

Net time-dependent ROC curves: a new method for evaluating the accuracy of a marker to predict mortality related to end-stage renal disease in kidney transplant recipients

M. Lorent, Y. Foucher and M. Giral*

Inserm U1064, Transplantation, Urology and Nephrology Institute (ITUN), 30 bd Jean Monnet, 44093 Nantes, France
Department of Biostatistics EA 4275, 1 rue Gaston Veil, 44035 Nantes, France. Labex Transplantex
*magali.giral@chu-nantes.fr



UNIVERSITÉ DE NANTES

INTRODUCTION

- **Prognostic markers** of mortality in transplantation is essential for:
 - ▷ determining patients at high-risk of death
 - ▷ optimizing medical management

PROGNOSTIC SCORE OF HERNANDEZ ET AL. [1]

- **Objective:**
 - ▷ **To develop a score predicting the long-term survival of kidney transplant recipients beyond the first year post transplantation.**
- **Method:**
 - ▷ Retrospective study conducted on 2348 Spanish adult patients receiving a kidney allograft in 1990, 1994, 1998 and 2002.
 - ▷ Score obtained by using a multivariate **Cox regression model** based on baseline and emergent comorbidity within the first post-transplant year.
- **Results:**
 - ▷ The score is based on 8 variables: 3 at baseline and 5 within the first post transplantation year.
 - ▷ The **largest positive coefficients** corresponded with recipient age and 1-year daily proteinuria → Important role in global mortality prediction.
 - ▷ Prognostic capacity: **C-index: 0.74** (95% CI: [0.70;0.77])

Table : Multivariate analysis of risk factors for death beyond 1 year of renal transplantation obtained using a Cox model in the study by Hernández (n = 2348).

Variables	Coefficients	HR	CI95%
Age (ref: <40 years)			
40-50 years	0.80	2.2	[1.5;3.3]
50-60 years	1.32	3.7	[2.6;5.4]
>60 years	1.91	6.7	[4.6;9.9]
Pretransplant diabetes	0.58	1.8	[1.1;2.9]
Positive HCV antibodies	0.44	1.5	[1.1;2.1]
NODAT at 1-year	0.45	1.5	[1.1;2.3]
Serum creatinemia at 1-year (mg.dl ⁻¹)	0.56	1.7	[1.5;2.1]
Proteinuria >1g at 1-year	0.99	2.7	[1.8;4.0]
Use of tacrolimus at the first year	-0.48	0.6	[0.4;0.9]
Use of MMF at the first year	-0.78	0.4	[0.3;0.6]

- **Limits:**
 - ▷ Main result of the study: elderly recipients are more at-risk of death than younger patients.
 - ▷ An important part of the mortality is not directly related to the chronic disease but to the natural patient ageing.

OBJECTIVE

- **To create a score intended to predict excess mortality specifically related to kidney transplant recipients.**
- **To evaluate its capacity to predict the disease-related mortality.**

MATERIALS AND METHODS

- Patients were selected from the French prospective DIVAT cohort of Nantes (www.divat.fr/en).
 - ▷ Adult recipients
 - ▷ Transplanted from 1996 to 2009
 - ▷ Patients receiving a kidney transplant alone
 - ▷ Living patients with functioning graft at 1-year post-transplant
- **1230 patients included**
- Development of a score predicting the **excess mortality**.
 - ▷ Separation of the initial cohort into 2 samples (training/validation).
 - ▷ Adaptation of the scoring system of Hernandez by maintaining the 8 variables in the model (from training set).
 - ▷ New weights obtained by using an **additive relative survival model** to remove the expected mortality as in the general population.
 - ▷ The objective of such models is to estimate the **net survival**.

