Time-dependent ROC analysis for a three-class prognostic

Application on the kidney transplant recipients

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Introduction (1)

Context

- The 1-year creatinine clearance (CrCl) is today an accepted surrogate marker of the long-term evolution of kidney transplant recipient.
- The CrCl is used in many protocols of clinical research as the principal outcome.
- Problem: Based on the usual receiver operating characteristic (ROC) curves, Kaplan et al. [1] demonstrated that the CrCl does not constitute a good predictive marker.

Two methodological issues of using the usual ROC curves

- Three possible prognostics: the death, the return in dialysis and the functional graft.
- The longitudinal data can be incomplete with right-censoring
Introduction (2)

Recent developments

- ROC curves for a diagnostic with more than 2 classes:
  - Mossman [2], Heckerling [3] and He et al. [4]
- The time-dependant ROC theory in the context of survival data:
  - Heagerty et al. [5, 6, 7]

Objective

- To adapt the ROC approach to a three-class prognostic with censoring data
- To evaluate the predictive capacity of the 1-year CrCl to predict the long-term evolution
The multi-state process (1)

Notations

- Two competitive failures $X (X = \{1, 2\})$
- Let $T$ be the failure time of the first event
- $Y$ the marker value at the origin of the follow-up ($Y \in \mathbb{R}$)
- $P_i$ denotes the probability that the first failure is $i$
  - Since $i = 1, 2$, then $P_1 = 1 - P_2 \in [0, 1]$
  - Logistic function: $P_1 = \exp(\alpha)/\{1 + \exp(\alpha)\}, \forall \alpha \in \mathbb{R}$
- According to the semi-markovian property [8], $S_i(t)$ is the specific survival function of the failure $i$
  - $S_i(t) = P(T > t|X = i)$
- Proportional hazard assumption: $S_i(t|Z_i) = S_{0i}(t)^{\exp(Z_i)}$
  - $S_{0i}(t)$ is the baseline survival function specific to the failure $i$
  - $\beta_i$ is the regression parameter associated with the failure $i$
  - $Z_i = \beta_i Y$ is the score of risk associated with the marker $Y$ and the failure $i$
The multi-state process (2)

Estimation

- The log likelihood is defined by:

\[
\sum_{j=1}^{N} \left\{ \sum_{i=1}^{2} \delta_{ij} \left\{ \log(P_i) + \log(\lambda_{0i}(t_j)) + z_{ij} - \exp(z_{ij})\Lambda_{0i}(t_j) \right\} \right. \\
\left. + \left( 1 - \sum_{i=1}^{2} \delta_{ij} \right) \log\left( \sum_{i=1}^{2} P_i S_{0i}(t_j) \exp(z_{ij}) \right) \right\}
\]

- \( \delta_{ij} = 1 \) if the end of the follow-up consists of failure \( i \) for the subject \( j \) and 0 otherwise.
- \( \lambda_{0i} \) is the baseline hazard function corresponding to \( S_{0i} \)
- \( \Lambda_{0i}(t) = \int_0^t \lambda_{0i}(u) du \)
Evaluations of the prognostic performances (1)

Suppose that \( \{Z_i > c_{i\tau}\} \) corresponds to the subgroup at risk of failure \( i \) before the time \( \tau \)

**The sensitivity (se) of \( Z_i \) for the prediction of the failure \( i \)**

\[
se_i(c_{i\tau}|\tau) = P(Z_i > c_{i\tau}|T \leq \tau, X = i) \\
= P(Z_i > c_{i\tau}, T \leq \tau|X = i)/P(T \leq \tau|X = i) \\
= \int_{c_{i\tau}}^{\infty} (1 - S_i(\tau|z_i))g(z_i)dz_i / \int_{-\infty}^{\infty} (1 - S_i(\tau|z_i))g(z_i)dz_i
\]

where \( g(z_i) \) is the probability density function of the score \( z_i \).
Evaluations of the prognostic performances (2)

The se of $Z_i \ (i = 1, 2)$ for the prediction of one of both failures

Let $c_\tau = (c_{1\tau}, c_{2\tau})$, $A = \{z_1 \leq c_{1\tau}, z_2 \leq c_{2\tau}\}$ and $\bar{A}$ is not $A$

$$se(c_\tau | \tau) = P(\bar{A} | T \leq \tau)$$

$$= P(A, T \leq \tau) / P(T \leq \tau)$$

$$= 1 - P(A, T \leq \tau) / P(T \leq \tau)$$

Total Probability Theorem

$$se(c_\tau | \tau) = 1 - \left\{ \sum_{i=1}^{2} P_i P(A, T \leq \tau | X = i) \right\} / \left\{ \sum_{i=1}^{2} P_i P(T \leq \tau | X = i) \right\}$$

