Assessing the Properties of an Adjusted Risk Difference for Survival Probabilities in Randomized Controlled Trials

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Outline

Adjustment in randomized controlled trials (RCTs)

- Four main reasons for doing **covariate adjustment** in RCTs (Hernández et al. 2006):
  - Correction of chance arisen imbalance
  - Quantification of heterogeneity of patients
  - Efficiency gain of the estimated treatment effect
  - Reduction of 'bias' ('attenuation' [Hauck et al. 1998]) when estimating treatment effects (in non–linear models)
- **Adjustment strategies** in RCTs (Hernández et al. 2006):
  - Prespecified adjustment
  - Significant–predictor adjustment
  - Significant–imbalance adjustment
- *Recommended*: Prespecified adjustment (Senn 2000, EMEA 2003)

Risk communication of survival data

- **Risk difference** (RD) may be a useful and comprehensible measure for communicating treatment effects of a RCT
- *Problem*: How to calculate a RD of a treatment effect which is adjusted for prespecified covariate(s)?
- *Two proposals*:
  - 'Average covariate method'
  - 'Corrected group prognostic survival curve' (Chang et al. 1982 and Makuch et al. 1982) or synonymously 'Direct adjusted survival curve' (Gail et al. 1986)
- *Recommended*: Method of **direct adjusted survival curves** (Lee et al. 1992)
- Direct adjusted RD for RCTs: Expected difference of the direct adjusted survival curves with and without treatment considering the whole distribution of the covariates

Definition of direct adjusted RD measure

- **Direct adjusted survival probabilities** are given by:
  - $S_F(t \mid Z = 1) = \int_{-\infty}^{\infty} S(t \mid Z = 1, \mathbf{x})F(\mathrm{d}\mathbf{x})$ for the **treatment** group
  - $S_F(t \mid Z = 0) = \int_{-\infty}^{\infty} S(t \mid Z = 0, \mathbf{x})F(\mathrm{d}\mathbf{x})$ for the **placebo** group
  - *where* Z is the treatment indicator and $\mathbf{x}$ is a covariate vector taken from distribution F
  - *where* $S(t \mid Z = 1, \mathbf{x})$ and $S(t \mid Z = 0, \mathbf{x})$ are the individual survival probabilities under treatment and placebo

Direct adjusted RD measure

$$\Delta(t) = S_F(t \mid Z = 1) - S_F(t \mid Z = 0)$$

- *assuming* w.l.o.g. $S_F(t \mid Z = 1) > S_F(t \mid Z = 0)$

Cox regression model

- Cox proportional hazards model (Cox, 1972):
  $\lambda(t \mid Z, \mathbf{X}) = \lambda_0(t) exp(\gamma Z + \boldsymbol{\beta}'\mathbf{X})$
- Estimated survival probability for a patient i conditional on her treatment $Z_i = z_i$ and observed covariates $\mathbf{X}_i = \mathbf{x}_i$:
  $$\hat{S}(t \mid Z_i = z_i, \mathbf{X}_i = \mathbf{x}_i) = \left[\hat{S}_0(t)\right]^{exp\left(\hat{\gamma} z_i + \hat{\boldsymbol{\beta}}'\mathbf{x_i}\right)}$$
  - *where* $\hat{S}_0(t)$ is the estimated baseline survival probability
  - *where* $\hat{\gamma}$ and $\hat{\boldsymbol{\beta}}'$ are the estimated regression coefficients
- *Assumptions:*
  - Right censored survival times T
  - Time–invariant treatment Z and time–invariant covariates $\mathbf{X}$
  - Censoring times C occur at random and are independent of the treatment Z and covariates $\mathbf{X}$
  - No stratified Cox model

Direct adjusted RD estimator

- **Direct adjusted survival probabilities** can be estimated by:
  - $\hat{S}_F(t \mid Z = 1) = n^{-1} \sum_{i=1}^{n} \hat{S}(t \mid Z_i = 1, \mathbf{X}_i = \mathbf{x}_i)$ for the **treatment** group
  - $\hat{S}_F(t \mid Z = 0) = n^{-1} \sum_{i=1}^{n} \hat{S}(t \mid Z_i = 0, \mathbf{X}_i = \mathbf{x}_i)$ for the **placebo** group

