Mortality Comparison of Endovascular versus Open Repair for Abdominal Aortic Aneurysm using Instrumental Variables

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Summary

Abdominal aortic aneurysm (AAA) is a pervasive condition with high morbidity, affecting 2-4% of adults in the U.S., with 85-90% mortality in ruptured AAA cases. Surgical repair can mitigate the risk of rupture, however open surgery is associated with high risk of complication. Endovascular aneurysm repair (EVAR) is a less invasive repair procedure, and is associated with lower short-term mortality, but it is not clear whether it has long-term benefits. There are concerns that EVAR is less effective in the long-term, leading to reinterventions. Clinical trials comparing the procedures are limited in size, scope, or follow-up. Hence we utilize a large Medicare enrollment dataset with long-term follow-up in our analysis. In order to establish causal estimates of the differences in long-term mortality outcomes, we develop novel instrumental variable approaches to survival analysis. In particular, we analyze the Medicare data based on the semiparametric accelerated failure time model. Inference regarding the causal effects is carried out using a weighted bootstrap approach.

Motivation
Abdominal Aortic Aneurysm

- **Surgical repair options**
  - Open repair - conventional treatment, more invasive, long recovery
  - Endovascular repair - less invasive, concerns about efficacy
- **Little convincing comparative effectiveness research**
  - Few randomized controlled trials enacted
    - Very small (10 AAA-related deaths) (Lederle et al., 2012)
    - Short follow-up (Prinssen et al., 2004)
  - Analysis of observational studies does not account for unmeasured confounding

Challenges of IVs in Survival Analysis

- Traditional IV methods rely on linearity
- For nonlinear models, other strong assumptions are necessary
- How to relax IV assumptions while retaining modeling flexibility?

Previous Work

- Fully specified parametric structural equation models: (Tang and Lee, 1998), (Muthen and Masyn, 2005), and (Chen et al., 2011)
- Two-stage residual inclusion-based approaches allow for consistent estimation for nonlinear models, with strong assumptions on endogenous variable
- Additive hazards instrumental variable approach of (Li et al., 2015) relies on linear structure for endogenous variable $X = \alpha_c + \alpha_Z Z + \boldsymbol{\alpha}_o' \mathbf{X}_o + \boldsymbol{\alpha}_u' \mathbf{U} + \epsilon$ and utilizes a two-stage procedure: estimate effects of Z and $\mathbf{X}_o$ on X using a linear model and use $\hat{X}$ in place of X in an additive hazards model
- There remains a need for IV methods which do not impose strong IV assumptions and still allow flexible survival modeling

Instrumental Variable Estimation in Censored Regression

- The linearity of the semiparametric accelerate failure time makes it suitable for IV estimation
- Relies only on core IV assumptions, no structural assumptions needed

Assumptions

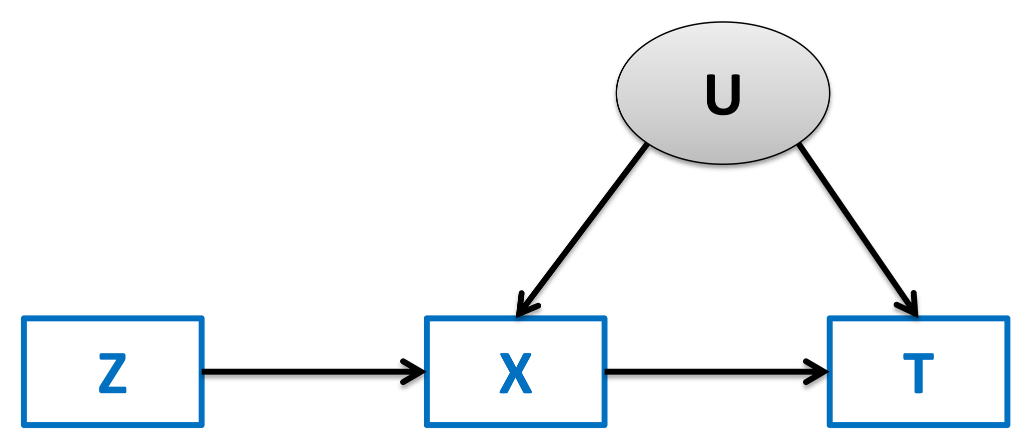
- True data-generating model:

$$\log \widetilde{T}_i = \beta X_i + U_i, i = 1, \ldots, n$$

- Where
  1. $Z_i \perp\!\!\!\perp U_i$
  2. $\widetilde{T}_i \perp\!\!\!\perp Z_i | X_i, U_i$
  3. $X_i \not\perp\!\!\!\perp Z_i$