If $\gamma = \beta_2 / \beta_1$ is positive, then:

$$se(c_\tau | \tau) = 1 - \left\{ \sum_{i=1}^{2} P_i \int_{-\infty}^{\omega_i} (1 - S_i(\tau | z_i)) g(z_i) dz_i \right\}$$

$$\times \left\{ \sum_{i=1}^{2} P_i \int_{-\infty}^{\infty} (1 - S_i(\tau | z_i)) g(z_i) dz_i \right\}^{-1}$$

where $\omega_1 = min(c_{1\tau}, \gamma^{-1} c_{2\tau})$ et $\omega_2 = min(\gamma c_{1\tau}, c_{2\tau})$. 
Evaluations of the prognostic performances (3)

The specificity (sp) of $Z_i$ for the prediction of no failure $i$

$$sp_i(c_{i\tau} | \tau) = \frac{\int_{-\infty}^{c_{i\tau}} S_i(\tau | z_i) g(z_i) dz_i}{\int_{-\infty}^{\infty} S_i(\tau | z_i) g(z_i) dz_i}$$

The sp of $Z_i$ ($i = 1, 2$) for the prediction of no failure

$$sp(c_{\tau} | \tau) = \left\{ \frac{\sum_{i=1}^{2} P_i \int_{-\infty}^{\omega_i} S_i(\tau | z_i) g(z_i) dz_i}{\sum_{i=1}^{2} P_i \int_{-\infty}^{\infty} S_i(\tau | z_i) g(z_i) dz_i} \right\}$$

$$\Rightarrow ROC_i(\tau), \quad ROC(\tau)$$

$$\Rightarrow AUC_i(\tau), \quad AUC(\tau)$$
Evaluations of the prognostic performances (4)

Determination of the optimal cutpoints of $Z_i$ ($i = 1, 2$)

- The optimal cutpoints minimize the cost function, denoted $C(c_\tau, \tau)$.
- Proportional to the number of false positive (FP) and negative (FN) for a prognostic at time $\tau$ using the cutpoints $c_\tau$
- Let $\phi_p$ and $\phi_n$ be the weights associated respectively with FP and FN
- Let $\phi_i$ be the weight of errors associated with the prognostic of $X_i$

$$
C(c_\tau, \tau) \propto \phi_p \left\{ \phi_1 \left( P_1 \int_{c_1 \tau}^{\infty} S_1(\tau|z_1)g(z_1)dz_1 + P_2 \int_{\gamma c_1 \tau}^{\infty} S_2(\tau|z_2)g(z_2)dz_2 \right) + \phi_2 \left( P_1 \int_{c_2 \tau / \gamma}^{\infty} S_1(\tau|z_1)g(z_1)dz_1 + P_2 \int_{c_2 \tau}^{\infty} S_2(\tau|z_2)g(z_2)dz_2 \right) \right\} \\
+ \phi_n \left\{ \sum_{i=1}^{2} \phi_i P_i \int_{-\infty}^{c_i \tau} (1 - S_i(\tau|z_i))g(z_i)dz_i \right\}
$$
Analysis of kidney transplant recipients (1)

Kidney transplant data

- What is the capacity of the 1-year CrCl to predict the evolution of kidney transplant recipients until the 10th anniversary of transplantation?
- The origin of the follow-up \( t = 0 \) is the first anniversary of transplantation
- The prognostic time \( \tau \) is equal to 9 years
- At any time, a patient can occupy one of the following three states:
  - Stable with a functional kidney
  - Returned to dialysis \((X = 1)\)
  - Died with a functional kidney \((X = 2)\).
- Prospective study of kidney transplant recipients (DIVAT)
- 2635 patients of more than 18 years of age and who received a kidney graft between January 1996 and September 2006
- 215 patients returned to dialysis and 95 died with a functional kidney
Analysis of kidney transplant recipients (2)

Modelling the survival part

- Generalized Weibull distribution of the baseline survival functions
  - \( S_{0i}(t) = \exp(1 - (1 + (\frac{t}{\sigma_i})^{\nu_i})^{\theta_i - 1}) \) \( \forall \nu_i, \sigma_i, \theta_i > 0 \)
  - if \( \theta_i = 1 \), the Weibull distribution is obtained
  - and if \( \nu_i = 1 \), the Exponential distribution is obtained

