Performance of statistical methods for analysing survival data in the presence of non-random noncompliance

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Noncompliance

- Effectiveness vs efficacy
- Low power
- Random noncompliance (non-informative)
  - NC not related to subject's characteristic predictive of survival

- Non-random noncompliance
  - Pr(noncomply) is correlated with individual frailty

- Classification:
  - All or nothing compliance
  - Partial compliance

Survival data

- Censoring
- ▷ Non informative

- Heterogeneity: induced bias
- ▷ Selection bias - covariates

- Unobserved covariates
- ▷ Random effects

Methods considered

- All or nothing compliance
  1. ITT - Cox PH model
  2. Simple regression
  3. C-Prophet
- Partial compliance
  1. Time adjust regression
  2. CACE_{PH}
  3. Dynamic compliance analysis (DCA)
- **Objective:** to compare performance of the 6 methods in terms of bias and MSE

All-or-nothing compliance

1. ITT: $h(t|\text{treat}) = h_0(t)\exp(\beta \text{ treat})$
2. Simple adjust: $h(t|\text{trt,nc}) = h_0(t)\exp[\beta_1 \text{ trt} + \beta_2 \text{ nc}]$
3. C-Prophet (Causal PROPortional Hazards Effect of Treatment) - Loeys and Goetghebeur (2003):

$$h(t|Z_i = 1, U_i = u) = h(t|Z_i = 0, U_i = u)\exp(\psi_0 u)$$

Partial compliance

1. Simple time adjust: NC treated as time-dependent covariate

$$h(t|\mathrm{trt},\mathrm{nc}) = h_0(t)\exp[\beta_1 \ \mathrm{trt} + \beta_2 \ \mathrm{nc}(t)]$$

2. $\mathrm{CACE_{PH}}$ (Complier Average Causal Effect for Proportional Hazards) - White et al. (2004):
   (a) short intervals (b) risks stay constant in each stratum

$$\mathrm{CACE_{PH}} \cong \mathrm{CACE_{adj}} = \frac{\mathrm{HR_{ITT}}(1-\lambda)}{1-\lambda \mathrm{HR_{ITT}}}$$

   where $\lambda \equiv$ proportion of the dead noncompliers in the treatment arm

3. DCA (Dynamic compliance analysis): randomization based efficacy estimation - Robins & Tsiatis (1992):

$$U_i(\psi) = \int_0^{T_i} \exp[\psi \cdot \mathrm{treatment}_i(t)]dt$$

Assumptions I: Hazard rates

- Two-arm trial
- Each subject has 2 potential hazard rates: λ_{0i} and λ_{1i}
- Fixed homogeneous risks: $\lambda_0 = 0.012$ and $\lambda_1 = 0.006$
  - ▷ True HR (THR) $= 0.5$
- Heterogeneous potential hazard rates:
- $\bar{\lambda}_0 = 0.012$, $\bar{\lambda}_1 = 0.006$ (THR$= 0.5$)
  - ▷ $\lambda_{0i} \sim$ gamma

Assumptions II: Non-compliance

- No treatments switches from control arm
- Noncompliers from the treatment arm revert to control hazards
- Decreasing probabilities of noncompliance with time (5%, 2%, 1%)
- Non-compliers remain so till end of study
- Pr(noncomply)= α_i are correlated with baseline risks λ_{0i}: $\alpha_i \sim$ log-normal

Test and power

- $\#$ of simulations$=2000$
- Sample size$=1000$
- Test: one-sided t-test ($\alpha = 0.05$)
- Bias=Mean HR-True HR
- Power: 90% to detect a bias ≥ 0.01

Results: Full compliance - THR=0.5, $\lambda_0 = \bar{\lambda}_0 = 0.12$

Rates	Effect†	Bias	MSE	Stat.‡	p-value
Hom.	0.500				
^{1}Het.	0.515	0.015	0.0002	3.002	0.001
^{2}Het.	0.500				

†Mean treatment effect; ‡Test statistics
^{1}Het: fixed effects model-ignoring heterogeneity
^{2}Het: random effects model-modelling heterogeneity

