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Net-benefit regression with censored cost-effectiveness data from randomized or observational studies

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Abstract

Cost-effectiveness analysis is an essential part of the evaluation of new medical interventions. While in many studies both costs and effectiveness (e.g., survival time) are censored, standard survival analysis techniques are often invalid due to the induced dependent censoring problem. We propose methods for censored cost-effectiveness data using the net-benefit regression framework, which allow covariate-adjustment and subgroup identification when comparing two intervention groups. The methods provide a straightforward way to construct cost-effectiveness acceptability curves with censored data. We also propose a more efficient doubly robust estimator of average causal incremental net benefit, which increases the likelihood that the results will represent a valid inference in observational studies. Lastly, we conduct extensive numerical studies to examine the finite-sample performance of the proposed methods, and illustrate the proposed methods with a real data example using both survival time and quality-adjusted survival time as the measures of effectiveness.

Keywords

Censored data; Cost-effectiveness analysis; Double robustness; Inverse-probability weighting; Net-benefit regression

1 | INTRODUCTION

Economic evaluation of new treatments is important given rising healthcare costs and limited resources. If a new medical intervention has higher costs but greater health benefit

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Web Appendices referenced in Sections 2–4 are available with this article online.

than its comparator (usual care), a decision must be made. This decision is informed with estimates of the new intervention's extra costs and extra effectiveness. A new intervention is cost-effective if the extra cost of an extra unit of effectiveness (e.g., one more year of life) is less than the decision maker's (maximum) willingness to pay (WTP) for it. There are two main summary statistics in cost-effectiveness analysis (CEA): the incremental cost-effectiveness ratio (ICER) and the incremental net benefit (INB). The ICER[1,2,3] is defined as the ratio of extra cost to extra effectiveness ΔCost/ΔEffect, where ΔCost and ΔEffect are differences in expected cost and expected effectiveness between new and conventional intervention groups.

However, statistical problems associated with ratio statistics are apparent in interpreting and making statistical inference with the ICER. For example, van Hout *et al.*[2] cite Fieller[4] in noting that, "the ratio of two normal distributed variables (i.e., ΔCost and ΔEffect) has neither a finite mean nor a finite variance." In addition, the ICER is a ratio statistic with a skewed distribution, and researchers need to be careful when handling the uncertainty of ICER. When the denominator of ICER is close to 0, its confidence interval (CI) may include infinite values, and an analyst who chooses to construct a CI for the ICER using bootstrapping – a popular method for handling uncertainty in CEA – may need to reorder the bootstrap replicates based on their positions from a cost-effectiveness plane to correctly obtain the tail cut-off points of the CI for the ICER.[5] However, the reordering process can be subject to error in an applied setting because, as Stinnett and Mullahy[6] note, "the negative portion of the probability distribution of (the ICER) does not lend itself to meaningful interpretation." Due to the problems associated with the ICER, attention has shifted to the INB.[2,7,8]

The INB requires the specification of the decision maker's WTP (denoted as λ) for an additional unit of effectiveness, and can be defined as $\mathrm{INB}(\lambda) \equiv \lambda \cdot \Delta\mathrm{Effect} - \Delta\mathrm{Cost}$. $\mathrm{INB}(\lambda) > 0$ means that the new intervention is cost-effective since the extra benefits outweigh the extra costs. The linear form of INB has more attractive statistical properties than the ICER and offers a simpler alternative for handling uncertainty in CEA, e.g., in construction of a 95% CI. In situations where the analyst wants to incorporate covariates in the analysis of a cost-effectiveness dataset, e.g., by adjusting for patient demographics, one can estimate INB using regression-based methods. For example, the use of covariate adjustment is essential for observational studies, since treatment assignments are likely related to covariates of patients, leading to potential confounding issues (e.g., the covariates affecting costs and effectiveness are imbalanced across treatment groups, potentially biasing the assessment of the new intervention). In clinical trials, covariates can also be used to adjust for imperfect randomization, to improve efficiency and to generate hypotheses about subgroups for whom a new intervention is especially cost-effective. The net-benefit regression framework[9,10] allows statistical CEA within a standard regression-type framework where advanced methods can be accommodated, like those for censored data.

Censoring brings unique challenges to CEA. In clinical studies, survival time and medical costs are frequently censored due to incomplete follow-up before the event of interest (e.g., due to study termination, deaths or disease relapses may not be observed). Analyzing censored cost data requires advanced statistical methodologies, due to the "induced

informative censoring" problem, first noted by Lin and colleagues.[11] For example, a healthier patient will accumulate costs slowly, and hence will have lower costs at both censoring time and event time, leading to violation of independent censoring assumption at cost scale. Therefore, traditional survival analysis methods, such as the Kaplan–Meier estimator and the Cox regression model, are no longer valid for analyzing cost (or quality-adjusted survival) data at the scale of cost (or quality-adjusted survival) directly. To handle censoring in a cost-effectiveness dataset, we propose to use inverse probability weighting[12] in a net-benefit regression framework, where the measure of effectiveness can be either survival time, quality-adjusted survival time or some other censored outcome variable.

Many cost-effectiveness datasets come from non-randomized sources such as administrative data, and it is desirable to handle data that are both censored and non-randomized. We propose a novel doubly robust estimator of average causal INB, which not only improves efficiency by utilizing cost history, but also increases the likelihood that the results will represent a valid inference for INB in observational studies, and therefore could provide a valuable tool for such datasets.

The remainder of the article is organized as follows. In Section 2, we first review net-benefit regression framework with uncensored data, and then propose the net-benefit regression methods for censored data. We also propose a doubly robust estimator of average causal INB based on our net-benefit regression, and discuss the connections between the proposed methods and other existing estimators. In Section 3, we conduct simulation studies to examine the finite-sample properties of the proposed methods. In Section 4, we apply the methods to a real data example from Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), a randomized clinical trial for cardiovascular disease. Finally, we discuss our findings in Section 5.

2 | METHODS

2.1 | Review of net-benefit regression and cost-effectiveness acceptability curves with uncensored data

Net-benefit regression[9,10] was originally proposed for uncensored data as a regression type framework for CEA. For subject i, denote Effect_i as the measurement of effectiveness, and Cost_i as cost. The net-benefit regression framework can be employed to estimate cost-effectiveness by calculating a net benefit (NB) value for each subject: $\text{NB}_i \equiv \lambda \cdot \text{Effect}_i - \text{Cost}_i$. The resulting NB_i is the ith individual's net benefit value, where λ denotes WTP for an additional unit of effectiveness. Let $\mathbf{U}_i$ be a vector of explanatory variables, which includes 1 for an intercept, $A_i = 1$ or 0 as the treatment indicator variable (taking the value one for the treatment under consideration and zero for the conventional treatment), $\mathbf{Z}_i = (Z_{i1}, \ldots, Z_{ip})^T$ as a vector of covariates such as patient demographics, and possibly $A_i \times \mathbf{Z}_i$ as the interaction of treatment indicator and covariates. For a given λ, the model can be

$$\text{NB}_i = \lambda \cdot \text{Effect}_i - \text{Cost}_i = \beta_0 + \beta_A A_i + \boldsymbol{\beta}_Z^T \mathbf{Z}_i + \boldsymbol{\beta}_{AZ}^T A_i \times \mathbf{Z}_i + \epsilon_i = \theta^T \mathbf{U}_i + \epsilon_i, \quad (1)$$

where $\theta = \left(\beta_0, \beta_A, \boldsymbol{\beta}_Z^T, \boldsymbol{\beta}_{AZ}^T\right)^T$, $\mathbf{U}_i = \left(1, A_i, \mathbf{Z}_i^T, A_i\mathbf{Z}_i^T\right)^T$, and ϵ_i is the error term without specified distribution. Note that, the coefficient $\boldsymbol{\theta}$ depends on λ, and hence the more accurate notation is $\boldsymbol{\theta}(\lambda) = (\beta_0(\lambda), \beta_A(\lambda), \boldsymbol{\beta}_Z(\lambda)^T, \boldsymbol{\beta}_{AZ}(\lambda)^T)^T$. In the following sections, we suppress (λ) in the coefficients for notational convenience as long as the context is clear. Large and statistically significant elements in $\boldsymbol{\beta}_{AZ}$ for interactions help identify important patient subgroups, which is essential for subgroup identification and hypothesis generation. These subgroups can be helpful to decision-makers who may need to focus funding on groups for whom treatment is especially cost-effective. When there is no censored data, the estimator of $\boldsymbol{\theta}$ can be obtained by the ordinary least squares method (for a given WTP value of λ), and the standard error estimate can be obtained by non-parametric bootstrapping or the standard Huber–White sandwich estimator,[13] which is robust to heteroscedastic errors.

