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Nonparametric inference for time-dependent incremental cost-effectiveness ratios

Laura M. Yee^{*,†} and Kwun Chuen Gary Chan

Department of Biostatistics, University of Washington, Seattle, WA 98195, U.S.A.

Abstract

As the costs of medical care increase, more studies are evaluating cost in addition to effectiveness of treatments. Cost-effectiveness analyses in randomized clinical trials have typically been conducted only at the end of follow-up. However, cost-effectiveness may change over time. We therefore propose a nonparametric estimator to assess the incremental cost-effectiveness ratio over time. We also derive the asymptotic variance of our estimator and present formulation of Fieller-based simultaneous confidence bands. Simulation studies demonstrate the performance of our point estimators, variance estimators, and confidence bands. We also illustrate our methods using data from a randomized clinical trial, the second Multicenter Automatic Defibrillator Implantation Trial. This trial studied the effects of implantable cardioverter-defibrillators on patients at high risk for cardiac arrhythmia. Results show that our estimator performs well in large samples, indicating promising future directions in the field of cost-effectiveness.

Keywords

cost-effectiveness analysis; Fieller bands; induced informative censoring; nonparametric estimation; randomized clinical trials; survival analysis

1. Introduction

It is becoming increasingly important to be able to assess the cost of effective treatments. The incremental cost-effectiveness ratio (ICER) is one measure of cost-effectiveness that has been widely used by biomedical researchers [1–3]. In the setting of randomized clinical trials, the ICER evaluates the difference in mean cost between a new treatment and standard practice, per unit of effectiveness gained by the new treatment. Two descriptors of effectiveness that are commonly employed are mean survival time and probability of survival. The ICER that uses the difference in mean cost as the measure of effectiveness can be interpreted as the additional cost per year of life saved. The ICER/100 that uses the difference in probability of survival as the measure of effectiveness can be interpreted as the additional cost per percentage point increase in survival probability.

The ICER has typically been evaluated at the end of follow-up [4, 5]. However, some biomedical researchers have noted that evaluating cost-effectiveness over time is also of

^{*}Correspondence to: Laura M. Yee, Department of Biostatistics, University of Washington, Seattle, WA 98195, U.S.A..

[†]Laura.Yee@fda.hhs.gov

interest [6]. Cost-effectiveness until death only measures long-term effectiveness, whereas the cost-effectiveness function over time measures both long-term and short-term effectiveness. Information on short-term effectiveness may help local healthcare providers make decisions on whether to implement new cost-effective technology or communicate to patients the costs and benefits of a given treatment. Van de Wetering noted that implementation of a cost-effective technology might be abandoned if short-term costs and effects are not well communicated [6]. In addition, cost-effectiveness analyses evaluated at the end of studies are not directly comparable across studies with different follow-up times. However, portions of the cost-effectiveness functions can still be compared across studies. For example, if two studies have follow-up periods of 3 and 5 years, the cost-effectiveness functions can still be compared up to 3 years.

The problem of cost-effectiveness changing over time has been highlighted in the implantable cardioverter-defibrillator (ICD) literature [1–3]. For example, in the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) [7], the initial cost of intervention is high, but benefits accumulate long after implantation. This pattern of high initial costs but accruing benefits would translate to high cost per unit of effectiveness early on, but lower costs per unit of effectiveness as time progresses. To our knowledge, the statistical problems associated with time-dependent cost-effectiveness have not yet been addressed explicitly. In this paper, we plan to address the problem of changing cost-effectiveness over time by evaluating a nonparametric estimator, $\widehat{ICER}(t)$.

When cost data is right censored, we encounter a problem known as induced informative censoring. Induced informative censoring has been documented at length on the cost scale [8–10] and has also been studied in other contexts, such as quality-adjusted life and mean number of recurrent events [10–13]. The nonparametric estimator proposed by Cook and Lawless estimated the mean number of recurrent events by weighting number of recurrent events by the probability of being censored [13]. This estimator can be applied to cost data and is a continuous version of the well-known partitioned estimator of Lin and others [8]. We employ the estimator of Cook and Lawless for our case of cost data [13] and derive analytical variance and covariance for the corresponding ICER functions using empirical process theory.

Once we have estimators for the corresponding variance and covariance components, we turn to creating pointwise intervals for the ICER. Some authors have discussed normal-based approximations, which yield symmetric intervals [14–17]. These intervals have drawbacks such as lower coverage probability when the ICER has a skewed distribution or has inappropriately finite interval values. In addition, symmetric intervals largely ignore the concept of the four quadrants of cost-effectiveness – namely, that a new treatment may be more effective but more costly (NE quadrant), more effective and less costly (SE quadrant), less costly but less effective (SW quadrant), or less effective and more costly (NW quadrant) [18–21]. For these reasons, some authors have applied the Fieller interval [4, 5, 15–18, 22, 23]. The Fieller interval is not symmetric and has been shown to have good coverage probabilities in many situations [16–18]. We will compare both types of intervals for our method.

Because we are interested in making inference over a period of time, we will construct simultaneous confidence bands. Lin, Fleming, and Wei proposed a method for creating confidence bands for proportional hazards regression [24]. They used a multiplier bootstrap algorithm to approximate the limiting distribution of the survival function, which they employed to create symmetric confidence bands. However, for the time-dependent ICER, it is of interest to define asymmetric confidence bands analogous to the pointwise Fieller interval. We therefore extend the method of Lin, Fleming, and Wei to construct Fieller-based confidence bands for our estimator of ICER(t).

The incremental net benefit (INB) is an alternative statistic for studying cost-effectiveness, which has been widely used to avoid some of the inherent difficulties of using the ICER, a ratio [25]. However, for a fixed time period, the INB is a function of λ , the monetary value per unit of effectiveness. The time-varying INB will be a bivariate function of (t, λ) , which may not be easily interpreted or presented graphically. On the other hand, the time-varying ICER is a univariate function of t , which can be readily plotted. For this reason, in this paper, we focus on the time-varying ICER.

