Time-dependent ROC analysis for a three-class prognostic

Application on the kidney transplant recipients

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Outline

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 ($Y \in \Re$)
- 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: $P_1 = exp(\alpha)/\{1 + exp(\alpha)\}, \forall \alpha \in \Re$
- 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
  - β_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.
- λ_{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 τ

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

$$\begin{aligned} se_i(c_{i\tau}|\tau) &= P(z_i > c_{i\tau}|T \leq \tau, X = i) \\ &= P(z_i > c_{i\tau}, T \leq \tau|X = i)/P(T \leq \tau|X = i) \\ &= \int_{c_{i\tau}}^{\infty} (1 - S_i(\tau|z_i))g(z_i)dz_i \Big/ \int_{-\infty}^{\infty} (1 - S_i(\tau|z_i))g(z_i)dz_i \end{aligned}$$

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 $\overline{A}$ is not A

$$\begin{aligned} se(c_\tau|\tau) &= P(\overline{A}|T \leq \tau) \\ &= P(\overline{A}, T \leq \tau)/P(T \leq \tau) \\ &= 1 - P(A, T \leq \tau)/P(T \leq \tau) \end{aligned}$$

Total Probability Theorem

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

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

$$\begin{aligned} se(c_\tau|\tau) &= 1 - \{\sum_{i=1}^{2} P_i \int_{-\infty}^{\omega_i} (1 - S_i(\tau|z_i))g(z_i)dz_i\} \\ &\times \{\sum_{i=1}^{2} P_i \int_{-\infty}^{\infty} (1 - S_i(\tau|z_i))g(z_i)dz_i\}^{-1} \end{aligned}$$

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

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

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

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

$$\Longrightarrow ROC_i(\tau),\ ROC(\tau)$$

$$\Longrightarrow AUC_i(\tau),\ AUC(\tau)$$

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 $\mathcal{C}(c_\tau, \tau)$.
- Proportional to the number of false positive (FP) and negative (FN) for a prognostic at time τ using the cutpoints c_τ
- Let ϕ_p and ϕ_n be the weights associated respectively with FP and FN
- Let ϕ_i be the weight of errors associated with the prognostic of X_i

$$\begin{aligned}
\mathcal{C}(c_\tau, \tau) \quad \propto \quad & \phi_p \Bigg\{ \phi_1 \left(P_1 \int_{c_{1\tau}}^{\infty} S_1(\tau|z_1) g(z_1) dz_1 + P_2 \int_{\gamma c_{1\tau}}^{\infty} S_2(\tau|z_2) g(z_2) dz_2 \right) \\
+ \quad & \phi_2 \left(P_1 \int_{c_{2\tau}/\gamma}^{\infty} S_1(\tau|z_1) g(z_1) dz_1 + P_2 \int_{c_{2\tau}}^{\infty} S_2(\tau|z_2) g(z_2) dz_2 \right) \Bigg\} \\
+ \quad & \phi_n \left\{ \sum_{i=1}^{2} \phi_i P_i \int_{-\infty}^{c_{i\tau}} (1 - S_i(\tau|z_i)) g(z_i) dz_i \right\}
\end{aligned}$$

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 10*th* anniversary of transplantation?
- The origin of the follow-up ($t = 0$) is the first anniversary of transplantation
- The prognostic time τ 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: ϕ_p and ϕ_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:

$$\phi_n = 1 - \phi_p = P(T > \tau) = \sum_{i=1}^{2} P_i \int_{-\infty}^{\infty} S_i(\tau|z_i) g(z_i) dz_i$$

Analysis of kidney transplant recipients (4)

Determination of the weights: ϕ_1 and ϕ_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

$$\phi_i = AUC_i(\tau) \quad (i = 1, 2)$$

Analysis of kidney transplant recipients (5)

The multi-state model

Parameters	Estimations	Standard Deviations	p-values*
α	0.41	0.59	.
σ_1	2.31	0.69	.
ν_1	1.30	0.08	.
σ_2	18.35	9.33	.
β_1	-0.06	0.01	$<$0.0001
β_2	-0.02	0.01	0.0075

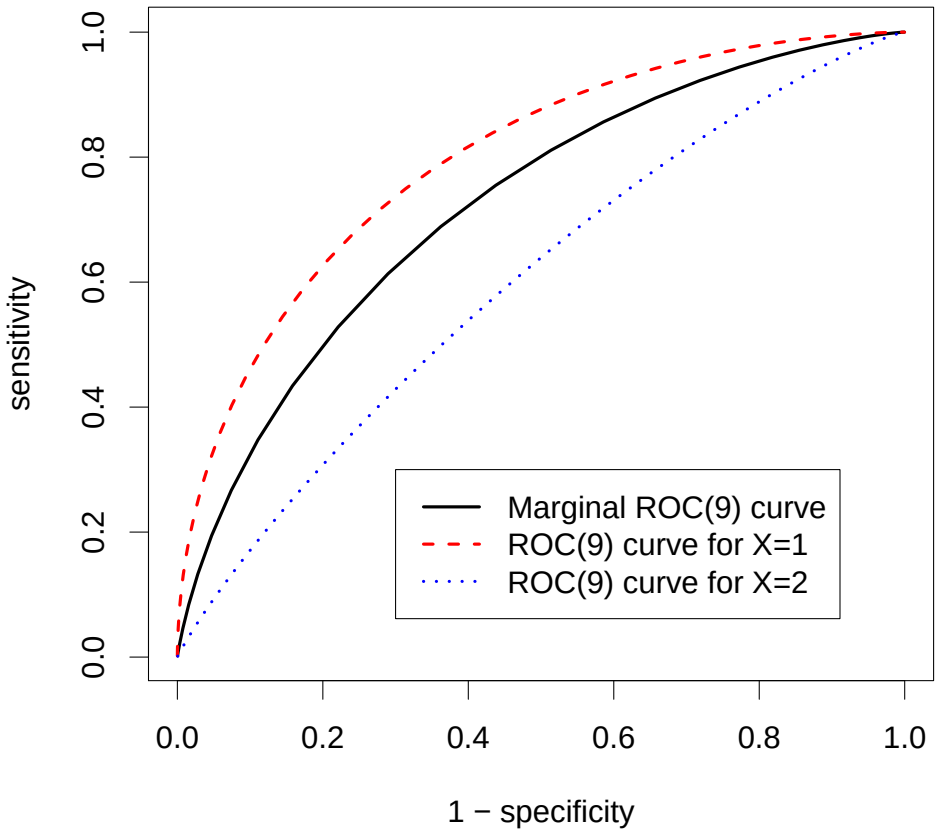
* Null hypothesis: the parameter is null (Wald test)

