Net time-dependent ROC curves: a solution for evaluating the accuracy of a marker to predict disease-related mortality

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Introduction (1)

Prognostic markers of all-cause mortality, essential to :

- identify subjects at high-risk of death
- optimize healthcare management

⇒ The capacity of a score to predict all-cause deaths is evaluated by using **time-dependent ROC curves** [1]

Limits

- an important part of the mortality not related to the chronic disease
- impossibility to identify excess deaths

⇒ Solution : distinguish between the expected mortality and the excess mortality, by using **additive net survival model**.

[1] Heagerty et al., Biometrics, 2000.

Introduction (2)

Objective

- Evaluate the capacity of a marker to predict disease-specific mortality, deaths for which medical specialists can act

Notations

- X : Random variable representing the prognostic marker
- x_j : Observation for the subject j
- n : Sample size, $j = 1, \ldots, n$
- T_{Ej} : Time to death related to the disease
- T_{Pj} : Time to expected death
- $T_j = min(T_{Ej}, T_{Pj})$: Time of the death
- C_j : Time of the last follow-up point (right censoring)
- $H(t)$, $H_E(t)$ and $H_P(t)$: Cumulative hazard functions of T, T_E and T_P at time t

Definition

New estimator : net time-dependent ROC curve

- represents the **net sensitivity** plotted against 1 - the **net specificity** for all the thresholds c of a marker X

  By defining a binary test at the cut-off c,

  - **Net sensitivity** : proportion of positive test ($X > c$) given that the disease-related death occurs before time t :

  $$se_t(c) = Pr(X > c | T_E \leq t)$$

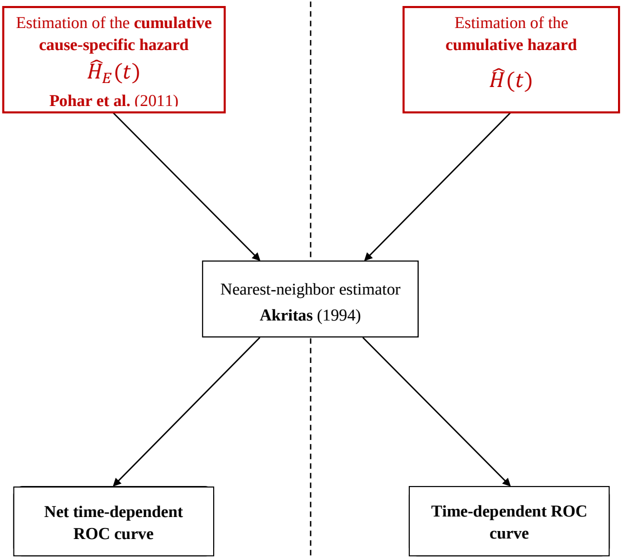
  - **Net specificity** : proportion of negative test ($X \leq c$) given that the disease-related death does not occur before time t :

  $$sp_t(c) = Pr(X \leq c | T_E > t)$$

⇒ **Question** : How estimate the net sensitivity and the net specificity ?

New estimator

Lorent et al. (submited) | **Heagerty et al.** (Biometrics, 2000)



Net sensitivity and net specificity

By adapting the approach of Heagerty (Biometrics, 2000)

the two probabilities can be developed :

- $se_t(c) = \{(1 - G_X(c)) - S_{X,E}(c,t)\}/\{1 - S_{X,E}(-\infty,t)\}$
- $sp_t(c) = 1 - \{S_{X,E}(c,t)/S_{X,E}(-\infty,t)\}$

Estimation of $S_{X,E}(c,t)$: bivariate survival function of X and T_E

⇒ implies to estimate $H_E(t|X = x_j)$, can be obtained from :

- $\hat{H}_E(t)$ [2]
- the calculation of the conditional at-risk and counting process (Use of Akritas estimator [3])
  - $Y_{jl}^{\pi}(t) = I(T_l > t, C_l > t, |\hat{G}_X(x_j) - \hat{G}_X(x_l)| < \pi)/S_{Pl}(t)$
  - $N_{jl}^{\pi}(t) = I(T_l \leq t, C_l \geq T_j, |\hat{G}_X(x_j) - \hat{G}_X(x_l)| < \pi)/S_{Pl}(t)$

[2] Pohar et al., Biometrics, 2011.
[3] Akritas, Annals of Statistics, 1994.