The goal of this paper is to introduce a nonparametric estimator for the ICER over time, ICER(t). In Section 2, we will discuss point estimation, derive pointwise interval estimation, and present how to evaluate confidence bands. Section 3 will demonstrate the performance of our estimators via simulation. In Section 4, we will present a data example using the MADIT-II data. Finally, we end with a discussion of our method in Section 5.

2. Methods

2.1. Notation

For individual i , $i = 1, \dots, n$, we define T_i to be the survival time, C_i to be the censoring time, and $X_i = \min(T_i, C_i)$. Let $Y_i(t)$ be the observed cumulative medical cost up to time t for individual i . That is, we define $Y_i(t) = Y_i^0(\min(t, C_i))$, where $Y_i^0(t)$ is the i th individual's true cumulative medical cost up to time t if no censoring were to occur. Let $\mu_Y(t) = E[Y^0(t)]$

be the true mean cumulative cost up to time t . Furthermore, let $\hat{Y}(t) = \frac{1}{n} \sum_{i=1}^n Y_i(t)$ be the sample mean of individual observed cumulative medical costs up to time t , and $Y(t) =$

$E[\hat{Y}(t)]$ be the mean observed cumulative cost up to time t . Assume that $(T_i, Y_i^0(\cdot)) \perp C_i$.

This requires that censoring is independent of survival time and cumulative medical cost, but allows T_i and $Y_i^0(\cdot)$ to be correlated.

We define $S(t) = P(T > t)$ to be the survival distribution, $K(t) = P(C > t)$ to be the survival distribution for the censoring times, $H(t) = E[I(T \leq t)I(C > t)]$ to be the average at-risk population at time t , and

$\Lambda_Y(t) = \int_0^t E[dY^0(s)|T \geq s] = \int_0^t E[dY(s)|X \geq s] = \int_0^t dY(s)/H(s-)$ to be analogous to the cumulative hazard for costs up to time t . Note that $H(t-)$ denotes the average at-risk

population at the moment before time t . We also define $\mu_T(t) = \int_0^t S(u)du$ to be the restricted mean survival time at time t .

Because our focus is on randomized clinical trials, we define a randomization variable, R_i . $R_i = 1$ if patient i was randomized to the new treatment and $R_i = 0$ for standard care. For notational ease, we will therefore employ the subscripts 1 and 0 to correspond to parameters and estimators that describe the treatment and standard groups, respectively.

In this paper, we evaluate cost-effectiveness beginning with some time after time zero, which is pre-specified to be of interest by study investigators. Thus, we restrict t to be larger than some clinically meaningful time, τ^0 . Furthermore, because of identifiability issues when estimating $\mu_Y(t)$ in the presence of censoring [8, 9, 26], we also only evaluate cost-effectiveness up to some time τ , where τ is chosen to be at or near the end of study observation. Therefore, we restrict t to $0 < \tau^0 \leq t \leq \tau$.

In the following sections, we will provide estimators, variance estimators, and a method to estimate confidence bands for ICER(t).

2.2. Estimation

Our parameters of interest are $\text{ICER}_T(t)$ and $\text{ICER}_S(t)$, where

$$\text{ICER}_T(t) = \frac{\mu_{Y_1}(t) - \mu_{Y_0}(t)}{\mu_{T_1}(t) - \mu_{T_0}(t)} \quad \text{and} \quad \text{ICER}_S(t) = \frac{\mu_{Y_1}(t) - \mu_{Y_0}(t)}{S_1(t) - S_0(t)}.$$

We can interpret $\text{ICER}_S(t)/100$ to be the increase in cost per one percentage increase in survival by time t , while $\text{ICER}_T(t)$ is the increase in cost per year of life saved up to time t .

We estimate $S(t)$ using the standard Kaplan–Meier estimator, $\hat{S}(t)$. Similarly, we estimate $\mu_T(t)$ by integrating the Kaplan–Meier estimator for survival times: $\hat{\mu}_T(t) = \int_0^t \hat{S}(u) du$. To estimate $\mu_Y(t)$, we employ the estimator of Cook and Lawless [13], which was originally proposed for estimating number of recurrent events. The estimation of the number of recurrent events and cumulative medical costs are similar because both are special cases of increasing stochastic processes [10]. For recurrent event counting processes, the jumps are always identical to 1, whereas the jumps are random medical costs for the cumulative cost process. The extension of the Cook and Lawless approach to medical cost is equivalent to a continuous-time version of Lin's discrete-interval estimator [8]. Zhao and others (2007) demonstrated that Lin's estimator is equivalent to the estimator of Zhao and Tian (2001) when the partition boundary is chosen at the censoring times [4, 27]. The continuous-time estimator is equivalent to a continuous-time version of the Zhao and Tian estimator. The weighted estimator of Cook and Lawless, adapted to estimate mean cost, can be written as follows:

$$\hat{\mu}_Y(t) = \int_0^t \frac{d\hat{Y}(u)}{\hat{K}(u-)} = \int_0^t \frac{\hat{S}(u-)}{\hat{H}(u)} d\hat{Y}(u) \quad \text{since } \hat{S}(u-) \hat{K}(u-) = \hat{H}(u) = \int_0^t \hat{S}(u-) d\hat{\Lambda}_Y(u).$$

Here, $\hat{K}(t)$ is the Kaplan–Meier estimator with X_i as the observed time variable and $I(X_i = C_i)$ as the event indicator, where $I(\cdot)$ is the indicator function. Furthermore,

$\hat{H}(t) = \frac{1}{n} \sum_{i=1}^n I(X_i \geq t)$ estimates the average observed risk set. Finally, $\hat{\Lambda}_Y(t) = \int_0^t \hat{Y}(ds) / \hat{H}(s-)$ can be estimated by plugging in the previously described estimators $\hat{H}(t)$ and $\hat{Y}(t)$.

