

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 interpretation¹
- 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 AR²
- 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 data³
- 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:

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

Where $\hat{\theta}^{-i}$ 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):

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

- Plus interaction:

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

- 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

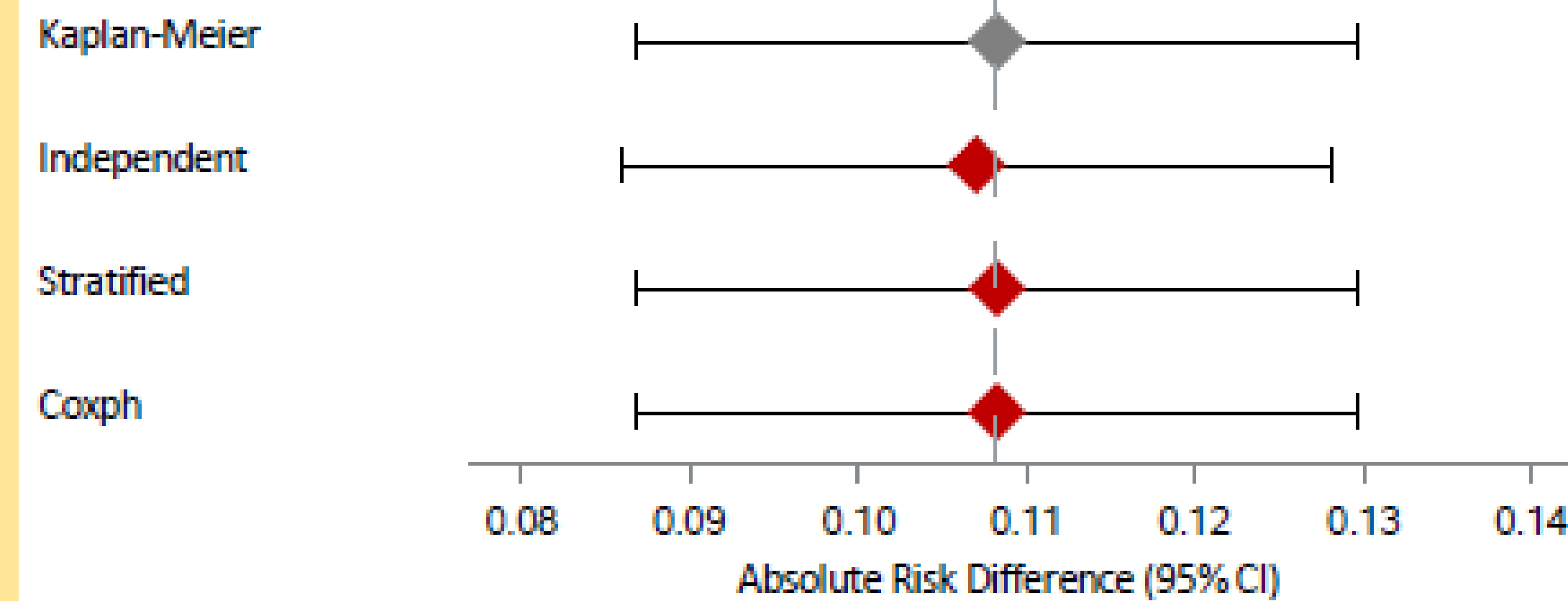


Figure 1. Absolute risk difference at 4 years between patients with CHF versus without CHF by different censoring methods for deriving pseudo-values

Estimating Adjusted Absolute Risk Differences Using Pseudo Values for Censored Data Across Time: Stratified Censoring

