On the equivalence of some medical cost estimators with censored data: Application to the MADIT-II trial

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Outline

- Background
- Statistical issues in medical cost data analysis
- Statistical methods: existing estimators for the “mean”
- Equivalences among estimators
- Example and Illustration: MADIT II
- Discussion
Methodological Background

- Incompleteness (due to censoring) is a key feature of most survival data.
- Numerous well established statistical methodologies and algorithms exist for analyzing censored survival data (e.g., Kaplan-Meir (KM), Cox model).
- However, informative censoring in medical cost invalidates the use of most standard analytic tools.
- Valid methods for analyzing censored medical costs have been actively developed (since 1st discovery by Lin, Feuer, Etzioni & Wax, Biometrics 1997).
Mean vs. Median, Cost-effectiveness (CE).
Mean: Most common. Total cost can be derived from mean, not median. CE analysis uses mean. Today’s talk is only about “MEAN” estimation.

“Induced or informative censorship” due to positive correlation between total cost at event and total cost at censoring even though event time and censoring are independent.

Thus, most standard statistics are invalidated (e.g., sample mean, t-test, ordinary least squares, KM estimates, Log-rank test, and Cox model, etc.)
Cumulative costs at survival and censoring times for 2 subjects in a heterogeneous population
Statistical methods: Notation and assumptions

- $T$=the patient's survival time or the time before all the cost data were available. Often, $T=\min(T, \tau)$ with the maximum follow-up time $\tau$.
- $M(t)$=the medical cost for a patient up to time $t$. Let $M(T)\equiv M$.
- Our goal is estimating “$E(M)$=expected value of $M$”.
- $C$=time to censoring, assumed to occur independently of all others.
- $[0=a_1, \tau=a_{K+1})$ is partitioned into $K$ sub-intervals $[a_k,a_{k+1})$ for $k=1,…K$ so partitioned costs are $M_k=M(a_{k+1})-M(a_k)$.
- Observed data: $\{X=\min(T,C), \Delta=I(T\leq C), M \text{ or } M_k\}$. 
Statistical methods:
Naïve approaches (old & wrong)

- All complete cost data (i.e., no censoring), no problem!
- Under right censoring, 3 naïve approaches are:
  1. Full sample mean: always underestimated. \( \frac{\sum_{i=1}^{n} M_i}{n} \)
  2. Complete (or uncensored) case mean: bias towards to cost with shorter survival. \( \frac{\sum_i \Delta_i M_i}{\sum_i \Delta_i} \)
  3. Mean derived from KM: biased.
Statistical methods: 
Existing estimators (new & correct)

  ---propose LinA/B when cost history (i.e., intermediate/partitioned cost information) is available and LinT otherwise.
  ---Known to be biased except discrete censoring times.

- Huang & Louis (Biometrika 1998): HL
  ---oriented for mark variable, estimating distribution
• Bang & Tsiatis (Biometrika 2000): BT, BTp, BTimp, BTpimp, where “p”
denotes partitioned (like LinA/B) and “imp” denotes improved (i.e.,
smaller variance)

\[
BT = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i M_i}{KM(T_i)}
\]

where KM(t) is the K-M estimate of P(C_i > t)

\[
BTp = \frac{1}{n} \sum_{k=1}^{K} \sum_{i=1}^{n} \frac{\Delta_i^k M_{ik}}{KM(T_i^k)}
\]

where \( \Delta_i^k = I(\min(T_i, a_k) \leq C_i) \) and \( T_i^k = \min(T_i, a_k) \).
Zhao & Tian (Biometrics 2001):

\[
ZT = \frac{1}{n} \left\{ \sum_{i=1}^{n} \Delta_i \frac{M_i}{KM(X_i)} + (1 - \Delta_i) \frac{(M_i - M_i^*)}{KM(X_i)} \right\}
\]

\[
= BT + \frac{1}{n} \left\{ \sum_{i=1}^{n} (1 - \Delta_i) \frac{(M_i - M_i^*)}{KM(X_i)} \right\}
\]

where $M_i^*$ is the average of M’s at $X_i$ from $i$ to $n$ when the data \{X,Δ,M\} have been sorted in ascending order based on X.

--- Thus, ZT=BT + efficiency term. ZT is easier to implement than BT’s improved estimators.
Pfeifer & Bang (J Int Marketing 2005): RR (Replace from the Right)

\[
RR = \frac{1}{n} \sum_{i=1}^{n} M_{i}^{replaced}
\]

- Sort \(\{X, \Delta, M\}\) in the ascending order of \(X\).
- Start with the largest lifetime (always uncensored) and move onto the left.
- If \(M\) is uncensored (i.e., \(\Delta=1\)), then use \(M\) for that subject.
  If \(M\) is censored (i.e., \(\Delta=0\)), replace \(M\) with the average of "downstream" replaced \(M\)'s.

