Causal inference for survival outcomes:

a censored edition

Bianca L De Stavola for STRATOS TG 7

Great Ormond Street Institute of Child Health, University College London

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STRATOS INITIATIVE

Topic group 7: Causal Inference

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STRATOS INITIATIVE

Aims: Overview of the principles that guide current developments in causal inference

- First guidance paper:

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TUTORIAL IN BIOSTATISTICS

Statistics in Medicine WILEY

Formulating causal questions and principled statistical answers

Els Goetghebeur[1,2] | Saskia le Cessie[3] | Bianca De Stavola[4] | Erica EM Moodie[5] | Ingeborg Waernbaum[6] | "on behalf of" the topic group Causal Inference (TG7) of the STRATOS initiative

- Short courses
- Website: ofcaus.org

Basic Principles

- To find a causal answer, start with a causal question. Then:
  1. specify exposure, outcome, population of interest, target causal effects (*e.g.* using potential outcomes)
  2. state assumptions for identification and estimation of effects from the data
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- These are indeed the principles guiding RCTs and, for observational studies, are referred to as "target trial emulation" (TTE).
- A major advantage of TTE: avoidance of errors in data manipulation (*e.g.* immortal time bias, treatment assignment).

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- Identification requires linking observed data to these hypothetical quantities *e.g.* invoking assumptions of no interference, consistency, and positivity.
- Choice of estimation methods: each requiring additional assumptions (*e.g.* no unmeasured confounding, correct (semi-)parametric models).

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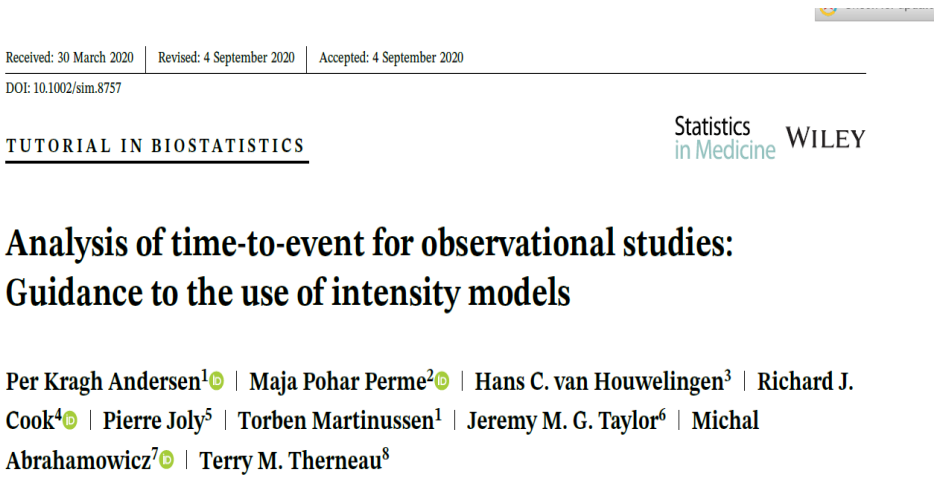
- Discussed by TG8-Survival Analysis:



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TUTORIAL IN BIOSTATISTICS

Statistics in Medicine WILEY

Analysis of time-to-event for observational studies: Guidance to the use of intensity models

Per Kragh Andersen[1] | Maja Pohar Perme[2] | Hans C. van Houwelingen[3] | Richard J. Cook[4] | Pierre Joly[5] | Torben Martinussen[1] | Jeremy M. G. Taylor[6] | Michal Abrahamowicz[7] | Terry M. Therneau[8]

Which aspects of time should we focus on when comparing alternative worlds?

Estimands

Let T_a be the potential survival time if we set A to take the value a by a well-defined (hypothetical) intervention.

(A) Risk scale:
Differences in survival probabilities at relevant times

$$\text{ACE}(t) \;=\; P(T_1 > t) - P(T_0 > t), \quad t \;\text{in}[0, \tau]$$

This is the difference in (marginal) survival functions of POs,

- Interpretation:
risk difference for no event by time t had random patient been treated versus not.

Estimands

(B) Hazard scale:

Contrast of hazards, for example $\frac{\lambda_1(t)}{\lambda_0(t)}$, where

$$\lambda_a(t) = lim_{h \to 0} \frac{1}{h} P(t \leq T_a < t + h | T_a \geq t)$$

- Complication:

  Interpretational difficulties because of the built-in selection due to the conditioning on different subgroups ($T_0 \geq t$ and $T_1 \geq t$)).

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(C) Other scales, *e.g.* speed from Accelerated Failure Time Models.

Comments

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- It depends on the source of censoring: for some it does not always make clinical sense to remove them,
  - Administrative reasons
  - Loss to follow-up
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  - Administrative reasons ✓
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  - Competing event ??