The marker distribution

- The distributions of the scores do not comply with any classic parametric law
- We use a Gaussian kernel density estimator with 1000 points
  \( (density \ function \ in \ R) \)

Computing details

- The analysis are realized with R
- The integral calculations are based on trapezoidal rule
Analysis of kidney transplant recipients (3)

Determination of the weights: $\phi_p$ and $\phi_n$

- The simplest solution is to suppose that $\phi_p = \phi_n$
  - irrespective of the intended application
- The priority of clinicians is to minimize the number of FN: $\phi_p < \phi_n$
- But, the majority of patients did not suffer any failure and the minimization of the total number of errors privileges the minimization of FP
- Since it is difficult for clinicians to precisely define both weights, we attribute greater importance of the false negatives according to the low frequency of observed failures:

$$\phi_n = 1 - \phi_p = P(T > \tau) = \sum_{i=1}^{2} P_i \int_{-\infty}^{\infty} S_i(\tau|z_i)g(z_i)dz_i$$
Determination of the weights: $\phi_1$ and $\phi_2$

- The simplest solution is to suppose that $\phi_1 = \phi_2$
  - irrespective of the intended application
- Death with a functional kidney is often due to a cause independent of the transplantation
- CrCl is a marker of the kidney activity and more predictive of a return in dialysis
- It is therefore more serious to not prognosticate return to dialysis than not prognosticate death
- The cost of an error associated with a certain failure is proportional to the accuracy of the marker to predict this failure

$$\phi_i = AUC_i(\tau) \ (i = 1, 2)$$
Analysis of kidney transplant recipients (5)

The multi-state model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimations</th>
<th>Standard Deviations</th>
<th>p-values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>0.41</td>
<td>0.59</td>
<td>.</td>
</tr>
<tr>
<td>$\sigma_1$</td>
<td>2.31</td>
<td>0.69</td>
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</tr>
<tr>
<td>$\nu_1$</td>
<td>1.30</td>
<td>0.08</td>
<td>.</td>
</tr>
<tr>
<td>$\sigma_2$</td>
<td>18.35</td>
<td>9.33</td>
<td>.</td>
</tr>
<tr>
<td>$\beta_1$</td>
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<td>0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>-0.02</td>
<td>0.01</td>
<td>0.0075</td>
</tr>
</tbody>
</table>

* Null hypothesis: the parameter is null (Wald test)

Table: Parameters of the semi-markovian model ($\log{\nu} = -1505.13$)

- The flexibility of the generalized Weibull distribution is useless
  - Weibull for the times until a return to dialysis
  - Exponential for the time until a death
- For returns in dialysis, an increase of 10 $ml/min$ divides the risk by 1.8
- For deaths, an increase of 10 $ml/min$ divides the risk by 1.2
- The estimated probability of returning to dialysis before dying equals 0.6
- 40% of the patients are expected to die with a functional kidney
Analysis of kidney transplant recipients (6)

Prognostic performances (1)

![ROC analysis graph]

- $AUC_1(9) = 0.81$
- $IC_{95\%} = [0.75, 0.85]$
- $AUC_2(9) = 0.62$
- $IC_{95\%} = [0.55, 0.69]$
- $AUC(9) = 0.75$
- $IC_{95\%} = [0.71, 0.78]$
Analysis of kidney transplant recipients (7)

Prognostic performances (2)

![Graph showing the observed 1-year CcCr value (ml/min) over time.](image)

- **Low Risk of Failure**: 41.8
- **At Risk of Return to Dialysis**: 18.9
- **At Risk of Return to Dialysis and Death**

**Time of Pronostic (years)**

**The Observed 1-Year CcCr Value (ml/min)**
Discussion

- We proposed a method for a three-class and time-dependant ROC analysis
- We also proposed a cost function to calculate the optimal cutpoints
  - The developments are based on the real problematic of the medical decision-making (definition of weights)
  - It can be difficult for experts to precisely define these weights according to the different kinds of errors
  - A solution is to grant the same importance to all errors
  - This solution is only useful from a statistical point of view (minimisation of the total number of errors)
- Adaptations can be proposed to this background methodology
  - Modelling the survival part: non-parametric model, competitive risk approach, accelerated failure time assumption...
  - The score can take into account more than one marker
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