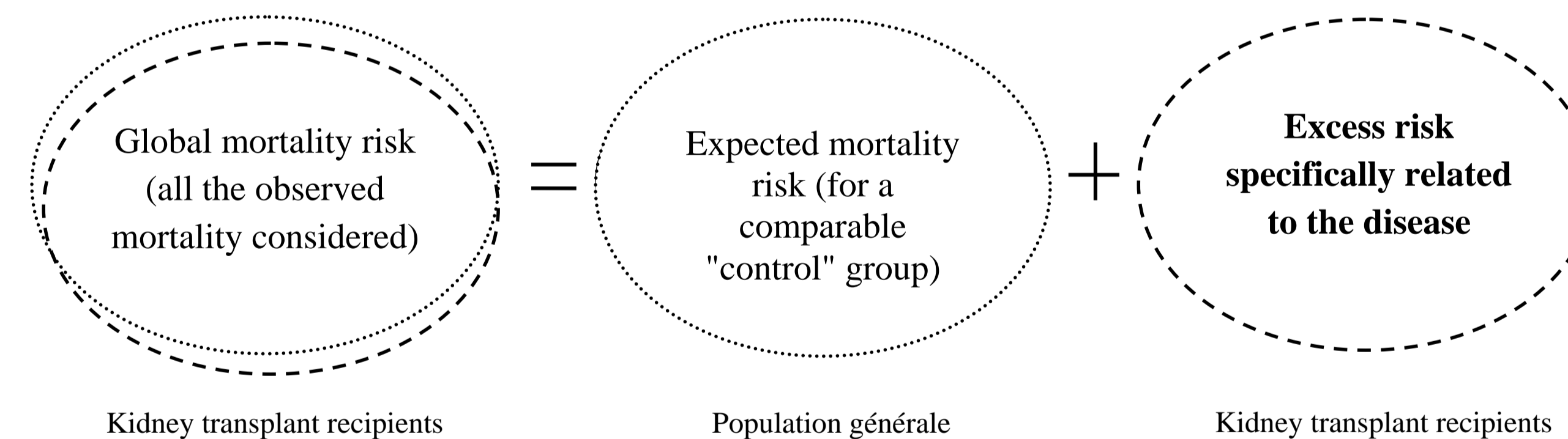


Figure : Additive relative survival model.

- Evaluation of the score capacity to predict the excess mortality.
 - **Proposed method: Net time-dependent ROC curves.**
 - ▷ Calculation of the area under the curve: **net AUC** (from validation set).

STUDY POPULATION

- Mean age at the time of the transplantation: 49.0 years (± 13.8)
- 62.4% of the patients were male
- Median follow-up: 4.9 years (interquartile range: from 2.1 to 7.9)
- 83 deaths observed
- At 10 years post-transplantation, **40% of observed deaths were unrelated to kidney transplant status.**

RESULTS

- It appears difficult to validate the score of Hernandez in the prediction of deaths specifically related to kidney transplant recipients (**net AUC=0.65**, **CI95%: [0.56;0.72]**).
- The capacity of the modified score to predict the disease-related mortality is acceptable (**net AUC=0.73**, **CI95%: [0.64;0.80]**).

Table : Results of the additive relative survival model.

Variables	Modified coef.	HR	CI95%
Age (ref: <40 years)			
40-50 years	1.00	2.7	[0.8;9.0]
50-60 years	0.54	1.7	[0.4;6.6]
>60 years	0.99	2.7	[0.7;10.0]
Pretransplant diabetes	1.61	5.0	[2.1;12.1]
Positive HCV antibodies	1.35	3.9	[1.5;10.3]
NODAT at 1-year	1.53	4.6	[1.5;14.8]
Serum creatinemia at 1-year (mg.dl ⁻¹)	0.65	1.9	[1.0;3.6]
Proteinuria >1g at 1-year	0.66	1.9	[0.6;6.6]
Use of tacrolimus at the first year	0.14	1.1	[0.5;2.6]
Use of MMF at the first year	0.18	1.2	[0.5;3.2]

