Assessing Life Extension from Medical Interventions

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Abstract

Comparing outcomes assessing performance of several types of treatments or interventions is an important task in clinical trials as well as in observational studies. Among various measurements in assessing life extension, the gain in life expectancy is one of performance measurements of interest. In this paper, we propose a framework for estimating this quantity by calculating the area between estimated survival curves from two comparative treatments respectively, for example, active treatment and control. We estimate the survival curves first via the non-parametric Kaplan-Meier estimator to reflect the observed survival probabilities in the study. We then use semi-parametric Cox proportional hazard model and obtain the direct adjusted survival curves. By doing this, we can adjust for any imbalance of covariates between the two treatments. In order to assess the variability of our estimate, we propose a new Bootstrap method for obtaining a bootstrap confidence interval for this quantity. We also propose the corresponding bootstrap testing procedure to test the null hypothesis that two treatments have the same expected survival. We conduct simulation studies to evaluate the effectiveness of this method and use it in a real data application.

1 Introduction

Comparing outcomes of several types of treatments or interventions is an important task in clinical trials as well as retrospective cohort studies in epidemiology. For simplicity and

without loss of generality, we compare two treatments and refer them as the active and the control respectively in this paper. Among various measurements in assessing the relative efficacy of the two treatments, the gain in life expectancy is often of interest. Such a gain is measured by estimating the average number of days that participants in the active group live longer than those in the control group, or equivalently by the area between the two survival curves from the two treatment arms [1, 2]. There are several steps in the estimating and testing of the survival gain: 1) estimating the survival probabilities for the subjects from the two treatment groups; 2) calculating the area under the two curves and its standard error; 3) computing the p-value of the null hypothesis that there is no survival gain between the two treatments.

In the first step, the Kaplan-Meier estimator is a straightforward method. It represents an observed survival probability and can be utilized to estimate the gain in survival quite accurately when the distributions of covariates in the two treatment arms are balanced. When there is an imbalance of the distributions, we need to adjust for the covariates using a regression approach such as a semi-parametric model (Cox regression) or parametric models (Weibull, exponential, etc.). Individual survival curves are predicted from the regression results and expected survival curves can be obtained in several ways such as the mean covariate method [4] or the direct adjustment method[6]. The mean covariate method applies the parameter estimates from a regression model to produce one survival curve in each treatment arm for a "typical" participant who assumes average values for all the covariates. Though it is easy to calculate, it lacks good interpretation and can be misleading in some circumstances [4, 5]. On the other hand, the direct adjustment method computes a weighted average of the individual survival curves, with weights proportional to the number of individuals at each level of the covariates. It offers a clear improvement over the average covariate method. As a result, we adopt the direct adjustment approach in this paper. As for the choices of regression models, parametric models are only occasionally used in the analysis of survival data. Although they may offer advantages over Cox model. However, they often involve stronger assumptions [7]. Therefore, we will consider the Cox regression model in this paper.

With the estimated survival curves from both treatment arms, the gain of survival is estimated by the difference of the area under them. Furthermore, we would like to estimate the precision of this estimation and conduct statistical hypothesis testing of no treatment effect. Because estimated survival probabilities are correlated, the variance estimation of

the survival curves is quite complicated [8] and it is even more so when we take consideration of entire time region and the difference of the area under two curves. To overcome this problem, we propose to adopt a Bootstrap sampling method [9] to obtain a bootstrap confidence interval of the survival gain and a bootstrap p-value to test a hypothesis that the two treatment arms have the same expected survival.

The rest of the paper is arranged as follows. After reviewing basic background in survival analysis, section 2 presents the framework to estimate survival curves, the area differences between curves, a bootstrap confidence intervals, and a p-value for hypothesis testing. Section 3 conducts simulation studies to evaluate the effectiveness of this framework. Section 4 analyzes a real data set from a clinical trial. Section 5 concludes the paper with a discussion and future research directions.