The cost-effectiveness acceptability curve (CEAC)[7,14] handles two uncertainty problems in cost-effectiveness. The first is which λ value for WTP to use, and the second is the probability that the new treatment is cost-effective for a given WTP value of λ. The CEAC shows the probability on the vertical axis as a function of the given WTP value of λ on the horizontal axis. While in theory the CEAC can be made with the ICER or the INB, in practice the INB is recommended (to avoid errors due to the ICER's nature as a ratio). When the INB is used to make the CEAC, the CEAC shows the probability that INB is positive for a given λ, that is, $\text{CEAC}(\lambda) \equiv \Pr(\lambda \cdot \Delta\text{Effect} - \Delta\text{Cost} > 0)$ (in a Bayesian sense). When there is no treatment-covariate interaction (i.e., $\boldsymbol{\beta}_{AZ}(\lambda) = \mathbf{0}$), the INB is $\beta_A(\lambda)$, and the CEAC is $\text{CEAC}(\lambda) = \Pr\{\beta_A(\lambda) > 0|\lambda\}$ (in a Bayesian sense). In the frequentist view, with a normal approximation for the distribution of $\hat{\beta}_A(\lambda)$, the adjusted CEAC (as a function of λ) can be estimated by

$$\text{CEAC}(\lambda) = \Phi\left\{\frac{\hat{\beta}_A(\lambda)}{\widehat{\text{SE}}\left(\hat{\beta}_A(\lambda)\right)}\right\},$$

where $\Phi(\cdot)$ is the cumulative distribution function of standard normal distribution, $\hat{\beta}_A(\lambda)$ is the estimate for $\beta_A(\lambda)$, and $\widehat{\text{SE}}\left(\hat{\beta}_A(\lambda)\right)$ is the Huber–White sandwich standard error estimator. When including treatment-covariate interaction (i.e., $\boldsymbol{\beta}_{AZ}(\lambda) \neq \mathbf{0}$), the cost-effectiveness is allowed to be heterogeneous across different patient subgroups, depending on covariates $\mathbf{Z}$. In this case, the INB for a patient subgroup with covariate $\mathbf{Z}$ is $\beta_A(\lambda) + \boldsymbol{\beta}_{AZ}(\lambda)^T\mathbf{Z}$, and $\mathbf{Z}$-specific CEAC is $\text{CEAC}(\lambda; \mathbf{Z}) = \Pr\{\beta_A(\lambda) + \boldsymbol{\beta}_{AZ}(\lambda)^T\mathbf{Z} > 0|\lambda, \mathbf{Z}\}$ (in a Bayesian sense). In the frequentist view, it can be estimated with a normal approximation by

$$\text{CEAC}(\lambda; \mathbf{Z}) = \Phi\left\{\frac{\hat{\beta}_A(\lambda) + \hat{\boldsymbol{\beta}}_{AZ}(\lambda)^T\mathbf{Z}}{\widehat{SE}\left(\hat{\beta}_A(\lambda) + \hat{\boldsymbol{\beta}}_{AZ}(\lambda)^T\mathbf{Z}\right)}\right\}.$$

When there is no interaction, this $\mathbf{Z}$-specific $\text{CEAC}(\lambda; \mathbf{Z})$ reduces to $\text{CEAC}(\lambda)$ by setting $\widehat{\boldsymbol{\beta}}_{AZ}(\lambda) = \mathbf{0}$, and is constant across all patients. Alternatively, bootstrap methods can be used to construct the CEAC if there is concern about the central limit theorem delivering normality with small sample size.[10]

2.2 | Net-benefit regression with censored data

2.2.1 | Notations and assumptions for censored data—We define T as the survival time from the beginning of the study until the occurrence of an event of interest (e.g., death or disease relapse), and C as censoring time. For subject i in the cohort, we observe follow-up time $X_i \equiv \min(T_i, C_i)$ and the failure indicator $\Delta_i \equiv I\{T_i \leq C_i\}$, where $I(\cdot)$ is indicator function. The cost accumulation process $M_i(t)$ tracks accumulated costs from time 0 to t. We use (potentially censored) survival time T_i as the measure of effectiveness (i.e., $\text{Effect}_i = T_i$), and total cost until time of failure event $M_i(T_i)$ as the measure of cost (i.e., $\text{Cost}_i = M_i(T_i)$). Note that both T_i and $M_i(T_i)$ are possibly censored. We will extend the methods to when quality-adjusted survival time serves as the effectiveness measure later.

Assume that censoring time C is independent of both survival time T and the cost accumulation process $M_i(t)$, $(0 \leq t \leq X)$, possibly conditional on covariates $\mathbf{Z}$ and treatment A. This assumption is adopted in most survival data analyses. In addition, the marginal distribution of costs may be nowhere identifiable without making some parametric assumptions due to the presence of censoring.[15] Hence, a limited time horizon is often required, for example, we measure life-years saved within a limited horizon of L years, and also costs within L years, where L is chosen such that a "reasonable number" of subjects are still being observed at that time. A consequence of applying such a restriction is that a survival time longer than L can be considered equivalently as having an event at time L; that is, we can redefine the survival time as $T^L = \min(T, L)$. However, we still use T instead of T^L for notational convenience.

2.2.2 | Method not using cost history: simple weighted method—Lin[16] proposed regression methods for cost data originally, based on the inverse probability weighting technique.[12,17,18] We extended the idea of Lin's method to net-benefit regression framework, and can estimate the coefficients by the simple weighted (SW) method,

$$\hat{\boldsymbol{\theta}}_{SW} = \underset{\boldsymbol{\theta}}{\operatorname{argmin}} \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} \left\{ \lambda T_i - M_i(T_i) - \boldsymbol{\theta}^T \mathbf{U}_i \right\}^2,$$

where $\hat{K}(T_i)$ is the Kaplan-Meier estimator for the survival function of the censoring variable C, $K(t) = \Pr(C > t)$, evaluated at T_i. The main idea is that one complete observation at T_i represents $1/K(T_i)$ potential people that might have been observed. Although K can be estimated in the entire population (when the distribution of censoring variable is the same across different treatments), stratifying the estimate of K by treatment group improves efficiency,[19,20] which uses $\hat{K}_1(t)$ and $\hat{K}_0(t)$ as Kaplan-Meier estimators within treatment group $A = 1$ and 0, respectively. Using the Kaplan-Meier estimator for the survival function of the censoring variable assumes that censoring time does not depend on covariates, which could be reasonable in well-conducted clinical trials where most censoring occurs due to staggered entry and study termination. An extension to allow covariate-dependent censoring is to replace the Kaplan-Meier estimator for $K(t)$ by the estimator from regression models such as Cox proportional hazards model.[21]

It is possible to obtain the closed form of SW estimator as

$$\widehat{\theta}_{SW} = \left\{ \sum_{i=1}^{n} \frac{\Delta_i}{\widehat{K}(T_i)} \mathbf{U}_i^{\otimes 2} \right\}^{-1} \sum_{i=1}^{n} \frac{\Delta_i}{\widehat{K}(T_i)} \{\lambda T_i - M_i(T_i)\} \mathbf{U}_i,$$

where $\mathbf{a}^{\otimes 2} = \mathbf{a}\mathbf{a}^T$. When there is no censoring, SW estimator reduces to the ordinary least squares estimator. To construct a confidence interval and the CEAC, bootstrap methods could be used. Alternatively, a normal approximation based on the robust estimator for the variance-covariance matrix of $\widehat{\theta}_{SW}$ (provided in Appendix A) can be used.

2.2.3 | Method using cost history: partitioned method—The SW estimator is good for the case when only the total accumulated costs, instead of the cost history, are available. Clearly the SW estimator is not efficient since it does not use the total costs from censored people, nor the cost histories from either censored or complete (uncensored) observations. By extending the idea of Lin's partitioned regression method[16] for cost data to our net-benefit regression framework, we partition time L into m intervals with partition points $0 = a_0 < a_1 < \cdots < a_m = L$. For the kth interval $(a_{k-1}, a_k]$, re-define survival time of the ith patient $T^*_{ki} = \min(T_i, a_k)$, event (e.g., death or clinical event) indicator $\Delta^*_{ki} = I(T^*_{ki} \le C_i)$, and follow-up time $X^*_{ki} = \min(T^*_{ki}, C_i)$. Denote observed follow-up time accumulated within interval $(a_{k-1}, a_k]$ as t^*_{ki}, and observed cost accumulated from a_{k-1} to a_k as M^*_{ki}. Note that $t^*_{ki} = M^*_{ki} = 0$ if $X_i < a_{k-1}$, and $t^*_{ki} = \min(X_i, a_k) - a_{k-1}$ and $M^*_{ki} = M_i\{\min(X_i, a_k)\} - M_i(a_{k-1})$ if $X_i \ge a_{k-1}$. Consequently, for a patient i censored after the kth interval (i.e., $C_i > a_k$), the cost within this interval is complete with $\Delta^*_{ki} = 1$. The procedure of redefinition is performed for each interval, and separate regressions will be done within each interval. The closed form of the partitioned estimator is $\widehat{\theta}_{PT} = \sum_{k=1}^{m} \widehat{\theta}_k$, where

$$\widehat{\theta}_k = \left\{ \sum_{i=1}^{n} \frac{\Delta^*_{ki}}{\widehat{K}(T^*_{ki})} \mathbf{U}_i^{\otimes 2} \right\}^{-1} \sum_{i=1}^{n} \frac{\Delta^*_{ki}}{\widehat{K}(T^*_{ki})} (\lambda t^*_{ki} - M^*_{ki}) \mathbf{U}_i,$$

By utilizing cost history, partitioned regression is expected to be more efficient than simple weighted regression in general. The robust estimator for the variance-covariance matrix of $\widehat{\theta}_{PT}$ is provided in Appendix A.

