

need estimate not only between-treatment differences with respect to cost and effect, but also their respective variances and covariance. Many researchers have proposed methods for estimating the mean medical costs and related variance, and most of them focus on the restricted medical costs, i.e., the costs accumulated within a time limit. A challenge comes when the terminating events for cost and survival are different. For example, a new strategy might prevent the heart failure event, but may not improve the overall survival time. Hence, it extends the heart failure free survival time, but not the overall survival time. Meanwhile, we are still interested in the cost estimation up to death. Although the construction for the CI of usual ICER with the same terminating points has been studied much, there are no theoretical results for research on the ICER and its CI which allow different terminating events.

The remainder of this chapter is organized as follows. We first review mean cost and mean survival estimator, as well as their variance estimators, and propose the modified form for mean heart failure free survival estimator. A consistent estimator for ICER with different terminating events will then be proposed, as well as the construction method of corresponding CI. As one of key steps, the covariance estimator between mean cost and heart failure free survival estimators are proposed together. This is followed by the numerical studies, which displays the performance of our proposed covariance formula, as well as the empirical coverage of CI for this special ICER. Finally, the application for this method and our future works will be discussed.

2. Method

2.1. Notation and Assumptions

For clinical trials, the death of patients may not be observed until study ends. Therefore, those patients are treated as censored subjects, with their survival time and

total costs unknown.

Moreover, assume the patients in study may suffer from heart failure, and a new treatment can reduce the risk of heart failure. Thus, patients with the new treatment tend to have longer time before heart failures, or even they may have no heart failures occurred during overall survival time. Therefore, we define heart failure free survival time as the time of heart failure or death, whichever occurs first. Since the new treatment can lower the risk of heart failure, but not extend the overall survival time, this heart failure free survival time can measure the effects of the treatment better. Meanwhile, the cost cumulation is until the overall survival time. Thus, there will be four types of patients: observing death without heart failure; observing heart failure first and then death; observing heart failure and then censored; censored before observing death or heart failure.

We first concentrate on patients in one arm of the study. For the ith person, let T_i denote the overall survival time, T_i^F denote the heart failure free survival time, i.e. $T_i^F = \min(HF_i, T_i)$, where HF_i is the time when a patient has a heart failure. C_i is the censoring time. Denote overall follow-up time $X_i = \min(T_i, C_i)$, and death indicator $\Delta_i = I(T_i \leq C_i)$. Similarly, $X_i^F = \min(T_i^F, C_i), \Delta_i^F = I(T_i^F \leq C_i)$, where $I(.)$ is the indicator function. Let $M_i(u)$ be the cost accumulated over time u. For simplicity, we denote $M_i = M_i(X_i)$ as the observed total cost.

We assume that the censoring times C_i is independent of the survival time T_i, the heart failure time HF_i, and the cost history process $\{M_i(u),\ u \leq T_i\}$. This assumption is reasonable for a well conducted clinical trial, where censoring is mainly caused by different entering times into the study, and cost collection is ended early due to reasons other than patients' health status. Due to the presence of censoring, it is impossible to estimate the cost over the entire health history. Therefore, we only consider cost accumulated up to a maximum of L units of time. This is equivalent to

redefining our survival time as $T_i^L = \min(T_i, L)$, and $T_i^{FL} = \min(T_i^F, L)$. For ease of notation, we suppress the superscript L of T_i^L and T_i^{FL} later.

For each of the two treatment groups, $k = 0, 1$, we observe the following identically distributed, independent data $\{X_i, \Delta_i, X_i^F, \Delta_i^F, M_i(X_i), i = 1, \cdots, n_k\}$; n_k is the number of patients for arm k. Our goal is to estimate the mean cost $\mu^M = E(M_i)$ and the mean heart failure free survival time $\mu^F = E(T_i^F)$ for each of the treatment groups, and then obtain the ICER and its confidence interval comparing the two treatment groups.

2.2. Estimating Mean Cost for Each Group

For estimation of mean cost accumulated over time L with censoring data, a consistent estimator was proposed by Bang and Tsiatis (2000) based on the inverse probability weighting technique:

$$\hat{\mu}_{BT}^M = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i M_i}{\hat{K}(T_i)}, \tag{3.1}$$

where M_i is the total observed cost for the ith individual, and $\hat{K}(T_i)$ is the Kaplan-Meier estimator for the survival function of the censoring time, $K(u) = Pr(C_i > u)$. $K(T_i)$ represents the probability that a subject is uncensored at T_i. The basic idea of this estimator is that each complete observation represents potential $1/\hat{K}(T_i)$ observations who might be censored.

When cost history is available, the BT estimator is not efficient since it does not use the cost information from censored ones. A more efficient estimator is proposed by Zhao and Tian (2001). We can estimate the mean cost by using their improved estimator:

$$\widehat{\mu}_{ZT}^M = n^{-1} \sum_{i=1}^{n} \frac{\Delta_i M_i}{\widehat{K}(T_i)} + n^{-1} \sum_{i=1}^{n} \int^{L} \frac{dN_i^C(u)}{\widehat{K}(u)} [M_i(u) - \widehat{G}^*\{M(u), u\}], \tag{3.2}$$

where $\widehat{K}(u)$ is the Kaplan-Meier estimator for survival distribution of C_i at time u,

$$N^C(u) = \sum_{i=1}^{n} N_i^C(u) = \sum_{i=1}^{n} I(X_i \leq u, \Delta_i = 0),$$

$$\widehat{G}^*\{M(u), u\} = \{\sum_{i=1}^{n} M_i(u) Y_i(u)\}/Y(u), \tag{3.3}$$

and $Y(u) = \sum_{i=1}^{n} Y_i(u) = \sum_{i=1}^{n} I(X_i \geq u)$.

The ZT estimator has the following simplified form (Pfeifer and Bang, 2005):

$$\hat{\mu}_{ZT}^M = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i M_i}{\hat{K}(T_i)} + \frac{1}{n}\sum_{i=1}^{n} \frac{(1-\Delta_i)[M_i(C_i) - \overline{M(C_i)}]}{\hat{K}(C_i)}, \tag{3.4}$$

where $\overline{M(C_i)} = \sum_{j=1}^{n} I(X_j \geq C_i) M_j(C_i) / \sum_{j=1}^{n} I(X_j \geq C_i)$, which is the average accumulative cost at time C_i of those subjects who are alive at C_i.