We can then use the aforementioned estimators to obtain

$$\widehat{ICER}_T(t) = (\hat{\mu}_{Y_1}(t) - \hat{\mu}_{Y_0}(t)) / (\hat{\mu}_{T_1}(t) - \hat{\mu}_{T_0}(t)) \text{ and}$$

$$\widehat{ICER}_S(t) = (\hat{\mu}_{Y_1}(t) - \hat{\mu}_{Y_0}(t)) / (\hat{S}_1(t) - \hat{S}_0(t)).$$

2.3. Variance and pointwise confidence intervals

Empirical process theory can be used to derive the asymptotic variances of $\widehat{ICER}_T(t)$ and $\widehat{ICER}_S(t)$. In this section, we present the consistent estimators for these asymptotic variances, which are derived in the Appendix.

For notational convenience, let $\hat{\gamma}(t) = \hat{\mu}_{Y_1}(t) - \hat{\mu}_{Y_0}(t)$ be the difference in estimated mean cost at time t , $\hat{s}(t) = \hat{S}_1(t) - \hat{S}_0(t)$ be the difference in estimated survival probability at time t , and $\hat{\tau}(t) = \hat{\mu}_{T_1}(t) - \hat{\mu}_{T_0}(t)$ be the difference in estimated mean survival time at time t . We will further simplify the difference in effectiveness measures to be $\hat{\kappa}(t)$ for measure K , $K \in \{S, T\}$, when appropriate. In the Appendix, we derive the influence functions of $\widehat{ICER}_K(t)$.

Based on the results, the variance estimators of $\widehat{ICER}_K(t)$ take the form

$$\widehat{Var}[\widehat{ICER}_K(t)] = \frac{1}{n} \sum_{i=1}^n \left[\frac{\hat{\eta}_i^Y(t)}{\hat{\Delta}_K(t)} - \hat{\eta}_i^K(t) \left(\frac{\hat{\Delta}_Y(t)}{[\hat{\Delta}_K(t)]^2} \right) \right]^2 = \frac{1}{n} \sum_{i=1}^n [\hat{\phi}_i^{ICER_K}(t)]^2,$$

where $\hat{\eta}_i^Y(t)$, $\hat{\eta}_i^T(t)$, $\hat{\eta}_i^S(t)$, and $\hat{\phi}_i^{ICER_K}(t)$ are the estimated influence functions for $\hat{\gamma}(t)$, $\hat{\tau}(t)$, $\hat{s}(t)$, and $\widehat{ICER}_K(t)$, respectively. The definitions and derivations of $\hat{\eta}_i^Y(t)$, $\hat{\eta}_i^T(t)$, $\hat{\eta}_i^S(t)$, and $\hat{\phi}_i^{ICER_K}(t)$ are described in detail in the Appendix.

Let $z_{\alpha/2}$ be the desired standard normal critical value. Then the symmetric pointwise confidence interval for $\widehat{ICER}_K(t)$ can therefore be formulated by normal approximation:

$$\widehat{ICER}_K(t) \pm z_{\alpha/2} \widehat{Var}^{\frac{1}{2}}[\widehat{ICER}_K(t)] / \sqrt{n}. \quad (1)$$

It has been noted that normal approximations tend to perform poorly when constructing confidence intervals for the ICER because its distribution is typically skewed and because in some cases the interval should not be finite [15–18, 23]. Therefore, it is also of interest to estimate Fieller intervals, which have been shown to perform well in a variety of situations [16–18]. To construct the pointwise Fieller intervals, we need to estimate the variances and covariances of $\hat{\gamma}(t)$, $\hat{\tau}(t)$, and $\hat{s}(t)$. Once again, using the empirical influence functions derived in the Appendix, for $K \in \{S, T\}$, we have that

$$\hat{\sigma}_Y^2(t) \equiv \widehat{Var}[\hat{\Delta}_Y(t)] = \frac{1}{n} \sum_{i=1}^n [\hat{\eta}_i^Y(t)]^2, \hat{\sigma}_K^2(t) \equiv \widehat{Var}[\hat{\Delta}_K(t)] = \frac{1}{n} \sum_{i=1}^n [\hat{\eta}_i^K(t)]^2, \text{ and}$$

$$\hat{\sigma}_{YK}(t) \equiv \widehat{Cov}[\hat{\Delta}_Y(t), \hat{\Delta}_K(t)] = \frac{1}{n} \sum_{i=1}^n [\hat{\eta}_i^Y(t) \hat{\eta}_i^K(t)].$$

The pointwise Fieller intervals are constructed as follows. Let

$$H_t(\rho) = \frac{\hat{\Delta}_Y(t) - \rho \hat{\Delta}_K(t)}{[\hat{\sigma}_Y^2(t) - 2 \times \rho \hat{\sigma}_{YK}(t) + \rho^2 \hat{\sigma}_K^2(t)]^{1/2}},$$

then $H_t(\rho)$ is asymptotically normal for a fixed ρ and t . The pointwise Fieller intervals at t are the collection of ρ such that

$$P[H_t(\rho) \leq z_{1-\alpha/2}^2] = 1 - \alpha. \quad (2)$$

Equation (2) can be rewritten as $P[Q_t(\rho) \leq 0] = 1 - \alpha$, where $Q_t(\rho) = q_0(t) - 2q_1(t)\rho + q_2(t)\rho^2$, and

$$q_0(t) = [\hat{\Delta}_Y(t)]^2 - z_{1-\alpha/2}^2 \hat{\sigma}_Y^2(t),$$

$$q_1(t) = \hat{\Delta}_Y(t) \hat{\Delta}_K(t) - z_{1-\alpha/2}^2 \hat{\sigma}_{YK}(t), \quad (3)$$

$$q_2(t) = [\hat{\Delta}_K(t)]^2 - z_{1-\alpha/2}^2 \hat{\sigma}_K^2(t).$$

Then the pointwise Fieller confidence intervals are the collection of ρ such that $Q_t(\rho) \leq 0$.