2.2.4 | Using quality-adjusted life years (QALYs) as effectiveness—In studies that evaluate new therapies for chronic diseases such as cancer or cardiovascular disease, extending overall survival time may not be the only goal. Improving patients' quality of life is also important. The quality-adjusted life year (QALY) is a measure which combines patients' quality of life and survival time together and provides a useful summary for evaluating the treatment effect.[22,23,24] A patient's health history is partitioned into different health states, e.g., toxicity state during cancer treatment, period of good health, and disease relapse state. Each state is assigned a utility weight, usually ranging from 0 (death) to

1 (good health). The ith individual's (possibly censored) QALY, $Q_i(T_i)$, is defined as the integration of utilities over the survival time T_i,

$$Q_i(T_i) = \int_0^{T_i} q_i(u)\mathrm{d}u,$$

where $q_i(u)$ is the utility weight for the ith individual at time u. Due to possible censoring, we can observe the history of accumulative QALY until follow-up time X_i, i.e., $Q_i(t) = \int_0^t q_i(u)\mathrm{d}u$, $(0 \le t \le X_i)$. Similar to costs and survival time, we only consider the QALYs accumulated within a time limit L, and assume that censoring is independent of the health history process and hence utility weights (possibly conditional on treatment A and covariates $\mathbf{Z}$). Like costs, QALYs are subject to the "induced informative censoring" issue even when censoring is completely at random. Our proposed censored net-benefit regression methods can be easily extended to the case when the QALY is the measure of effectiveness. The simple weighted estimator is

$$\hat{\theta}^Q_{SW} = \left\{ \sum_{i=1}^n \frac{\Delta_i}{\widehat{K}(T_i)} \mathbf{U}_i^{\otimes 2} \right\}^{-1} \sum_{i=1}^n \frac{\Delta_i}{\widehat{K}(T_i)} \{\lambda Q_i(T_i) - M_i(T_i)\}\mathbf{U}_i$$

and the partitioned estimator is $\hat{\theta}^Q_{PT} = \sum_{k=1}^m \hat{\theta}^Q_k$, where

$$\hat{\theta}^Q_k = \left\{ \sum_{i=1}^n \frac{\Delta^*_{ki}}{\widehat{K}(T^*_{ki})} \mathbf{U}_i^{\otimes 2} \right\}^{-1} \sum_{i=1}^n \frac{\Delta^*_{ki}}{\widehat{K}(T^*_{ki})} (\lambda Q^*_{ki} - M^*_{ki})\mathbf{U}_i,$$

Q^*_{ki} is the observed QALY accumulated from a_{k-1} to a_k. Note that $Q^*_{ki} = 0$ if $X_i < a_{k-1}$, and $Q^*_{ki} = Q_i\{\min(X_i, a_k)\} - Q_i(a_{k-1})$ if $X_i \ge a_{k-1}$. The robust estimators for the variance-covariance matrices of $\hat{\theta}^Q_{SW}$ and $\hat{\boldsymbol{\theta}}^Q_{PT}$ are provided in Appendix A.

2.2.5 | Doubly robust estimator of average causal INB—In observational studies, estimation of the average causal treatment effect on a patient's outcome should adjust for confounders that are associated with both treatment exposure and outcome. For two treatment options (e.g., new treatment and usual care), the propensity score[25,26] is the probability of a person receiving new treatment conditional on the observed covariates, which is commonly used to adjust for confounding in observational studies for causal inference. The propensity score can be used to construct weights for individual observations to adjust for confounding. Goldfeld[27] proposed a partitioned method to analyze cost-effectiveness based on a propensity score weighting method, which relies on a correctly specified propensity score model and tends to be biased if the propensity score model is mis-specified. Later, Wang and colleagues[28] proposed a doubly robust estimator for average causal treatment effect for censored medical costs, which is doubly robust in the sense that it remains consistent when either the model for the treatment assignment (i.e., propensity score model) or the regression model for the outcome (i.e., cost regression model) is correctly

specified. However, Wang *et al.* only used total costs from complete subjects and hence is not efficient when cost history is available. In addition, their method only estimated costs without handling cost-effectiveness. We propose a doubly robust estimator by utilizing cost (and QALY) history to improve efficiency, as well as extending to other outcome variables such as the QALY and the net benefit. Therefore, our proposed method is doubly robust, more efficient, and can perform CEA directly within our framework.

Denote the outcome of a patient as Y, which is the patient's total cost $M(T)$ in the original method proposed by Wang *et al.*[28] for estimating average causal treatment effect on costs. To estimate average causal INB, let the outcome Y be net benefit, which is $\lambda T - M(T)$ (if using survival time T as effectiveness) or $\lambda Q(T) - M(T)$ (if using QALY, $Q(T)$, as effectiveness). Let $Y^{(1)}$ and $Y^{(0)}$ be the potential outcomes if the corresponding treatment A were 1 and 0 respectively, which may be contrary to the fact. They are counterfactuals or potential outcomes because an individual can only receive one treatment, so A can only take one value (1 or 0) for this person. The actual outcome is $Y = AY^{(1)} + (1 - A)Y^{(0)}$. Similarly, let $Y_k^{(1)*}$ and $Y_k^{(0)*}$ be potential outcomes accumulated in the kth interval. The average causal treatment effect on outcome is defined as

$$\delta \equiv \mathrm{E}\left(Y^{(1)}\right) - \mathrm{E}\left(Y^{(0)}\right) = \mu_1 - \mu_0 = \sum_{k=1}^{m} \mathrm{E}\left(Y_k^{(1)*}\right) - \mathrm{E}\left(Y_k^{(0)*}\right).$$

Let $m_k(A, \mathbf{Z}) \equiv \mathrm{E}\left(Y_k^* \mid A, \mathbf{Z}\right)$ as the expectation of outcome accumulated in the kth interval of a person with treatment A and covariates $\mathbf{Z}$, where $Y_k^* = \lambda t_k^* - M_k^*$ (if using survival time as effectiveness) or $Y_k^* = \lambda Q_k^* - M_k^*$ (if using the QALY as effectiveness). The $m_k(A, \mathbf{Z})$ is unknown and can be estimated using our partitioned net-benefit regression. When the net-benefit regression does not include a treatment-covariate interaction and is correctly specified, it is easy to see $\delta = \beta_A = \sum_{k=1}^{m} m_k(1, \mathbf{Z}) - m_k(0, \mathbf{Z})$.

Assume treatment A is independent of $\left\{Y_k^{(1)*}, Y_k^{(0)*}, T_k^{(1)*}, T_k^{(0)*}\right\}$ given covariates $\mathbf{Z}$, which is the conditional ignorable treatment assignment assumption commonly made in causal inference. Assume $0 < \pi(\mathbf{Z}) < 1$, where $\pi(\mathbf{Z}) = \Pr(A = 1|\mathbf{Z})$ is the propensity score, which makes sure that each individual has positive probability to be assigned to one of the treatments. The propensity score $\pi(\mathbf{Z})$ is usually unknown and estimated by a model (e.g., logistic model or probit model).

We propose the doubly robust estimator for δ as $\hat{\delta} = \sum_{k=1}^{m} (\hat{\mu}_{k1} - \hat{\mu}_{k0})$, where

$$\hat{\mu}_{k1} = \sum_{i=1}^{n} \frac{\Delta_{ki}^*}{\widehat{K}_{A_i}(T_{ki}^*)} \left\{ \frac{A_i Y_{ki}^*}{\hat{\pi}(\mathbf{Z}_i)} - \frac{A_i - \hat{\pi}(\mathbf{Z}_i)}{\hat{\pi}(\mathbf{Z}_i)} \cdot \hat{m}_k(1, \mathbf{Z}_i) \right\} / \sum_{i=1}^{n} \frac{\Delta_{ki}^*}{\widehat{K}_{A_i}(T_{ki}^*)},$$

and

$$\hat{\mu}_{k0} = \sum_{i=1}^{n} \frac{\Delta_{ki}^*}{\widehat{K}_{A_i}(T_{ki}^*)} \left\{ \frac{(1-A_i)Y_{ki}^*}{1-\hat{\pi}(\mathbf{Z}_i)} + \frac{A_i - \hat{\pi}(\mathbf{Z}_i)}{1-\hat{\pi}(\mathbf{Z}_i)} \cdot \hat{m}_k(0, \mathbf{Z}_i) \right\} / \sum_{i=1}^{n} \frac{\Delta_{ki}^*}{\widehat{K}_{A_i}(T_{ki}^*)},$$

where $\widehat{K}_{A_i}(t)$ is $\widehat{K}_1(t)$ or $\widehat{K}_0(t)$ for treatment group $A = 1$ or 0 respectively (i.e., Kaplan-Meier estimators stratified by treatment group), and $\hat{m}_k(A, \mathbf{Z})$ is the estimator for $m_k(A, \mathbf{Z}) = \mathrm{E}(Y_k^* \mid A, \mathbf{Z})$ based on our partitioned net-benefit regression.

This estimator remains consistent when either the treatment propensity score model or the net-benefit regression model is correctly specified. This property of double robustness provides twice the chances to obtain consistent estimates in observational studies, and can always obtain consistent estimates in randomized trials (since the propensity scores is known in randomized trials). The proof of double robustness of the proposed estimator is provided in Appendix B, and the corresponding variance estimator is provided in Web Appendix A.

2.2.6 | Relationship with other estimators—Our proposed methods unify many existing methods in the net-benefit framework as special cases. Currently, there is no method available for censored cost-effectiveness data to do cost-effectiveness directly in a single model incorporating covariates, cost (and QALY) history, and double robustness, so implementation would entail considerable effort using existing methods. On the other hand, our proposed method handles these within one framework.

In the absence of covariates, the proposed net-benefit regression model reduces to an unadjusted net-benefit regression (i.e., a simple model only including the intercept and treatment indicator variable). An alternative way to perform unadjusted CEA is stratified analysis within each treatment group separately, by estimating mean effectiveness, mean cost, and their variances and covariance between cost and effectiveness within each treatment group.[17,18,29] These estimators can be used to estimate unadjusted INB and construct CEAC. The stratified analysis based on SW mean estimators[17,18,29] can be viewed as a special case of our SW net-benefit regression when no covariate is adjusted in our regression. Similarly, the stratified analysis based on partitioned mean estimators[17] is a special case of our partitioned net-benefit regression when no covariate is adjusted.

When only a categorical covariate and its interaction with treatment are included in net-benefit regression, our proposed model includes an intercept, the treatment indicator A, a categorical covariate Z, and the interaction between A and Z. An alternative way is to perform separate subgroup analysis within each subgroup defined by Z, by estimating mean effectiveness and mean cost of each treatment group within each subgroup. When the same $\widehat{K}$ is used, the two methods will obtain the same INB estimates. Therefore, performing separate subgroup analyses can be viewed as a special case of the proposed net-benefit regression.

The doubly robust estimator for cost estimation proposed by Wang *et al.*[28] can be viewed as a special case of our estimator. When there is no partition ($m = 1$) and the outcome is cost (i.e., $\lambda = 0$ in our net-benefit regression), our proposed doubly robust estimator reduces

to the estimator proposed by Wang *et al.*. The proposed propensity score-adjusted method by Goldfeld[27] to analyze cost-effectiveness using partitioned method will perform similarly to our doubly robust estimator when the propensity score model is correctly specified (e.g., in randomized studies). However, our method is consistent even when the propensity score model is mis-specified, as long as the net-benefit model is correctly specified, while the method by Goldfeld tends to be inconsistent if the propensity score model is mis-specified.