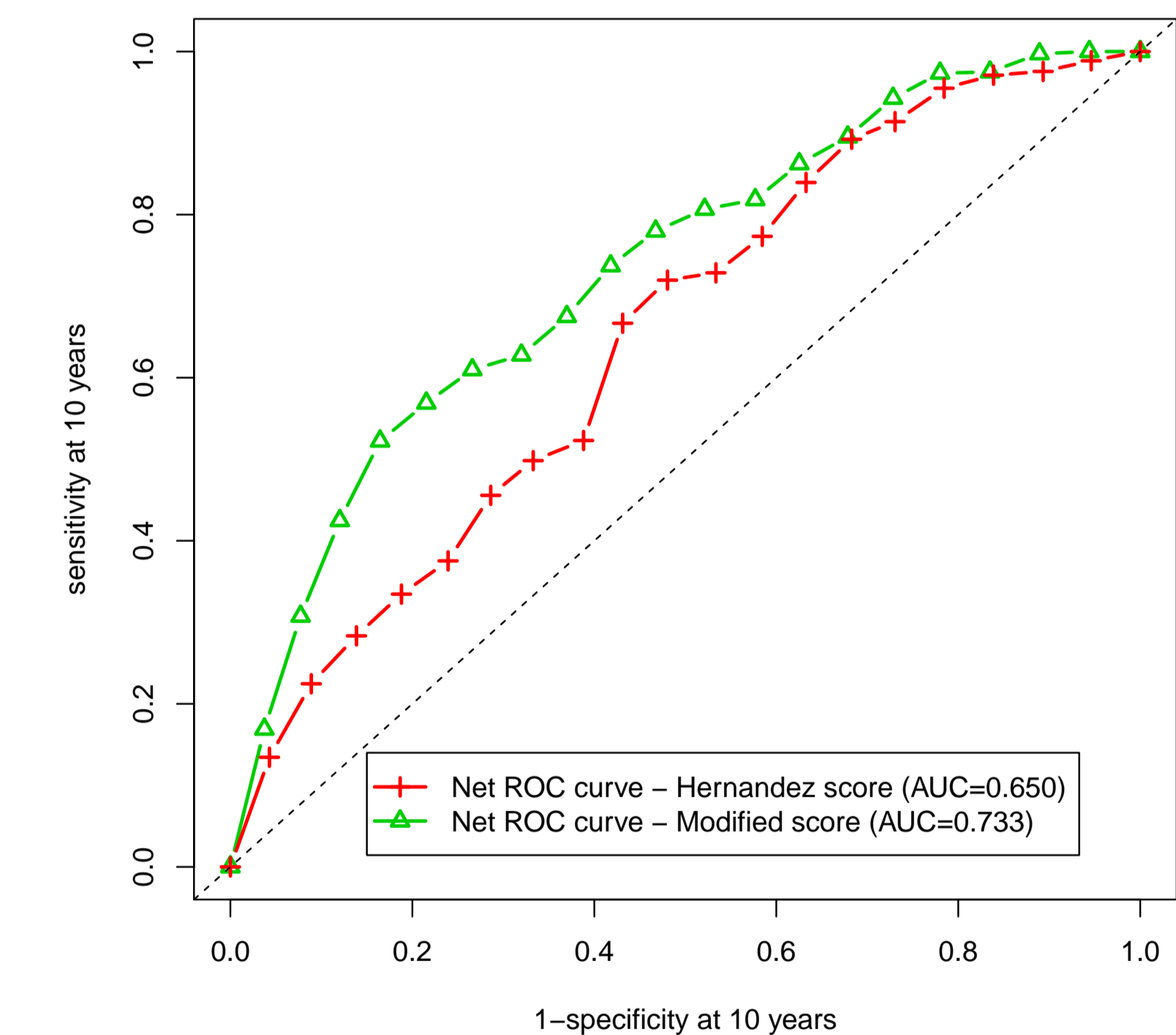


Figure : Net time-dependent ROC curves for a prognosis of mortality up to 10 years.

CONCLUSION

- **Pretransplant diabetes, HCV antibodies and NODAT at 1-year** → Important role in disease-related mortality prediction.
- The new method is useful for predicting disease-related deaths and more relevant for medical decision making.

REFERENCE

[1] D. Hernandez, A. Sanchez-Fructuoso, J.M. Gonzalez-Posada, et al.
A novel risk score for mortality in renal transplant recipients beyond the first posttransplant year.
Transplantation, 88:803-809, 2009.