Define $D(t) = q_1^2(t) - q_0(t)q_2(t)$ and $l_1(t) = (q_1(t) - \sqrt{D(t)})/q_2(t)$ and

$l_2(t) = (q_1(t) + \sqrt{D(t)})/q_2(t)$, which are defined when $D(t) \geq 0$. Then, the Fieller interval is defined for the following cases:

Case 1. If $D(t) \geq 0$ and $q_2(t) > 0$, we have a finite interval $[l_1(t), l_2(t)]$.

Case 2. If $D(t) \geq 0$ and $q_2(t) < 0$, we have an infinite interval $(-\infty, l_2(t)] \cup [l_1(t), \infty)$.

Case 3. If $D(t) < 0$, the interval is defined as the whole real line $(-\infty, \infty)$.

It is possible that finite intervals are obtained for some time periods, while infinite intervals are obtained for other time periods. In fact, finite intervals are obtained for t such that the difference in effectiveness is statistically significant at the $\alpha\%$ significance level, while infinite intervals are obtained for t such that the equality of effectiveness is not rejected at $\alpha\%$ significance level. We note that these Fieller confidence intervals reduce to the case considered by Willan and O'Brien (1996) when the effectiveness outcome is binary instead of a survival outcome [18].

2.4. Confidence bands

We can construct pointwise confidence intervals using either the symmetric approach of Equation (1) or the Fieller approach. Because we are describing the ICER over time, it is also of interest to assess simultaneous confidence bands so that we can make inference over the entire time span (τ^0, τ) . We aim to replace the $z_{\alpha/2}$ of Equations (1) and (3) with larger values, b_S and b_F , respectively. These larger critical values are used to yield the simultaneous coverage probabilities in each situation.

We outline methods for computing b_S and b_F , which are based on a formulation of a confidence band for the Cox proportional hazards model [24]. To compute b_S based on the standard symmetric approach, we complete the following steps:

1. Generate random multipliers $\{G_i, i = 1, \dots, n\}$, which are independent and standard normally distributed. Define $W(t) = \frac{1}{\sqrt{n}} \sum_{i=1}^n G_i \varphi_i^{ICER_K}(t) / \widehat{Var}^{1/2}[\widehat{ICER}_K(t)]$.
2. Choose a number of m , which will represent the number of multiplier bootstrap replications that will be completed. Repeat step 1 m times to obtain $W_l(t), l = 1, \dots, m$.
3. Obtain b_S , the $(100-\alpha)$ percentile of $\max_{(\tau^0, \tau)} \{|W_l(t)|\}$.

The symmetric confidence band is then constructed by replacing $z_{1-\alpha/2}$ in (1) using b_S . This approach is based on a normal assumption of the whole ratio, which may not hold because the ICER often has a skewed distribution, as noted previously. Therefore, we also consider computing b_F , which is based on normal approximations for a linear combination of the numerator and the denominator. We modify the aforementioned steps as follows:

1. Generate random multipliers $\{G_i, i = 1, \dots, n\}$ which are independent and standard normally distributed. Define $Z(t) = \frac{1}{\sqrt{n}} \sum_{i=1}^n G_i [\hat{\eta}_i^Y(t) - \widehat{ICER}_K(t) \hat{\eta}_i^K(t)] / [\hat{\sigma}_Y^2(t) - 2 \times \widehat{ICER}_K(t) \hat{\sigma}_{YK}(t) + \widehat{ICER}_K^2(t) \hat{\sigma}_K^2(t)]^{1/2}$.
2. Choose a number of m , which will represent the number of multiplier bootstrap replications that will be completed. Repeat step 1 m times to obtain $Z_l(t), l = 1, \dots, m$.
3. Obtain b_F , the $(100-\alpha)$ percentile of $\max_{(\tau^0, \tau)} \{|Z_l(t)|\}$.

The Fieller confidence band is constructed by replacing $z_{1-\alpha/2}$ in (3) using b_F . Because $b_F > z_{1-\alpha/2}$, it is possible that $q_2(t) > 0$ for a particular t for pointwise Fieller intervals but $q_2(t) < 0$ for the Fieller band. In such cases, the pointwise intervals have finite length but the bands would have infinite length. Statistical codes are available upon request.

3. Simulation

In this section, we present simulation studies that evaluate the proposed ICER(t) and variance estimators. We also provide the empirical coverage of the simultaneous confidence

bands. We use a simulation setup similar to that of Zhao and Tian [4], which has also been employed to some degree in other cost-related studies [8–10, 28].

The total cost for each individual was composed of a diagnostic cost (incurred at the beginning of the study), a yearly cost (incurred randomly within each year), and an end of life cost (incurred randomly in the year before death). We considered two cost simulation setups – one in which cost was generated using uniform distributions and one in which cost was generated with gamma distributions. The uniform cost simulation was as follows: for the treatment group, the diagnostic cost was uniform on [20,000, 30,000], the yearly cost was uniform on [1000, 2000], and the end of life cost was uniform on [5000, 10,000]. For the standard group, the costs were uniform on [1000, 3000], uniform on [1000, 3000], and uniform on [5000, 10,000], respectively. For the treatment group, this setup therefore assigns a high diagnostic cost, but lower average yearly costs thereafter. In addition to uniform cost distributions, we considered right-skewed cost distributions generated from gamma distributions with the same means and variances as the uniform distribution setup.