  A key difference from typical survival assumptions:

  4. $C_i \perp\!\!\!\perp (X_i, Z_i, U_i, \widetilde{T}_i)$ (The typical assumption is $C_i \perp\!\!\!\perp \widetilde{T}_i | X_i$)
- No structural assumptions regarding the relationship between X and Z



Rank-based estimator for the standard AFT model

$$U_n(\beta) = \sum_{i=1}^{n} \int \rho(t, \beta) \{X_i - \overline{X}(t, \beta)\} \, \mathrm{d}N_i(t, \beta)$$

where $\overline{X}(t, \beta) \equiv \frac{1}{n} \sum_{j=1}^{n} X_j I(\epsilon_j^{\beta} \geq t) \,/\, \frac{1}{n} \sum_{j=1}^{n} I(\epsilon_j^{\beta} \geq t)$ and

$\epsilon_i^{\beta} = \log T_i - \beta X_i$ is the residual for subject i and

$N_i(t, \beta) = I(\epsilon_i^{\beta} \leq t, \Delta_i = 1)$

Rank-based IV estimator for the AFT model

Key Difference: instead of comparing X_i with the average X in the residual risk set, we compare Z_i with the average Z in the residual risk set

$$U_n^{IV-IPCW}(\beta) = \sum_{i=1}^{n} \int \rho(t, \beta) \{Z_i - \overline{Z}_{G_C}(t, \beta)\} \frac{\mathrm{d}N_i(t, \beta)}{G_C(t + \beta X_i)}$$

where $\overline{Z}_{G_C}(t, \beta) \equiv \frac{1}{n} \sum_{j=1}^{n} \frac{Z_j I(\epsilon_j^{\beta} \geq t)}{G_C(t + \beta X_j)} \,/\, \frac{1}{n} \sum_{j=1}^{n} \frac{I(\epsilon_j^{\beta} \geq t)}{G_C(t + \beta X_j)}$ and

$\epsilon_i^{\beta} = \log T_i - \beta X_i$ is the residual for subject i and G_C is the Kaplan-Meier estimator for the survival function of C

We need to use inverse probility of censoring weighting to account for induced dependence of C_i on ϵ_i^{β}

Inference via Bootstrap

Challenge: Too computationally demanding to resample the data and solve a resampled equation many times

Instead: Relate the variance of $\sqrt{n}(\hat{\beta} - \beta)$ to the variance of $n^{-1/2} U_n^{IV-IPCW}(\beta)$

The approach of (Zeng and Lin, 2008) only involves evaluations of the estimating equation

Simulation

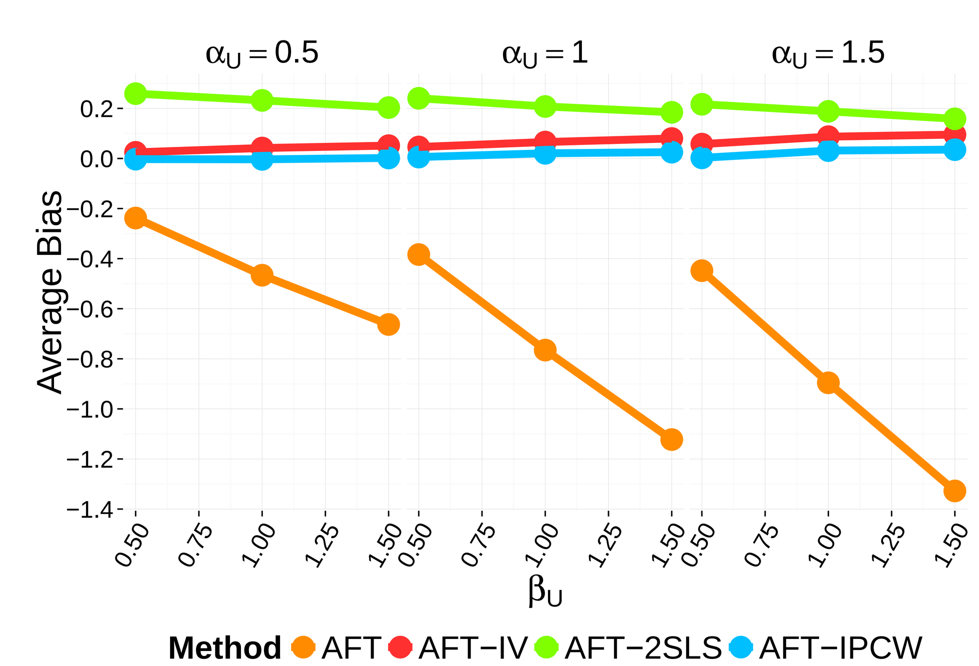
- $T = \exp\{X + \beta_U U + \epsilon\}$