It was shown that this estimator is consistent, and asymptotically normally distributed with variance that can be estimated consistently by

$$\begin{aligned}
\widehat{Var}(\widehat{\mu}_{ZT}^M) \;=\; & \frac{1}{n^2}\sum_{i=1}^{n} \frac{\Delta_i (M_i - \widehat{\mu}_{ZT}^M)^2}{\widehat{K}(T_i)} + \frac{1}{n^2}\int_0^L \frac{dN^C(u)}{\widehat{K}(u)^2}\{\widehat{G}(M^2, u) - \widehat{G}(M, u)^2\} \\
& - \frac{2}{n^2}\int_0^L \frac{dN^C(u)}{\widehat{K}(u)^2}[\widehat{G}\{MM(u), u\} - \widehat{G}(M, u)\widehat{G}\{M(u), u\}] \\
& + \frac{1}{n^2}\int_0^L \frac{dN^C(u)}{\widehat{K}(u)^2}[\widehat{G}^*\{M(u)^2, u\} - \widehat{G}^*\{M(u), u\}^2],
\end{aligned} \tag{3.5}$$

where

$$\widehat{G}(Z, u) = \frac{1}{n\widehat{S}(u)}\sum_{i=1}^{n} \frac{\Delta_i}{\widehat{K}(T_i)} Z_i I(T_i \geq u), \tag{3.6}$$

for any random variable Z, and $\widehat{S}(u)$ is the Kaplan-Meier estimator for $S(u)$, the survival distribution of T at time u, using data $(X_i, \Delta_i, i = 1, \cdots, n)$.

$$\widehat{G}^*\{Z, u\} = \{\sum_{i=1}^{n} Z_i Y_i(u)\}/Y(u), \tag{3.7}$$

and $Y(u) = \sum_{i=1}^{n} Y_i(u) = \sum_{i=1}^{n} I(X_i \geq u)$.

This formula for variance, given by Zhao and Tian (2001); Zhao and Wang (2010), is a simplified form of original formula.

2.3. Estimating Mean Heart Failure Free Survival Time for Each Group

The mean survival time can be obtained by the area under the survival function, i.e.,

$$\widehat{\mu}^T = \int_0^L \hat{S}(x)dx, \tag{3.8}$$

where $\hat{S}(x)$ is the Kaplan-Meier estimator for $S(u) = Pr(T > u)$. This mean survival time estimator can be equivalently estimated by (Satten and Datta, 2001):

$$\widehat{\mu}^T = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i T_i}{\widehat{K}(T_i)}. \tag{3.9}$$

Similarly, the mean heart failure free survival time can be estimated by

$$\widehat{\mu}^F = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i^F T_i^F}{\widehat{K}^F(T_i^F)}, \tag{3.10}$$

where $\widehat{K}^F(u)$ is the Kaplan-Meier estimator for $K(u) = Pr(C > u)$, the survival distribution of C at time u, using data $(X_i^F, \Delta_i^F, i = 1, \cdots, n)$. Following Zhao and Tian (2001), its variance can be estimated consistently by

$$\frac{1}{n^2}\sum_{i=1}^{n} \frac{\Delta_i^F (T_i^F - \widehat{\mu}^F)^2}{\widehat{K}^F(T_i)} + \frac{1}{n^2}\int_0^L \frac{dN^F(u)}{\widehat{K}^F(u)^2}\{\widehat{G}^F(T^{F2}, u) - \widehat{G}^F(T^F, u)^2\}, \tag{3.11}$$

where

$$N^F(u) = \sum_{i=1}^{n} N_i^{C_F}(u) = \sum_{i=1}^{n} I(X_i^F \le u, \Delta_i^F = 0),$$

$$\widehat{G}^F(Z, u) = \frac{1}{n\widehat{S}^F(u)}\sum_{i=1}^{n} \frac{\Delta_i^F}{\widehat{K}^F(T_i^F)} Z_i I(T_i^F \ge u), \tag{3.12}$$

$\widehat{S}^F(u)$ is the Kaplan-Meier estimator for $S^F(u) = \Pr(T_i^F > u)$.

As discussed in Zhao and Tian (2001), discounting of future years of survival time

and costs at a specific annual rate can be easily accommodated in the above formulae.

2.4. Estimating the ICER and Its Confidence Interval

To compare two treatments, the ICER is the ratio between difference of their costs and difference of effects. Here we use mean of heart failure free survival time as the measure of effectiveness.

For a two-arm trial (k, $k = 0, 1$), denote μ_k^M as the mean cost and μ_k^F as the mean heart failure Free survival time, each limited to a window of time [0, L]. We consider the ICER as the additional cost for a new treatment for saving one year of heart failure free lifetime and define it as

$$\gamma = \frac{\mu_1^M - \mu_0^M}{\mu_1^F - \mu_0^F},$$

which can be estimated by

$$\widehat{\gamma} = \frac{\widehat{\mu}_1^M - \widehat{\mu}_0^M}{\widehat{\mu}_1^F - \widehat{\mu}_0^F}, \tag{3.13}$$

where, $\widehat{\mu}_k^M$ is the ZT estimator for the mean cost and $\widehat{\mu}_k^F$ is the estimator for mean heart failure free life time for group k.

We use Fieller's Theorem to obtain confidence intervals for the ICER, similarly as in Zhao and Tian (2001). Assuming that asymptotically $x = \widehat{\mu}_1^M - \widehat{\mu}_0^M$ and $y = \widehat{\mu}_1^F - \widehat{\mu}_0^F$ are bivariate normally distributed, the $100(1 - 2\alpha)$ percent confidence limits for the ICER γ are

$$\frac{xy - z_\alpha^2 s_{xy} \pm \{(xy - z_\alpha^2 s_{xy})^2 - (x^2 - z_\alpha^2 s_{xx})(y^2 - z_\alpha^2 s_{yy})\}^{1/2}}{y^2 - z_\alpha^2 s_{yy}}, \tag{3.14}$$

where s_{xx}, s_{yy}, s_{xy} are respectively the variances of x and y, and the covariance of x and y, z_α is the cut-off point with tail area α of the standard normal distribution. If the denominator of equation (3.14) is positive, the CI is finite. When the denomina-

tor is negative, which means the difference between effects of two treatments is not significant (i.e., zero belongs to the CI of the divisor), the CI for ICER is exclusive and thus infinite.