We also examined two different situations of survival time distributions. In the first situation, the survival time of the treatment group followed an exponential distribution with a mean of 8 years, while the standard group followed an exponential distribution with a mean of 5 years. In the second situation, the survival time of the treatment group followed an exponential distribution with a mean of 12.8 years, and the standard group followed a Weibull distribution with a mean of 7 years (scale = 7.29, shape = 1.11). The first situation is an example similar to that of Zhao and Tian [4]. The second situation is more realistic and is based on the parameters obtained from a Weibull survival regression of the MADIT-II data.

We examined cost and survival up to $\tau = 10$ years. Censoring time was uniformly distributed on [0, 12.5], which resulted in censoring at 10 years of 37% for standard care and 51% for new treatment in the first survival time example and 49% for standard care and 65% for new treatment in the second survival time example. A τ^0 of 1.5 years was chosen for all simulation examples. The results are based on 1000 simulation runs. Sample size was 500 per treatment group. Confidence band critical values are based on 1000 resamples.

Tables I and II present $ICER_5(t)$ and $ICER_7(t)$ estimates, bias, pointwise estimated standard error, pointwise sample standard error, and 95% coverage probability of the estimated confidence bands over time. In particular, Table I presents the uniformly generated costs, while Table II presents the gamma-distributed costs.

In the first set of simulations – where $T_1 \sim \text{Exp}(8)$ and $T_0 \sim \text{Exp}(5)$ – we see that our estimates are slightly biased, but the bias becomes less pronounced over time. The estimated standard error tends to be lower than the sample standard error early in the study, but our estimated standard error does quite well after the first few years of observation. We see similar patterns in the second set of simulations – where $T_1 \sim \text{Exp}(12.8)$ and $T_0 \sim \text{Weib}(\text{scale} = 7.3, \text{shape} = 1.1)$. Here, the estimates and standard error estimates perform more poorly at 2 years, but perform well in subsequent years. The poorer performance in the earlier years is

due to the small difference in effectiveness at those times, thus leading to unstable estimation of the ratios.

We observed improved coverage when using the Fieller bands (Fb_F) over the symmetric bands (Sb_S). In both survival scenarios and both cost generation examples, empirical coverage probabilities for the Fieller bands were close to nominal values (0.95) while the symmetric bands showed varying levels of under coverage.

4. Second multicenter automatic defibrillator implantation trial

The second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) was a clinical trial in which patients at risk for cardiac arrhythmia were randomized to receive ICD or standard medical treatment in an attempt to prevent sudden cardiac death [7]. ICDs have a high initial cost, but their benefits accrue for years after implantation. For this reason, the ICD has often been the focus of cost-effectiveness analyses [1–3].

The second Multicenter Automatic Defibrillator Implantation Trial was conducted from 1997 to 2002. Participants were enrolled from 76 hospitals in the US and Europe. Participants were considered for inclusion in the study if they had experienced a previous heart attack and had a left ventricular ejection fraction less than or equal to 0.30. Additional exclusion criteria and details about the study design are documented in the original report [7]. We illustrate our methods with the 664 ICD participants and 431 standard therapy participants who were analyzed in the cost-effectiveness paper by Zwanziger and others [3]. For our analyses, both costs and survival times were discounted at a 3% yearly rate. Before embarking upon our analysis, we chose a τ^0 of 1.5 years after randomization, and we chose τ to be 4.

Figure 1 shows the following: (a) estimated mean cost, (b) estimated probability of survival, and (c) estimated mean survival time for participants in the ICD and standard treatment groups. In Figure 1(a), we see that there is a high initial cost for the ICD group relative to the standard treatment group because of the high cost of intervention. However, cost accrual remains similar in ICD and standard groups after randomization. Figure 1(b) and (c) shows that the differences in probability of survival and mean survival time grow larger over time.

Figure 2 shows the estimated (a) $ICER_T(t)$ and (b) $ICER_S(t)$ along with the 95% symmetric confidence band (thin line). The Fieller confidence bands calculated with the Fieller critical value (Fb_F , dotted line) are also depicted on each graph. The estimated $ICER_T$ (Figure 2(a), thick line) decreases over time, showing that ICDs become more cost-effective over time. In our example, we see that the symmetric confidence bands – which are not recommended for use because of their low coverage probability as seen in Section 3 – often cross below zero. We now inspect the corresponding Fieller-based confidence band (Fb_F) for the estimated $ICER_T(t)$. The upper band in this case is infinite before 3.3 years, which means that when we account for making simultaneous probability statements over time, we are not able to rule out large values of $ICER_T$ before 3.3 years. In terms of our previously defined Fieller interval types, the upper confidence band belongs to Case 2 of Section 2.3 between $\tau^0 = 1.5$ and 3.3 years, and belongs to Case 1 between 3.3 and 4 years. At 4 years, the $ICER_T(t)$ is estimated to be \$164,000. Here, the lower confidence band only goes as low as \$79,700,

indicating that it would be unlikely for the cost of ICD per year of life saved to go below \$79,700.

The estimated $ICER_S$ (Figure 2(b), thick line) also decreases slightly over time, but tends to jump up and down. The jumps occur because the differences in Kaplan–Meier estimated survival probabilities take large jumps, mostly because of the sample size of the MADIT-II data. As in the $ICER_T(t)$ example, we note that the upper Fieller confidence band is infinite before 3.7 years and only goes as low as \$4,400,000 (not depicted). Here, the upper confidence band belongs to Case 2 between 1.5 and 3.7 years and belongs to Case 1 between 3.7 and 4 years. The lower band does not reach below \$114,000, indicating that it would be unlikely for the cost of the ICD per 100 percentage point increase in survival probability to go below \$114,000. Note that the 100 percentage point increase in survival probability compares the scenario of a 100 percent survival probability to 0 percent, but the estimate may be scaled (for example, divided by 100) to yield a more meaningful increase in survival probability. Additional recommendations about which ICER estimate to employ are explored in the discussion.

