Dynamic propensity scores matching to evaluate the impact of time-dependent treatment from real life data: illustration with the HFNO-Weaning study

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Plan

Acute respiratory failure and oxygen therapy in critical car unit

- High-flow nasal oxygen therapy (HFNO) is the recommended technique.
- The right time for HFNO weaning is an important to prevent unnecessarily long sojourn (saturation of critical care units, significant cost, etc.).
- It will require a set of randomized clinical trials between weaning and continuing HFNO, with different inclusion criteria, in particular different HFNO durations.

Objective of the HFNO-Weaning study

Clinical trial emulation for comparing the prognosis of early weaning versus delaying the decision.

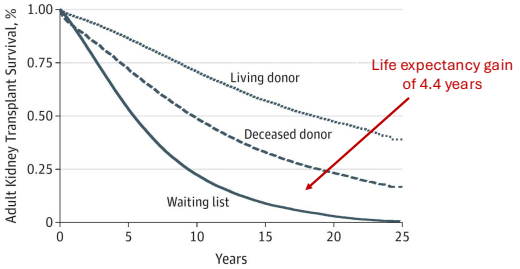
How the impact of two different treatments $(A = 1, 0)$ from real life data ?

- Re-baseline the database at the time of the treatment deliverance : $T = 0$.
- Structure the important characteristics of the patients at $T = 0$, especially the confounders X (causes of both the treatment allocation) and the outcomes.
- Calculate the outcomes, for instance studied events such $D(t) = 1$ if the event occurs before t $(T < t)$ and 0 otherwise.
- Perform statistical analyses such as :
  - Multivariate modelling of the outcomes : $S(t \mid A, X)$.
  - Propensity score (PS)-based approaches with $P(A = 1 \mid X)$.

Example of application in another context : the kidney transplantation

Survival Benefit of Solid-Organ Transplant in the United States

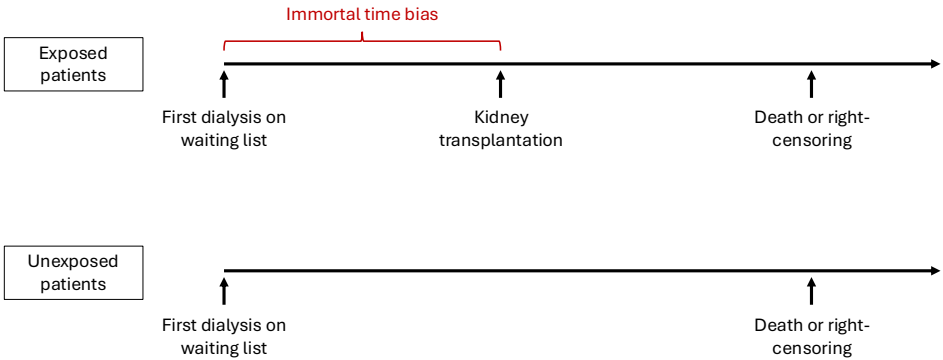
Abbas Rana, MD; Angelika Gruessner, PhD; Vatche G. Agopian, MD; Zain Khalpey, MD, PhD; Irbaz B. Riaz, MBBS; Bruce Kaplan, MD; Karim J. Halazun, MD; Ronald W. Busuttil, MD, PhD; Rainer W. G. Gruessner, MD



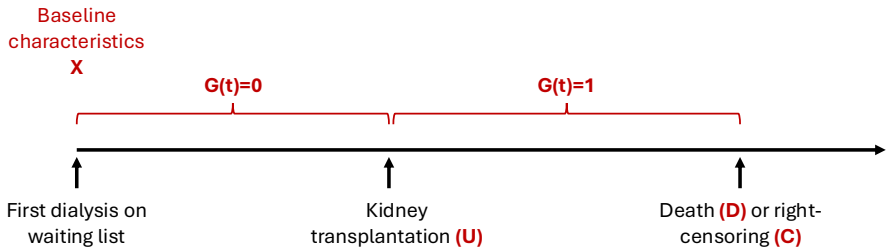
No. at risk

Waiting list	239162	43202	7083	1472	275	32
Deceased donor	148292	74561	27850	8576	1859	16
Living donor	87387	50125	19255	5275	1115	8