The variance of x and y can be obtained from results mentioned earlier, assuming independent samples. To find the covariance between x and y, we need to find the covariance between $\widehat{\mu}_k^M$ and $\widehat{\mu}_k^F$. The mean heart failure free survival time estimator and the mean cost estimators can both be described by martingale forms (Zhao and Tian, 2001), and the covariance between them can be derived based on the counting process and the general theory for missing data process (Fleming and Harrington, 1991; Robins and Rotnitzky, 1992; Robins et al., 1994). In Appendix B we show that the covariance between the improved estimator for cost and the estimator for mean heart failure free survival time for each arm can be estimated consistently by

$$\begin{aligned}
& \frac{1}{n^2}\sum_{i=1}^{n}\frac{\Delta_i M_i T_i^F}{\widehat{K}(T_i)} - \frac{1}{n^3}\sum_{i=1}^{n}\frac{\Delta_i M_i}{\widehat{K}(T_i)}\sum_{i=1}^{n}\frac{\Delta_i^F T_i^F}{\widehat{K}^F(T_i^F)} \\
+ \quad & \frac{1}{n^2}\int_0^L \frac{dN^{C_F}(u)}{\widehat{K}^F(u)^2}\{\widehat{G}^{F_0}(T^F M, u) - \widehat{G}^{F_0}(M,u)\widehat{G}^{F_0}(T^F,u)\} \\
- \quad & \frac{1}{n^2}\int_0^L \frac{dN^{C_F}(u)}{\widehat{K}^F(u)^2}\{\widehat{G}^{F_0}\{T^F M(u), u\} - \widehat{G}^{F_0}\{M(u),u\}\widehat{G}^{F_0}(T^F,u)\},
\end{aligned}$$

where

$$\widehat{G}^{F_0}(Z,u) = \frac{1}{n\widehat{S}^F(u)}\sum_{i=1}^{n}\frac{\Delta_i}{\widehat{K}(T_i)} Z_i I(T_i^F \geq u), \tag{3.15}$$

As mentioned before, the bootstrap methods can also be used for CI construction, but they take more time, and not necessarily better than the Fieller's method, which can also be seen from the numerical comparison conducted by Wang and Zhao (2008).

3. Numerical Studies

As commonly used in scenarios for simulation, survival time is simulated by exponential distribution. The overall survival time $T \sim exp(10)$ for both two groups with different treatments. The heart failure time $HF \sim exp(6)$ for Group 0, and $HF \sim exp(12)$ for Group 1 with a more effective treatment to prevent heart failure. T and HF are simulated independently and truncated at L=10, and heart failure free survival time is $T^F = min(T, HF)$. The censoring time $C \sim Unif(0, 15)$ with 42% heavy censoring for overall survival time and 24%-30% censoring rate for heart failure free survival time. The true mean heart failure free survival time for Group 0 and Group 1 are 3.49 and 4.58 respectively. Figure 7 shows the survival functions of T^F for two groups. The survival function of Group 1 is above Group 0, which indicates the patients in Group 1 tend to have a larger heart failure free survival time.

U-shaped sample paths for the costs are considered. The entire time period [0, 10] is partitioned into 10 equal intervals. There are initial diagnostic cost at time 0, and terminal cost during the last year before death. Within each time interval, there are fixed annual cost (which fixes for each patient) and random annual cost (which varies from year to year). We considered two settings of scenarios with uniform costs and log normal costs. For uniform setting, the diagnostic cost, fixed annual cost, random annual cost, and terminal cost are uniform distribution with respective parameters $(1000, 3000)$, $(1000, 2600)$, $(0, 400)$, $(10000, 20000)$ for Group 0, and $(20000, 30000)$, $(1000, 1600)$, $(0, 400)$, $(10000, 20000)$ for Group 1. For log normal setting, the diagnostic cost, fixed annual cost, random annual cost, and terminal cost are log normal distribution with respective parameters $(9, 0.245^2)$, $(6.5, 0.245^2)$, $(4, 0.245^2)$, and $(9, 0.632^2)$ for Group 0, and $(10, 0.245^2)$, $(6, 0.245^2)$, $(4, 0.245^2)$, and $(9, 0.632^2)$ for Group 1. The true mean cost for Group 0 and Group 1 are 23646 and 43505 under

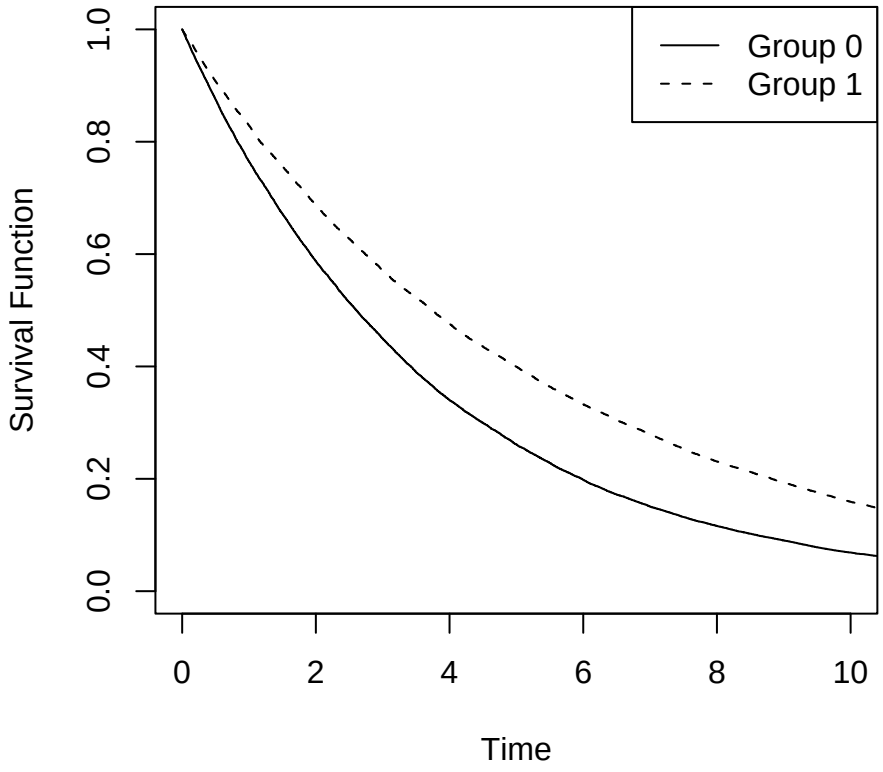

Figure 7. The survival functions of heart failure free survival time for two groups.