In our analysis of the MADIT-II data, we see that the confidence bands often include very large values. This reflects our uncertainty about the $ICER(t)$ estimates. It should be noted that the original study design was powered for detecting a difference in survival and cost-effectiveness was a secondary analysis [7]. As such, larger sample sizes or longer follow-up time might yield cost-effectiveness results that are more conclusive. In this example, we also did not discuss current guidelines for cost-effectiveness. Although this is not the focus of the paper, one possible recommendation – put forth by the World Health Organization [29] – suggests that a treatment might be considered cost-effective if an additional year of disability-free life costs less than three times the annual per-capita GDP of the country in which it is being used. Given our current analysis and assuming a 2002 per capita GDP of \$38,000 USD [30], ICD does not appear to reach this goal, but again, our study was limited by length of follow-up, sample size, and a lack of disability information.

5. Discussion

In this paper, we have presented a nonparametric method to evaluate the ICER over time. We presented an estimator, derived an analytical variance formula, and formulated confidence bands.

Several authors have used bootstrapping to estimate confidence intervals for the ICER [15, 16, 31, 32]. However, as was noted by Lin, Fleming, and Wei, it is not clear how to justify using the bootstrap for estimating a function over time [24]. We therefore employed analytical interval formulas and applied a resampling method to calculate critical values for our confidence bands.

Our simulation results summarized the performance of our estimators using a rather large sample size. We believe that suggesting a larger sample size for our method is reasonable because we are interested in the whole time period (τ^0, τ) rather than just at τ . It should be noted that $\widehat{ICER}_S(t)$ and its corresponding confidence bands can be quite unstable, as we

saw in the data example. This is due to the fact that the difference in Kaplan–Meier-estimated survival probabilities may jump substantially when the sample size is small. In comparison, the $\widehat{ICER}_T(t)$ is more stable because a single event will not have such a large effect on the estimated mean survival time. The $ICER_S(t)/100$ can be interpreted as the increase in cost per percent increase in survival probability by time t , while $ICER_T(t)$ is the increase in cost per year of life saved by time t . Given its more desirable interpretation, many biomedical authors have employed the $ICER_T(t)$. We also recommend using this estimator because of the instability of the estimates and bands for $ICER_S(t)$.

A reviewer suggested that when effectiveness is non-significant, a common approach is to conduct a cost-minimization analysis that ignores the denominator in the ICER. This is an intuitive approach to understanding the data when the denominator of the ICER is close to zero and avoids the problem of ICER approaching infinity.

Although it is clear that cost-effectiveness may change over time, statistical literature in the area has been lacking. We provided a starting point for this research by proposing a nonparametric estimator, variance, and confidence bands for the time-dependent ICER. Future work in this area might develop methodology for the INB, another measure of cost-effectiveness, or might extend regression methods so that researchers may account for covariates.

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Appendix A

We wish to find the influence functions of $\widehat{ICER}_S(t)$ and $\widehat{ICER}_T(t)$. To do so, we will first find the influence function of $\Lambda_Y(t)$. We will then use this influence function to find the influence functions of $\hat{\mu}_Y(t)$ and $\hat{\mu}_T(t)$. Finally, we will find the influence functions of $\widehat{ICER}_S(t)$ and $\widehat{ICER}_T(t)$. We use notation from Sections 2.1–2.3 of the main paper.

A.1. Influence function for $\hat{\Lambda}_Y(t)$

In this section, we wish to find the influence function of $\Lambda_Y(t)$, where

$\Lambda_Y(t) = \int_0^t dY(s)/H(s-)$. $\Lambda_Y(t)$ depends on the pair $(\hat{Y}(t), \hat{H}(t))$ through two maps:

$$(A, B) \rightarrow \left(A, \frac{1}{B}\right) \rightarrow \int_0^t \frac{1}{B} dA.$$

Then the derivative of these maps at (Y, H) is as follows:

$$(\alpha, \beta) \rightarrow \left(\alpha, -\frac{\beta}{H^2}\right) \rightarrow \int_0^t \frac{d\alpha}{H} - \int_0^t \frac{\beta dY}{H^2}.$$

Let $\alpha = \hat{Y}(t) - Y(t)$ and $\beta = \hat{H}(t) - H(t)$. Then, by the functional delta method [33], we have

$$\begin{aligned}\hat{\Lambda}_Y(t) - \Lambda_Y(t) &= \int_0^t \frac{1}{H(s)} [\hat{Y}(ds) - Y(ds)] - \int_0^t \frac{\hat{H}(s) - H(s)}{H^2(s)} Y(ds) + o_p\left(\frac{1}{\sqrt{n}}\right) \\ &= \int_0^t \frac{\hat{Y}(ds)}{H(s)} - \int_0^t \frac{\hat{H}(s)}{H^2(s)} Y(ds) + o_p\left(\frac{1}{\sqrt{n}}\right) \\ &= \frac{1}{n} \sum_{i=1}^n \left[\int_0^t \frac{\hat{Y}_i(ds)}{H(s)} - \int_0^t \frac{I(X_i \geq s) Y(ds)}{H^2(s)} \right] + o_p\left(\frac{1}{\sqrt{n}}\right) \\ &= \frac{1}{n} \sum_{i=1}^n \phi_i^{\Lambda_Y}(t) + o_p\left(\frac{1}{\sqrt{n}}\right).\end{aligned}$$

A consistent estimator for $\phi_i^{\Lambda_Y}(t)$ can be calculated by plugging in $\hat{H}(t)$ and $\hat{Y}(t)$ for $H(t)$ and $Y(t)$, respectively.

