Apprentissage machine: projet applications en recherche clinique

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Plan

The problematic of the method choice for survival prediction

- The prediction of the probability that a subject experienced an event is often of interest.
- Several regressions can be used for right-censored data. :
  - Most of the studies use proportional hazard (PH)-based assumption.
  - Other models such as accelerated failure time (AFT) approaches are not frequent.
- Machine learning is increasingly used and avoids such modeling assumptions :
  - Random survival forests.
  - Survival neural networks.
  - Support-vector machines.
  - Etc.

A super learner (SL) allows us to combine regressions and algorithms

- In 2011, Polley and van der Laan proposed a survival SL (right censoring). [1]
- Two R packages are available :
  - The first one was proposed by Golmakani et al. (2020). It allows us to obtain the linear predictor of a PH regression.
  - The second one was developed by Westling et al. (2021) with additional learners : several parametric PH models, a generalized additive Cox regression, and a random survival forest.
- **We aimed to extend these packages to additional learners and loss functions.**

1. Super Learning for Right-Censored Data. In MJ van der Laan, S Rose (eds.), Targeted Learning, Springer Series in Statistics.

The survival SL is estimated by minimizing the cross-validated loss function

- $S_m(.)$ is the survival function obtained by the m^{th} learner ($m = 1, ..., M$).
- w_m is the corresponding weight with respect to $\sum_1^M w_m = 1$ and $0 \leq w_m \leq 1$.
- The sample is randomly divided into V cross-validated sub-samples.
- For each of the folds, one can estimate the M learners from the training subjects and predict $\tilde{S}_m(.)$ of the leaving subjects.
- The weights $\hat{w}_m$ are then obtained by minimizing the loss function, i.e., distance between the observations and the predictions $\tilde{S}_{sl}(t \mid Z) = \sum_{m=1}^M w_m \tilde{S}_m(t \mid Z)$.
- The final survival SL is obtained by $\hat{S}_{sl}(t \mid Z) = \sum_{m=1}^M \hat{w}_m \hat{S}_m(t \mid Z)$, where $\hat{S}_m(t \mid Z)$ are estimated on the entire sample.

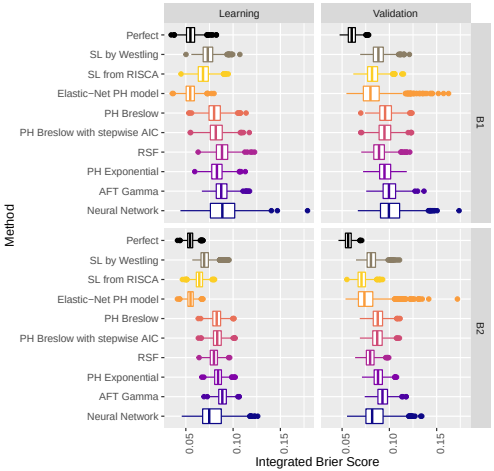
The implemented learners

- Parametric AFT models. (Weibull, Gamma and generalized Gamma distributions).
- Parametric PH models (Exponential or Gompertz distributions).
- Semiparametric PH models with a non-parametric baseline hazard function estimated by using the Breslow estimator (with an option for covariates selection by forward AIC-based selection).
- Penalized PH models (Lasso, Ridge, or Elastic-Net). The quantitative covariates are transformed with B-splines to relax the log-linear assumption.
- Random survival forests.
- Survival neural networks (NN). The linear predictor of the previous semi-parametric PH model is obtained by a single hidden layer network with non-linear activation functions.

The implemented loss functions

- The Brier Score (BS) for right-censored data and a prediction at time t.
- The negative binomial log-likelihood (BLL) for a prognostic at time t.
- The integrated BS and BLL up to the maximum follow-up time.
- The restricted integrated BS and BLL up to a time t.

The performances of the survival SL



Our recent implementation of neural network for survival data in R : the partial logistic regression approach (PLANN)

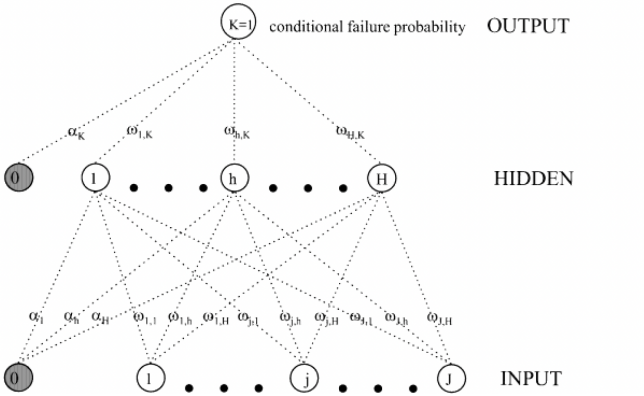


FIGURE – Biganzoli et al. Feed forward NN for t censored survival data. Stat Med. (1998)