2 Methods

2.1 Notations

Assume that there are n subjects receiving a same treatment in a study, which studies an event of interest, for example, death due to some cause. Let T_i denote the survival time for the ith subject. Assume $T_1, ..., T_n$ are continuous random variables, which are identically distributed with a cumulative distribution function $F(.)$ and a density function $f(.)$. Define the survival function

$$S(t) = P(T > t) = 1 - F(t) = \int_t^\infty f(u)du. \tag{1}$$

Since time to event data is sometimes censored due to end of the follow-up period of the study or dropout of subjects from the study, we generally observe a sample of pairs (T_i, δ_i), $i = 1, ..., n$ where $\delta_i = 1$ if the subject has an event and $\delta_i = 0$ if the subject is censored. Note that there are several types of censorship [11]. In this paper we focus on the right censoring type of time to event data. In addition we observe a list of covariates denoted by X_i that identify a collection of demographic and medical characteristics of the ith patient.

In connection with $f(.)$ and $S(.)$, we define the hazard function $h(.)$ as

$$h(t) = \frac{f(t)}{S(t)} = -\frac{d}{dt} \log S(t), \tag{2}$$

which is the ratio of the density function to the survival function. Hence, the hazard function is related to the survival function: $S(t) = \exp[-\int_0^t h(u)du]$.

2.2 Estimating survival functions

Assume that observed times for the n subjects are $t_1 \leq t_2 \leq ... \leq t_n$. For each t_i, we denote n_i as the number at risk just prior to time t_i, and d_i as the number of deaths at time t_i. The Kaplan-Meier estimator [10] is a nonparametric maximum likelihood estimate of $S(t)$ with a product of the form

$$\hat{S}(t) = \prod_{t<t_i} \frac{n_i - d_i}{n_i} \tag{3}$$

Note that when there is no censoring, n_i is just the number of survivors just prior to time t_i. With censoring, n_i is the number of survivors less the number of losses (censored cases). Therefore, n_i is only for those surviving cases that are still being observed (have not yet been censored), or "at risk" of an observed death.

Clinical studies often put participants in more than one (often two) treatment group so that the difference of the treatments can be observed and studied. We can use (3) to estimate and compare survival probability in each treatment group. This method works quite well when covariates in the two treatment arms are balanced. When we have imbalance in the distributions of the covariates, we need to adjust for the covariates with regression models. The semi-parametric Cox proportional hazard model [12] incorporates covariates X in the form:

$$h(t|X) = h_0(t)\exp(\beta^T X), \tag{4}$$

where β is a vector of regression coefficients and $h_0(t)$ is a baseline survival function. The survival function can be written in terms of a base survival function $S_0(t) = \exp[-\int_0^t h_0(u)du]$:

$$S(t|X) = \exp\Big(-\int_0^t h_0(u)\exp(\beta^T X)du\Big) = S_0(t)^{\exp(\beta^T X)} \tag{5}$$

This can be estimated by $\hat{S}(t|X) = \hat{S}_0(t)^{\exp(\hat{\beta}^T X)}$ where $\hat{S}_0(t)$ is the estimated baseline survival function by the Aalen-Nelson estimator [13] and $\hat{\beta}$ is the estimated parameters from Cox regression based on a partial likelihood approach.

From (5), we estimate the survival function for each subject in a treatment arm. Based on the direct adjustment method [6], we can obtain the average survival curves for all the

subjects in a treatment arm by averaging the individual curves as

$$\hat{S}(t|X) = \frac{1}{n}\sum_{i=1}^{n} \hat{S}_0(t)^{\exp(\hat{\beta}^T X_i)} \tag{6}$$

When some of the predictors do not satisfy proportional hazards assumption, we may stratify them to get around the problem. In the case of a stratified Cox regression model [14], the above becomes

$$\hat{S}(t|X) = \frac{1}{n}\sum_{j=1}^{J}\sum_{i=1}^{n_j} \hat{S}_0^j(t)^{\exp(\hat{\beta}^T X_{ij})}, \tag{7}$$

where J is the number of strata, n_j is the number of subjects in the jth stratum, n is the total number of subjects, $\hat{S}_0^j(t)$ is the estimated baseline survival function for the jth stratum.