Direct adjusted RD estimator

$$\hat{\Delta}(t) = \hat{S}_F(t \mid Z = 1) - \hat{S}_F(t \mid Z = 0)$$

- *assuming* w.l.o.g. $\hat{S}_F(t \mid Z = 1) > \hat{S}_F(t \mid Z = 0)$

Limiting distribution

- Limiting process of $W(\cdot) = \sqrt{n}\left\{\hat{\Delta}(\cdot) - \Delta(\cdot)\right\}$ behaves *asymptotically* as zero mean Gaussian processes with finite variance (using cumulative baseline hazard estimator of Breslow)
  - Counting process martingale theory under specified regularity assumptions (Andersen et al. 1982, Andersen et al. 1993)
  - Functional delta method (Andersen et al. 1993)
  - Corollary VII.2.6 of Andersen et al. 1993

Preliminaries I

- Define the **counting process** $N_i(t) = I(T_i \leq t, D_i = 1)$ for patient i where $D_i = I(T_i \leq C_i)$ is the event indicator with T_i as observed time–to–event time and C_i as censoring time
- Let $\hat{\Sigma}$ be the **estimated observed information matrix**
- Let $S^{(k)}(\gamma, \boldsymbol{\beta}, t) = n^{-1} \sum_{i=1}^{n} J_i(t)(Z_i\, \mathbf{X}_i)^{\otimes k} exp(\gamma Z_i + \boldsymbol{\beta}' \mathbf{X}_i)$ be **'norming factors'** (Andersen et al. 1982)
    - for $k = 0, 1, 2$, where for a column vector a, $a^{\otimes 0} = 1$, $a^{\otimes 1} = a$ and $a^{\otimes 2} = aa'$
    - where $J_i(t) = I(T_i \geq t)$ is the process whether the subject i is **at risk** at time t
- $E(\gamma, \boldsymbol{\beta}, t) = \frac{S^{(1)}(\gamma, \boldsymbol{\beta}, t)}{S^{(0)}(\gamma, \boldsymbol{\beta}, t)}$

Preliminaries II

- For notational simplicity, let

$$
\begin{aligned}
\hat{\xi}(t \mid Z_i = 1, \mathbf{X}_i = \mathbf{x}_i) &= \hat{S}(t \mid Z_i = 1, \mathbf{X}_i = \mathbf{x}_i) exp(\hat{\gamma} + \hat{\boldsymbol{\beta}}' \mathbf{x}_i), \\
\hat{\xi}(t \mid Z_i = 0, \mathbf{X}_i = \mathbf{x}_i) &= \hat{S}(t \mid Z_i = 0, \mathbf{X}_i = \mathbf{x}_i) exp(\hat{\boldsymbol{\beta}}' \mathbf{x}_i), \\
\hat{\nu}(t \mid Z_i = 1, \mathbf{X}_i = \mathbf{x}_i) &= \hat{\xi}(t \mid Z_i = 1, \mathbf{X}_i = \mathbf{x}_i) \\
&\qquad \int_0^t \left[(Z_i = 1 \; \mathbf{x}_i) - E(\hat{\gamma}, \hat{\boldsymbol{\beta}}, u) \right] \frac{\mathrm{d} \sum_{i=1}^n N_i(u)}{n S^{(0)}(\hat{\gamma}, \hat{\boldsymbol{\beta}}, u)}, \\
\hat{\nu}(t \mid Z_i = 0, \mathbf{X}_i = \mathbf{x}_i) &= \hat{\xi}(t \mid Z_i = 0, \mathbf{X}_i = \mathbf{x}_i) \\
&\qquad \int_0^t \left[(Z_i = 0 \; \mathbf{x}_i) - E(\hat{\gamma}, \hat{\boldsymbol{\beta}}, u) \right] \frac{\mathrm{d} \sum_{i=1}^n N_i(u)}{n S^{(0)}(\hat{\gamma}, \hat{\boldsymbol{\beta}}, u)}.
\end{aligned}
$$

