A multiplicative-regression model to compare the risk factors associated with time to graft failure between a first and second renal transplant

K. Trébern-Launay, Y. Foucher, J. Dantal 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
*mgiral@chu-nantes.fr

INTRODUCTION

- The prognosis of **second kidney transplant recipients (STR)** compared to **first kidney transplant recipients (FTR)** has been frequently studied.
  - But no study has addressed the issue of **comparing the risk factors associated with the time to graft failure between both groups**.
- The limits of classical survival models:
  - A comparison of risk factors between both groups is possible but would imply testing interactions of all the factors with the graft rank.
  - STR-specific covariates (survival time of the first transplant, time in dialysis before retransplantation or transplantectomy) cannot be analyzed, despite the knowledge that their use would improve risk evaluation.

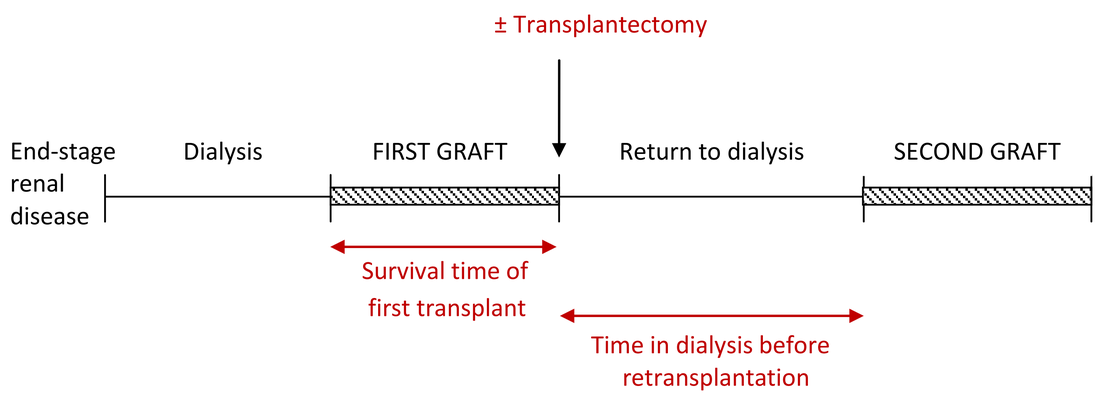

Figure: Clinical trajectory before second graft.

- Andersen et al. [1] proposed for this purpose a multiplicative model for relative survival based on expected mortality rates, using life tables.
  - But the applications to endpoints other than mortality, with a reference group without a life time, has never been explored.

OBJECTIVE

- **To evaluate difference in risk factors associated with time to graft failure between a specific group** (STR) **and a reference group** (FTR).

MATERIALS AND METHODS

- Patients were selected from the French DIVAT (www.divat.fr/en) multicentric prospective cohort.
  - Centers: Nantes, Necker, Nancy, Toulouse, Montpellier, Lyon
  - Adult recipients
  - Transplanted from 1996 to 2010
  - Under mycophenolate mofetil and steroids at transplantation
    - 566 STR (group of interest) and 2206 FTR (reference group)
- The main endpoint was the patient-and-graft survival, it means that the event of interest was the time between the date of transplantation and the date of graft failure, which was the first event between return to dialysis and patient death with a functioning graft.