uniform setting, and 18998 and 31651 under log normal setting. Thus, the more effective treatment adopted by Group 1 saves more heart failure free lifetime, while costs much more than Group 0 by a large amount of diagnostic cost. Figure 8 shows the kernel densities of costs for two groups, which indicates the mean cost of Group 1 is more than Group 0. It can also be seen that the distribution of log normal costs is more skew than the uniform costs.

The simulation results for variance and covariance estimation based on 2000 replica-

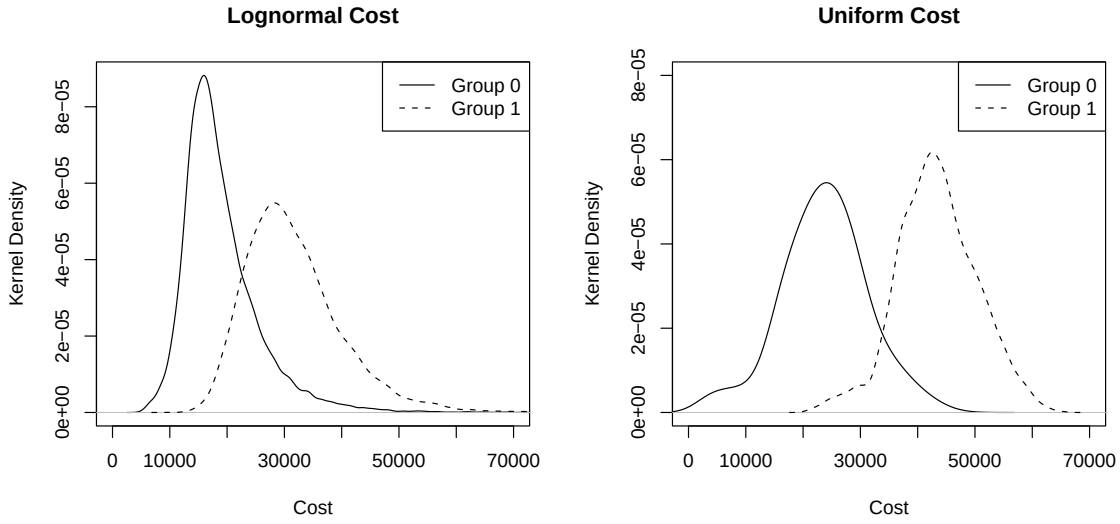

Figure 8. The kernel densities of cost for two groups in simulation.

tions are summarized in Table 1, where SVar is the sample variance of the estimator, EVar is the mean of estimated variance, SCov is the sample covariance of $\hat{\mu}^M$ and $\hat{\mu}^F$, and ECov is the mean of estimated covariance. The results show that the estimated variance and covariance are close to the sample variance and sample covariance, and the biases of estimators are small. Thus, the simulations display the consistency of those estimators. The empirical coverage under different scenarios are shown in Table 2, in which we can find the coverage is approaching to nominal level as the sample size increases.

4. Conclusion

Censoring brings challenges to estimating ICER and calculating its CI in cost-effectiveness analysis, since usually failures can not be observed for all patients during clinical trials. Another new challenge comes from the different terminating events, which is

Table 1

Summary of variance and covariance estimation from 2000 replications

			$\hat{\mu}^M$			$\hat{\mu}^F$			Cov($\hat{\mu}^M$, $\hat{\mu}^F$)	
Cost	n	k	Bias	SVar	EVar	Bias	SVar	EVar	SCov	ECov
Lnorm	100	0	19	770464	772142	-0.014	0.118	0.106	9.4	13.3
		1	-30	1072544	1063645	0.005	0.145	0.141	-24.2	-23.7
	200	0	20	385962	389229	-0.003	0.055	0.053	2.0	2.9
		1	-28	525137	532257	-0.005	0.070	0.071	-11.8	-13.0
	400	0	15	196160	195746	-0.003	0.026	0.026	1.1	1.5
		1	11	264317	266563	-0.008	0.036	0.035	-7.3	-6.9
Unif	100	0	18	933790	895854	-0.016	0.116	0.106	69.2	75.4
		1	21	778935	768607	-0.011	0.148	0.140	44.1	42.3
	200	0	-20	438629	444898	0.006	0.052	0.053	31.8	34.5
		1	22	372260	384993	0.005	0.068	0.070	18.1	19.1
	400	0	-17	214646	222930	0.003	0.026	0.027	17.7	16.9
		1	6	191395	192043	0.004	0.035	0.035	8.0	8.7

commonly encountered when the treatment aims to low risk of some events, for instance, heart failure in our article, but not the extension of the overall survival time. Therefore, statistical inference for ICER allowing different terminating events are needed for practitioners to evaluate such a new treatment.

In this chapter, we provide a consistent estimator for ICER with different terminating events, as well as a method to construct its CI. Our method not only handles censoring problem well, but also allows different terminal events. Simulation studies showed that our covariance estimator and the constructed CI perform very well for

Table 2

Empirical coverage of confidence intervals for ICER from 2000 replications

Sample Size	Nominal level	Log normal Cost	Uniform Cost
100	0.95	0.935	0.936
	0.90	0.884	0.879
	0.80	0.781	0.779
200	0.95	0.948	0.945
	0.90	0.895	0.899
	0.80	0.801	0.798
400	0.95	0.953	0.954
	0.90	0.908	0.902
	0.80	0.803	0.793

some practical settings. Thus, our method provides an effective way to make statistical inference for such data and is easy to implement. Furthermore, our proposed covariance estimator can be used not only in the construction of CI for ICER, but also other cases which require the covariance estimator.