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

- 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)

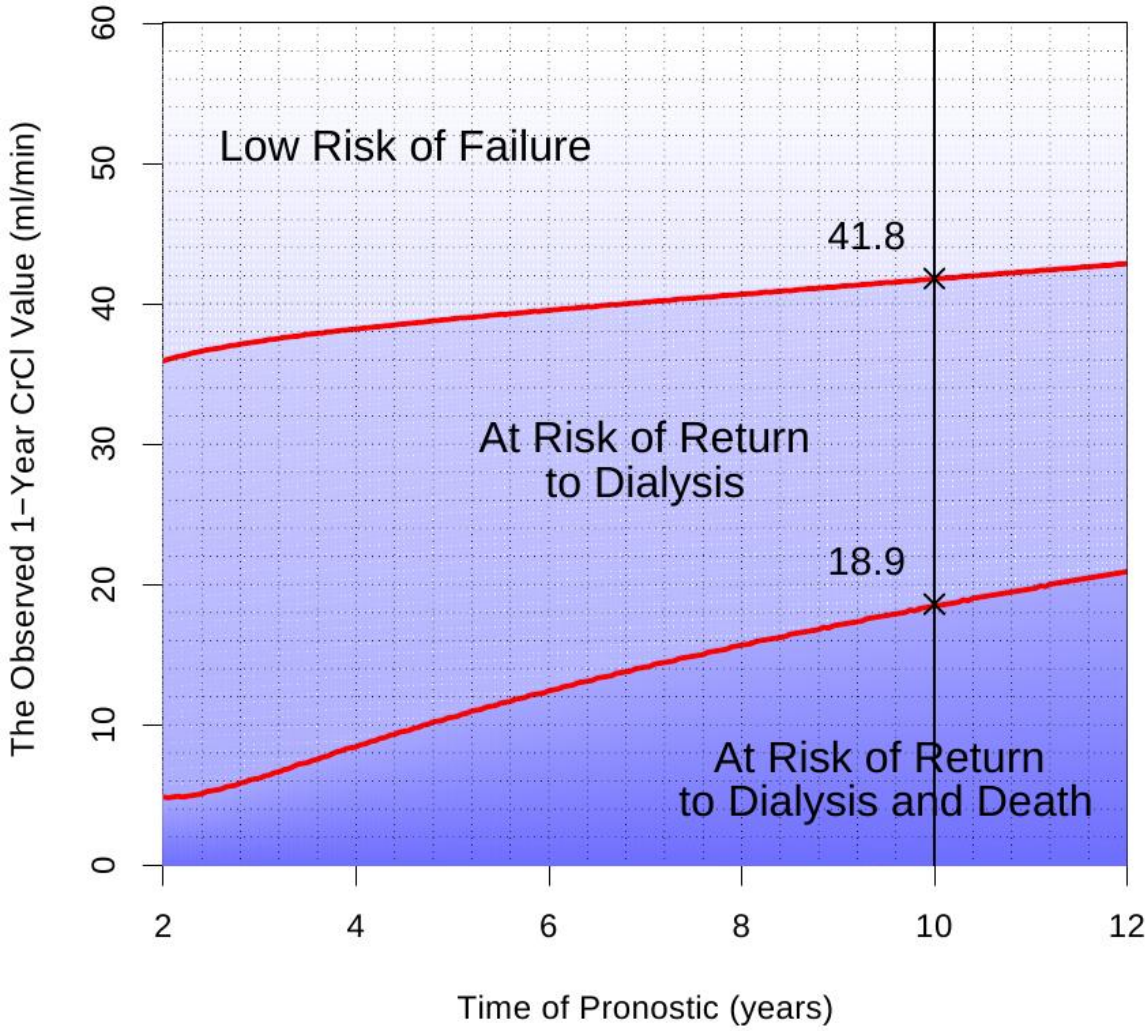
Prognostic performances (1)



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

Analysis of kidney transplant recipients (7)

Prognostic performances (2)



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 numbre 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

References

B. Kaplan, J. Schold, and H.U. Meier-Kriesche.

Poor predictive value of serum creatinine for renal allograft loss.

American Journal of Transplantation, 3:1560–1565, 2003.

D. Mossman.

Three-way roc.

Medical Decision Making, 19:78–89, 1999.

P.S. Heckerling.

Parametric three-way receiver operating characteristic surface analysis using mathematica.

Medical Decision Making, 21:409–417, 2001.

X. He, C.E. Metz, B.M. Tsui, J.M. Links, and E.C. Frey.

Three-class roc analysis-a decision theoretic approach under the ideal observer framework.

IEEE Transactions on Medical Imaging, 25:571–581, 2006.

P.J. Heagerty, T. Lumley, and S.P. Pepe.

Time-dependent roc curves for censored survival data and a diagnostic marker.

Biometrics, 56:337–344, 2000.