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On Projection of Costs and Incremental Cost-Effectiveness Ratios: A Data Example

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Abstract

Cost and cost-effectiveness analysis has been more and more important to both policy makers and clinicians in assessing health care delivery. The incremental cost-effectiveness ratio (ICER) is widely used inpractice to evaluate the relative health benefit of one treatment over another. Due to the short time span ofclinical trials, the cost estimated from observed data are often right censored. The ICERs obtained from observed data are thus limited to a short time window. But for some intervention it is life time costs and benefits that health decision makers need to calculate the true cost effectiveness. Thus it is necessary to project the ICERs to a longer time horizon based on available data. In order to project ICER, we need to first project both the cost and health effectsince ICER is a ratio betweenthe two. Two difficulties encountered in projecting costs using monthly cost data are the death cost, which has to be counted backward, and the last month cost which is always incomplete. Using data from a four-year multi-center clinical trial study, we describe a method of projecting the future medical costs, using a mixed effect model from observed data. Combined with a method of projecting the survival distribution for different hypothetical scenarios, we are able to project future ICERs.

Keywords: Incremental Cost-Effectiveness Ratio; Survival; Censoring; Projection

1. Introduction

With medical cost dramatically increasing and the restriction of limited resources, evaluation of the cost and cost-effectiveness of therapies is a very important aspect in the decisionmaking (Russelletal., 1996).

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Accurate estimates of health carecosts and cost-effectiveness are of growing importance to both health policy makers and clinicians.

There are some challenges in analyzing medical cost data. First, medical cost data are usually right censored. In long-term clinical or observational studies, patients are recruited over time and the study terminates before all the patients reach the endpoints of interest so that their medical costs are not fully observed, which results in the right censoring problem of the cost data. Second, the distribution of health care costs data usually is highly right skewed, with a few very high-cost individuals on the tail. Third, healthy people may incur no costs in a given time period. Fourth, it has been shown that the assumption of homoscedasticity is not valid. Anumber of statistical methods has focused on how to analyzing medicalcost, for example in Linetal. (1997), Bang and Tsiatis (2000), Zhao and Tian (2001), Lin (2003), Wang and Zhao (2006), Zhaoetal. (2007), and Liuetal. (2007).

In cost-effectiveness analysis in order to compare different treatments and eval- uate the economic impact of new treatment options, there are two measure of cost- effectiveness: incremental net benefit (INB) and incremental cost-effectiveness ratio (ICER) (Willan and Briggs 2006). The INB is equivalent to the difference between the extra cost and the λ multiply the extraeffectiveness. The INB is mathematically more convenient to deal with, but it depends upon decision makers willingness-to-pay for an additional unit ofeffectiveness λ, which is usually unknown or not well defined. Here we will focus on the ICER. The incremental cost-effectiveness ratio (ICER), is a ratio between the difference in mean cost and the difference in the effectiveness for two therapies. It is a measure that describes the new therapy in terms of the additional cost for each incremental unit of health effect, such as per life of year saved, has been widely used in evaluating the relative health benefits from new treatments. Many researchers have used it (e.g., Phelps and Mushlin, 1991; Mushlinetal., 1998; Marketal., 2000) to assess the cost of new therapies relative to health benefits. Because the ICER involves the estimating of mean cost and mean effectiveness (usually survival time or quality-adjusted-lifetime), the estimating of ICER unavoidably faces the same challenge as that in estimating mean medical cost.

Clinical trials are often expensive, and it takes long time to obtain every subject's information if the end point is related to patient's survival time. Intheory, one could follow all participants until death. However, in reality it is very rare that a clinical trial will not finish until every participant's death is observed.

The time frame of clinical trials is usually limited to a short time span, e.g., 3 years or 5 years. The cost and survival estimation are usually obtained within a restricted time period. A cost-effectiveness ratio evaluated from a clinical trial thus is confined to a short time window. However, health policy makers and health care providers are often interested in seeing the cost-effectiveness outcome for a long term. In reality, the ICER often changes rapidly over time. Hence, it is important to project the current estimate of ICER to future years. The projected future ICER provides an assessment of how much money the health care program would have to pay for a better treatment for a longer time horizon.