Further work may be conducted to compare our method with Bootstrap method, and investigate how ICER changes with different groups. Besides, ICER with heart failure Free Quality-Adjusted lifetime (QAL) can also be studied similarly.

CHAPTER IV

SUMMARY

In this thesis, several innovative methods are proposed for cost estimation and cost-effectiveness analysis with censored data. Censoring brings unique challenges to this field, since we cannot observe complete data for all the subjects in the study. Even though it is reasonable to assume that the censoring and the potential event time are independent (or conditionally independent) for most studies, the "induced informative censoring" problem makes the cost evaluation more difficult, since many standard methods for survival analysis are not appropriate for cost evaluation any more.

We first extend the research conducted by Zhao et al. (2011) who provided a link between the BT estimator and an intuitive RR estimator for estimating mean costs with censored data. Our proposed RRimp estimator utilizes the cost history and therefore is generally more efficient than the RR estimator. We establish the mathematical equivalency between the RRimp estimator and an improved mean cost estimator, the ZT estimator. Thus, we are able to provide an intuitive explanation for how the ZT estimator works. We believe our effort enables a better understanding of the theoretically derived mean cost estimators, the BT and ZT estimators, and meanwhile provides justification for the simple, intuition based RR and RRimp estimators.

It is more challenging to derive an intuitive estimator for the survival function of costs. Motivated by the original idea of redistribute-to-the right algorithm (Efron, 1967) for explaining the Kaplan-Meier estimator, we construct a RR^S survival estimator, which can be shown to be equivalent to the SW survival estimator for costs. We also propose a RRimp^S survival estimator which has the desirable property of being monotone, and more efficient than the RR^S survival estimator, but unfortunately, this estimator is not always consistent. Since the bias seems to be quite small

from many simulations we conduct, it may be considered as an alternative survival estimator for costs in a real setting when the sample size is not very large and cost history information is available. Further research needs to be conducted in order to find a survival estimator for costs which is monotone, consistent and efficient.

In performing cost-effectiveness analysis with censored data, a new challenge arises from having the different terminating events for survival and cost estimation. Therefore, statistical inference for ICER allowing different terminating events is desirable for practitioners to deal with such data. We propose a consistent estimator for this special ICER, as well as a method to construct its CI. The conducted simulation studies show that our method performs very well for some practical settings. Thus, our method provides an effective way to make statistical inference for such data and is easy to implement. Further work for ICER and corresponding CI may be conducted to compare our method with the Bootstrap method, and investigate how ICER changes with different groups.

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APPENDIX A

PROOF FOR THE EQUIVALENCY OF THE ZT MEAN COST ESTIMATOR AND THE RRIMP METHOD

Suppose we have observed the following survival and cost history data

$$[\{X_i, \Delta_i, M_i, M_i(t_j), \quad j = 1, \cdots, J\}, \quad i = 1, \cdots, n],$$

where i denotes individuals, $t_j (j = 1, \cdots, J)$ denotes the ordered distinctive censoring times. Let Y_j indicate the number of people who have observation times greater than t_j (i.e., $Y_j = \sum_{i=1}^{n} I(X_i > t_j)$), and n_j represent the number of people who are censored at time t_j. If an event occurs at a censoring time t_j, we assume this event happens shortly before t_j. Therefore, the set $\{X_i = t_j\}$ consist only of censored data.

First, for the subject i who is censored at t_j (note that we allow multiple subjects who are censored at time t_j), define $\delta M_i(t_j)$ as the difference between the observed cost at time t_j for the ith subject and the average accumulated cost at t_j for subjects who are still alive at t_j:

$$\delta M_i(t_j) = M_i(t_j) - \overline{M(t_j)} = M_i(t_j) - \frac{\sum_{i:X_i \geq t_j} M_i(t_j)}{Y_j + n_j}. \tag{A.1}$$

Define $M^*(t_j)$ as the sum of $\delta M_i(t_j)$ over all subjects who are censored at t_j:

$$\begin{aligned} M^*(t_j) &= \sum_{i:X_i = t_j} \delta M_i(t_j) = \sum_{i:X_i = t_j} M_i(t_j) - n_j \overline{M(t_j)} \\ &= \sum_{i:X_i = t_j} M_i(t_j) - \frac{n_j}{Y_j + n_j} \sum_{i:X_i \geq t_j} M_i(t_j). \end{aligned} \tag{A.2}$$

Starting from the largest censoring time t_J, there are Y_J subjects who have complete costs and whose survival times are greater than t_J. Hence, the RRimp cost for the

kth subject censored at t_J is

$$M_{J,k}^{RRimp} = M_k(t_J) + \frac{1}{Y_J} \sum_{i:X_i > t_J} \{M_i - M_i(t_J)\}.$$

Recall that the replacement cost from RR method for the kth subject censored at time t_J is

$$M_J^{RR} = \frac{1}{Y_J} \sum_{i:X_i > t_J} M_i,$$

thus, the sum of difference between $M_{J,k}^{RRimp}$ (in RRimp method) and M_J^{RR} (in RR method) at t_J is

$$\begin{aligned}
& \sum_{k:X_k=t_J} (M_{J,k}^{RRimp} - M_J^{RR}) \\
= & \sum_{k:X_k=t_J} M_k(t_J) + \frac{n_J}{Y_J} \sum_{i:X_i>t_J} \{M_i - M_i(t_J)\} - \frac{n_J}{Y_J} \sum_{i:X_i>t_J} M_i \\
= & \sum_{i:X_i=t_J} M_i(t_J) - \frac{n_J}{Y_J} \sum_{i:X_i>t_J} M_i(t_J) \\
= & (1 + \frac{n_J}{Y_J}) \sum_{i:X_i=t_J} M_i(t_J) - \frac{n_J}{Y_J} \sum_{i:X_i \geq t_J} M_i(t_J) \\
= & (1 + \frac{n_J}{Y_J}) \{ \sum_{i:X_i=t_J} M_i(t_J) - \frac{n_J}{Y_J + n_J} \sum_{i:X_i \geq t_J} M_i(t_J) \} \\
= & (1 + \frac{n_J}{Y_J}) M^*(t_J). \qquad \text{(A.3)}
\end{aligned}$$