Two separate regressions for effectiveness and costs could be fitted to perform CEA with censored data, proposed by Willan and colleagues.[30] Later, Pullenayegum and Willan[20] further derived the semi-parametric efficient parameter estimates for this 2-regression method. In their works, the two separate regressions need to be fitted for effectiveness and cost respectively, and the covariance between effectiveness and cost must be estimated to construct the CEAC. In Web Appendix E, we provided the proof of equivalence between the 2-regression approach and our net-benefit regression, when using the same set of covariates and same partition intervals for costs and effectiveness. In practice, using our net-benefit regression is a more straightforward way to construct the CEAC, since the researchers only need to examine the estimated coefficient on the treatment indicator variable in a single regression. On the other hand, the 2-regression method also can estimate CEAC, but is more laborious, which needs to fit two separate regressions and estimate the covariance between cost and effectiveness models. In addition, it is more straightforward to obtain our proposed doubly robust estimator of average causal INB based on the net-benefit regression framework than the 2-regression method.

3 | SIMULATION STUDY

Treatment A and patient characteristic Z were generated independently from a Bernoulli distribution with $\Pr(A = 1) = 0.5$ and $\Pr(Z = 1) = 0.5$. Survival time T was generated from an exponential distribution with the rate parameter of $1/\exp(2.2 - 0.5Z + 0.1A + 1.2A \times Z)$. Survival time was then truncated at time $L = 10$. Motivated by the data generation process used by Lin[11] and Zhao and Tian,[18] U-shaped sample paths for the cost distribution were adopted, where the entire time period of $L = 10$ years was partitioned into 10 equal intervals. Each individual's costs consisted of random initial diagnostic costs incurred at time 0, random terminal costs incurred at the failure (death) time, fixed annual costs (which vary from individual to individual), and random annual costs (which vary from year to year). The random annual costs and terminal costs for all patients were generated from log-normal distributions with parameters $(4, 0.2^2)$ and $(9, 0.6^2)$, respectively. The diagnostic costs were generated from log-normal distributions with parameters $(9.5, 0.2^2)$ and $(8.5, 0.2^2)$ for the treatment group ($A = 1$) and the conventional group ($A = 0$), respectively. The fixed annual costs were generated from log-normal distributions with parameters $(7, 0.2^2)$, $(6.8, 0.2^2)$, $(6, 0.2^2)$ and $(4.5, 0.2^2)$ for $Z = 0$, $A = 0$ group, $Z = 1$, $A = 0$ group, $Z = 0$, $A = 1$ group, and $Z = 1$, $A = 1$ group, respectively. To reflect common real world data such as the MADIT-CRT data, the new treatment had higher initial diagnostic costs for performing treatment, but lower fixed annual costs subsequently.

We also considered two scenarios for the distribution of the censoring time C. C was generated independently from a uniform distribution on [0,25] years for light censoring, or [0,14] for heavy censoring, leading to censoring rates of about 25% and 48%, respectively.

The true values of mean effectiveness $E(T|A, Z)$ and mean costs $E\{M(T)|A, Z\}$ were derived theoretically (details provided in Web Appendix D) based on their distributions for all combinations of treatments and subgroups, which were listed in Table 1. Based on these values, we calculated the true coefficient $\theta = \left(\beta_0, \beta_A, \boldsymbol{\beta}_Z^T, \boldsymbol{\beta}_{AZ}^T\right)^T$ in net-benefit regression for a given WTP λ.

We evaluated the estimated coefficient $\hat{\theta}$ using different methods. In particular, we were most interested in estimating β_A (i.e., INB in subgroup $Z = 0$) and $\beta_A + \beta_{AZ}$ (i.e., INB in subgroup $Z = 1$). We consider the following estimation methods: (1) the ordinary least squares method that uses only complete-case (uncensored) data (CC); (2) the ordinary least squares method that uses both censored and uncensored data ignoring censoring status (AL); (3) the simple weighted estimator (SW); and (4) the partitioned estimator (PT) using yearly data. Approaches (1) and (2) are naive estimators ignoring censoring, whereas (3) and (4) provide consistent estimators. For (3) and (4), estimation of K was stratified by treatment group to improve efficiency.

Table 2 summarizes the results based on 2,000 runs for different sample sizes and levels of censoring, for the subgroup of $Z = 1$. It is clear that the naive approach using all data (AL) is biased and yields incorrect coverage probabilities for the 95% CIs for the coefficient of interest. The naive approach using complete-case data only (CC) is apparently biased with heavy censoring, while it seems to produce reasonable coverage probabilities for most light censoring scenarios. However, since this estimator uses only the complete observations, which tend to consist of those with short survival times, the costs can be biased downward (or upward) when people with shorter survival times have smaller (or larger) costs. Therefore, the CC method is not recommended since the net benefit value (NB= $\lambda \cdot$ Effect − Cost) will also be biased generally for most values of λ, with the exception when $\lambda \cdot$ bias(Effect) − bias(Cost) is close to 0. The coverage probabilities of the two naive methods do not improve with increased sample sizes, but deteriorate when the sample size increases, especially for the heavy censoring case. The SW method and the more efficient partitioned method (PT) produce coverage probabilities that are close to the nominal value. The estimated standard errors (SEs) of the PT estimator are close to the empirical SEs. The SEs of the SW estimator are slightly overestimated, leading to higher coverage probabilities than those of the PT estimator, especially under heavy censoring. The SE becomes smaller as the sample size increases from 200 to 800. We also notice that the SEs for the partitioned method generally are smaller than those for the simple weighted method, and the difference becomes more pronounced when the censoring is heavier. Hence it would be advantageous to use the partitioned estimator when the censoring is heavy and cost history data are available. The summary of results for subgroup of $Z = 0$ is provided in Web Appendix B with similar conclusions. During the simulation, we also compared the 2-regression approach from Willan *et al.*[30] to confirm the equivalence between the 2-regression method

and our proposed method. More details about equivalence will be discussed in Section 4 for the MADIT-CRT study.

We also performed additional numerical studies for the proposed doubly robust estimator, where the simulation scenario tried to mimic an observational study. The results demonstrate that the proposed estimators are doubly robust, and the partitioned method improved efficiency over the SW method. The details of the simulation and results are in Web Appendix C. The results also indicated that the doubly robust estimator may be biased when both propensity score and outcome models are mis-specified. To minimize the bias of the proposed doubly robust estimator when the two models might be both mis-specified, machine learning techniques (e.g., neural networks, boosting, Super Learner) could be employed to better estimate the two models.[31,32,33]

4 | A REAL DATA EXAMPLE: MADIT-CRT

The Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronization Therapy (MADIT-CRT) was a multicenter clinical trial designed to evaluate the potential health benefit of cardiac resynchronization therapy (CRT) when added to the implantable cardiac defibrillator (ICD) in patients with mild cardiac symptoms.[34] Patients were recruited into the study over time and were randomized into either the ICD arm or the CRT with an ICD (CRT-ICD) arm in a 2:3 ratio. After the trial was completed, it was shown that CRT-ICD reduces the risk of the occurrence of heart failure or death, especially in patients with left bundle branch block (LBBB) conduction disturbance.

Due to the huge costs associated with the implantation of ICD, a cost-effectiveness analysis was also conducted based on patients from the US centers, with 503 patients in the ICD arm and 748 in the CRT-ICD arm.[35] There were 859 LBBB patients among them. Health care utilization data were collected by phone and at follow-up visits at one month after randomization, and at three month intervals after that. Cost assessment processes were similar to the MADIT-I and MADIT-II studies.[36,37] The patient health-related quality of life was assessed using the EQ-5D instrument,[38] prior to randomization and at 6 months intervals after that. Costs data were collected with available cost history, discounted at 3% annual rate. The utility weights were collected at 6 month intervals. We assume utility remains the same until the next measurement, and it becomes zero at death. Each patient's survival time and QALY were also discounted at 3% annual rate.

We performed partitioned net-benefit regressions within a 4-year limit, using life years (LYs) or QALYs as effectiveness. The monthly costs were used to perform partitioned regression. The regression included LBBB status, treatment indicator, and their interaction as explanatory variables. Estimation of K was stratified by treatment group to improve efficiency. The estimated coefficients for different WTP values of λ are summarized in Table 3 using LYs as effectiveness. In contrast, the 2-regression method from Willan *et al.*[30] fits the two models with $\lambda = 0$ and infinity (NA in the table), and estimates the covariance between costs and effectiveness. Denote $\widehat{\theta}_{\text{Effect}}$ as the estimated coefficient from the regression for effectiveness (i.e., regression with dependent variable to be LY or QALY), and $\widehat{\theta}_{\text{Cost}}$ from the regressions for costs (i.e., regression with dependent variable as Cost,

which can be obtained by simply flipping the sign of estimated coefficients from our net-benefit regression with $\lambda = 0$). The 2-regression method is equivalent to our net-benefit regression in the sense that $\widehat{\theta}_{\text{NBR}} = \lambda\widehat{\theta}_{\text{Effect}} - \widehat{\theta}_{\text{Cost}}$, where $\widehat{\theta}_{\text{NBR}}$ is the estimated coefficients from our net-benefit regression for a given λ, which can be mathematically proven (this was demonstrated for a simple linear regression estimated by ordinary least squares for uncensored randomized data,[39] and we provide a detailed proof for censored scenario in Web Appendix E) and easily verified in Table 3. Taking $\lambda = 20$ as an example, the estimated coefficient of interaction between LBBB and treatment is 13.4 by the partitioned estimator given $\lambda = 20$, which equals $20 \times 0.27 - (-7.9)$, where 0.27 is the estimated coefficient of interaction by the partitioned estimator with λ =NA (for Effect), and 7.9 is the estimated coefficient of interaction by the partitioned estimator with $\lambda = 0$ (for -Cost, where "-" is used to flip the sign of coefficient since the dependent variable here is -Cost instead of Cost).