B.1. Influence functions for $\hat{\mu}_Y(t)$ and $\hat{\mu}_T(t)$

Here, we wish to find the influence functions of $\hat{\mu}_Y(t)$ and $\hat{\mu}_T(t)$. First, note that the influence function for $\hat{S}(t)$ is written as follows:

$$\phi_i^{KM}(t) = S(t) \left[\frac{\Delta_i I(X_i \leq t)}{H(X_i)} - \int_0^t \frac{I(X_i \geq s)}{H^2(s)} dF_1(s) \right],$$

where $X_i = \min(T_i, C_i)$, $\Delta_i = I(T_i \leq C_i)$, and $F_1(x) = P(X \leq x, \Delta = 1)$. Employing steps similar to those in Appendix A, we use both $\phi_i^{\Lambda_Y}(t)$ and $\phi_i^{KM}(t)$ to obtain the following influence functions:

$$\begin{aligned}\hat{\mu}_Y(t) - \mu_Y(t) &= \int_0^t S(s-) [\hat{\Lambda}_Y(ds) - \Lambda_Y(ds)] + \int_0^t [\hat{S}(s-) - S(s-)] \Lambda_Y(ds) + o_p\left(\frac{1}{\sqrt{n}}\right) \\ &= \frac{1}{n} \sum_{i=1}^n \left[\int_0^t S(s-) \phi_i^{\Lambda_Y}(ds) + \int_0^t \phi_i^{KM}(s-) \Lambda_Y(ds) \right] + o_p\left(\frac{1}{\sqrt{n}}\right) \\ &= \frac{1}{n} \sum_{i=1}^n \phi_i^{\mu_Y}(t) + o_p\left(\frac{1}{\sqrt{n}}\right), \quad \text{and}\end{aligned}$$

$$\hat{\mu}_T(t) - \mu_T(t) = \int_0^t [\hat{S}(u) - S(u)] du = \frac{1}{n} \sum_{i=1}^n \left[\int_0^t \phi_i^{KM}(u) du \right] + o_p\left(\frac{1}{\sqrt{n}}\right) = \frac{1}{n} \sum_{i=1}^n \phi_i^{\mu_T}(t) + o_p\left(\frac{1}{\sqrt{n}}\right).$$

Define $\hat{F}_1(x) = \frac{1}{n} \sum_{i=1}^n I(X_i \leq x, \Delta_i = 1)$ to be the empirical estimator of $F_1(x)$. Then consistent estimators for $\phi_i^{KM}(t)$, $\phi_i^{\mu_Y}(t)$, and $\phi_i^{\mu_T}(t)$ can be calculated by replacing $F_1(x)$ for $\hat{F}_1(x)$, $\hat{H}(t)$ for $H(t)$, $\hat{S}(t)$ for $S(t)$, $\hat{\Lambda}_Y(t)$ for $\Lambda_Y(t)$, and $\hat{\phi}_i^{\Lambda_Y}(t)$ for $\phi_i^{\Lambda_Y}(t)$ in the aforementioned formulas.

C.1. Influence functions for $\widehat{ICER}(t)$

First, let n_1 and n_0 denote the number of participants on treatment and standard, respectively, such that $n = n_1 + n_0$. Using notation in Sections 2.1–2.3 of the paper, we find the influence function for $\hat{\Delta}_Y(t)$:

$$\begin{aligned}\hat{\Delta}_Y(t) - \Delta_Y(t) &= [\hat{\mu}_{Y_1} - \hat{\mu}_{Y_0}] - [\mu_{Y_1} - \mu_{Y_0}] \\ &= \frac{1}{n} \sum_{i=1}^n \left[\frac{n}{n_1} R_i \phi_i^{\mu_Y}(t) - \frac{n}{n_0} (1 - R_i) \phi_i^{\mu_Y}(t) \right] + o_p \left(\frac{1}{\sqrt{n}} \right) \\ &= \frac{1}{n} \sum_{i=1}^n \eta_i^Y(t) + o_p \left(\frac{1}{\sqrt{n}} \right).\end{aligned}$$

Similarly, the influence functions for $\hat{S}(t)$ and $\hat{T}(t)$ take the form

$$\eta_i^S(t) = \frac{n}{n_1} R_i \phi_i^{KM}(t) - \frac{n}{n_0} (1 - R_i) \phi_i^{KM}(t), \text{ and}$$

$$\eta_i^T(t) = \frac{n}{n_1} R_i \phi_i^{\mu_T}(t) - \frac{n}{n_0} (1 - R_i) \phi_i^{\mu_T}(t).$$

Now, by the functional delta method once again, we obtain the influence functions of $\widehat{ICER}_S(t)$ and $\widehat{ICER}_T(t)$. With $K \in \{S, T\}$, $\widehat{ICER}_K(t)$ takes the following format:

$$\begin{aligned}\widehat{ICER}_K(t) - ICER_K(t) &= \frac{\hat{\Delta}_Y(t) - \Delta_Y(t)}{\hat{\Delta}_K(t)} - [\hat{\Delta}_K(t) - \Delta_K(t)] \frac{\hat{\Delta}_Y(t)}{\hat{\Delta}_K^2(t)} \\ &= \frac{1}{n} \sum_{i=1}^n \left[\frac{\eta_i^Y(t)}{\hat{\Delta}_K(t)} - \eta_i^K(t) \frac{\hat{\Delta}_Y(t)}{\hat{\Delta}_K^2(t)} \right] + o_p \left(\frac{1}{\sqrt{n}} \right) \\ &= \frac{1}{n} \sum_{i=1}^n [\varphi_i^{ICER_K}(t)] + o_p \left(\frac{1}{\sqrt{n}} \right).\end{aligned}$$

Finally, the consistent estimators for $\eta_i^Y(t)$, $\eta_i^S(t)$, $\eta_i^T(t)$, $\varphi_i^{ICER_S}(t)$, and $\varphi_i^{ICER_T}(t)$ are calculated by replacing $\hat{\phi}_i^{\mu_Y}(t)$, $\hat{\phi}_i^{KM}(t)$, and $\hat{\phi}_i^{\mu_T}(t)$ for $\phi_i^{\mu_Y}(t)$, $\phi_i^{KM}(t)$, and $\phi_i^{\mu_T}(t)$, respectively, in the aforementioned formulas.