Now we move to the 2nd largest censoring time t_{J-1}, where the number of subjects surviving longer than t_{J-1} is Y_{J-1}. The RRimp cost for the kth censored subject at

t_{J-1} is

$$
\begin{aligned}
& M_{J-1,k}^{RRimp} \\
= \; & M_k(t_{J-1}) + \frac{1}{Y_{J-1}} \sum_{i:X_i > t_{J-1}} \{M_i - M_i(t_{J-1})\} \\
= \; & M_k(t_{J-1}) + \frac{1}{Y_{J-1}} \{ \sum_{i:X_i > t_{J-1}} \Delta_i [M_i - M_i(t_{J-1})] + \sum_{i:X_i = t_J} [M_{J,i}^{RRimp} - M_i(t_{J-1})] \} \\
= \; & M_k(t_{J-1}) + \frac{1}{Y_{J-1}} \{ \sum_{i:X_i > t_{J-1}} \Delta_i M_i - \sum_{i:X_i > t_{J-1}} \Delta_i M_i(t_{J-1}) - \sum_{i:X_i = t_J} M_i(t_{J-1}) \\
& + \sum_{i:X_i = t_J} M_i(t_J) + \frac{n_J}{Y_J} \sum_{i:X_i > t_J} \Delta_i [M_i - M_i(t_J)] \} \\
= \; & M_k(t_{J-1}) + \frac{1}{Y_{J-1}} \{ \sum_{i:X_i > t_J} \Delta_i M_i + \sum_{i:t_{J-1} < X_i \le t_J} \Delta_i M_i - \sum_{i:X_i > t_{J-1}} M_i(t_{J-1}) \\
& + \sum_{i:X_i = t_J} M_i(t_J) + \frac{n_J}{Y_J} \sum_{i:X_i > t_J} \Delta_i M_i - \frac{n_J}{Y_J} \sum_{i:X_i > t_J} M_i(t_J) \} \\
= \; & \frac{1}{Y_{J-1}} (1 + \frac{n_J}{Y_J}) \sum_{i:X_i > t_J} \Delta_i M_i + \frac{1}{Y_{J-1}} \sum_{i:t_{J-1} < X_i \le t_J} \Delta_i M_i + M_k(t_{J-1}) \\
& - \frac{1}{Y_{J-1}} \sum_{i:X_i > t_{J-1}} M_i(t_{J-1}) + \frac{1}{Y_{J-1}} \sum_{i:X_i = t_J} M_i(t_J) - \frac{n_J}{Y_J Y_{J-1}} \sum_{i:X_i > t_J} M_i(t_J)
\end{aligned}
$$

where the first two terms $\frac{1}{Y_{J-1}}(1 + \frac{n_J}{Y_J}) \sum_{i:X_i > t_J} \Delta_i M_i + \frac{1}{Y_{J-1}} \sum_{i:t_{J-1} < X_i \le t_J} \Delta_i M_i = M_{J-1}^{RR}$ (Zhao et al. 2011). Thus, the sum of difference between $M_{J-1,k}^{RRimp}$ and M_{J-1}^{RR} at

t_{J-1} is

$$\begin{aligned}
&\sum_{k:X_k=t_{J-1}} (M^{RRimp}_{J-1,k} - M^{RR}_{J-1}) \\
= &\sum_{i:X_i=t_{J-1}} M_i(t_{J-1}) - \frac{n_{J-1}}{Y_{J-1}} \sum_{i:X_i>t_{J-1}} M_i(t_{J-1}) + \frac{n_{J-1}}{Y_{J-1}} \sum_{i:X_i=t_J} M_i(t_J) \\
&-\frac{n_{J-1}n_J}{Y_{J-1}Y_J} \sum_{i:X_i>t_J} M_i(t_J) \\
= &(1+\frac{n_{J-1}}{Y_{J-1}}) \sum_{i:X_i=t_{J-1}} M_i(t_{J-1}) - \frac{n_{J-1}}{Y_{J-1}} \sum_{i:X_i\geq t_{J-1}} M_i(t_{J-1}) \\
&+\frac{n_{J-1}}{Y_{J-1}}(1+\frac{n_J}{Y_J}) \sum_{i:X_i=t_J} M_i(t_J) - \frac{n_{J-1}n_J}{Y_{J-1}Y_J} \sum_{i:X_i\geq t_J} M_i(t_J) \\
= &(1+\frac{n_{J-1}}{Y_{J-1}})M^*(t_{J-1}) + \frac{n_{J-1}}{Y_{J-1}}(1+\frac{n_J}{Y_J})M^*(t_J) \qquad \text{(A.4)}
\end{aligned}$$

Similarly, we have

$$\begin{aligned}
&\sum_{k:X_k=t_{J-2}} (M^{RRimp}_{J-2,k} - M^{RR}_{J-2}) \\
= &(1+\frac{n_{J-2}}{Y_{J-2}})M^*(t_{J-2}) + \frac{n_{J-2}}{Y_{J-2}}(1+\frac{n_{J-1}}{Y_{J-1}})M^*(t_{J-1}) \\
&+\frac{n_{J-2}}{Y_{J-2}}(1+\frac{n_{J-1}}{Y_{J-1}})(1+\frac{n_J}{Y_J})M^*(t_J) \qquad \text{(A.5)}
\end{aligned}$$