Assumptions

For identification of causal effects for a time-to-event outcome:

- No interference, consistency and positivity of the exposure
- No unmeasured confounding (NUC), *i.e.* : sufficient covariate information regarding treatment assignment confounding
- In the presence of censoring we also require: sufficient covariate information regarding (possibly time-varying) 'common causes' of censoring and event.

The simulation learner

Inspiration: the Rotterdam study [Royston & Lambert, 2009; Sjolander, 2016]

- About 3000 women who had undergone surgery for breast cancer and, for some, hormonal therapy was offered in 1978 to 1993
- Outcome of interest: overall mortality
- Strong negative confounding of the association between therapy and mortality
- Informative loss to follow-up driven by age and year of surgery
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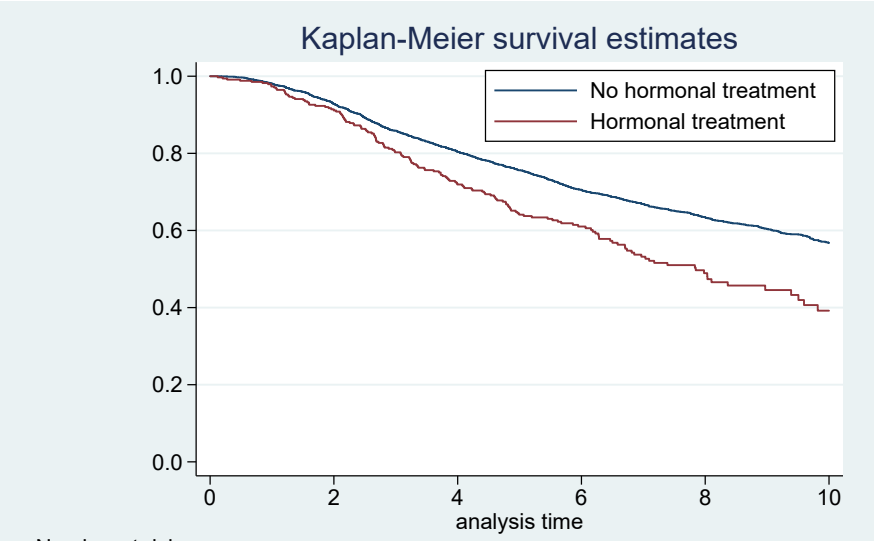
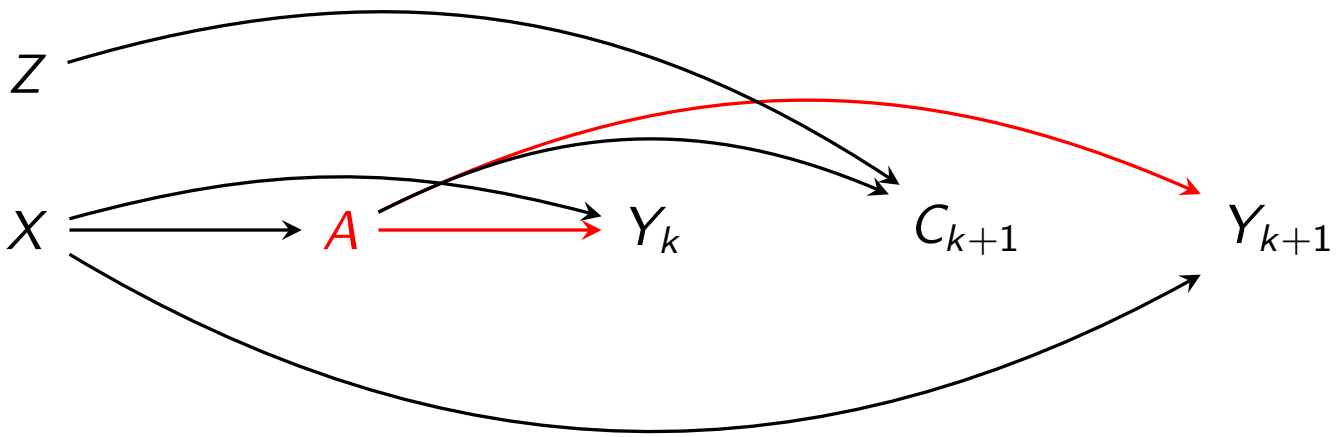