2.3 Estimation of the area between two survival curves

One important issue in analyzing survival data is to compare the survival function $S_{trt}(t)$ of a treatment group with that of a control group $S_{ctr}(t)$. One quantity to compare is the expectation of time to event variable T. Since

$$E(T) = \int_0^\infty uf(u)du = \int_0^\infty (1 - F(u))du = \int_0^\infty S(u)du, \tag{8}$$

which is the area under the survival curve, therefore treatment survival gain (TSG) is defined as

$$E(T_{trt} - T_{ctr}) = \int_0^\infty (S_{trt}(u) - S_{ctr}(u))du \tag{9}$$

which is the area between two survival curves from the two treatment groups. When covariates are involved, (6) or (7) shows that the estimated survival function depends on the values of X. When the distribution of X is not balanced for the two treatment arms, the KM estimator approach produces misleading results which compares the survival gains between two difference groups of subjects.

We estimate TSG in the following steps:

1. Obtain the two estimated curves $\hat{S}_{trt}(t)$ and $\hat{S}_{ctr}(t)$ either by their corresponding Kaplan-Meier estimators or by direct adjusted survival curves from Cox regression in Section 2.2. In general, the two estimated curves are expressed as step functions. We

assume that $\hat{S}_{trt}(t)$ takes value y_i in the interval $[t_{i-1}, t_i)$ for $i = 1, ..., n$ and $t_0 = 0$; $\hat{S}_{ctr}(t)$ takes value z_j in the interval $[s_{j-1}, s_j)$ for $j = 1, ..., m$ and $s_0 = 0$.

2. Suppose that $s_m > t_n$ then we set the interval for the integral to be $[0, s_m]$, $t_{n^*} = s_m$, and $y_{n^*} = y_n$. Essentially we take the longest time for both arms and extend the last estimated survival function in the treatment group to that time. Note that $n^* = n+1$.

3. Estimate TSG by the trapezoidal method over the interval $[0, t_{n^*}]$:

$$\widehat{TSG} = \sum_{t=1}^{n^*} y_i(t_i - t_{i-1}) - \sum_{t=1}^{m} z_i(s_i - s_{i-1}) \tag{10}$$

Note the above is easy to be modified when the follow-up of the control arm ends earlier or $s_m < t_n$. This algorithm uses the fact that the survival curves are step functions and hence the area under the curve can be calculated without error as a sum of rectangular areas.

2.4 Bootstrap confidence interval and p-value

Efron [9] proposed to bootstrap the survival function by sampling the pairs of censoring indicators and observed times to event with replacement. He also showed that this is equivalent to sample from the distribution of survival times (denote x_i^* as the samples), and sample from the observed survival time (denote u_i^* as the samples), and then assign $t_i^* = \min(u_i^*, x_i^*)$, $\delta_i^* = 1$ if $t_i^* = x_i^*$ and 0 otherwise. This algorithm has been applied by Utzek and Sanchez [15] to estimate a bootstrap confidence envelop of the survival curve.

Denote the upper bound in follow-up times for both arms as w. Here we apply Efron's algorithm to estimate a confidence interval of the area between two survival curves as follows:

1. Use Efron's method to select two bootstrap samples $\{(\delta_i^*, t_i^* : i = 1, \cdots, n)\}$ and $\{(\nu_j^*, s_j^* : j = 1, \cdots, m)\}$ the treatment group and the control group respectively. Order the pairs by the t_i^*'s and the s_j^*'s. If $t_n^* < w$, we add the pair (y_n^*, w) to the estimated survival curve for the treatment sample and do the same operation to the bootstrap control sample.

2. Calculate the survival gain from the bootstrap sample - TSG^b over the interval $[0, w]$ using algorithm in Section 2.3.