These results show that there is no significant interaction between LBBB and treatment for costs ($\lambda = 0$), but the interaction is significant when WTP λ is larger, with LBBB subjects achieving higher net benefits from CRT-ICD treatment in comparison to their non-LBBB counterparts. The results for simplified unadjusted analysis are also presented, which ignored covariates and the potential for heterogeneous cost-effectiveness across patient subgroups (equivalent to stratified analysis based on mean cost and effectiveness estimators within each treatment group). We also performed the two naive biased methods using complete-case (uncensored) data only (CC) and using all data but ignoring censoring (AL), which produced quite different estimates from our consistent partitioned estimator. The CC method also has a much larger standard error due to discarding censored patients. The results for QALY as effectiveness are in Web Appendix B with similar findings.

Next, the estimated CEACs based on the fitted net-benefit regressions appear in Figure 1. The curves demonstrate the probabilities that the CRT-ICD is cost-effective compared to the ICD only, given different WTP values of λ for an additional LY or QALY. Due to the fact that much higher costs were associated with CRT-ICD while the survival time was not prolonged among non-LBBB patients, the CEAC curves for non-LBBB are close to 0. Among LBBB patients, the probability that the CRT-ICD is cost-effective is much higher than the probability among non-LBBB patients, indicating heterogeneous cost-effectiveness across different patient subgroups. As a comparison, the unadjusted CEACs for all patients are illustrated in the plots, which is the special case of net-benefit regression with only an intercept and a treatment indicator in the model, i.e., $\mathbf{U} = (1, A)$. We also performed net-benefit regression adjusted by LBBB status, i.e., a special case when $\mathbf{U} = (1, A, Z)$ where Z is the indicator of LBBB. The adjusted curve is similar to the unadjusted curve, which is as expected for a randomized clinical trial and indicates no major randomization issues. As an example to show equivalence between the 2-regression method and net-benefit regression, we also included the CEAC by the 2-regression method adjusted by LBBB in Figure 1, which produced the same CEAC curves with our LBBB-adjusted net-benefit regression method. However, to estimate the CEAC, the 2-regression method needs additionally to estimate the covariance between cost and effectiveness models and hence is not as straightforward as our net-benefit regression.

We estimated the LBBB-adjusted ICERs along with the 95% confidence intervals based on the LBBB-adjusted regressions, which were 74.1 (95% CI: $(-\infty, -335.8) \cup (9.4, \infty)$, LY as effectiveness) and 56.4 (95% CI: $(-\infty, -924.2) \cup (5.6, \infty)$, QALY as effectiveness). Note that, the confidence intervals of the ICERs included infinity due to the fact that the denominators of ICERs were close to 0. Furthermore, analysts must be extremely cautious to apply the correct cost-effectiveness definition if using the ICER.[6,40] For example, the standard definition of cost-effectiveness is that the ICER is smaller than a pre-determined WTP, which does not apply when $\Delta\text{Effect} < 0$ (e.g., if the ICER > 0 but $\Delta\text{Cost} < 0$ and $\Delta\text{Effect} < 0$ then the decision rule of cost-effectiveness must be inverted to be that the ICER is greater than a pre-determined WTP). Likewise, ICER < 0 must be investigated closely to determine if this results from $\Delta\text{Cost} < 0$ and $\Delta\text{Effect} > 0$ or $\Delta\text{Cost} > 0$ and $\Delta\text{Effect} < 0$, which occurs for the CIs of ICERs in the MADIT-CRT example. Therefore, the interpretation of the ICER and its confidence interval needs more carefulness and it is recommended to examine the ICER on a cost-effectiveness plane to prevent mis-interpretation. On the other hand, a CEAC based on the INB is less problematic. In Web Appendix B, we provided more explanation about the LBBB-adjusted ICER and its connection with the CEAC in the MADIT-CRT study.

Our net-benefit regression framework is a flexible way to adjust for covariates and identify subgroup effects defined by LBBB status, and can easily incorporate more covariates. Note that, the net-benefit regression might suffer from a potentially mis-specified regression model and we could use the proposed double robust estimator, which can always obtain consistent estimates on average causal INB for randomized trials such as MADIT-CRT, since the propensity scores were known. Since LBBB status is binary, the mis-specification issue is minimal in this application. However, the doubly robust estimator might be worthy to consider when the researcher would like to account for more covariates (especially continuous covariates) and their interactions to improve estimation efficiency for randomized trials.

5 | DISCUSSION

We proposed a unified net-benefit regression framework for censored cost-effectiveness data from either randomized or observational studies, which allows covariate-adjustment and helps identify subgroups when comparing two treatment options, where the measure of effectiveness is either survival time or the QALY. Our proposed censored net-benefit regression framework unifies many existing methods as special cases, and is straightforward to construct the cost-effectiveness acceptability curve in practice. These methods provide valuable tools for the economic evaluation of new treatments, especially when the data are subject to censoring, as is common in prospective studies.

Our simulation results demonstrate that naive methods that either ignore censoring or fail to account for it properly (by using either uncensored data only, or treating censored data as if they were not censored) produce biased results. Use of these methods should be avoided in the analysis of censored cost-effectiveness data. The simple weighted estimator can be useful and convenient when we have only the total costs and QALYs at the end point for

each subject. In contrast, when cost (and quality of life) history data are available, the partitioned estimator can be more efficient, especially when the censoring rate is high.

Many cost-effectiveness datasets come from non-randomized sources (e.g., administrative data). Our proposed doubly robust estimator utilizes both the propensity score and net-benefit regression models, and is consistent when either model is correctly specified. Compared with existing methods, our proposed estimator is doubly robust and uses cost (and quality of life) history to improve efficiency, which provides a tool to address the challenges of both observational and censored data in a net-benefit regression framework when history data are available. This is a major advantage for comparative effectiveness research using data that are both censored and non-randomized, providing a strong option for "real world" cost-effectiveness analysis using administrative data routinely collecting payer cost and patient outcomes.

The linear models might not be appropriate for some applications. By combining the ideas of Lin's generalized linear models for cost data[41] with the proposed methods of this paper, we may develop net-benefit regression methods for cost-effectiveness analyses using generalized linear models. Some have compared various advanced econometric techniques including generalized method of moments (GMM) for uncensored cost-effectiveness data and these might be extended to a scenario with censored data that were not randomized.[42] Additionally, EEE models developed by Basu and Rathouz[43] seem promising as they extend the estimating equations in generalized linear models to estimate parameters in the link function and variance structure simultaneously with regression coefficients. While simulation studies by Willan *et al*.[44] examined the effect of skewing on statistical inference based on least squares methodology and concluded, "Apart from the confidence intervals for treatment effect being a little conservative (i.e. a little too wide), there appears to be no real cause for concern, even when cost data are log-normal and the total sample size is as small as 100", guidance is needed in this area for censored data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Sample R programs for the proposed methods with the simulated data are available online. While the data transfer and use agreements prohibit making the MADIT-CRT datasets publicly available, Boston Scientific may share the data with qualified researchers, available at https://www.bostonscientific.com/en-US/data-sharing-requests.html.

APPENDIX A |: VARIANCE-COVARIANCE MATRIX ESTIMATORS FOR NET-BENEFIT REGRESSION COEFFICIENT ESTIMATORS

Following the idea of Lin[16] which was originally proposed for cost regression, the robust estimators for the variance-covariance matrices of the estimated regression coefficients can be obtained as follows in practice.

The robust estimator for the variance-covariance matrix of $\widehat{\theta}_{SW}$ can be obtained by $\widehat{\mathrm{Var}}\left(\widehat{\theta}_{SW}\right) = \frac{1}{n}\hat{I}_0^{-1}\hat{I}_1\hat{I}_0^{-1}$, where

$$\hat{I}_0 = \frac{1}{n}\sum_{i=1}^{n}\mathbf{U}_i^{\otimes 2}, \tag{A1}$$

and

$$\hat{I}_1 = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{\Delta_i}{\widehat{K}(T_i)}\left\{\lambda T_i - M_i(T_i) - \hat{\theta}_{SW}^T\mathbf{U}_i\right\}\mathbf{U}_i + (1-\Delta_i)G(X_i) - \sum_{j=1}^{n}\frac{(1-\Delta_j)I(X_j \le X_i)G(X_j)}{\sum_{l=1}^{n} I(X_l \ge X_j)}\right]^{\otimes 2},$$

$$G(t) = \frac{\sum_{i=1}^{n}\left[\frac{\Delta_i}{\widehat{K}(T_i)}I(T_i > t)\left\{\lambda T_i - M_i(T_i) - \hat{\theta}_{SW}^T\mathbf{U}_i\right\}\mathbf{U}_i\right]}{\sum_{i=1}^{n} I(X_i \ge t)}.$$

The robust estimator for the variance-covariance matrix of $\widehat{\theta}_{PT}$ can be obtained by $\widehat{\mathrm{Var}}\left(\widehat{\theta}_{PT}\right) = \frac{1}{n}\hat{I}_0^{-1}\hat{I}_2\hat{I}_0^{-1}$, where $\hat{I}_0$ can be calculated by (A1), $\hat{I}_2 = \sum_{k=1}^{m}\sum_{k=1}^{m}\hat{I}_{kl}$, $\hat{I}_{kl} = \frac{1}{n}\sum_{k=1}^{m}\hat{\xi}_{ki}\hat{\xi}_{li}^T$,

$$\hat{\xi}_{ki} = \frac{\Delta_{ki}^*}{\widehat{K}(T_{ki}^*)}\left(\lambda t_{ki}^* - M_{ki}^* - \hat{\theta}_k^T\mathbf{U}_i\right)\mathbf{U}_i + \left(1-\Delta_{ki}^*\right)G_k\left(X_{ki}^*\right) - \sum_{j=1}^{n}\frac{\left(1-\Delta_{kj}^*\right)I\left(X_{kj}^* \le X_{ki}^*\right)G_k\left(X_{kj}^*\right)}{\sum_{l=1}^{n} I\left(X_{kl}^* \ge X_{kj}^*\right)},$$

$$G_k(t) = \frac{\sum_{i=1}^{n}\left\{\frac{\Delta_{ki}^*}{\widehat{K}(T_{ki}^*)}I\left(T_{ki}^* > t\right)\left(\lambda t_{ki}^* - M_{ki}^* - \hat{\theta}_k^T\mathbf{U}_i\right)\mathbf{U}_i\right\}}{\sum_{i=1}^{n} I\left(X_{ki}^* \ge t\right)}.$$