The current developments of R packages

- The survival neural network (PLANN) :

`https://github.com/chupverse/survivalPLANN`
`https://cran.r-project.org/package=survivalPLANN`

- The survial super learner :

`https://github.com/chupverse/survivalSL`
`https://cran.r-project.org/package=survivalSL`

Plan

Context

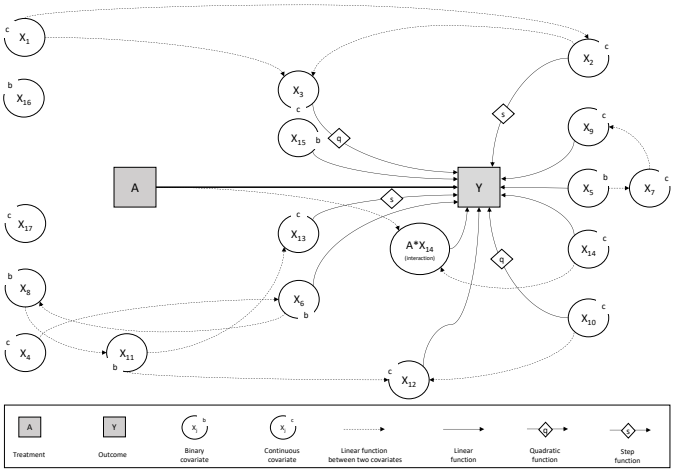
- In a randomized clinical trial with individual randomization (RCT), the random treatment allocation aims to balance the prognostic factors.
- But residual differences due to chance may persist, namely near-confounders.
- Three categories of methods for estimating marginal effects : propensity score, G-computation, and doubly robust estimators).
- Regarding our previous results in observational studies, [2] we hypothesized that G-computation associated with ML could be suitable for RCTs.

2. Le Borgne et al. G-computation and machine learning for estimating the causal effects of binary exposure statuses on binary outcomes. Sci Rep (2021)

The G-computation

- Let (Y, A, X) the binary outcome , the 1 :1 randomized treatment, and the set of baseline prognostic factors.
- Fit the outcome model.
- Predict the potential outcomes as if the subjects were included in the two arms.
- Compute the difference of the mean of the potential outcomes.
- We considered several models and algorithms as outcome models : Lasso and Elasticnet logistic regression, neural networks, support vector machine, and super learner of the previous methods.

The simulations



The simulations

Sample size	mOR*	Method	Absolute mean bias				log mÔR				
			$\hat{\pi}_0$	$\hat{\pi}_1$	log mÔR	$\hat{\Delta}$	RMSE	VEB	Coverage	Error†	RSS
$n = 200$	1.9	Unadjusted	0.03%	-0.02%	0.0044	-0.05%	0.29	-0.43%	94.57%	42.58%	0.00%
		Elasticnet	-0.10%	0.03%	0.0108	0.13%	0.24	0.61%	94.54%	26.07%	31.07%
		Lasso	-0.11%	-0.07%	0.0071	0.04%	0.24	3.59%	95.24%	27.19%	27.53%
		Neural network	1.36%	-2.27%	-0.1439	-3.63%	0.27	-5.14%	93.07%	48.56%	-30.94%
		Support vector machine	0.80%	-1.78%	-0.1034	-2.59%	0.24	-9.94%	90.88%	31.22%	18.18%
		Super learner	1.71%	-0.58%	-0.0890	-2.29%	0.24	-7.09%	92.22%	29.16%	22.86%
	1.3	Unadjusted	0.00%	-0.06%	0.0000	-0.06%	0.29	-1.19%	91.96%	86.69%	0.00%
		Elasticnet	-0.11%	-0.08%	-0.0030	0.02%	0.24	-0.42%	95.04%	82.20%	32.90%
		Lasso	-0.13%	-0.12%	0.0025	0.01%	0.24	2.23%	94.65%	83.34%	30.28%
		Neural network	0.55%	-1.73%	-0.0899	-2.27%	0.23	3.16%	94.14%	92.03%	-79.15%
		Support vector machine	0.73%	-0.33%	-0.0415	-1.06%	0.21	-3.04%	94.80%	83.42%	25.90%
		Super learner	1.37%	0.20%	-0.0456	-1.17%	0.21	-3.01%	93.57%	83.94%	20.42%
	1.0	Unadjusted	-0.03%	0.02%	0.0020	0.05%	0.29	-1.38%	94.09%	5.93%	-
		Elasticnet	-0.13%	-0.08%	0.0020	0.05%	0.24	0.21%	94.39%	5.61%	-
		Lasso	-0.15%	-0.09%	0.0024	0.06%	0.24	2.72%	94.83%	5.17%	-
		Neural network	-0.05%	-1.25%	-0.0493	-1.20%	0.21	10.24%	95.76%	4.24%	-
		Support vector machine	0.58%	0.67%	0.0036	0.09%	0.20	-0.02%	94.20%	5.80%	-
		Super learner	1.10%	0.80%	-0.0131	-0.30%	0.20	-0.05%	94.01%	5.99%	-