Variance estimaton of direct adjusted RD

Variance estimator of direct adjusted RD

$$\hat{\sigma}^2(t) = \left\{ n^{-1} \sum_{i=1}^{n} \left[\hat{\xi}(t \mid Z_i = 1, \mathbf{X}_i = \mathbf{x}_i) - \hat{\xi}(t \mid Z_i = 0, \mathbf{X}_i = \mathbf{x}_i) \right] \right\}^2$$

$$\int_0^t \frac{\mathrm{d} \sum_{i=1}^{n} N_i(u)}{[nS^{(0)}(\hat{\gamma}, \hat{\boldsymbol{\beta}}, u)]^2} + \left\{ n^{-1} \sum_{i=1}^{n} \left[\hat{\nu}(t \mid Z_i = 1, \mathbf{X}_i = \mathbf{x}_i) \right.\right.$$

$$\left.\left. - \hat{\nu}(t \mid Z_i = 0, \mathbf{X}_i = \mathbf{x}_i) \right] \right\}' \hat{\Sigma}^{-1}$$

$$\left\{ n^{-1} \sum_{i=1}^{n} \left[\hat{\nu}(t \mid Z_i = 1, \mathbf{X}_i = \mathbf{x}_i) - \hat{\nu}(t \mid Z_i = 0, \mathbf{X}_i = \mathbf{x}_i) \right] \right\}.$$

- **Asymptotic (pointwise) confidence interval**: $\hat{\Delta}(t) \pm z_{\alpha/2} \hat{\sigma}(t)$,
  - where $z_{\alpha/2}$ is the $\alpha/2$ upper percentile of the standard normal distribution

Design

- Generation of simulated data and parameters varied:
  - Sample sizes: $n \in \{100, 200, 500, 1000\}$
  - Distribution of treatment Z: $B(n, 0.5)$
  - Treatment effect: $\gamma \in \{log(0.7), log(0.9)\}$
  - Distribution of covariate X: $N(65, \sigma_X)$ where $\sigma_X \in \{3, 9\}$
  - Covariate effect: $\beta \in \{log(1.01), log(1.03)\}$
  - Proportion of censored observations: $p_c \in \{0.1, 0.25\}$
  - Types of hazard function: constant, increasing, decreasing, 'bathtub', upside–down 'bathtub' (logistic–exponential hazard function [Lan et al. 2008]) with follow–up of 3 years
- Number B of simulation runs: accuracy of $\hat{\Delta}(t)$ (Burton et al. 2006)
- Analyzing simulated data:
  - Prespecified adjustment strategy
  - Adjusted RD $\hat{\Delta}(t)$ and unadjusted $\hat{\Delta}^{\star}(t)$ at $t \in \{1a, 2a, 3a\}$, adjusted regression coefficient of treatment effect $\hat{\gamma}$, unadjusted regression coefficient of treatment effect $\hat{\gamma}^{\star}$ and corresponding 95% confidence intervals (CI)
- Performance measures calculated: Empirical relative precision (ERP), coverage probability (CP) and sample mean of regression coefficients

ERP for RD at $t = 2a$ for $p_c = 0.25$

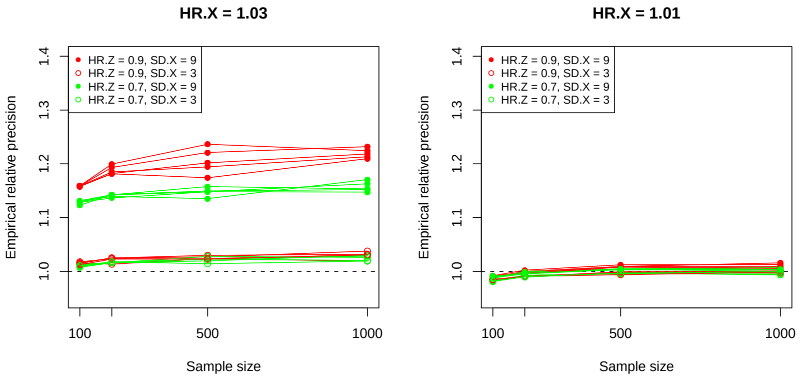

Figure: ERP for RD stratified by γ and σ_X of the covariate X each for β

CP for $\hat{\Delta}(t)$ at $t = 2a$

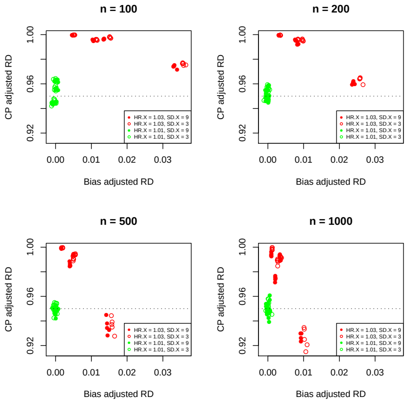

Figure: CP for $\hat{\Delta}(t)$ stratified by HR_Z and σ_X of the covariate X each for n