3. Repeat steps 2 and 3 B (at least 1000) times and order the sample increasingly as $TSG^b_{(1)} \leq TSG^b_{(2)} \leq \cdots \leq TSG^b_{(B)}$. Then $(TSG^b_{(0.025B)}, TSG^b_{(0.975B)})$ is a 95% bootstrap confidence interval (CI) for TSG.

We also propose a similar algorithm for testing the null hypothesis that $TSG = 0$ or there is no survival gain in the two arms, vs the one-sided alternative hypothesis that $TSG > 0$. This algorithm is an adaptation of the general bootstrap testing algorithm that can be found in [16]. We modify the above algorithm as follows

- 2*. Using Efron's method select two bootstrap samples $\{(\delta^*_i, t^*_i)\}$ and $\{(\nu^*_i, s^*_i)\}$ of sizes n and m respectively from the control sample $\{(\mu_i, s_i)\}$. If $t^*_n < w$ then add the pair (y_n*, w) to the estimated survival curve for the treatment sample and do the same operation to the bootstrap control sample.
- 4*. Repeat steps 2* and 3 B times, where B is a large number at least 1000. Observe the sample $\{TSG^b_1, ..., TGS^b_B\}$ from which we estimate the bootstrap one-sided p-value as the $\#\{TSG^b_j > \widehat{TSG}\}/B$, where $\widehat{TSG}$ is from (10).

3 Simulations

In this section, we present simulation studies to demonstrate that proposed bootstrap method can effectively estimate TSG, its confidence interval, and p-value for hypothesis testing. Intuitively, factors such as size of a study number, censoring rates of lifetime, etc. can directly impact the estimation accuracy and power. Here, we will study how those factors affect the estimation performances.

3.1 Bias of estimation from Kaplan-meier estimator and Cox regression with balanced design

Assume life time $y_{trt} \sim \exp(\gamma_{trt})$ for a treatment group, where $\gamma_{trt} = \gamma_0 \exp(\alpha + \beta x_{trt})$; life time $y_{ctr} \sim \exp(\gamma_{ctr})$ for a control group, where $\gamma_{ctr} = \gamma_0 \exp(\beta x_{ctr})$; covariate $x_{trt} \sim normal(\mu_{trt}, \sigma^2_{trt})$ for the treatment group; covariate $x_{ctr} \sim normal(\mu_{ctr}, \sigma^2_{ctr})$ for the control

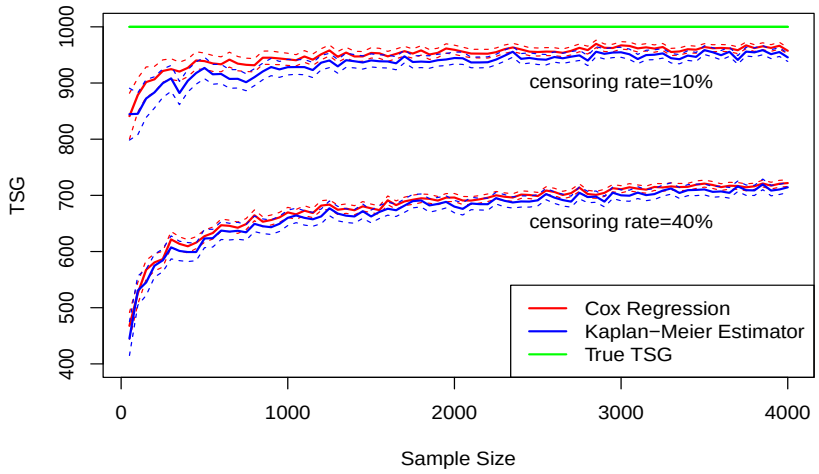
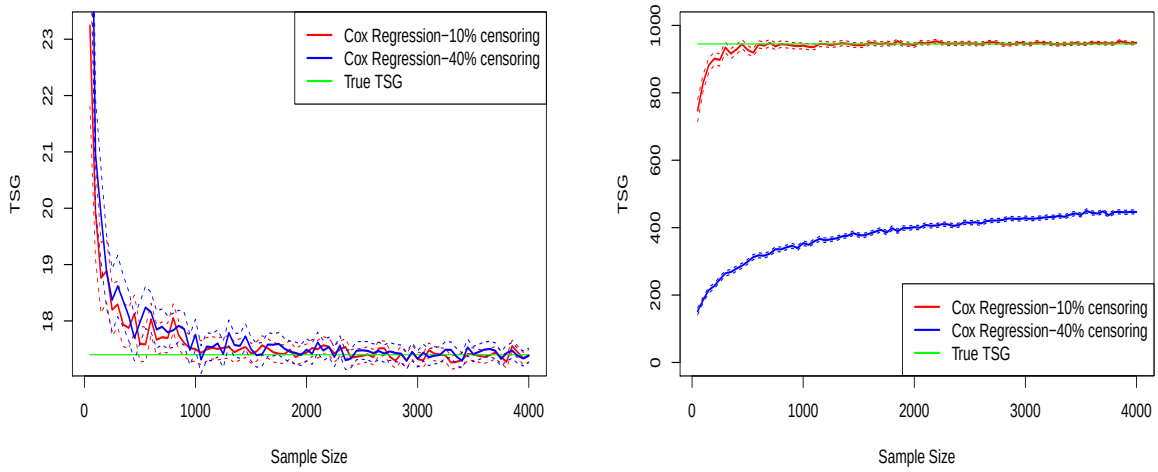