Net time-dependent ROC curve

Estimation of $se_t(c)$ and $sp_t(c)$

- the conditional cumulative excess hazard function is estimated by :

$$\hat{H}_E(t|X = x_j) = \int_0^t \frac{dN_{j.}^{\pi}(u)}{Y_{j.}^{\pi}(u)} - \int_0^t \frac{\sum_{l=1}^{n} Y_{jl}^{\pi}(u) dH_{Pj}(u)}{Y_{j.}^{\pi}(u)}$$

$\Rightarrow$ Allows to obtain :

- an estimation of $S_{X,E}(c, t)$
- an estimation of the net sensitivity and the net specificity for all the thresholds c

$\Rightarrow$ Representation of the net time-dependent ROC curve
Area under the curve = net AUC

Simulations (1)

Objective : validate the proposed estimator

3 different scenarios were considered

- Expected ages of death in general population were simulated to establish life tables
- Excess times-to-death were simulated

$\Rightarrow$ Distinction is possible between expected deaths and excess deaths

$\Rightarrow$ Calculation of the cause-specific AUC by censoring the expected deaths

$\Rightarrow$ Comparison between the traditional AUC, the cause-specific AUC and the net AUC for each sample

Simulations (2)

Censoring rate	Effective	All-cause AUCt	Cause-specific AUCt	Net AUC
≈ 0.30	n=100	0.769 (0.049)	0.955 (0.015)	0.891 (0.089)
	n=250	0.774 (0.035)	0.963 (0.008)	0.906 (0.061)
	n=500	0.773 (0.024)	0.963 (0.006)	0.912 (0.049)
	n=1000	0.772 (0.017)	0.964 (0.004)	0.910 (0.038)
≈ 0.50	n=100	0.756 (0.056)	0.945 (0.017)	0.872 (0.094)
	n=250	0.766 (0.034)	0.954 (0.010)	0.886 (0.067)
	n=500	0.764 (0.024)	0.953 (0.007)	0.888 (0.051)
	n=1000	0.765 (0.018)	0.955 (0.005)	0.889 (0.037)
≈ 0.70	n=100	0.747 (0.063)	0.940 (0.020)	0.839 (0.105)
	n=250	0.754 (0.043)	0.941 (0.014)	0.850 (0.073)
	n=500	0.752 (0.032)	0.944 (0.009)	0.846 (0.057)
	n=1000	0.750 (0.019)	0.943 (0.006)	0.843 (0.034)

Results

⇒ The net AUC provide significant correction of the all-cause AUC

⇒ The net AUC is closer to the cause-specific AUC

Kidney transplantation

Definition

- Disease associated = End stage renal disease
- Choice treatment = Kidney transplantation
- Possible trajectories after kidney graft :
  - return to dialysis
  - patient death related to the disease or not. Distinction is often impossible

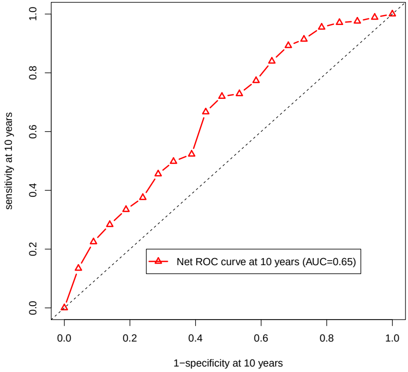
$\Rightarrow$ Endpoint studied in the following applications : patient death related to the disease

Kidney transplant recipients data (1)

Prognostic score of mortality of Hernandez [4]

- tested by using DIVAT cohort from Nantes Hospital (n=1230)
- 10 years prognostic, *net AUC* = 0,65, IC_{95}% = [0,56 - 0,72]

⇒ Difficult to validate the score in the prediction of excess deaths



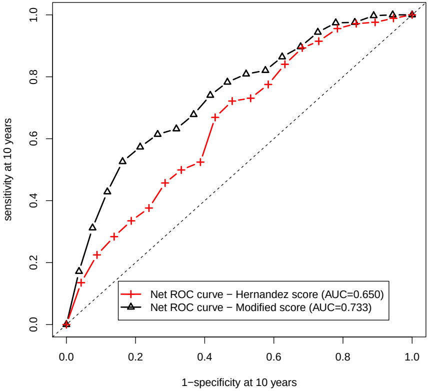
[4] Hernandez, Transplantation, 2009.

Kidney transplant recipients data (2)

Other prognostic score of mortality, created from DIVAT cohort

- 10 years prognostic, *net AUC* = 0,73, $IC_{95}\%$ = [0,64 - 0,80]

⇒ Capacity of this score to predict the disease-related mortality : acceptable



Interest of this method

Net time-dependent ROC curve

- useful when attribution of the deaths is impossible
- *net AUC* at time *t* is interpretable :

  for two patients randomly selected, probability that the patient with the higher value of the marker dies because of the disease, before the patient with the lower value.
- can be applied to others areas of medicine and biology
- implemented in an R package `ROCt` available at : http ://www.divat.fr/en/softwares/roct

Limits

Limits

- When a distinction is feasible between deaths related to the disease and those that are not $\Rightarrow$ competing risk model
- When all the observed mortality is related to the disease $\Rightarrow$ time-dependent ROC curve **OR** net time-dependent ROC curve
- The use of the proposed estimator in the presence of informative censoring $\Rightarrow$ noticeable effect on the results

Thank you for your attention !

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