Estimating Adjusted Absolute Risks Differences Using Pseudo Values for Censored Data: Application, Interpretation, and Software Development

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INTRODUCTION

- In clinical and epidemiologic research, associations of interest are commonly summarized with hazard ratios. Time-specific absolute risks (AR) and absolute risk differences (ARD) can complement hazard ratios for improved clinical interpretation[1]
- The common Kaplan-Meier (KM) approach only provides unadjusted estimates of AR and ARD. Recent developments have introduced a risk modeling approach based on pseudo-values for censored data to estimate multivariable adjusted AR[2]
- Our goal: to apply this approach in a clinical dataset, compare models for censoring mechanisms, and extend SAS macros

PSEUDO VALUES MODELING

- Allows direct regression modeling of the survival function, restricted mean survival time, and the cumulative incidence function, for standard time-to-event as well as competing risks
- The general idea of pseudo-values is to think of censored observation as a particular kind of missing data[3]
- This allows direct estimation of a regression model for the AR given covariates
- First, a model for the missing values (i.e. censored observations) is defined (pseudo-values imputation)
  - The i^{th} pseudo-observation is defined as:

$$\widehat{\theta}_i = n \cdot \hat{\theta} - (n-1)\,\widehat{\theta^{-i}},$$

Where $\widehat{\theta^{-i}}$ is the "leave-one-out" estimator for based on $X_j, j \neq i$ [4]

- Second, a linear model for the risk is fitted
  - With one continuous/binary covariate and a set of confounders (C):

$$AR(t)=\beta_0+\beta_1 X+\beta C \qquad (1)$$

  - Plus interaction:

$$AR(t)=\beta_0+\beta_1 X_1+\beta_2 X_2+\beta_3 X_1 X_2+\beta C \qquad (2)$$

  - The test for β_3 (2) is a test for additive interaction

Unadjusted ARD from Models with Different Censoring Mechanisms as Compared to KM Estimate

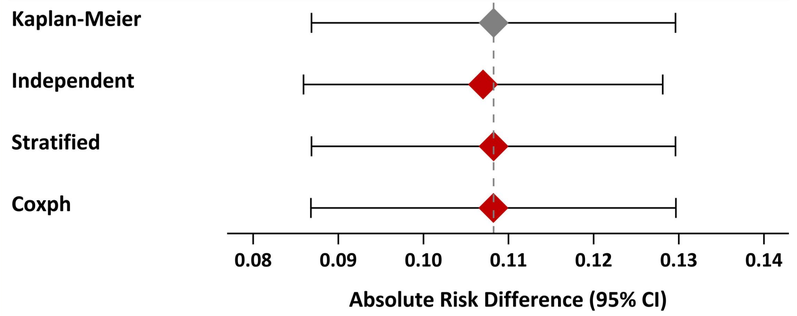

Figure 1. Absolute risk difference at 4 years between patients with CHF versus without CHF by different censoring methods for deriving pseudo-values

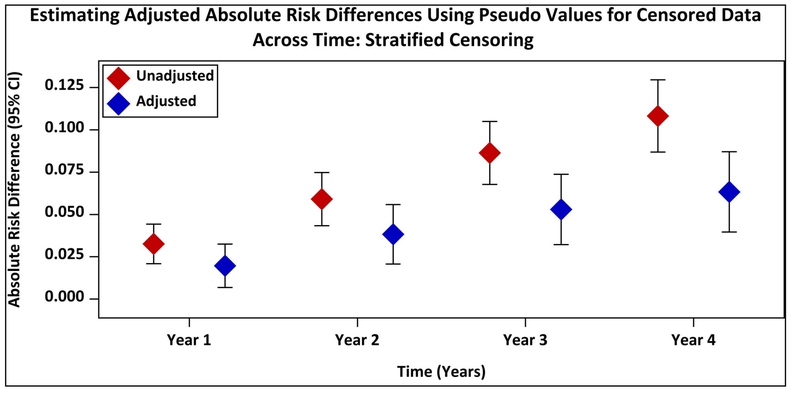

Figure 2. ARD (β_1 estimates) between patients with CHF versus without CHF across time. Adjusted estimates are adjusted for age and NTproBNP

ILLUSTRATIVE EXAMPLE

- AR and ARD estimation of Major Adverse Cardiovascular Events in a clinical trials of patients with type-2 diabetes
- Primary exposure (binary): History of congestive heart failure (CHF)
- Continuous covariates: Age and N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP)

PSEUDO-VALUES DERIVATION

- Three main approaches for pseudo-values derivation (Fig 1):
  - Independent censoring
  - Stratified censoring
  - Cox Proportional Hazard (Coxph) censoring
- Stratified censoring by a binary covariate coincides with ARD estimated from KM

ESTIMATING MULTIPLE TIME POINTS

- KM provides unadjusted estimates of survival at a specific timepoint. Hazard ratios summarize the instantaneous event risk over time
- In addition to providing adjusted AR and ARD, risk regression based on pseudo-values can also model the ARD over time (Fig 2)

CONCLUSIONS

- Risk regression based on pseudo-values is a valuable and novel approach to derive adjusted estimates of AR and ARD in survival analyses and thus provide formal testing and inference on the risk scale
- We illustrated its application and interpretation under different models for censoring mechanisms
- We extended SAS macros and material for deriving pseudo values, available at our GitHub page (scan QR code)

Contact: mgpalazzolo@bwh.harvard.edu

GitHub: https://github.com/andreabellavia/RCSplines

http://timi.org/biostatistics

References:

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