Figure 1: TSG's from the Kaplan-meier and Cox regression approaches

group; and censoring time $y_{cen} \sim \exp(\gamma_{cen})$. Then the theoretical survival gain is $E(y_{trt}) - E(y_{ctr}) = 1/\gamma_0 \exp(-\alpha - \mu_{trt}\beta - 0.5\beta^2\sigma_{trt}^2) - 1/\gamma_0 \exp(-\mu_{ctr}\beta - 0.5\beta^2\sigma_{ctr}^2)$.

We vary n from 50 to 4000. For each n, we generate the y_{trt} or y_{ctr} (denoted by y) with the equal probability using $\alpha = \log(0.5), \beta = 1, \mu_{trt} = \mu_{ctr} = 2, \sigma_{trt} = \sigma_{ctr} = 1, \gamma_0 = 2.23 \times 10^{-4}, \gamma_{cen} = 10^{-4}$. Then the observed time to event $t = \min(y, y_{cen})$, censoring indicator $\delta = I\{y \geq y_{cen}\}$ where $I(.)$ is an indicating function which takes the value of 1 when the argument is no less than zero, and 0 otherwise. For each value of n, calculate $\widehat{TSG}_{km}$ and $\widehat{TSG}_{cox}$. Repeat this for 2000 times to get the mean of estimates and their standard errors. The true TSG is calculated as 1000 with censoring rate of 0.11. Thus we plot in Figure1 the true TSG, $\widehat{TSG}_{km}$, $\widehat{TSG}_{cox}$, and their 95% confidence bands. We observe that 1) when sample size increases, the estimates from both methods get close to the true value; 2) Cox regression tends to achieve less bias and produce narrower confidence bands though the two methods do not differ significantly.

To examine the effects of censoring, we repeat the simulations using the same settings as above except for $\gamma_{cen} = 7.14 \times 10^{-4}$. The censoring rate increases to 40%. We plot the results in the same figure and observe that the bias is bigger when the censoring is more severe.



(a) $X = 2$ (b) $X = -2$

Figure 2: TSG in imbalanced trials

3.2 Bias of estimation from Cox regression with imbalanced design

When the design is not balanced in the two treatment arms, the result from KME is not easy to interpret. Cox regression method, on the other hand, can be applied to estimate the TSG on a particular subgroup of subjects from both arms.

Assume that a covariate X takes values of 0 and -2 with equal probability in the active treatment arm, 0 and 2 in the control arm. We might be interested to know the TSG when X takes on -2 or 2. To do so, we can fit a Cox regression model to available data, then using the concept of "counter-factual" by assigning a different treatment type to the same subgroup of subjects.