In (A.3), the contribution of $M^*(t_j)$ is $(1+\frac{n_J}{Y_J})$. In (A.4), its contribution is $\frac{n_{J-1}}{Y_{J-1}}(1+\frac{n_J}{Y_J})$. For (A.5), the contribution is $\frac{n_{J-2}}{Y_{J-2}}(1+\frac{n_{J-1}}{Y_{J-1}})(1+\frac{n_J}{Y_J})$. If we generalize the conclusion and sum up the equations from J to 1, we can find the contribution of $M^*(t_J)$ is

$$\left(1+\frac{n_J}{Y_J}\right) + \left(1+\frac{n_J}{Y_J}\right)\cdot\frac{n_{J-1}}{Y_{J-1}} + \cdots + \left(1+\frac{n_J}{Y_J}\right)\cdots\left(1+\frac{n_2}{Y_2}\right)\cdot\frac{n_1}{Y_1} = \prod_{j=1}^{J}\left(1+\frac{n_j}{Y_j}\right).$$

Similarly, the contribution of $M^*(t_j)$ is

$$\left(1+\frac{n_j}{Y_j}\right)+\left(1+\frac{n_j}{Y_j}\right)\cdot\frac{n_{j-1}}{Y_{j-1}}+\cdots+\left(1+\frac{n_j}{Y_j}\right)\cdots\left(1+\frac{n_2}{Y_2}\right)\cdot\frac{n_1}{Y_1}=\prod_{l=1}^{j}\left(1+\frac{n_l}{Y_l}\right).$$

Hence,

$$\begin{aligned}
&\hat{\mu}_{RRimp}\\
=\;&\frac{1}{n}\{\sum_{i=1}^{n}\Delta_i M_i+\sum_{k:X_k=t_J}M_{J,k}^{RRimp}+\sum_{k:X_k=t_{J-1}}M_{J-1,k}^{RRimp}+\cdots+\sum_{k:X_k=t_1}M_{1,k}^{RRimp}\}\\
=\;&\frac{1}{n}\{\sum_{i=1}^{n}\Delta_i M_i+\sum_{k:X_k=t_J}M_{J}^{RR}+\sum_{k:X_k=t_{J-1}}M_{J-1}^{RR}+\cdots+\sum_{k:X_k=t_1}M_{1}^{RR}\}\\
&+\frac{1}{n}\{\prod_{j=1}^{J}(1+\frac{n_j}{Y_j})M^*(t_J)+\prod_{j=1}^{J-1}(1+\frac{n_j}{Y_j})M^*(t_{J-1})+\cdots+(1+\frac{n_1}{Y_1})M^*(t_1)\}\\
=\;&\hat{\mu}_{RR}+\frac{1}{n}\{\prod_{j=1}^{J}(1+\frac{n_j}{Y_j})M^*(t_J)+\prod_{j=1}^{J-1}(1+\frac{n_j}{Y_j})M^*(t_{J-1})+\cdots+(1+\frac{n_1}{Y_1})M^*(t_1)\}
\end{aligned}$$

Where $\hat{\mu}_{RR}=\hat{\mu}_{BT}$ is already known, and $M^*(t_j)=\sum_{i:X_i=t_j}[M_i(t_j)-\overline{M(t_j)}]$ according to its definition. It can also be shown that the Kaplan-Meier estimator for $K(t_j)$ is

$$\hat{K}(t_j)=\prod_{l=1}^{j}\frac{Y_l}{Y_l+n_l},$$

which means

$$\frac{1}{\hat{K}(t_j)}=\frac{1}{\prod_{l=1}^{j}\frac{Y_l}{Y_l+n_l}}=\prod_{l=1}^{j}\left(1+\frac{n_l}{Y_l}\right).$$

Thus,

$$
\begin{aligned}
& \hat{\mu}_{RRimp} \\
= \; & \hat{\mu}_{BT} + \frac{1}{n}\{\frac{\sum_{i:X_i=t_J}[M_i(t_J) - \overline{M(t_J)}]}{\hat{K}(t_J)} + \frac{\sum_{i:X_i=t_{J-1}}[M_i(t_{J-1}) - \overline{M(t_{J-1})}]}{\hat{K}(t_{J-1})} \\
& + \frac{\sum_{i:X_i=t_{J-2}}[M_i(t_{J-2}) - \overline{M(t_{J-2})}]}{\hat{K}(t_{J-2})} + \cdots + \frac{\sum_{i:X_i=t_1}[M_i(t_1) - \overline{M(t_1)}]}{\hat{K}(t_1)}\} \\
= \; & \hat{\mu}_{BT} + \frac{1}{n}\sum_{i=1}^{n}\frac{(1-\Delta_i)[M_i - \overline{M(C_i)}]}{\hat{K}(C_i)} \\
= \; & \hat{\mu}_{ZT}.
\end{aligned}
$$

We have proved that the RRimp estimator is the same as the ZT estimator for estimating the mean cost.

APPENDIX B

ESTIMATING THE COVARIANCE BETWEEN THE MEAN COST AND THE MEAN HEART FAILURE FREE SURVIVAL TIME

For ease of notation, we confine our attention to one arm of the study. We define two martingales based on the censoring variable for the survival time and heart failure free survival time, T_i and T_i^F, respectively. For the ith individual, the martingale for the censoring variable for survival time T_i is defined as $M_i^C(u) = N_i^C(u) - \int_0^u \lambda^C(t) Y_i(t) dt$, where $\lambda^C(u)$ is the hazard function for C, $\lambda^C(u) = \lim_{h \to 0} \frac{1}{h} \Pr(C < u + h | C \geq u)$, $Y_i(u) = I(X_i \geq u)$, $N_i^C(u) = I(X_i \leq u, \Delta_i = 0)$. Similarly, the martingale for the censoring variable for heart failure free survival T_i^F is defined as $M_i^{C_F}(u) = N_i^{C_F}(u) - \int_0^u \lambda^C(t) Y_i^F(t) dt$, where $Y_i^F(u) = I(X_i^F \geq u)$, $N_i^{C_F}(u) = I(X_i^F \leq u, \Delta_i^F = 0)$. The filtration $\mathcal{F}(u)$ is defined as the increasing sequence of $\sigma-$algebras generated by

$$\sigma\{I(C_i \leq x), x \leq u; I(T_i \leq s), I(T_i^F \leq s), M_i(s), 0 \leq s < \infty, i = 1, \ldots, n\}.$$

Using results from Zhao and Tian (2001), the improved cost estimator can be expressed approximately by

$$\begin{aligned} & n^{\frac{1}{2}}(\widehat{\mu}^M - \mu^M) \\ = \; & n^{-\frac{1}{2}} \sum_{i=1}^{n} (M_i - \mu^M) - n^{-\frac{1}{2}} \sum_{i=1}^{n} \int_0^L \frac{dM_i^C(u)}{K(u)} \{M_i - G(M, u)\} \\ & + n^{-\frac{1}{2}} \sum_{i=1}^{n} \int_0^L \frac{dM_i^C(u)}{K(u)} [M_i(u) - G\{M(u), u\}] + o_p(1), \end{aligned}$$

where μ^M is the true mean cost, $G(Z, u) = E\{Z_i I(T_i \geq u)\}/S(u)$, for any random variable or functional Z.