Intuitively, the easiest way of projecting the ICERs over time is to fit a parametric curve over the observed ICERs, then extend the curve to a new time horizon assuming the existing relationship between the ICER and the time holds for the future. However, due to the feature of medical cost data-right censored, right-skewed, involve a Substantial proportion of zero values, and heteroscedasticity-no simple parametric distribution is suitable for describing the cost data. Then any parametric assumption of the ICER seems difficult to justify. Other existing methods use Markov transition models. These models make assumptions about the underlying disease processes (e.g., BlueCross-BlueShield Association, 2004). However, the validity of the assumptions is hard to verify from the existing data.

In this paper, we describe a way of projecting the future costs and ICERs, and illustrate our method by using data from the Multi-center Automatic Defibrillator Implantation Trial II (MADIT-II). MADIT-II was designed to evaluate the potential survival benefit of aprophylactically implanted defibrillator (Mossetal., 2002). Patients with a prior myocardial infarction and advanced left ventricular dysfunction were randomly assigned to receive either a prophylactically implanted ICD (ICD arm) or conventional medical therapy (CONV arm). There were 664 patients in the ICD arm and 431 in the CONV arm. The average followup time was 22 months. It was shown that the ICD improves survival as compared with conventional medical therapy. Because of the highinitial cost of a defibrillator, a cost-benefit analysis was performed (Zwanzigeretal, 2006; Wang and Zhao, 2006).

Since few patients had four or more years of follow-up, the primary cost-effectiveness analysis for MADIT-II was performed at year 3.5. However, it is of greatinterest for policy makers and health care providers to know the long term cost-effectiveness outcome of the ICD.

We project the future costs and ICERs to a time horizon of 12 years based on available data. Here we consider the ICER as the additional cost of ICD for saving one year of life. Our approach utilizes the projected survival curve and monthly costs for survivors to obtain the projected overall mean costs. It has beenobserved that The health care costs tend to rise dramatically in the period prior to an individual's death (Scitovsky and Capron 1986; Diehretal. 1999). A common practice when people model the cost data is that the last month's costisd is carded (e.g., Liu et al. 2008), which affect the estimate of monthly cost. Our proposed method will take into consideration the death cost in our modeling for cost data. From the economic point of view, today's cost in dollars and health benefit in life years saved will not be the same years later. Thus it is customary to discount future cost and health benefit (Goldetal.,1996) in cost-effectiveness analysis. We also incorporate the discounting of cost and survival in our proposed method.

The rest of this paper is organized as follows. In Section 2, we briefly describe how the survival curve in MADIT II was projected up to a horizon of 12 years. In Section 3, we estimate the monthly costs for survivors using a mixed effect regression model on observed monthly cost data. The projected mean costs are obtained by multiplying the estimated monthly costs by the estimated probability of survival through that month, making adjustment for subjects dying in the middle of the interval. The results are presented in Section 3. This is followed by results in Section 4 on projected ICERs obtained from our proposed method and discounted years of life saved. Finally, some concluding remarks are given in Section 5.

2. Projecting Survival Curves

In MADIT-II cost-effectiveness analysis (Zwanziger et al., 2006), there were 1095 patients, with 664 in the ICD arm and 431 in the CONV arm. The follow-up ranged from 11 days to 55 months, averaging 22 months. All-cause mortality rates were 21% in CONV arm and 15% in the ICD arm. More details on the projected survival curves can be found in Zwanziger et al., 2006. In summary, the Kaplan-Meier estimates were used for the first 3.5 years.

The life-table method was used to project the survival curve up to 12 years. Three alternative but related methods were used to project ICD arm's survival depending on the choice of the hazard ratio of the ICD arm relative to CONV arm. ICD1 assumes that this hazard ratio remains the same till 12 years.

ICD2 assumes the hazard ratio increases linearly at 3.5 years to 1 at 12 years. ICD3 assumes the hazard ratio increases from 3.5 years to 1 at 7.1 years and to 1.094 at 12 years so that the two survival curves meet at 12 years. The hazard ratio from the observed data at year 3.5 is fixed for three methods.

For each of the projected survival curves, the survival probability till 12 years at each month was calculated, i.e., S_i, i = 0, 1, 2, ..., 144. Assuming an annual rate of discount of b (= 3%), the monthly discount rate is $\alpha = b/12$. The projected discounted mean survival time up to L months was:

$$T^{pred} = \sum_{i=1}^{L} S_i e^{-ai}$$

3 Projecting Costs

3.1 Projecting Costs for Survivors

In MADIT-II, patients' costs are assembled on a daily basis. These data are first grouped into monthly costs (30 days) with the last month often consisting of less than 30 days. Due to the high costs of the defibrillators, we subtract the device cost and associated procedure cost from the total monthly costs for patients who received the implantation. Some ICD patients later received a second procedure for replacement ICDs and these replacement costs are also subtracted from the monthly costs. These ICD related costs are added back later in projections.