Conclusions

- G-computation with Elasticnet and splines when appropriate represents a relevant approach for increasing the power of RCTs.
- This approach is particularly effective when the outcome model has significant predictive capacities.
- It remains robust even with very small sample sizes ($n = 60$).
- We should avoid complex outcome models when the sample size is small.

Plan

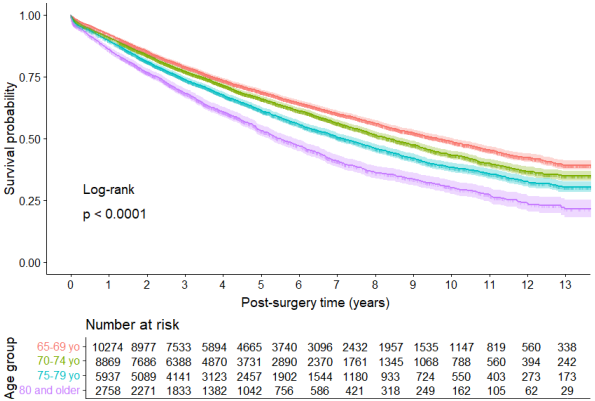
Context

- There has been an increase in the incidence of cancers but a decrease in associated mortality.
- Interest in predicting probability of cure and time to cure for the right to be forgotten and the patient information
- Two competing deaths : $Y = (E, P)$ due or not to the cancer.

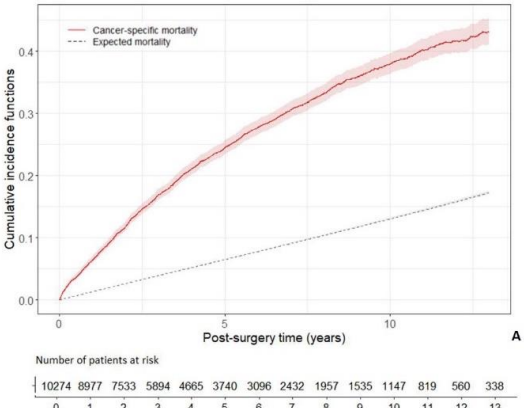
$$\lambda_O(t \mid X_P, X_E) = \tilde{\lambda}_P(t \mid X_P) + \lambda_E(t \mid X_E)$$

  - $\lambda_O(t \mid .)$ is the overall instantaneous hazard at time t.
  - $\tilde{\lambda}_P(t \mid X_P)$ is the population hazard and X_P the predictors : age, sex, and year of diagnosis.
  - $\lambda_E(t \mid X_E)$ the excess hazard and X_E the predictors : age, sex, and type of cancer.

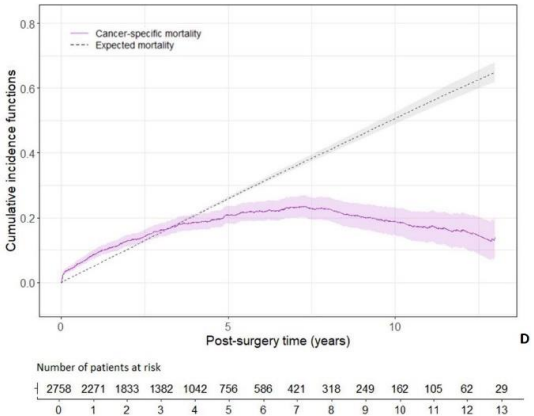
Current application : post-surgery lung cancer (French EPITHOR registry)