The simulation learner

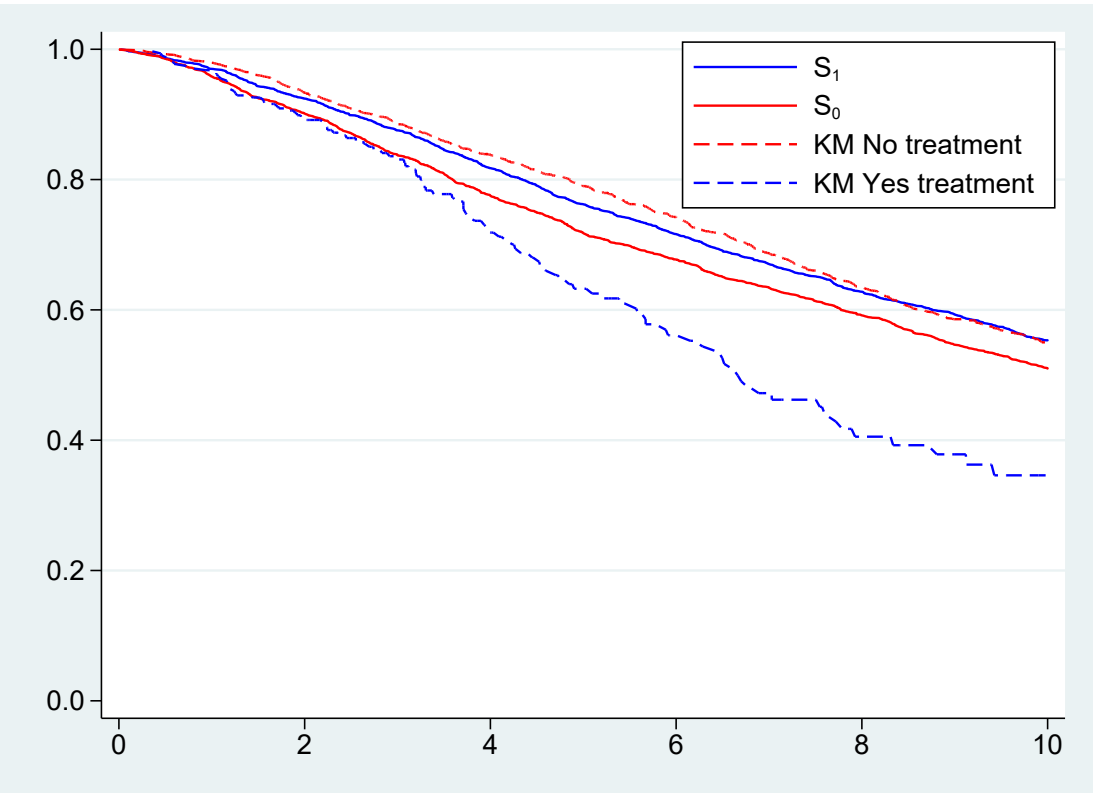
- Excluded women younger than 40 and with surgery before 1982
- Retained all the original confounders data



For a subset of the follow-up:

X: baseline confounders; Z: baseline predictors of censoring and death; A: treatment; C_k: censoring indicator at time t_k; Y_k: outcome at time t_k.

The simulation learner



Estimation of ACE(t)

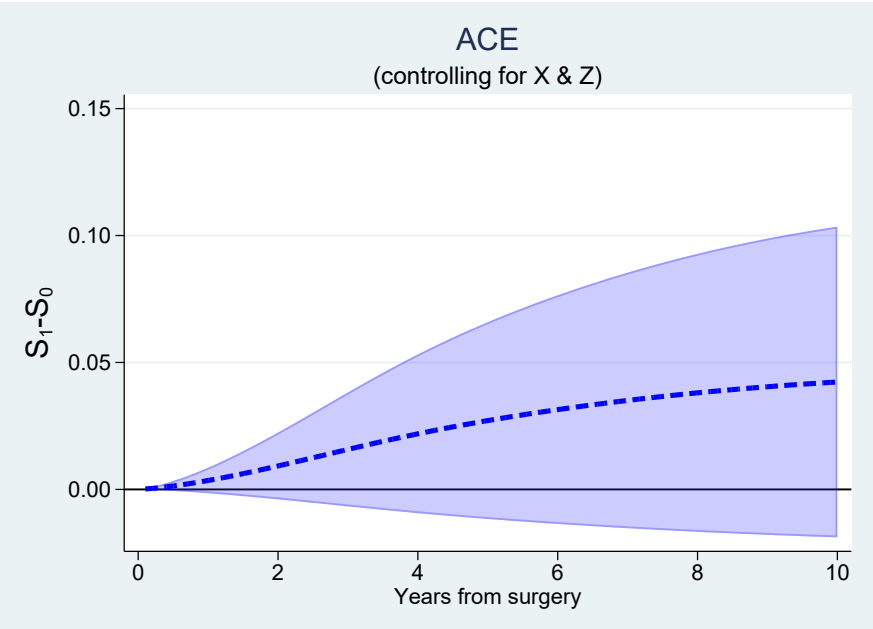
1. Model-based marginal counterfactual survival curves:
   - (Sufficiently) flexible hazard models
   - Derive individual-level predicted potential survival curves
   - Standardisation to the distribution of the observed confounders
   - Compute difference at selected values of t