The mean heart failure free survival time estimator can be approximated by

$$\begin{aligned} & n^{\frac{1}{2}}(\widehat{\mu}^F - \mu^F) \\ = \; & n^{-\frac{1}{2}} \sum_{i=1}^{n} (T_i^F - \mu^F) - n^{-\frac{1}{2}} \sum_{i=1}^{n} \int_0^L \frac{dM_i^{C_F}(u)}{K(u)} \{T_i^F - G^F(T^F, u)\} + o_p(1), \end{aligned}$$

where μ^F is the true heart failure free survival time, $G^F(Z,u) = E\{Z_i I(T_i^F \geq u)\}/S^F(u)$, for any random variable or functional Z.

To derive the covariance formula between the cost estimator and the survival time estimator, we need to calculate the covariance between the two different martingale processes $< dM_i^C(u), dM_i^{C_F}(u) >$. Define

$$dM_i^{C*}(u) = dN_i^{C*}(u) - \lambda^C(u) I(C_i \geq u) du$$

where $N_i^{C*}(u) = I(C_i \leq u)$. We can show that

$$dM_i^C(u) = I(T_i > u) dM_i^{C*}(u),$$

$$dM_i^{C_F}(u) = I(T_i^F > u) dM_i^{C*}(u),$$

and

$$\mathrm{Var}\{dM_i^{C*}(u) | \mathcal{F}(u)\} = I(C_i > u) \lambda^C(u) du.$$

Hence,

$$\begin{aligned} & \mathrm{Cov}\{dM_i^C(u), dM_i^{C_F}(u) | \mathcal{F}(u)\} \\ = \; & I(T > u) I(T^F > u) \mathrm{Var}\{dM_i^{C*}(u) | \mathcal{F}(u)\} \\ = \; & Y_i^F(u) \lambda^C(u) du. \end{aligned}$$

The covariance between the mean cost estimator μ^M and the mean heart failure

free survival time estimator μ^F becomes

$$
\begin{aligned}
& \mathrm{Cov}\{n^{\frac{1}{2}}(\widehat{\mu}^M - \mu^M), n^{\frac{1}{2}}(\widehat{\mu}^F - \mu^F)\} \\
= \; & \mathrm{Cov}(M_i, T_i^F) + \mathrm{E}\int_0^L \{T_i^F - G^F(T^F, u)\}\{M_i - G(M, u)\}\frac{Y_i^F(u)}{K(u)^2}\lambda^C(u)du \\
& -\mathrm{E}\int_0^L \{T_i^F - G^F(T^F, u)\}\{M_i(u) - G\{M(u), u\}\}\frac{Y_i^F(u)}{K(u)^2}\lambda^C(u)du. \\
= \; & \mathrm{Cov}(M_i, T_i^F) + \mathrm{E}\int_0^L [\{T_i^F - G^F(T^F, u)\}\{M_i - G(M, u)\}I(T_i^F \geq u)]\frac{\lambda^C(u)}{K(u)}du \\
& -\mathrm{E}\int_0^L [\{T_i^F - G^F(T^F, u)\}\{M_i(u) - G\{M(u), u\}\}I(T_i^F \geq u)]\frac{\lambda^C(u)}{K(u)}du. \\
= \; & \mathrm{Cov}(M_i, T_i^F) + \int_0^L [G^F\{T^F M, u\} - G^F\{M, u\}G^F(T^F, u)]\frac{S^F(u)\lambda^C(u)}{K(u)}du \\
& -\int_0^L [G^F\{T^F M(u), u\} - G^F\{M(u), u\}G^F(T^F, u)]\frac{S^F(u)\lambda^C(u)}{K(u)}du
\end{aligned}
$$

This can be estimated consistently by

$$
\begin{aligned}
& \frac{1}{n}\sum_{i=1}^n \frac{\Delta_i M_i T_i^F}{\widehat{K}(T_i)} - \frac{1}{n^2}\sum_{i=1}^n \frac{\Delta_i M_i}{\widehat{K}(T_i)}\sum_{i=1}^n \frac{\Delta_i^F T_i^F}{\widehat{K}^F(T_i^F)} \\
+ \; & \frac{1}{n}\int_0^L \frac{dN^{C_F}(u)}{\widehat{K}^F(u)^2}\{\widehat{G}^{F_0}(T^F M, u) - \widehat{G}^{F_0}(M, u)\widehat{G}^{F_0}(T^F, u)\} \\
- \; & \frac{1}{n}\int_0^L \frac{dN^{C_F}(u)}{\widehat{K}^F(u)^2}\{\widehat{G}^{F_0}\{T^F M(u), u\} - \widehat{G}^{F_0}\{M(u), u\}\widehat{G}^{F_0}(T^F, u)\},
\end{aligned}
$$

where

$$
\widehat{G}^{F_0}(Z, u) = \frac{1}{n\widehat{S}^F(u)}\sum_{i=1}^n \frac{\Delta_i}{\widehat{K}(T_i)} Z_i I(T_i^F \geq u), \tag{B.1}
$$

Although some of G can be estimated by

$$
\widehat{G}^F(Z, u) = \frac{1}{n\widehat{S}^F(u)}\sum_{i=1}^n \frac{\Delta_i^F}{\widehat{K}^F(T_i)} Z_i I(T_i^F \geq u), \tag{B.2}
$$

which seems to adopt more data information when available, using the same form of

$\widehat{G}$ achieves more efficiency in numerical studies. Thus, we suggest to use the same estimator for G.

VITA

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