Full compliance

- With homogeneous rates, fixed effects model provided unbiased TE estimate
- Fixed effects model that ignored heterogeneity when present introduced significant bias
- Modelling heterogeneity via random-effects model provided unbiased TE estimate

Predicting bias due to heterogeneity (Aalen, 1998)

$$\text{Predicted HR} = R\left[\frac{1+\delta H(t)}{1+R\ \delta H(t)}\right],$$

where $R \equiv$HR, $\delta \equiv$ variance, $H(t) = \int_0^T \lambda(u)\,du$

$$\text{Predicted HR} = \begin{cases} 0.517 & \text{if } \bar{\lambda}_0 = 0.012,\ \delta = 0.5 \text{ and} \\ 0.632 & \text{if } \bar{\lambda}_0 = 0.12,\ \delta = 0.5 \end{cases}$$

PHR$\equiv$predicted HR if using PH model which ignored heterogeneity

Random noncomply: Hom. rates THR$= 0.5, \lambda_0 = 0.012$

Method	Comply	Effect[†]	Bias	MSE	Stat[‡].	p-value
ITT	Ign	0.637	0.137	0.019	30.845	< 0.001
$\text{Simple}_{\text{adj}}$	AON[¶]	0.576	0.076	0.006	13.812	< 0.001
C-Prophet	AON	0.500				
Time_{adj}	vary	0.495	-0.005	0.00006	0.909	0.182
DCA	vary	0.489	-0.011	0.0002	1.380	0.084
CACE_{PH}	vary	0.509	0.009	0.0002	0.703	0.241
CACEadj	vary	0.500				

[†]Mean treatment effect; [‡]Test statistics ; ¶All-or-nothing

Random noncomply: Het. rates THR$= 0.5, \bar{\lambda}_0 = 0.012$, PHR$= 0.517$

Method	Comply	Effect[†]	Bias	MSE	Stat[‡].	p-value
ITT	Ign	0.626	0.109	0.012	23.133	< 0.0001
$\text{Simple}_{\text{adj}}$	AON[¶]	0.559	0.042	0.002	7.462	< 0.0001
C-Prophet	AON	0.483	-0.034	0.001	4.978	< 0.001
Time_{adj}	vary	0.490	-0.027	0.001	4.770	< 0.0001
DCA	vary	0.489	-0.028	0.001	3.514	0.0002
CACE_{PH}	vary	0.489	-0.028	0.001	3.096	0.001
CACEadj	vary	0.485	-0.032	0.001	4.819	< 0.001

[†]Mean treatment effect; [‡]Test statistics ; ¶All-or-nothing

AON non-random noncomply: Het. rates, THR$= 0.5, \bar{\lambda}_0 = 0.012$

Method	Attained[§] corr(α_i, λ_{0i})			
	0.150	0.261	0.442	-0.126
ITT	0.558	0.566	0.576	0.532
Simple$_{\mathrm{adj}}$	0.506	0.494	0.471	0.535
C-Prophet	0.518	0.518	0.515	0.513

[§] Set correlations: $0.3, 0.5, 0.8$ and -0.5 respectively

Partial non-random noncompliance: Het. rates, THR$= 0.5, \bar{\lambda}_0 = 0.012$

Method	Attained[§] corr(α_i, λ_{0i})			
	0.150	0.261	0.442	-0.126
Time_{adj}	0.499	0.487	0.465	0.527
DCA	0.487	0.485	0.484	0.482
CACE_{PH}	0.508	0.510	0.518	0.492
CACE_{adj}	0.516	0.514	0.510	0.513

[§]Set correlations: $0.3, 0.5, 0.8$ and -0.5 respectively

- Predicted bias due to heterogeneity $= 0.017$

Summary/conclusion

- ITT produced large bias
- Simple and time-varying noncompliance regression adjustments produced bias:
  - bias appears sensitive to correlation, i.e. opposite and larger bias for negative correlation compared to positive correlation
- C-Prophet and CACE_{adj} performed well: ▷ bias is of order expected from models which ignore heterogeneity

- DCA consistently produced bias in opposite direction - bias is small

- For mild positive correlation levels, CACE_{adj} is a good approximation of CACE_{PH}

Thank you