An overestimation of the kidney transplantation benefit



The updated Cox model as a solution for dealing with immortal time bias



$$\lambda(d \mid X, G(d)) = \lambda_0(d)\exp(\beta X + \gamma(d-u)G(d))$$

- $\lambda_0(.)$ is the baseline hazard function of the time-to-death.
- β are the regression coefficients associated with the baseline characteristics.
- $\gamma(.)$ is a time-dependent function according to the post-transplantation time.

Wolfe et al., New England Journal of Medicine 1999 ; 341 :1725-1730

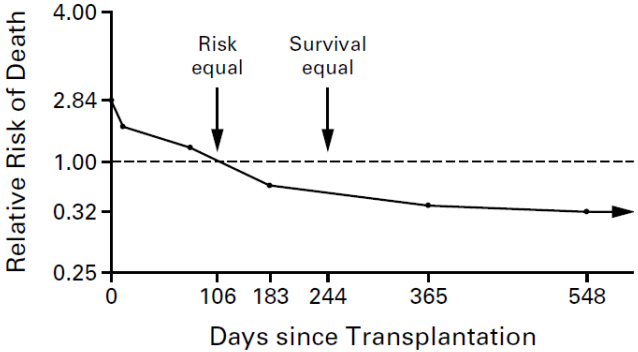


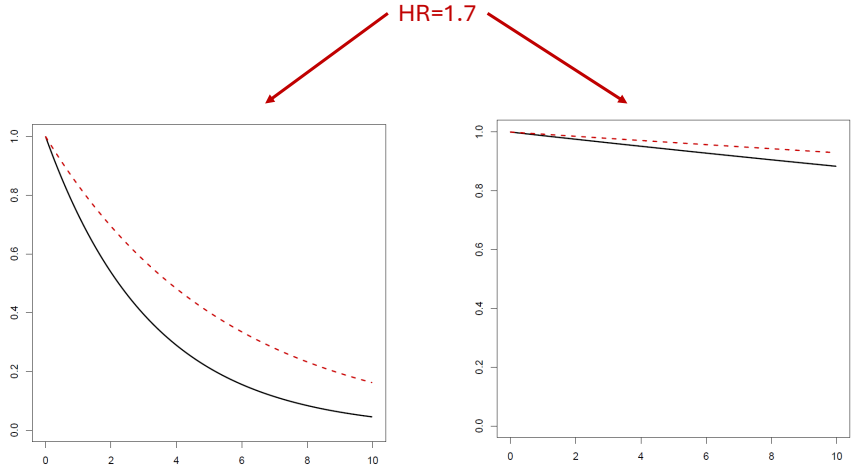
Figure 2. Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

The main limits of results from such an updated Cox model

$$\lambda(d \mid X, G(d)) = \lambda_0(d) \exp(\beta X + \gamma(d-u)G(d))$$

- Post-registration confounders $X(d)$ may bias the results.
- One can expect an overestimation of the KT effect : patients with a deteriorating health are less likely to be transplanted.
- The magnitude of the transplantation effect is difficult to interpret for Hazard Ratio (HR).