With a similar setup as the previous setting except for the construction of covariate X and $\gamma_0 = 7.8 \times 10^{-3}$, we will have the true overall $TSG = 1000$, the true TSG for the subgroup is 945.0 for $X = -2$, 17.3 for $X = 2$. With $\gamma_{cen} = 4000$, the censoring is set to 10%. We repeat the simulations with $\gamma_{cen} = 350$ to achieve 40% censoring. The estimated TSGs for both subgroups are shown in Figure 2. We observe that the censoring rate makes a difference in estimating TSG for subset $X = -2$ while no difference for the other subset.

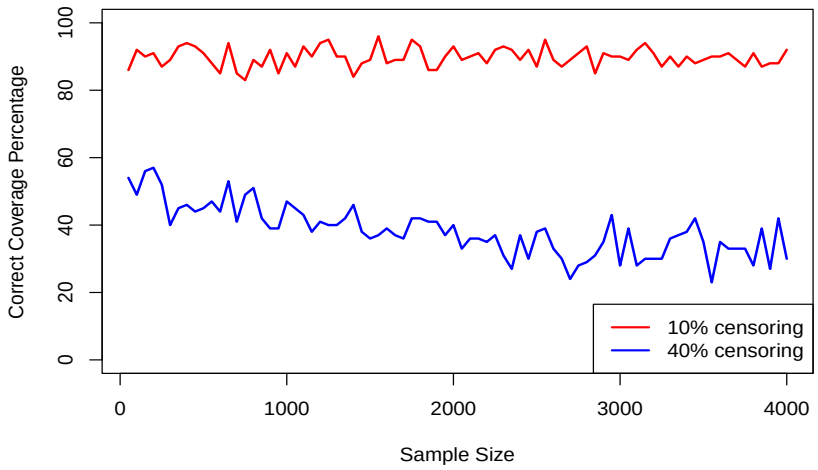


Figure 3: Bootstrap confidence interval coverage rates

3.3 Bootstrap confidence interval coverage and testing power

Here, we are interested in studying the accuracy of the Bootstrap method. We concentrate on the case when the covariates are balanced in both treatment arms and use the KME approach. Under the similar setup, we use Bootstrap steps to obtain a 95% confidence interval (CI) and check if the CI covers the true TSG. Repeat these steps 100 times, we can calculate the percentage of a correct coverage of the CI. We plot the results in Figure 3.

We observe that censoring rate of the life time data plays an important role in the correct coverage of the Bootstrap CI. For example, with a low censoring rate of 10%, the coverage percentage achieves 90% to 95% with a moderate sample size. However, the higher censoring rate of 40% makes the coverage percentage stay below 50%.

Next, we evaluate the Bootstrap p-value calculation for hypothesis testing. We use the same simulation setting as before and obtain the percentage of Bootstrap p-value less than 0.05 as the power of hypothesis test in Figure 4. We observe that the testing power increases rapidly to 0.9 and above with small sample sizes and low censoring rate data achieves high powers than the high censoring rate data. We also try other settings with different true TSG with similar power curves.

