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.

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\(^1\) Heagerty et al., Biometrics, 2000.
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. (submitted)

Estimation of the cumulative cause-specific hazard
\( \hat{H}_E(t) \)

Pohar et al. (2011)

Nearest-neighbor estimator
Akritas (1994)

Heagerty et al. (Biometrics, 2000)

Estimation of the cumulative hazard
\( \hat{H}(t) \)

Net time-dependent ROC curve

Time-dependent ROC curve
By adapting the approach of Heagerty (Biometrics, 2000) the two probabilities can be developed:

- \(\text{set}(c) = \{(1 - G_X(c)) - S_{X,E}(c, t)\}/\{1 - S_{X,E}(-\infty, t)\}\)
- \(\text{sp}(c) = 1 - \{S_{X,E}(c, t)/S_{X,E}(-\infty, t)\}\)

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

\(\Rightarrow\) 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\(^3\))

\(Y_{j\pi}(t) = I(T_i > t, C_i > t, |\hat{G}_X(x_j) - \hat{G}_X(x_l)| < \pi)/S_{Pl}(t)\)
\(N_{j\pi}(t) = I(T_i \leq t, C_i \geq T_j, |\hat{G}_X(x_j) - \hat{G}_X(x_l)| < \pi)/S_{Pl}(t)\)

\(^2\)Pohar et al., Biometrics, 2011.
Estimation of $se_t(c)$ and $sp_t(c)$

- the conditional cumulative excess hazard function is estimated by:

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

⇒ 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 $c$

⇒ Representation of the net time-dependent ROC curve
Area under the curve = net AUC
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

⇒ Distinction is possible between expected deaths and excess deaths

⇒ Calculation of the cause-specific AUC by censoring the expected deaths

⇒ Comparison between the traditional AUC, the cause-specific AUC and the net AUC for each sample
### Results

- **The net AUC provide significant correction of the all-cause AUC**
- **The net AUC is closer to the cause-specific AUC**

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

⇒ Endpoint studied in the following applications: patient death related to the disease
Kidney transplant recipients data (1)

Prognostic score of mortality of Hernandez

- tested by using DIVAT cohort from Nantes Hospital (n=1230)
- 10 years prognostic, net $AUC = 0.65$, $IC_{95\%} = [0.56 - 0.72]$

$\Rightarrow$ Difficult to validate the score in the prediction of excess deaths

![Net ROC curve at 10 years (AUC=0.65)](image)

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 **RO Ct** available at:
  
  http://www.divat.fr/en/softwares/roct
Limits

• When a distinction is feasible between deaths related to the disease and those that are not ⇒ competing risk model

• When all the observed mortality is related to the disease ⇒ time-dependent ROC curve OR net time-dependent ROC curve

• The use of the proposed estimator in the presence of informative censoring ⇒ noticeable effect on the results
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