Similarly, the robust estimator for the variance-covariance matrix of $\widehat{\theta}_{SW}^Q$ can be obtained by $\widehat{\mathrm{Var}}\left(\widehat{\theta}_{SW}^Q\right) = \frac{1}{n}\hat{I}_0^{-1}\hat{I}_1^Q\hat{I}_0^{-1}$, where

$$\hat{I}_1^Q = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{\Delta_i}{\hat{K}(T_i)}\left\{\lambda Q_i(T_i) - M_i(T_i) - \left(\hat{\theta}_{SW}^Q\right)^T \mathbf{U}_i\right\}\mathbf{U}_i + (1-\Delta_i)G^Q(X_i) - \sum_{j=1}^{n}\frac{(1-\Delta_j)I(X_j \le X_i)G^Q(X_j)}{\sum_{l=1}^{n} I(X_l \ge X_j)}\right]^{\otimes 2},$$

$$G^Q(t) = \frac{\sum_{i=1}^{n}\left[\frac{\Delta_i}{\hat{K}(T_i)} I(T_i > t)\left\{\lambda Q_i(T_i) - M_i(T_i) - \left(\hat{\theta}_{SW}^Q\right)^T \mathbf{U}_i\right\}\mathbf{U}_i\right]}{\sum_{i=1}^{n} I(X_i \ge t)}.$$

The robust estimator for the variance-covariance matrix of $\hat{\theta}_{PT}^Q$ can be obtained by $\widehat{\mathrm{Var}}\left(\hat{\theta}_{PT}\right) = \frac{1}{n}\hat{I}_0^{-1}\hat{I}_2^Q\hat{I}_0^{-1}$, where $\hat{I}_2^Q = \sum_{k=1}^{m}\sum_{l=1}^{m}\hat{I}_{kl}^Q$, $\hat{I}_{kl}^Q = \frac{1}{n}\sum_{i=1}^{n}\hat{\xi}_{ki}^Q\left(\hat{\xi}_{li}^Q\right)^T$,

$$\hat{\xi}_{ki}^Q = \frac{\Delta_{ki}^*}{\hat{K}(T_{ki}^*)}\left\{\lambda Q_{ki}^* - M_{ki}^* - \left(\hat{\theta}_k^Q\right)^T \mathbf{U}_i\right\}\mathbf{U}_i + (1-\Delta_{ki}^*)G_k^Q(X_{ki}^*) - \sum_{j=1}^{n}\frac{(1-\Delta_{kj}^*)I(X_{kj}^* \le X_{ki}^*)G_k^Q(X_{kj}^*)}{\sum_{l=1}^{n} I(X_{kl}^* \ge X_{kj}^*)},$$

$$G_k^Q(t) = \frac{\sum_{i=1}^{n}\left[\frac{\Delta_{ki}^*}{\hat{K}(T_{ki}^*)} I(T_{ki}^* > t)\left\{\lambda Q_{ki}^* - M_{ki}^* - \left(\hat{\theta}_k^Q\right)^T \mathbf{U}_i\right\}\mathbf{U}_i\right]}{\sum_{i=1}^{n} I(X_{ki}^* \ge t)}.$$

APPENDIX B |: DOUBLE ROBUSTNESS OF THE PROPOSED DOUBLY ROBUST ESTIMATOR FOR AVERAGE CAUSAL INB

Following the idea of Wang *et al.*,[28] we now show the double robustness of the proposed estimator $\hat{\mu}_{k1}$, i.e., $\hat{\mu}_{k1}$ is a consistent estimator of μ_{k1} if either the model for the propensity score $\pi(\mathbf{Z}) = \pi(\mathbf{Z}; \phi)$ is correct or the regression model $\mathrm{E}(Y_k^* \mid A = 1, \mathbf{Z}) = m_k(A = 1, \mathbf{Z}; \theta_k)$ is correct, where ϕ and θ_k are true parameters for propensity score model and regression model, respectively. Denote estimator $\hat{\pi}_n(\mathbf{Z}) = \pi\left(\mathbf{Z}; \hat{\phi}_n\right)$, and $\hat{m}_{k,n}(A = 1, \mathbf{Z}) = m_k\left(A = 1, \mathbf{Z}; \hat{\theta}_{k,n}\right)$. Let $\hat{\phi}_n \to_p \phi^*$ and $\hat{\theta}_{k,n} \to_p \theta_k^*$. If the propensity score model is correct, then $\phi^* = \phi$; if the regression models are correct, then $\theta_k^* = \theta_k$.

By the uniform consistency of the Kaplan–Meier estimator, we have

$$\begin{aligned}
\hat{\mu}_{k1} &= \mathrm{E}\left[\frac{\Delta_k^*}{K_A(T_k^*)}\left\{\frac{AY_k^*}{\pi(\mathbf{Z};\phi^*)} - \frac{A-\pi(\mathbf{Z};\phi^*)}{\pi(\mathbf{Z}_i;\phi^*)}\cdot m_k(1,\mathbf{Z};\theta_k^*)\right\}\right] + o_p(1)\\
&= \mathrm{E}\left(\mathrm{E}\left[\frac{\Delta_k^*}{K_A(T_k^*)}\left\{\frac{AY_k^*}{\pi(\mathbf{Z};\phi^*)} - \frac{A-\pi(\mathbf{Z};\phi^*)}{\pi(\mathbf{Z};\phi^*)}\cdot m_k(1,\mathbf{Z};\theta_k^*)\right\}\right.\right.\\
&\quad \left.\left. \mid \left\{Y_k^{(1)*}, Y_k^{(0)*}, T_k^{(1)*}, T_k^{(0)*}, \mathbf{Z}, A\right\}\right]\right) + o_p(1)\\
&= \mathrm{E}\left\{\frac{AY_k^*}{\pi(\mathbf{Z};\phi^*)} - \frac{A-\pi(\mathbf{Z};\phi^*)}{\pi(\mathbf{Z};\phi^*)}\cdot m_k(1,\mathbf{Z};\theta_k^*)\right\}\frac{K_A\left(T_k^{(A)*}\right)}{K_A\left(T_k^{(A)*}\right)} + o_p(1)\\
&= \mathrm{E}\left(Y_k^{(1)*}\right) + \mathrm{E}\left[\frac{A-\pi(\mathbf{Z};\phi^*)}{\pi(\mathbf{Z};\phi^*)}\cdot\left\{Y_k^{(1)*} - m_k(1,\mathbf{Z};\theta_k^*)\right\}\right] + o_p(1).
\end{aligned}$$

If $\phi^* = \phi$,

$$\begin{aligned}
&\mathrm{E}\left[\frac{A-\pi(\mathbf{Z};\phi^*)}{\pi(\mathbf{Z};\phi^*)}\cdot\left\{Y_k^{(1)*}-m_k\left(1,\mathbf{Z};\theta_k^*\right)\right\}\right]\\
&=\mathrm{E}\left[\frac{A-\pi(\mathbf{Z})}{\pi(\mathbf{Z})}\cdot\left\{Y_k^{(1)*}-m_k\left(1,\mathbf{Z};\theta_k^*\right)\right\}\right]\\
&=\mathrm{E}\left(\mathrm{E}\left[\frac{A-\pi(\mathbf{Z})}{\pi(\mathbf{Z})}\cdot\left\{Y_k^{(1)*}-m_k\left(1,\mathbf{Z};\theta_k^*\right)\right\}\mid Y_k^{(1)*},\mathbf{Z}\right]\right)\\
&=\mathrm{E}\left[\frac{\pi(\mathbf{Z})-\pi(\mathbf{Z})}{\pi(\mathbf{Z})}\cdot\left\{Y_k^{(1)*}-m_k\left(1,\mathbf{Z};\theta_k^*\right)\right\}\right]=0.
\end{aligned}$$

If $\theta_k^* = \theta_k$,

$$\begin{aligned}
&\mathrm{E}\left[\frac{A-\pi(\mathbf{Z};\phi^*)}{\pi(\mathbf{Z};\phi^*)}\cdot\left\{Y_k^{(1)*}-m_k\left(1,\mathbf{Z};\theta_k^*\right)\right\}\right]\\
&=\mathrm{E}\left[\frac{A-\pi(\mathbf{Z};\phi^*)}{\pi(\mathbf{Z};\phi^*)}\cdot\left\{Y_k^{(1)*}-m_k(1,\mathbf{Z};\theta_k)\right\}\right]\\
&=\mathrm{E}\left(\mathrm{E}\left[\frac{A-\pi(\mathbf{Z};\phi^*)}{\pi(\mathbf{Z};\phi^*)}\cdot\left\{Y_k^{(1)*}-m_k(1,\mathbf{Z})\right\}\mid A,\mathbf{Z}\right]\right)\\
&=\mathrm{E}\left[\frac{A-\pi(\mathbf{Z};\phi^*)}{\pi(\mathbf{Z};\phi^*)}\cdot\left\{E\left(Y_k^{(1)*}\mid A,\mathbf{Z}\right)-m_k(1,\mathbf{Z})\right\}\right]=0.
\end{aligned}$$

So $\hat{\mu}_{k1} \to_p \mu_{k1}$ for both cases. Similarly, we have $\hat{\mu}_{k0} \to_p \mu_{k0}$ when either $\phi^* = \phi$ or $\theta_k^* = \theta_k$. Because $\hat{\delta}_n = \sum_{k=1}^{m}(\hat{\mu}_{k1} - \hat{\mu}_{k0})$, we have $\hat{\delta}_n \to_p \sum_{k=1}^{m}(\mu_{k1} - \mu_{k0}) = \mu_1 - \mu_0$ when either $\phi^* = \phi$ or $\theta_k^* = \theta_k (k = 1, \ldots, m)$. That is, $\hat{\delta}_n$ is doubly robust when either the propensity score model or the outcome regression model is correct.