Cumulative incidence functions in patients in-between 60 and 69 years old



Cumulative incidence functions in patients older than 80 years



The current flexible strategy for time-to-cure estimation [3]

- Maximum likelihood estimation for each stratum s, c :

$$\lambda_E(t \mid sex = s, cancer = c, age = a) = \lambda_{b,s,c}(t) \exp\Big(\sum_i \beta_{s,c,i}(t) \mathbb{1}\{a \in A_i\}\Big)$$

  - $\lambda_{s,c}(t)$, strata-specific baseline hazard function by cubic splines (4 internal nodes).
  - $A_1 = [45; 55[$, $A_2 = [55; 65[$, $A_3 = [65; 75[$
  - $\beta_{s,c,i}(t)$, strata-specific function by cubic splines (2 internal nodes).

- Avoid assumptions of log-linearity and hazards proportionality.

3. Boussari et al. A new approach to estimate time-to-cure from cancer registries data. Cancer Epidemiology 2018.

Method limitations : small effective per stratum [4]

Cancer site	15-44 years		45-54 years		55-64 years		65-74 years	
	P (95% CI)	TTC (95% CI)	P (95% CI)	TTC (95% CI)	P (95% CI)	TTC (95% CI)	P (95% CI)	TTC (95% CI)
Breast	72 (71-74)	12.1 (11.5-12.7)	80 (80-81)	10.6 (10.0-11.1)	79 (78-79)	11.2 (10.6-11.8)	73 (71-74)	12.3 (11.7-12.9)
Central nervous system	38 (33-42)	10.4 (6.2-14.5)	19 (15-23)	10.8 (3.3-18.3)	NC	NC	NC	NC
Cervix uteri	77 (75-79)	6.5 (4.3-8.7)	63 (60-67)	8.5 (4.6-12.5)	49 (45-53)	11.0 (7.6-14.5)	46 (42-51)	10.7 (6.3-15.2)
Colon [a]	62 (58-66)	7.4 (3.8-11.1)	62 (59-64)	6.8 (4.5-9.2)	58 (56-60)	8.1 (6.1-10.1)	55 (53-57)	8.6 (6.9-10.2)
Colon and Rectum	62 (59-65)	7.6 (4.8-10.4)	59 (57-61)	8.1 (6.2-10.0)	58 (57-60)	8.5 (7.1-10.0)	53 (52-55)	9.2 (7.9-10.5)
Corpus uteri	81 (75-86)	6.8 (0.3-13.3)	77 (73-79)	8.4 (3.6-11.8)	75 (73-77)	8.8 (6.5-11.1)	63 (60-65)	10.9 (8.8-13.0)

FIGURE – Proportion of cured patients (P)and time-to-cure (TTC) in women.

4. Romain et al. Time-to-cure and cure proportion in solid cancers in France. A population based study. Cancer Epidemiology, 2019.

Our proposal : estimate $\lambda_{O,i}(.)$ by ML and deduce the other quantities

- Excess hazard function

$$\lambda_{E,i}(t \mid X_{Ei}) = \lambda_{O,i}(t \mid X_{Ei}, X_{Pi}) - \tilde{\lambda}_{P,i}(t \mid X_{Pi})$$

- Cumulative incidence functions ($k = E, P$) :

$$F_{k,i}(t \mid X_{Ei}, X_{Pi}) = Pr(T_i \leq t, Y_i = k) = \int_0^t S_{O,i}(u- \mid X_{Ei}, X_{Pi}) \tilde{\lambda}_{k,i}(u \mid X_{Pi}) du$$

- Probability of being cured, i.e. , dying from another cause :

$$P_i(X_{Ei}, X_{Pi}) = F_{P,i}(\infty \mid X_{Ei}, X_{Pi})$$

- Probability of being cured in patients alive at time t :

$$Pr(Y_i = P \mid T_i \geq t) = \frac{Pr(T_i \geq t \mid Y_i = P) Pr(Y_i = P)}{Pr(T_i \geq t)} = \frac{P_i(X_{Ei}, X_{Pi})}{S_{E,i}(t \mid X_{Ei})}$$

Application in patients with colon cancer in the Slovene registry (R data)

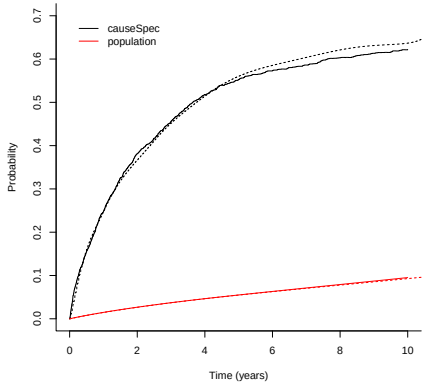


FIGURE – Marginal cumulative incidence functions $F_P(t)$ and $F_E(t)$. Solid line : the Pohar-Perm non-parametric estimation. Dotted line :the Survival Neural Network.