Interpretation of Hazard Ratios



Key methodological issues for time-depend exposure

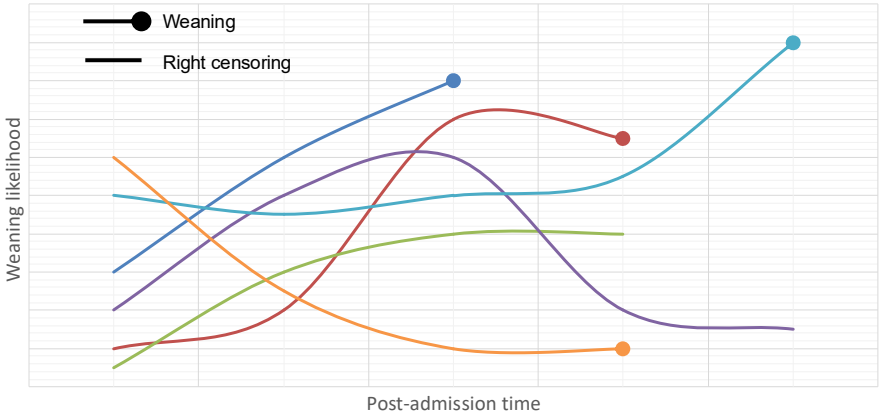
- Several categories of time-dependent treatment :
  - To compare a group of early treated patients ($A = 1$) versus a comparable group not treated patients ($A = 0$).
  - To compare a group of early switched patients ($A = 1$) versus a comparable group maintaining treatment ($A = 0$).
- No baseline $T = 0$ in the control groups ($A = 0$).
- No identification of the confounders (X) at this unknown time.

Plan

Time-dependent PS will be used to :

- Construct the weaning group ($A = 1$), i.e. patients weaned from ventilation at times U.
- Construct the awaiting group ($A = 0$), i.e. comparable patients who were not weaned at same times U.
- Estimate the difference in the number of days without hospitalization for a 90-day follow-up from time U (primary outcome).
- Identify the characteristics at time U that can modify this difference.

We will adapt the method proposed by Lu (Biometrics ; 2005 ;61 :721-728)



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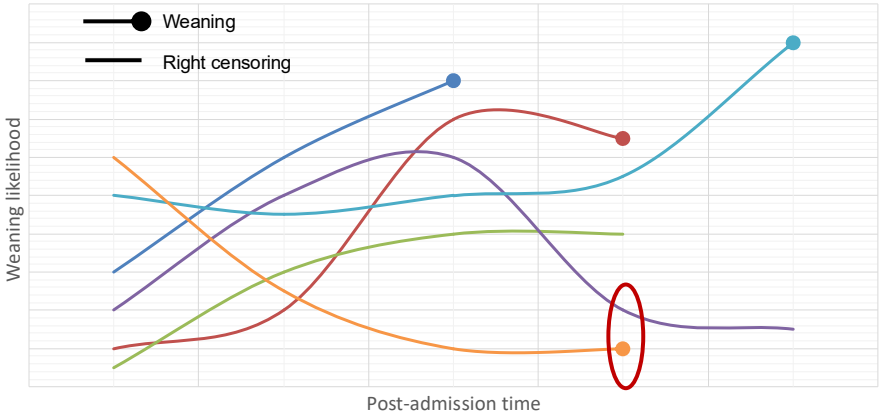

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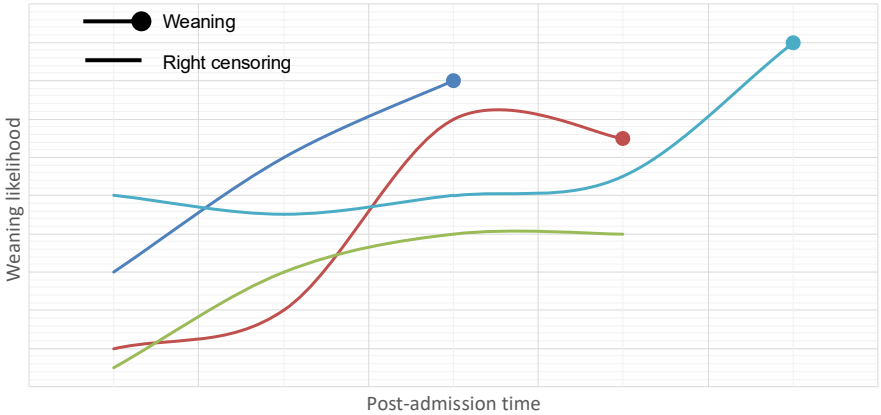