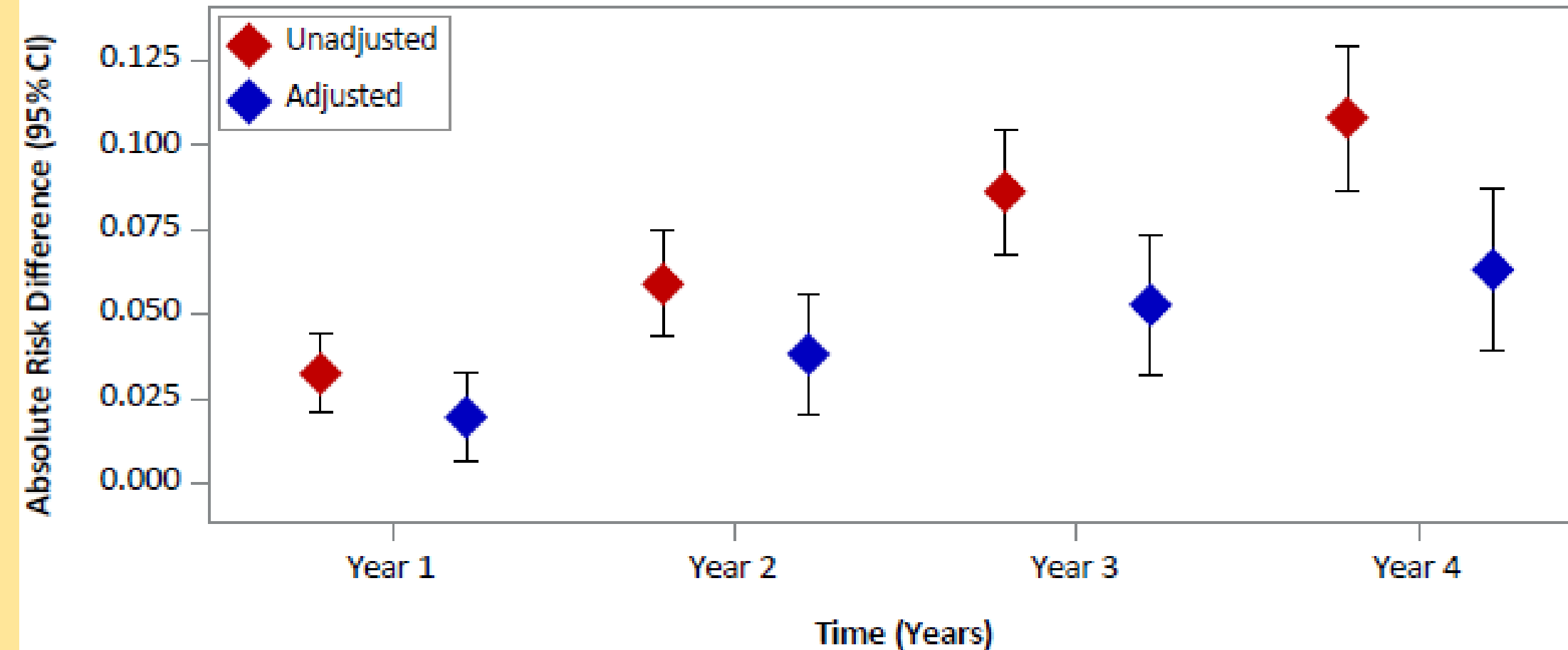


Figure 2. ARD (β_1 estimates) between patients with CHF versus without CHF across time. Adjusted estimates are adjusted for age and NTproBNP

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

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

<http://timi.org/biostatistics>



References:

- Bellavia A, Murphy SA. Summarizing primary results in clinical trials with a time-to-event end point: complementing different measures for a comprehensive assessment of treatment effect. *Circulation*. 2024 Apr 9;149(15):1154-6
- Gerds TA et al. Absolute risk regression for competing risks: interpretation, link functions, and prediction. *Stat in medicine*. 2012.
- Andersen PK, Pohar Perme M. Pseudo-observations in survival analysis. *Statistical methods in medical research*. 2010 Feb;19(1):71-99.
- Klein JP, et al.. SAS and R functions to compute pseudo-values for censored data regression. *Computer methods and programs in biomedicine*. 2008