The current developments of R packages

- The survival neural network with relative survival :

`https://github.com/chupverse/survivalPLANN`
`https://cran.r-project.org/package=survivalPLANN`

- The flexible B-spline approach :

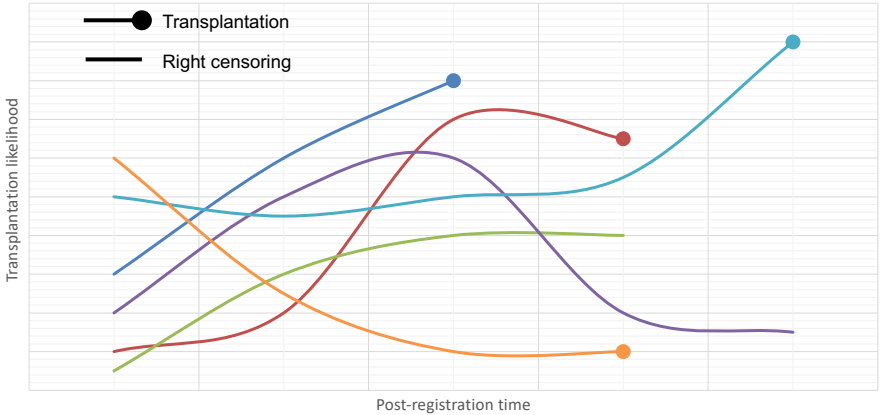
`https://github.com/chupverse/survivalNET`

Plan

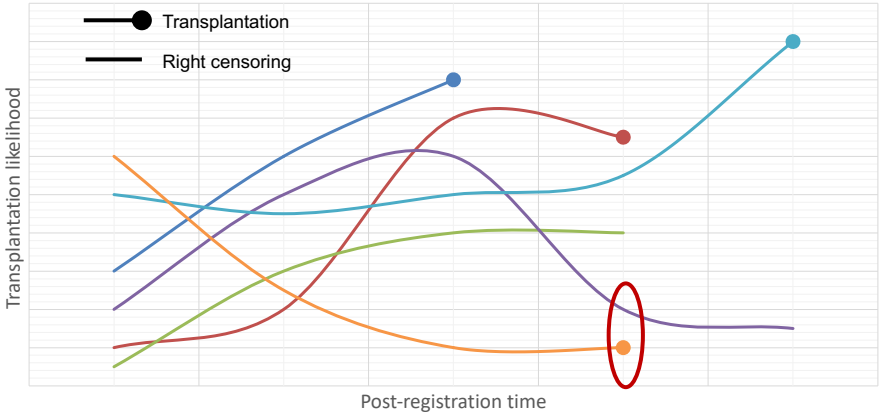
Context

- The estimation of the impact of a treatment/exposure versus no intervention from real life data.
- Example : the impact of transplantation compared to waiting in dialysis.
- Two main issues :
  - The unbalanced time-dependent confounders at the time of the decision.
  - The absence of event to determine the baseline in the non-intervention group.

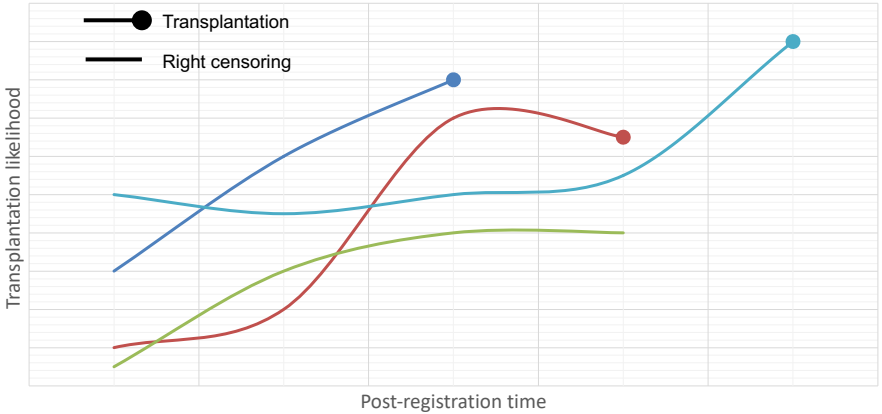
Matching on time-dependent propensity scores