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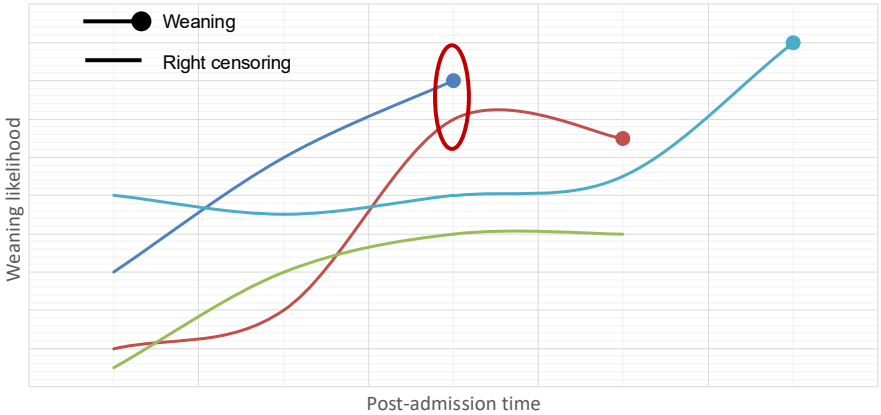

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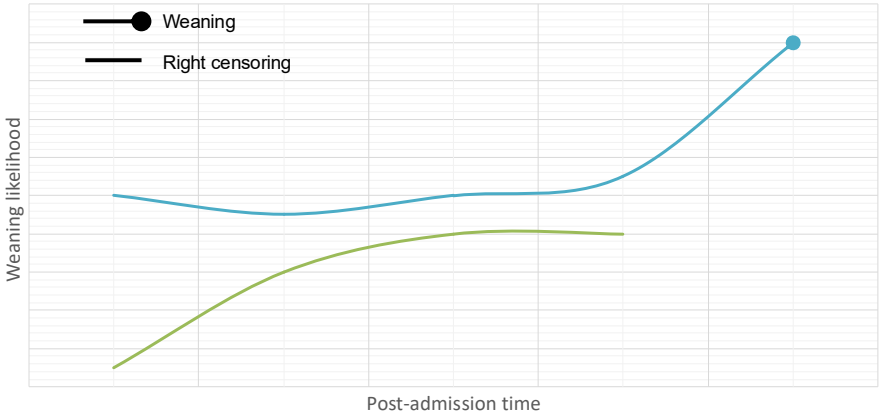

The first step : estimating the time-dependent likelihood of transplantation

- The hazard of HFNO weaning at time u can be estimated by using an updated Cox model :

$$\lambda(u \mid X(u)) = \lambda_0(u) \exp(\beta X(u))$$

- Death will be right-censored.
- We considered :
  - time-fixed observed covariates : age, sex, etc..
  - time-dependent covariates : heart rate, respiratory rate, FiO2, etc.

The second step : matching pairs

- Because the baseline hazard function constant at each matching time point, one can match on the linear predictor $\beta X(u)$ from the Cox model.
- We will use the nearest neighbor matching algorithm with a maximum caliper of 0.20.
- Exact matching was considered for the unbalanced covariates.
- We used random matching without replacement, meaning that once matched, a patient could not be matched again in another pair.

The third step : analysing the matched cohort

- The matching time corresponded to the pseudo-randomization between $A = 1$ or $A = 0$.
- From this baseline, we will compute the mean differences in the outcomes :
  - Number of days without hospitalization for a 90-day follow-up.
  - Critical care length of stay (in days).
  - Critical care mortality (cumulative probability).
  - Patient survival up to 90 days.
- Multivariate models with interactions with A will allow to identify patients profiles with more or less benefit of the switch.