Estimation of ACE(t)

2. Weighted Kaplan-Meier curves:
   - Fit propensity score model for A and save predicted scores
   - Fit pooled logistic regression model for C and save predicted (time-varying) probabilities
   - Combine the weights
   - Estimate K-M curves using the inverse of these combined values as weights

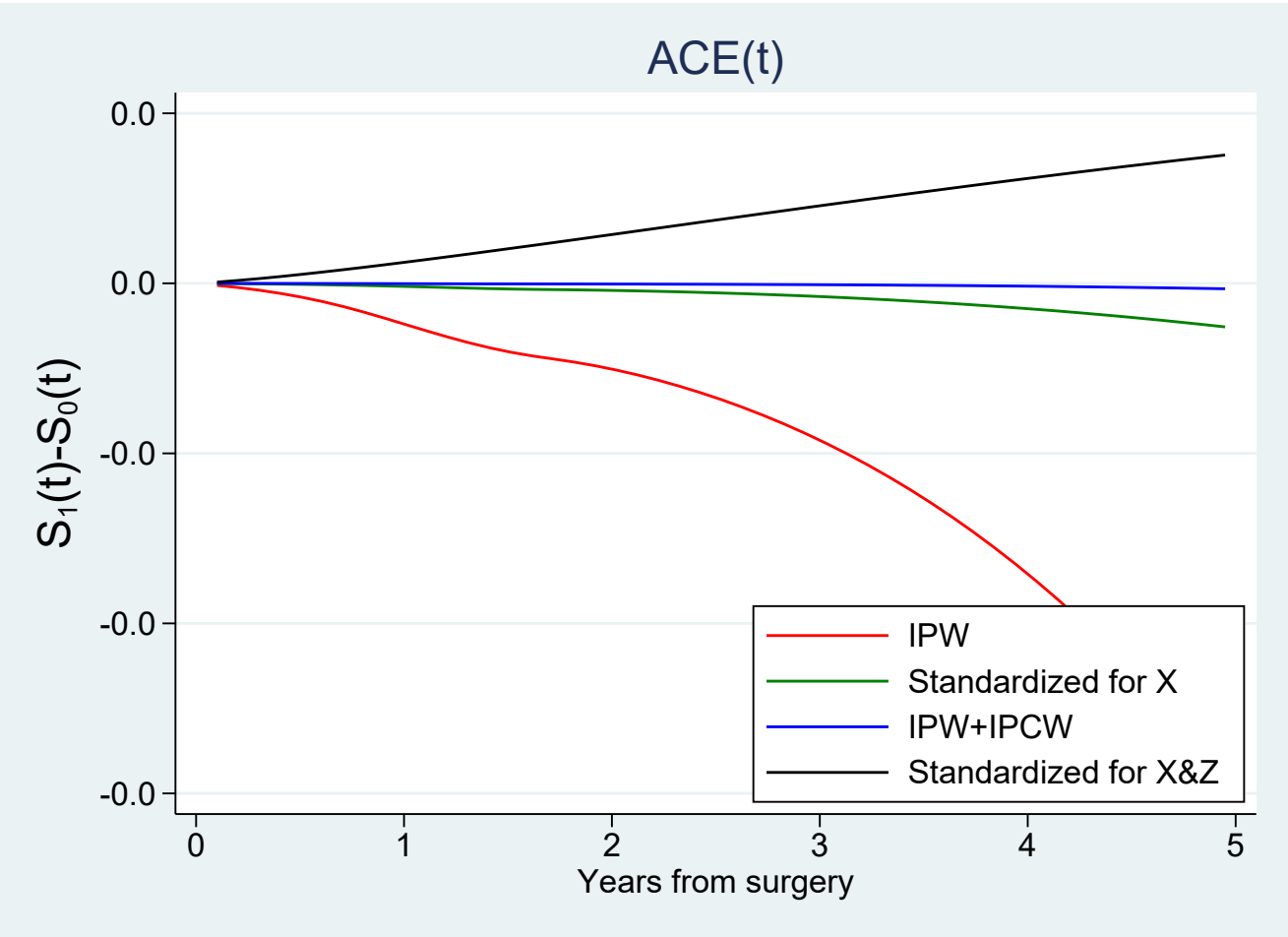
Results

Model-based marginal counterfactual survival curves



Results

All methods together



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- Counterfactual-based causal inference has shifted the focus from model-based parameters to estimands defined irrespectively of any model: we should choose meaningful, clinically relevant quantities
- This should free us from necessarily wanting to express causal effects on the hazard scale:
  - challenges to be interpreted causally
  - useful for deriving the causal estimates of interest.
- Dealing with censoring calls upon a careful choice of potential outcomes.