--- This RR algorithm has been used for survival times & KM (Efron 1967)
Summary/overview

- When only total costs are available, we may use
  - LinT
  - BT
  - RR (easy to compute)
  - HL

- When individual cost histories are available, we may use
  - LinA/B
  - BTp, BTimp, BTpimp
  - ZT
Some equivalences previously shown

- O’Hagan and Stevens (J Health Econ 2004) showed BT=LinT analytically but via infinitesimal partitions.
- Pfeifer and Bang (2005) showed 1) RR=BT and 2) ZT=LinA/B numerically and 2) proposed a simpler expression of ZT.
New relationships revealed

Zhao, Bang, Wang and Pfeifer (In Press, Stat Med) proved analytically:

- LinT = BT
- LinA/B = BTP = ZT

if non-overlapping partitions are formed by distinct censoring times such as

\[(0 = t_0^C, t_1^C], (t_1^C, t_2^C], \ldots, (t_f^C, t_{f+1}^C = \tau].\]
An example: The MADIT-II

- The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) was designed to study the potential survival benefit of a prophylactically implanted defibrillator in patients with a prior myocardial infarction and a left ventricular ejection fraction \( \leq 0.03 \) (Moss et al. NEJM 2002; Zwanziger et al. J Am Col Cardiology 2006).

- In contrast, the original MADIT-I considered patients who were at high risk for ventricular arrhythmia (Moss et al. NEJM 1996, Mushlin et al. Circulation 1998).
More on The MADIT-II

- The MADIT-II started on July 1997.
- Randomized into either the implantable cardiac defibrillator (ICD) arm vs. the conventional therapy arm.
- It was shown that ICD has a survival advantage with estimated hazard ratio of 0.69 (95% CI=0.51-0.93 with p=0.016).
- Due to high cost with the defibrillator and the implementation process, the CE analysis to evaluate the cost implication of the new treatment was needed.
- N=664 subjects in the ICD arm and 431 in the conventional arm.
- The average follow-up time was 22 months.
- Zwanziger et al. (2006) examined the costs accumulated over 3.5 years, equivalently, 1,278 days.
- For an illustrative purpose, we used 1,260 days and computed mean only, not CE ratio.
- We tried two methods of partitions: 1) 6 months (180 days) intervals and 2) boundaries matching with the distinct censoring times.
Various estimates (in US $) by arm for the MADIT-II

<table>
<thead>
<tr>
<th>Estimators</th>
<th>Conventional therapy mean (standard error)</th>
<th>ICD mean (standard error)</th>
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<tr>
<td></td>
<td><strong>Using 6-month intervals for boundaries</strong></td>
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<tr>
<td>LinT</td>
<td>50,065 (5,497)</td>
<td>84315 (4,921)</td>
</tr>
<tr>
<td>BT</td>
<td>49,796 (5,483)</td>
<td>84353 (4,948)</td>
</tr>
<tr>
<td>LinA</td>
<td>39,578 (3,164)</td>
<td>77539 (2,900)</td>
</tr>
<tr>
<td>LinB</td>
<td>47,855 (4,168)</td>
<td>84315 (3,392)</td>
</tr>
<tr>
<td>BTP</td>
<td>46,803 (3,474)</td>
<td>83887 (2,862)</td>
</tr>
<tr>
<td>ZT</td>
<td>44,666 (3,664)</td>
<td>83629 (2,921)</td>
</tr>
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Results

- LinA/B, Lin T, BTp depend on the intervals we choose.
- With 6 month intervals, LinA is smaller than other estimates ----shown to always underestimate the true mean.
- With the censoring times as partition boundaries, we have LinT=BT and LinA/B=BTp=ZT.
- Since LinA/B, BTp and ZT use more information, they are more efficient than LinT and BT that use only total cost information.
Summary and Conclusions

- Standard statistical methods for survival data analysis SHOULD not be used for medical cost data ----Proved 10 years ago!
- Question/observations for many years: Several estimators have been developed from different theoretical backgrounds. They behave similarly. Why?
- Different estimators are needed for different data conditions.
• This research has limited impacts on applications but is mathematically/theoretically important!

• When you think that you invented a new thing, you should check if this is really new or at least if there are some advantages in it (e.g., offer easy variance estimation, or more intuitive or user-friendly formula).

• Limitation: No Software. Consult with a statistician.
Reference

Zhao, Bang, Wang & Pfeifer
On the equivalence of some medical cost estimators with censored data. Accepted to Stat Med.