The monthly average data show that there are large monthly costs in the early months and in the later months prior to death, whereas the costs are relatively flat during the other time. Hence, for our regression model we assume that patients have some initial costs C_{IC} in the first month. In addition, patients accumulate monthly average costs, called the monthly base costs C_{BC}.

For patients whose death was observed, we assume there are some death costs C_{DC1}–C_{DC6}, extra costs accumulated in the last 6 months prior to death. In our initial model selections, we have considered initial costs in the first 3 months, death costs in the last 18 months prior to death, and time trends in monthly costs. However, we find statistically insignificance of any time-trend in monthly costs, death costs earlier than 6 months prior to death and initial costs beyond the first month.

Since monthly costs data from the same subject are correlated, we fit a mixed effect model to these data. The fixed effects include C_{IC}, C_{BC} (same for each month), C_{DC1} −C_{DC6}, and their interactions with treatment. The random effects include only the monthly base costs CBC, but allows the variability of CBC to be different for different treatment groups.

There are two difficulties for mixed effect model analysis with the monthly cost data. One is due to the fact that the last month is often incomplete, having less than 30 days. It is not realistic to assume that the last month's cost has the same variability as the previous month if the last month consists of cost data from a few days, rather than 30 days.

The other difficulty is that the death costs are counted backward, e.g., starting from the patient's death time, and going backward in time.

Our strategy is as follows. If the last month has less than 15 days, it is combined with the previous month. Since the death costs C_{DC1} − C_{DC6} start from the day of death and count backward, the costs from a given month closest to death are contributed by two consecutive death costs C_{DCJ} and $C_{DC(J+1)}$, where J can be a number between 1 and 5.

Our method can be illustrated using the following hypothetical data:

If a patient dies on day 130, he would have data for 5 months and the last month contained only 10 days. Let $fr \equiv \frac{10}{30}$. Denote the costs of month i as mi. The following data are generated to fit our mixed effect model.

days	month	cost	C_{IC}	C_{BC}	C_{DC1}	C_{DC2}	C_{DC3}	C_{DC4}	C_{DC5}
1−30	1	m_1	1	1	0	0	0	1−fr	fr
31−60	2	m_2	0	1	0	0	1−fr	fr	0
61−90	3	m_3	0	1	0	1−fr	fr	0	0
91−130	4	$m_4 + m_5$	0	1+fr	1	fr	0	0	0

In our preliminary analyses, we find that death costs are common to the two arms and are constant over prior months 2 to 4 and over prior months 5 and 6.

We then combine C_{DC2}, C_{DC3}, C_{DC4} as C_{DCC2} and C_{DC5}, C_{DC6} as C_{DCC3}. Our final model has the monthly base cost C_{BC0} (CONV arm) and CBC1 (ICD arm) as two random effects; C_{IC}, C_{BC0}, C_{BC1}, C_{DC1}, C_{DCC2}, C_{DCC3}, the interaction of C_{IC} and the treatment as fixed effects. Details of the estimates of the parameters from our regression model will not be shown here.

3.2 Projecting Mean Costs

Using the estimates from the fitted regression model, we project accumulated costs beyond 3.5 years. The projected accumulated costs at time t, using an annual discount rate of β (=3%), is equalto $\int_0^t C(u))\ S_u e^{-\beta u} du$, where C(u) represents the costs incurred at at time *u* if patients survive beyond *u*, and S_u is the survival probability at time u.

For patients from each arm, their estimated monthly costs might contain the initial costs, device costs, death costs, and replacement costs. Under different survival models described in the previous section, for different treatment arms, patients' expected total costs can be obtained by multiplying the estimated monthly costs by the estimated probability of survival through that month. The detail is as follows. In discrete time, the projected accumulated discounted costs at time t (= L month) can be approximated by

$$\sum_{i=1}^{L} C(i) S_i e^{-\beta i}$$

Assuming that the costs are projected up to L (L = 144) months, we could express the expected total discounted costs as:

$$E(C^d) = C_{IC}^{pred} + C_{BC}^{pred} + C_{DC}^{pred} + C_{RC}^{pred} + C_{Device}^{pred}$$

whereC_{IC}^{pred}represents the predicted initial costs, $C_{BC}^{pred}$the predicted total monthly base costs, $C_{DC}^{pred}$the predicted total death costs, C_{RC}^{pred} the predicted generator replacement costs, and $C_{Device}^{pred}$the predicted device cost and the associated procedure cost for patients who received implantation in the ICD arm.