Abbreviations:

CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
ICER	incremental cost-effectiveness ratio
INB	incremental net benefit
LY	Life Years
NB	net benefit
SW	simple weighted
QALY	Quality-Adjusted Life Years
WTP	willingness to pay

References

1. O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: Issues in the design and analysis of statistic cost effectiveness studies in health care. Medical Care 1994; 32: 150–163. [PubMed: 8302107]
2. van Hout BA, Al MJ, Gordon GS, Rutten FFH. Costs, effects and C/E-ratios alongside a clinical trial. Health Economics 1994; 3: 309–319. [PubMed: 7827647]

3. Chaudhary MA, Sterns SC. Estimating confidence intervals for cost-effectiveness ratios: An example from a randomized trial. Statistics in Medicine 1996; 15: 1447–1458. [PubMed: 8841654]
4. Fieller EC. The distribution of the index in a normal bivariate population. Biometrika 1932: 428–440.
5. Wang H, Zhao H. A Study on Confidence Intervals for Incremental Cost-Effectiveness. Biometrical Journal 2008; 50: 505–514. [PubMed: 18663759]
6. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Medical Decision Making 1998; 18(2_suppl): S68–S80. [PubMed: 9566468]
7. Löthgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. Health Economics 2000; 9(7): 623–630. [PubMed: 11103928]
8. Heitjan DF. Fieller's method and net health benefits. Health Economics 2000; 9: 327–335. [PubMed: 10862076]
9. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health economics 2002; 11(5): 415–430. [PubMed: 12112491]
10. Hoch JS, Rockx MA, Krahn AD. Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from a trial of external loop recorders versus Holter monitoring for ambulatory monitoring of "community acquired" syncope. BMC Health Services Research 2006; 6(1): 1–8. [PubMed: 16403235]
11. Lin DY, Feuer EJ, Etzioni R, Wax Y. Estimating medical costs from incomplete follow-up data. Biometrics 1997; 53: 419–434. [PubMed: 9192444]
12. Horvitz D, Thompson D. A generalization of sampling without replacement from a finite universe. Journal of the American Statistical Association 1952; 47: 663–685.
13. Kleiber C, Zeileis A. Applied econometrics with R. Springer Science & Business Media. 2008.
14. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics 2001; 10(8): 779–787. [PubMed: 11747057]
15. Huang Y Calibration regression of censored lifetime medical cost. Journal of the American Statistical Association 2002; 97: 318–327.
16. Lin DY. Linear regression of censored medical costs. Biostatistics 2000; 1: 35–47. [PubMed: 12933524]
17. Bang H, Tsiatis AA. Estimating medical costs with censored data. Biometrika 2000; 87: 329–343.
18. Zhao H, Tian L. On estimating medical cost and incremental cost-effectiveness ratios with censored data. Biometrics 2001; 57: 1002–1008. [PubMed: 11764238]
19. Robins J, Rotnitzky A. Recovery of information and adjustment for dependent censoring using surrogate markers.. In: Jewell N, Dietz K, Farewell V., eds. AIDS Epidemiology-Methodological Issues Boston: Birkhauser. 1992 (pp. 297–331).
20. Pullenayegum EM, Willan AR. Semi-parametric regression models for cost-effectiveness analysis: improving the efficiency of estimation from censored data. Statistics in Medicine 2007; 26(17): 3274–3299. [PubMed: 17309112]
21. Cox D Regression models and life tables. Journal of the Royal Statistical Society, Series B 1972; 34: 187–220.
22. Goldhirsch A, Gelber RD, Simes RJ, Glasziou P, Coates AS. Costs and benefits of adjuvant therapy in breast cancer: a quality-adjusted survival analysis. Journal of Clinical Oncology 1989; 7(1): 36–44. [PubMed: 2642538]
23. Glasziou P, Simes R, Gelber R. Quality adjusted survival analysis. Statistics in Medicine 1990; 9(11): 1259–1276. [PubMed: 2277877]
24. Gelber RD, Cole BF, Gelber S, Goldhirsch A. Comparing treatments using quality-adjusted survival: the Q-TWiST method. The American Statistician 1995; 49(2): 161–169.
25. Rosenbaum PR. Model-based direct adjustment. Journal of the American Statistical Association 1987; 82(398): 387–394.

26. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Statistics in Medicine 2004; 23(19): 2937–2960. [PubMed: 15351954]
27. Goldfeld K Twice-weighted multiple interval estimation of a marginal structural model to analyze cost-effectiveness. Statistics in Medicine 2014; 33(7): 1222–1241. [PubMed: 24151161]
28. Wang X, Beste LA, Maier MM, Zhou XH. Double robust estimator of average causal treatment effect for censored medical cost data. Statistics in Medicine 2016; 35(18): 3101–3116. [PubMed: 26818601]
29. Satten G, Datta S. The Kaplan-Meier Estimator as an Inverse-Probability-of-Censoring Weighted Average. The American Statistician 2001; 55: 207–210. [PubMed: 28845048]
30. Willan AR, Lin DY, Manca A. Regression methods for cost-effectiveness analysis with censored data. Statistics in Medicine 2005; 24: 131–145. [PubMed: 15515137]
31. Hastie TJ, Tibshirani RJ, Friedman JH. The elements of statistical learning: data mining, inference, and prediction. Springer series in statisticsNew York: Springer. 2009.
32. Laan V. dMJ, Polley EC, Hubbard AE. Super learner. Statistical applications in genetics and molecular biology 2007; 6(1).
33. Li J, Vachani A, Epstein A, Mitra N. A doubly robust approach for cost–effectiveness estimation from observational data. Statistical Methods in Medical Research 2018; 27(10): 3126–3138. [PubMed: 29298637]
34. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. New England Journal of Medicine 2009; 361(14): 1329–1338. [PubMed: 19723701]
35. Noyes K, Veazie P, Hall WJ, et al. Cost effectiveness of cardiac resynchronization for the prevention of heart failure. Journal of Cardiovascular Electrophysiology 2013; 24: 66–74. [PubMed: 22913474]
36. Mushlin AI, Hall WJ, Zwanziger J, et al. The cost-effectiveness of automatic implantable cardiac defibrillators: Results from MADIT. Circulation 1998; 97: 2129–2135. [PubMed: 9626173]
37. Zwanziger J, Hall WJ, Dick AW, et al. The cost-effectiveness of implantable cardiac defibrillators: Results from MADIT II. Journal of the American College of Cardiology 2006; 47: 2310–2318. [PubMed: 16750701]
38. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Medical Care 2005; 43: 203–220. [PubMed: 15725977]
39. Hoch JS, Dewa CS. Lessons from trial-based cost-effectiveness analyses of mental health interventions. Pharmacoeconomics 2007; 25(10): 807–816. [PubMed: 17887803]
40. Tambour M, Zethraeus N, Johannesson M. A note on confidence intervals in cost-effectiveness analysis. International journal of technology assessment in health care 1998; 14(3): 467–471. [PubMed: 9780533]
41. Lin DY. Regression analysis of incomplete medical cost data. Statistics in Medicine 2003; 22: 1181–1200. [PubMed: 12652561]
42. Hoch JS, Chaussé P. Econometric considerations when using the net benefit regression framework to conduct cost-effectiveness analysis. In: Emerald Publishing Limited. 2018.
43. Basu A, Rathouz PJ. Estimating marginal and incremental effects on health outcomes using flexible link and variance function models. Biostatistics 2005; 6(1): 93–109. [PubMed: 15618530]
44. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. Health Economics 2004; 13(5): 461–475. [PubMed: 15127426]

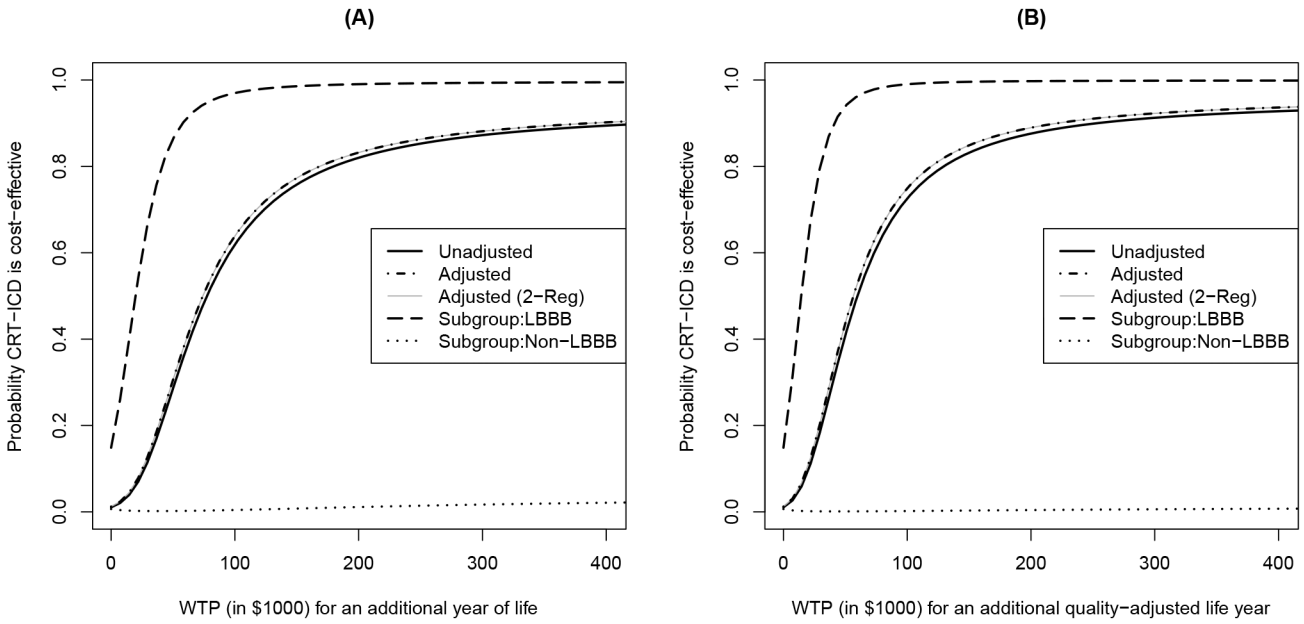

FIGURE 1.