Further results

- **Direct adjusted RD**
  - ERPs for simulation scenarios with $p_c = 0.1$ similar to these with $p_c = 0.25$
  - All presented results for RD hold for all points in time t
- **Regression coefficient of treatment effect**
  - Slight loss of precision for adjusted $\hat{\gamma}$ which nearly vanishes with increasing n for *all* simulation scenarios
  - Sample mean of $\hat{\gamma}^{\star}$ is more attenuated toward 0 than sample mean of $\hat{\gamma}$ for *all* simulation scenarios
  - CP of 95% CIs for $\hat{\gamma}$ and $\hat{\gamma}^{\star}$ close to 95% in *all* simulation scenarios

EORTC 62961/ESHO RHT–95

- RCT concerning high–risk soft tissue sarcomas in adults (Issels et al. 2009, unpublished manuscript)
- $n = 341$ patients
- **Primary endpoint**: Local progression–free survival (132 events)
- **Treatment** Z: Neoadjuvant chemotherapy combined with regional hyperthermia (EIA + RHT) *vs.* neoadjuvant chemotherapy alone (EIA)
- Prognostically strong **covariates** $\mathbf{X}$:
  - Extremity vs. non–extremity
  - Predefined high–risk groups (S1, S2, S3)
- **Cox models**:
  - $exp(\hat{\gamma}^{\star}) = 0.64$ (95% CI: $[0.45, 0.90]$, $p = 0.01$)
  - $exp(\hat{\gamma}) = 0.59$ (95% CI: $[0.42, 0.83]$, $p = 0.003$)

Direct adjusted RD

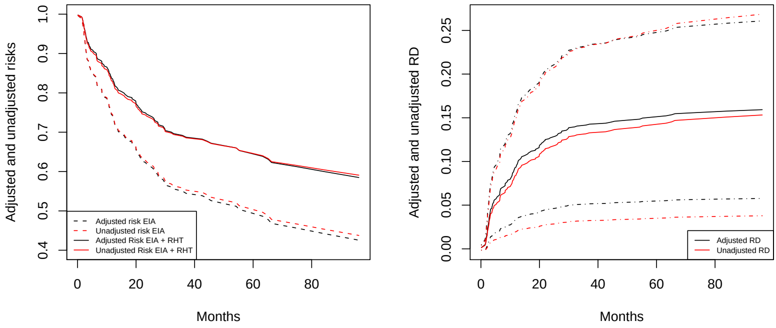

Figure: Adjusted and unadjusted risks separated by treatment groups [left plot] and $\Delta(t)$ and $\Delta^\star(t)$ estimates with 95% confidence intervals (dot–dashed lines) [right plot]

- **Summary**:
  - RD useful to present study results and for risk communication
  - Sometimes, covariates have to bo taken into account: Direct adjusted survival curves
  - Extension to survival data and to the Cox model: $\Delta(t)$
  - Precision gains especially for prognostically strong covariates
  - Disadvantages:
    - Sometimes, serious over- and undercoverage for CIs of $\Delta(t)$ (well–known fact [e.g. Andersen et al. 1996])
    - Flaws of the Cox model (Freedman 2008)
- **Literature review**:
  - Difference of direct adjusted curves for stratified Cox model (Zhang et al. 2007)
  - In evaluation research: '*A*verage *T*reatment *E*ffect' (ATE)
- **Extensions**:
  - Finding transformations for the CI of $\Delta(t)$ to yield better CPs
  - Evaluating properties of $\hat{\Delta}(t)$ using different baseline hazard estimators
  - Derivation of asymptotic bias, asymptotic relative precision (and asymptotic relative efficiency?)
  - $\Delta(t)$ can be transformed to an adjusted '*N*umber *N*eeded to *T*reat' (NNT) for survival data (Altman et al. 1999)

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