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Figure 1. (a) Estimated mean cost, (b) probability of survival, and (c) mean survival time for the second Multicenter Automatic Defibrillator Implantation Trial data. ICD, implantable cardioverter-defibrillator.

Figure 2.

(a) Estimated $ICER_T(t)$ and (b) $ICER_S(t)$ along with the 95% simultaneous confidence bands. Sb_S denotes the symmetric confidence band calculated with the symmetric critical value, while Fb_F denotes the Fieller confidence band calculated with the Fieller-based critical value. ICER, incremental cost-effectiveness ratio.

Summary of simulation results for $\widehat{ICER}_T(t)$ and $\widehat{ICER}_S(t)$ for two different survival time scenarios when cost was simulated using the uniform distribution.

Table 1

t (Yrs)	Ests (\$1000s)	Bias (%)	SSE (\$1000s)	ESE (\$1000s)	Cov. Sb _S	Cov. Fb _F
$\widehat{ICER}_T(t); T_1 \sim \text{Exp}(8), T_0 \sim \text{Exp}(5)$						
2	197.3	10.2	139.6	96.1	0.87	0.95
4	58.3	6.4	17.5	15.2		
6	30.4	4.5	7.4	6.5		
8	21.0	3.5	4.4	4.0		
10	16.5	3.0	3.1	3.0		
$\widehat{ICER}_S(t); T_1 \sim \text{Exp}(8), T_0 \sim \text{Exp}(5)$						
2	222.1	11.0	136.9	92.6	0.79	0.95
4	144.1	6.1	38.9	36.7		
6	130.9	4.9	34.4	31.4		
8	137.5	5.3	38.0	35.1		
10	157.6	8.1	57.0	50.0		
$\widehat{ICER}_T(t); T_1 \sim \text{Exp}(12.8), T_0 \sim \text{Weib}(\text{scale}=7.3, \text{shape}=1.1)$						
2	420.3	16.7	1016.9	1631.0	0.89	0.95
4	85.9	5.9	22.5	29.1		
6	36.4	3.2	6.6	8.9		
8	21.9	2.1	3.3	4.4		
10	15.4	1.5	2.0	2.8		
$\widehat{ICER}_S(t); T_1 \sim \text{Exp}(12.8), T_0 \sim \text{Weib}(\text{scale}=7.3, \text{shape}=1.1)$						
2	360.7	11.1	171.7	186.5	0.86	0.94
4	165.4	4.1	34.1	45.3		
6	117.9	2.3	18.8	26.1		
8	103.1	2.0	15.8	21.5		

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t (Yrs)	Ests (\$1000s)	Bias (%)	SSE (\$1000s)	ESE (\$1000s)	Cov. Sb _S	Cov. Fb _F
10	98.8	1.6	16.2	21.5		

The table describes estimation, bias, sample standard error (SSE), estimated standard error (ESE), and coverage probability for simultaneous confidence bands using the symmetric-based critical value b in the symmetric interval (Sb_S) and the Fieller-based b in the Fieller interval (Fb_F). Results reflect 1000 replications; confidence bands are based on $m = 1000$ resamples; and there are $n = 500$ people in each treatment group.

Table II

Summary of simulation results for $\widehat{ICER}_T(t)$ and $\widehat{ICER}_S(t)$ for two different survival time scenarios when cost was simulated using the Gamma distribution.

t (Yrs)	Ests (\$1000s)	Bias (%)	SSE (\$1000s)	ESE (\$1000s)	Cov. Sb_S	Cov. Fb_F
$\widehat{ICER}_T(t); T_1 \sim \text{Exp}(8), T_0 \sim \text{Exp}(5)$						
2	186.0	3.9	49.0	43.6	0.91	0.95
4	55.9	2.0	10.2	9.4		
6	29.5	1.4	4.4	4.2		
8	20.5	1.0	2.7	2.6		
10	16.1	0.8	2.0	2.0		
$\widehat{ICER}_S(t); T_1 \sim \text{Exp}(8), T_0 \sim \text{Exp}(5)$						
2	207.3	3.6	48.6	43.9	0.84	0.95
4	138.5	1.9	24.1	23.0		
6	126.6	1.5	19.6	19.9		
8	133.0	1.8	23.1	22.1		
10	151.0	3.6	33.7	30.1		
$\widehat{ICER}_T(t); T_1 \sim \text{Exp}(12.8), T_0 \sim \text{Weib}(\text{scale} = 7.3, \text{shape} = 1.1)$						
2	382.1	6.1	872.6	1212.9	0.87	0.96
4	84.0	3.5	19.9	27.5		
6	35.7	1.2	6.0	8.5		
8	21.5	0.4	3.0	4.3		
10	15.2	0.0	1.9	2.7		
$\widehat{ICER}_S(t); T_1 \sim \text{Exp}(12.8), T_0 \sim \text{Weib}(\text{scale} = 7.3, \text{shape} = 1.1)$						
2	352.3	8.5	145.9	170.8	0.81	0.96
4	162.0	1.9	31.0	43.3		
6	115.8	0.5	17.9	25.1		
8	101.5	0.4	14.4	20.7		

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t (Yrs)	Ests (\$1000s)	Bias (%)	SSE (\$1000s)	ESE (\$1000s)	Cov. SbS	Cov. FbF
10	97.9	0.6	15.1	21.0		

The table describes estimation, bias, sample standard error (SSE), estimated standard error (ESE), and coverage probability for simultaneous confidence bands using the symmetric-based critical value b in the symmetric interval (SbS) and the Fieller-based b in the Fieller interval (FbF). Results reflect 1000 replications; confidence bands are based on $m = 1000$ resamples; and there are $n = 500$ people in each treatment group.