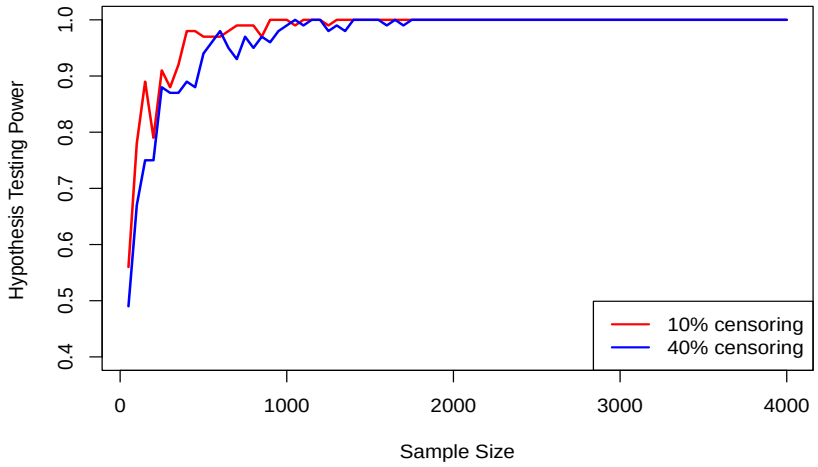


Figure 4: Bootstrap testing power

4 Application to a real data set

4.1 Data

The Systolic Hypertension in the Elderly Program (SHEP) was a randomized, double-blind placebo controlled trial in older patients with isolated systolic hypertension with the primary endpoint of fatal or non-fatal stroke. The investigators randomized 4736 participants (56.8% women) with systolic blood pressure (SBP) 160 mm Hg or higher and diastolic blood pressure 90 mm Hg or lower to stepped care antihypertensive therapy based on chlorthalidone or matching placebo.

Recruitment of the study begun on March 1, 1984 and vital status, date of death and cause of death were ascertained using the NDI through the end of 2006. The total duration of follow-up was 21 years and 10 months. Death was classified as cardiovascular if it was due to *International Classification of Diseases, Ninth Revision* codes 290 to 459 or *International Statistical Classification of Disease, 10th Revision* codes I00 to I99.

4.2 Analyses and Results

In order to access the efficacy of the treatment, we estimates the net gain in life expectancy free from cardiovascular death in the active therapy group.

First, we fit Kaplan-Meier survival curves free of cardiovascular (CV) death separately on the treatment group and control group. We calculate the areas under the two curves and take the difference and follow the Bootstrap steps to obtain the confidence interval and p-value for testing whether there is no difference in the two groups in term of survival gains. We repeat the same set of analyses for the end point of all-cause mortality. The results are shown in Table 1:

Table 1: TSG from Kaplan-Meier approach.

		Bootstrap		
End Point	TSG	Mean	95% CI	pvalue
All-Cause death	104.7	105.6	(-39.2, 241.8)	0.073
CV death	158.9	157.6	(36.4, 286,6)	0.009

Next we use Cox partial regression approach to correct any imbalance of the covariates between the two treatment groups. After using all the significant variables and checking the proportional hazard assumption, we stratify age using two categories of older than 71 and the rest, and race with 3 categories of white, black and others. The two covariates are sex and indicator of whether the patient previously has myocardial infarction (histmi). For the end point of cardiovascular death, we stratify age and use sex and race as covariates. The results are in Table 2.

From the results in Table 1 and 2, chlorthalidone reduces CV death significantly and does not reduce all-cause mortality. The Cox partial regression approach achieves a slightly tighter confidence interval of the TSG for CV death. The estimated TSG for all-cause death differs quite a lot from the two methods.

Table 2: TSG from Cox partial regression.

	Covariates		Bootstrap		
End Point	(besides treatment)	TSG	Mean	95% CI	pvalue
All-cause death	sex, histmi (race and age-stratified)	64.9	67.1	(-62.6, 190.7)	0.158
CV death	sex, race (age-stratified)	146.0	145.5	(14.9, 276.1)	0.016

5 Discussions

This paper proposes a bootstrap-based method to estimate the survival gain of a treatment vs its control and assess the precision of this estimator. The Kalplan-meier approach is straightforward and less computational intensive. Under the assumption of balanced study covariates, we can use this approach to estimate the survival gains for a similar group of participants. However, when this assumption does not hold, the Kaplan-meier method produces misleading results. To solve this problem, we propose an alternative Cox partial regression approach. With that, we can deal with the possible imbalance between the two groups. Furthermore, we can make inference of the survival gain of a hypothetical participant or group of participants with similarity to the counterfactural causal inference framework. Due to the size limit of this paper, we do not include in this paper the proof of the consistency property of this proposed bootstrap method.

The length of follow-up time for a study limits our goal of assessing its life extension. The survival function beyond follow-up needs to be estimated and extrapolated. By doing so, we can more accurately access the survival gain of a treatment.

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