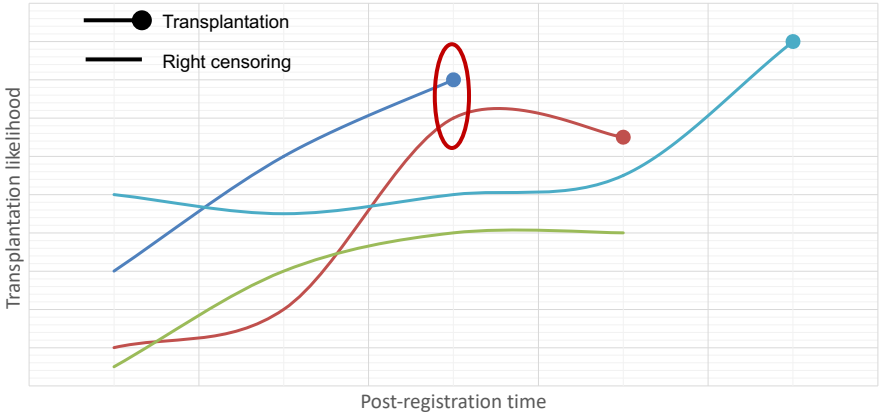
Matching on time-dependent propensity scores



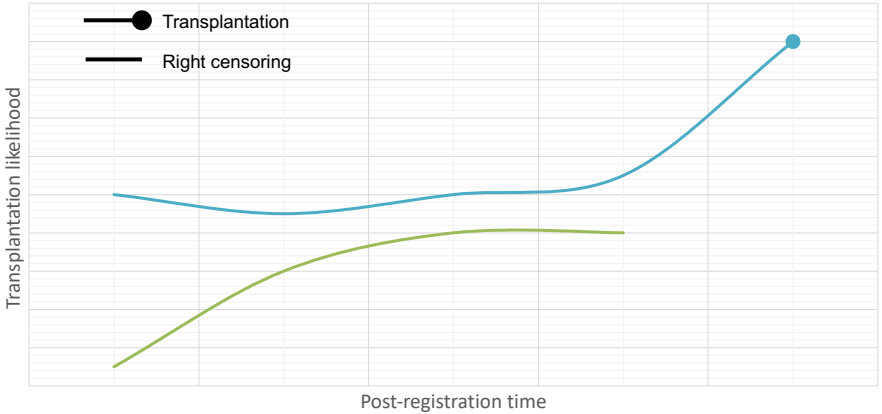
Matching on time-dependent propensity scores



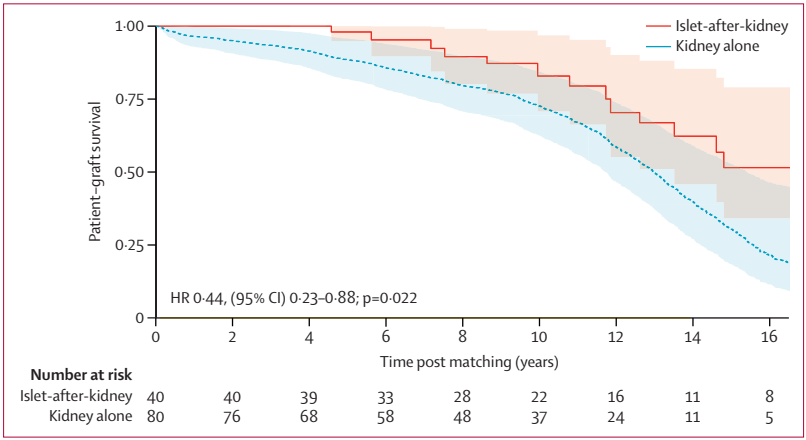
Matching on time-dependent propensity scores



Matching on time-dependent propensity scores



Islet-after-kidney transplantation versus kidney alone (type 1 diabetes) [5]



5. Maanaoui, et al. The Lancet Diabetes and Endocrinology, 2024.

The issue when modeling time-dependent propensity scores

- The time-dependent predictors : $X(t)$.
- The time-varying effects of the time-dependent predictors : $\beta(t)$.

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

- The "manual" modeling of such an updated Cox model is complex.
- Its construction cannot be included in the estimation of confidence intervals by bootstrapping.

Our objective

- To describe the interest of survival SL for estimating the time-dependent propensity scores.

Acknowledgments

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