  where
- $X = \alpha_Z \exp\{Z\} + \alpha_U U + \epsilon^*$ where $\epsilon, \epsilon^* \sim N(0, 1)$, $\epsilon \perp\!\!\!\perp \epsilon^*$
- $C \sim$ exponential with rate parameter 1

Nonlinearity between Z and X to demonstrate structural assumptions not necessary

Two other methods investigated:

- Rank-based IV estimator without inverse weighting (not theoretically justified)
- Two stage procedure; replace X with predictions of X using linear model with Z



			AFT		AFT IV		AFT 2SLS		AFT IPCW	
			Sample Size		Sample Size		Sample Size		Sample Size	
α_u	β_u	α_I	500	5000	500	5000	500	5000	500	5000
0.5	0.5	0.5	0.542	0.000	0.848	0.874	0.902	0.296	0.928	0.970
		1	0.742	0.026	0.844	0.920	0.762	0.012	0.936	0.970
	1	0.5	0.100	0.000	0.838	0.852	0.912	0.544	0.924	0.938
		1	0.422	0.000	0.880	0.888	0.842	0.086	0.906	0.966
1	0.5	0.5	0.146	0.000	0.798	0.858	0.938	0.638	0.910	0.960
		1	0.406	0.000	0.840	0.866	0.808	0.050	0.924	0.968
	1	0.5	0.002	0.000	0.826	0.774	0.964	0.808	0.920	0.948
		1	0.054	0.000	0.856	0.786	0.872	0.184	0.906	0.938

Table: Empirical Coverage, 95% Level. Simulations based on 500 simulated datasets, 1000 bootstrap replications

Analysis of Medicare Enrollment Data

- Approximately 100k patients
- Approximately 44k deaths
- Surgeries performed between 2001 and 2008 and followed up until 2009
- Data includes 2,853 cases of abdominal aortic rupture
- Primary outcome is all-cause survival time
- Demographic information as well as medical information, including chronic conditions

- **AAA Background**
  - Randomized controlled trials suggest
    - a short term mortality reduction for EVAR (Prinssen et al., 2004)
    - little difference long-term (Lederle et al., 2012)
  - Observational studies utilizing propensity score-matched cohorts (Schermerhorn et al., 2008) suggest
    - EVAR has short-term benefits
    - older patients benefit more from EVAR
    - reinterventions are more common after EVAR
- **Instrumental variable**
  - Proportion of EVAR surgeries to open surgeries at the institution in which the patient received treatment
  - Predictive of actual surgery received, indicating moderate instrument strength
  - Potential weaknesses:
    - possibly institutions which perform one type of surgery often see more ill patients
    - institutions which perform one type of surgery more often could perform them better than other institutions

Analysis

Four approaches:

- Standard AFT
- AFT with IV and no inverse probability of censoring weighting
- AFT two stage procedure (analogous to 2SLS)
- AFT with IV and inverse probability of censoring weighting (our proposed method)

Estimates of EVAR Effect

Estimator	$\hat{\beta}_{EVAR}$	(95% Conf.	Interval)
AFT	0.047	−0.063	0.144
AFT-IV	−0.169	−0.420	0.080
AFT-2SLS	−0.175	−0.432	0.074
AFT-IV-IPCW	−0.156	−0.364	0.052

Table: Estimates of the effect of EVAR vs. open repair for rupture cases

Conclusions

- Analysis adjusting for unmeasured confounding suggests there may be some benefit for open repair for rupture cases
- Suggests that more comprehensive treatment provided by open repair leads to reduction in mortality for more serious AAA cases
- Rupture cases are more serious than typical AAA cases; conclusion may be different for non-rupture cases
- Our analysis is consistent with a recent study of ruptured AAA which provides sensitivity analysis to bias due to unmeasured confounding (Edwards et al., 2014)

Remaining Challenges

- Our estimating equation is not monotone and often has poor behavior in small samples
  - Monotonicity would also improve computation dramatically
  - Could alleviate difficulties in analyzing entire dataset
- Sensitivity of the bootstrap procedure

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