The predicted total arm-specific monthly base costs up to L months are:

$$C_{BC}^{pred} = \sum_{i=1}^{L} \Big[E(C_{BC} | T \geq i) \Pr(T \geq i) + \frac{1}{2} E(C_{BC} | i-1 \leq T < i) \Pr(i-1 \leq T < i) \Big]$$

$$= \sum_{i=1}^{L} [S_i C_{BC} e^{\{-\beta(i-0.5)\}} + \frac{(S_{i-1} - S_i) C_{BC}}{2} e^{\{-\beta(i-0.5)\}}]$$

$$= \sum_{i=1}^{L} [\frac{(S_{i-1} + S_i) C_{BC}}{2} e^{\{-\beta(i-0.5)\}}]$$

The predicted death costs up to L months are:

$$C_{DC}^{pred} = \sum_{i=1}^{L} \left[(S_{i-1} - S_i) \sum_{j=1}^{6} \left[C_{DCj} e^{\{-\beta(i-j)\}} I(i > j) + \frac{C_{DCj}}{2} I(j = i) e^{\{-\beta(i-j)\}} \right] \right]$$

$$= \sum_{i=1}^{L} \left[(S_{i-1} - S_i) \sum_{j=1}^{6} \left[C_{DCj} e^{\{-\beta(i-j)\}} I(i > j) + \frac{C_{DCj}}{2} I(j = i) \right] \right]$$

The calculation of C_{BC}^{pred} and C_{DC}^{pred} makes adjustment for subjects dying in the middle of the timeintervals, and discounts the costs accordingly.

The defibrillator was assumed to have a life time of 5 years. Based on generator and associated medical cost data from 32 early replacements, we calculate the generator replacement costs C_{RC} and assume them to take place at years 5 and 10 for ICD arm patients surviving up to those horizon time points. Then the predicted replacement costs up to L months for the ICD arm are:

$$\begin{aligned} \mathcal{C}_{RC}^{pred} &= I(L \geq 60) \mathcal{C}_{RC} \Pr(T \geq 60) + I(L \geq 120) \mathcal{C}_{RC} \Pr(T \geq 120) \\ &= I(L \geq 60) S_{60} \mathcal{C}_{RC} e^{(-60\beta)} + I(L \geq 120) S_{120} \mathcal{C}_{RC} e^{(-120\beta)}. \end{aligned}$$

If the patient is in CONV arm, then C_{RC}^{pred} is 0. Finally, the predicted total costs are obtained by summing the above 5 items.

4. Projecting ICERs

With the projected discounted survival time and discounted costs obtained from the previous section, for any time horizon, we calculate the difference of projected discounted costs (ICD arm minus CONV arm) as well as the discounted years of life saved. The projected ICER can be obtained by the ratio of the difference of costs and the corresponding difference of projected years of life saved.

5 Discussion

In this paper we have described a method to project future costs and ICERs, based on the projected survival curves. By using data from MADIT-II, we apply a mixed effect regression model to the available cost data to obtain the monthly costs for survivors. By multiplying the estimated survival probability with the estimated monthly costs, we can obtain the projected costs, thus the projected ICER for any time point within our time span. We have used the survival time in calculating the ICERs. There are some medical interventions that do not result in life years saved but address the quality of life. Our method can be easily extended to obtain the projected ICERs using quality-adjusted lifetime. The quality-adjusted lifetime can be discounted similarly as the survival time.

The projected survival probability assumes that the aging effect in the MADIT-II population is the same as that in the US population. In our mixed effect regression model, we have not taken into consideration any covariates which may affect the monthly costs. If we have some knowledge about the covariate effects, we may incor- porate them into our model and obtain a better estimation of the monthly costs. We have not considered the aging effects in cost, since we only have 3.5 years' observed data. In the mixed-effect regression model, we only count backward 6 months' death costs for those patients whose death are observed. Death costs for patients who are censored but who might be close to their death points are not considered. If we dis- card the last 6 months' data for those censored patients, we may lose some efficiency in our estimation due to throwing away a lot of data, since more than half of the patients in MADIT-II are censored observations. The best way of projection is still

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