Cost-effectiveness acceptance curves (CEAC) for the MADIT-CRT study limited to a 4-year time horizon, from fitted partitioned net-benefit regression, using (A) life years (LYs) or (B) quality-adjusted life years (QALYs) as effectiveness. The solid curve is from unadjusted regression including the treatment indicator only. The dash-dotted curve is from regression adjusted by LBBB status (i.e., including the treatment indicator and LBBB status). The dashed curve and dotted curve are for LBBB and non-LBBB patients, respectively, from the regression including treatment indicator, LBBB, and their interaction. The thin solid gray curve is from the 2-regression method adjusted by LBBB status, which shows the equivalence to our method numerically.

TABLE 1

Mean (standard deviation) of effectiveness and cost for different treatment A and patient subgroup Z in simulated data.

		Treatment A		
		0	1	
Measurement	**Subgroup Z**	**Mean (SD)**	**Mean (SD)**	**Mean Difference Between Treatment 1 and 0**
Effectiveness (Survival)	0	6.04 (3.6)	6.31 (3.6)	0.27
	1	4.59 (3.4)	7.88 (3.2)	3.29
Costs (in $1000)	0	18.61 (6.1)	22.72 (6.8)	4.11
	1	17.62 (6.6)	18.60 (6.5)	0.98

TABLE 2

Summary for estimated incremental net benefit (in $1000) in subgroup Z=1 (i.e., $\hat{\beta}_A + \hat{\beta}_{AZ}$) with different WTP values of λ (in $1000) based on 2,000 runs.

			Light Censoring		Heavy Censoring	
n	**λ**	**Method**	**Bias (SEE, ESE)**	**95% CP**	**Bias (SEE, ESE)**	**95% CP**
200	15	CC	−1.8 (12.3, 12.1)	0.941	−9.2 (14.8, 14.5)	0.897
		AL	−13.2 (10.4, 10.1)	0.755	−23.1 (9.6, 9.3)	0.295
		SW	−0.6 (11.5, 11.7)	0.949	−0.5 (14.1, 14.8)	0.942
		PT	−0.5 (11.1, 11.0)	0.945	−0.5 (12.0, 12.0)	0.941
	30	CC	−2.8 (24.2, 23.7)	0.940	−16.2 (28.9, 28.3)	0.907
		AL	−25.6 (20.8, 20.0)	0.769	−44.7 (19.1, 18.5)	0.317
		SW	−1.0 (22.7, 23.0)	0.948	−0.8 (27.6, 29.0)	0.943
		PT	−1.0 (21.8, 21.6)	0.943	−1.0 (23.6, 23.5)	0.941
400	15	CC	−1.3 (8.6, 8.6)	0.948	−8.7 (10.5, 10.3)	0.864
		AL	−12.7 (7.2, 7.2)	0.569	−22.7 (6.6, 6.6)	0.069
		SW	−0.2 (8.0, 8.3)	0.956	−0.1 (9.6, 10.5)	0.962
		PT	−0.1 (7.8, 7.8)	0.951	−0.1 (8.4, 8.5)	0.952
	30	CC	−1.8 (16.7, 16.8)	0.948	−15.2 (20.5, 20.1)	0.874
		AL	−24.6 (14.2, 14.2)	0.592	−43.8 (13.1, 13.1)	0.081
		SW	−0.4 (15.7, 16.3)	0.956	−0.1 (18.7, 20.6)	0.963
		PT	−0.3 (15.2, 15.3)	0.950	−0.2 (16.3, 16.7)	0.953
800	15	CC	−1.4 (6.1, 6.1)	0.941	−9.0 (7.3, 7.3)	0.772
		AL	−13.0 (5.1, 5.1)	0.276	−23.0 (4.6, 4.7)	0.002
		SW	−0.1 (5.8, 5.9)	0.957	−0.1 (6.8, 7.4)	0.966
		PT	−0.1 (5.6, 5.5)	0.951	−0.1 (6.0, 6.0)	0.950
	30	CC	−2.1 (11.9,11.9)	0.945	−16.0 (14.2, 14.3)	0.806
		AL	−25.1 (10.0, 10.0)	0.296	−44.4 (9.2, 9.3)	0.002
		SW	−0.2 (11.3, 11.5)	0.959	−0.3 (13.4, 14.5)	0.969
		PT	−0.2 (10.9, 10.8)	0.954	−0.3 (11.8, 11.8)	0.950

Note:“Bias” is the absolute bias, i.e., difference between the mean estimate and the true value; “SEE” is the empirical standard error of the estimates; “ESE” is the mean of the estimated standard errors; column “95% CP” gives the proportion containing the true value within 95% confidence interval; “CC” uses only uncensored data; “AL” uses both censored and uncensored data ignoring censoring status; “SW” is simple weighted estimator; and “PT” is partitioned estimator.

TABLE 3

Coefficient estimates (standard errors) (in $1000) and p-values from net-benefit regression with different WTP values of λ (in $1000) for the MADIT-CRT data using life years (LYs) as effectiveness.

WTP λ (in $1000)	Explanatory Variables	Partitioned Est (SE) [p-value]	Partitioned (Unadjusted) Est (SE) [p-value]	Naive (CC) Est (SE) [p-value]	Naive (AL) Est (SE) [p-value]
0	Intercept	−57.5 (3.5) [< 0.001]	−57.0 (1.8) [< 0.001]	−61.5 (6.0) [< 0.001]	−47.4 (2.1) [< 0.001]
	LBBB (dummy)	0.8 (4.1) [0.852]	-	−1.0 (7.0) [0.891]	−0.6 (2.5) [0.822]
	CRT-ICD (dummy)	−10.7 (4.3) [0.013]	−5.3 (2.3) [0.021]	−9.2 (7.9) [0.243]	−9.7 (2.6) [< 0.001]
	LBBB×CRT-ICD	7.9 (5.1) [0.120]	-	14.0 (9.1) [0.122]	6.6 (3.1) [0.035]
20	Intercept	14.6 (3.8) [< 0.001]	13.9 (2.0) [< 0.001]	−3.5 (7.8) [0.654]	−2.5 (2.3) [0.286]
	LBBB (dummy)	−0.9 (4.4) [0.835]	_	−5.6 (9.3) [0.543]	−1.8 (2.8) [0.504]
	CRT-ICD (dummy)	−13.3 (4.7) [0.005]	−3.9 (2.5) [0.121]	−20.5 (10.6) [0.053]	−9.1 (2.9) [0.002]
	LBBB×CRT-ICD	13.4 (5.6) [0.016]	-	35.1 (12.3) [0.004]	7.1 (3.5) [0.041]
50	Intercept	122.7 (4.6) [< 0.001]	120.1 (2.6) [< 0.001]	83.6 (14.5) [< 0.001]	64.9 (3.8) [< 0.001]
	LBBB (dummy)	−3.4 (5.6) [0.538]	-	−12.6 (17.1) [0.460]	5.4 (4.5) [0.231]
	CRT-ICD (dummy)	−17.3 (6.0) [0.004]	−1.9 (3.3) [0.571]	−37.4 (19.5) [0.055]	−8.1 (4.7) [0.083]
	LBBB×CRT-ICD	21.6 (7.2) [0.003]	-	66.8 (22.7) [0.003]	7.8 (5.7) [0.169]
100	Intercept	302.9 (6.6) [< 0.001]	297.2 (4.1) [< 0.001]	228.6 (27.6) [< 0.001]	177.2 (7.0) [< 0.001]
	LBBB (dummy)	−7.7 (8.4) [0.360]	-	−24.3 (32.3) [0.451]	11.5 (8.5) [0.176]
	CRT-ICD (dummy)	−23.8 (9.0) [0.009]	1.5 (5.1) [0.762]	−65.7 (36.7) [0.073]	−6.6 (8.7) [0.451]
	LBBB×CRT-ICD	35.2 (10.9) [0.001]	-	119.5 (42.5) [0.005]	9.1 (10.6) [0.388]
NA (Effect only)	Intercept	3.60 (0.05) [< 0.001]	3.54 (0.04) [< 0.001]	2.90 (0.28) [< 0.001]	2.25 (0.07) [< 0.001]
	LBBB (dummy)	−0.08 (0.07) [0.224]	-	−0.23 (0.32) [0.462]	0.12 (0.09) [0.159]
	CRT-ICD (dummy)	−0.13 (0.08) [0.085]	0.07 (0.04) [0.113]	−0.56 (0.36) [0.117]	0.03 (0.09) [0.717]
	LBBB×CRT-ICD	0.27 (0.09) [0.003]		1.05 (0.41) [0.011]	0.03 (0.11) [0.809]

Note: “Est” is Coefficient Estimates; “SE” is estimated standard errors. When λ = 0, dependent variable = -Cost. When λ =NA, dependent variable = Effect (does not belong to net-benefit regression). “Partitioned” is our partitioned net-benefit regression, “Partitioned (Unadjusted)” only includes intercept and treatment in our partitioned net-benefit regression, “Naive (CC)” is the regression using complete-case (uncensored) cases only, “Naive (AL)” is the regression using all data ignoring censoring status. The intercept is interpreted as the estimated net benefit of non-LBBB patients who underwent ICD only.