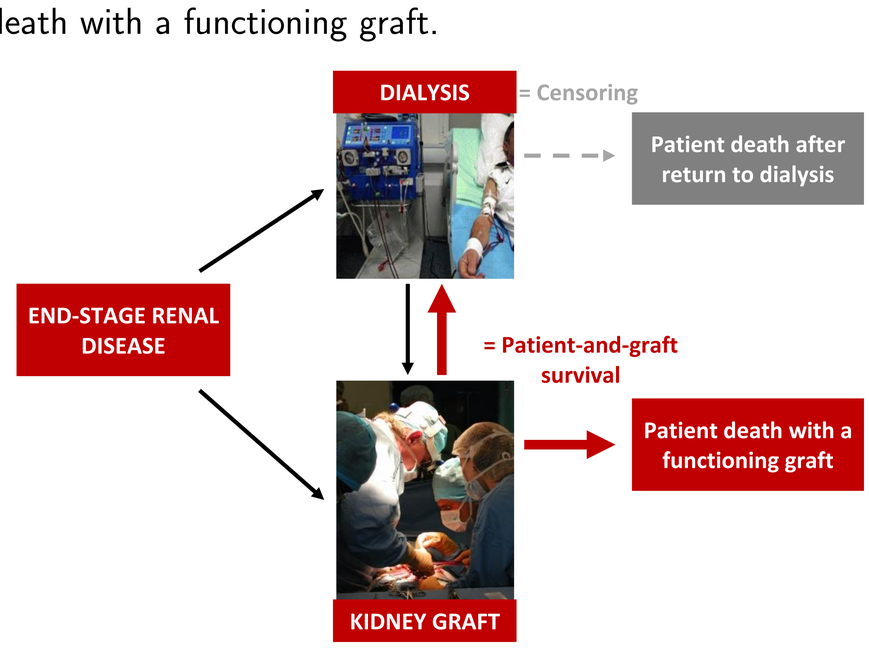

Figure: Definition of patient-and-graft survival.

- We developped a new multiplicative-regression model for relative survival [2, 1] applied to graft failure and with an expected hazard estimated from reference individuals (FTR) with similar characteristics to individuals of the relative group (STR).

STUDY POPULATION

Table: Demographic characteristics at the date of transplantation

Demographic characteristics	FTR (N = 2206) Number	(%)	STR (N = 566) Number	(%)	p-value
Male recipient	1362	(61.7)	343	(60.6)	0.6536
Recipient $\geq$ 55 years of age	994	(45.1)	181	(32.0)	<0.0001
Donor $\geq$ 55 years of age	973	(44.1)	199	(35.2)	0.0002
Recipient BMI $\geq$ 30 kg.m^{-2}	235	(10.7)	28	(4.9)	<0.0001
History of diabetes	306	(11.0)	37	(6.5)	0.0002
HLA-A-B-DR incompatibilities > 4	326	(14.8)	39	(6.9)	<0.0001
Potentially recurrent causal nephropathy	666	(30.2)	240	(42.4)	<0.0001
History of cardiac disease	686	(31.1)	217	(38.3)	0.0012
History of malignancy	147	(6.7)	81	(14.3)	<0.0001
History of hepatitis B or C	96	(4.4)	72	(12.7)	<0.0001
Cold ischemia time $\geq$ 24h	552	(25.0)	202	(35.7)	<0.0001
Positive anti-class I PRA	355	(16.1)	351	(62.0)	<0.0001
Positive anti-class II PRA	319	(14.5)	414	(73.1)	<0.0001
Lymphocyte-depleting induction therapy	793	(35.9)	430	(76.0)	<0.0001
First graft survival < 1 year	-	-	131	(24.1)	-
Time before retransplantation $\geq$ 3 years	-	-	272	(49.8)	-
Transplantectomy of the first graft	-	-	220	(38.9)	-

BMI, body mass index; PRA, panel reactive antibody; HLA, human leukocyte antigen

RESULTS

- Donor gender and waiting time before re-transplantation were not taken into account in the expected hazards (as they were not risk factors for FTR):
  - The risk of graft failure was 1.5-fold higher for STR with grafts from males compared to STR with grafts from females (p = 0.0320).
  - The risk of graft failure was 1.9-fold higher for STR with a long time before retransplantation compared to STR with a short waiting time (p < 0.0001).
- Regarding the hazard ratios (HR) observed in the FTR (gray column), expected HRs associated with recipient and donor age would be respectively 1.39 and 1.34 in the STR. In fact, the relative model showed that both variables appeared to be differently associated with the risk of graft failure between STR and FTR:
  - The HR associated with recipient age $\geq$ 55 years was 1.6-fold higher for STR compared to FTR (p = 0.0480).
  - The HR associated with donor age $\geq$ 55 years was nearly 2-fold lower for STR compared to FTR (p = 0.0440).

Table: Results of the relative survival model. The gray column provides the expected HR obtained for the FTR.

	Cox model (FTR)	Relative model (STR)		
	Expected HR	HR	[95% CI]	p-value
Transplantation < 2005	1.33	0.97	[0.55-1.74]	0.9360
Male recipient	1.17	0.61	[0.38-1.05]	0.0720
Recipient age $\geq$ 55 years	1.39	1.65	[1.01-2.72]	0.0480
Donor age $\geq$ 55 years	1.34	0.59	[0.33-0.99]	0.0440
Male donor	-	1.53	[1.03-2.48]	0.0320
Waiting time >3 years	-	1.92	[1.22-3.00]	<0.0001

CONCLUSION

- The adverse effect of recipient age was enhanced for STR
  - A cumulative effect of the risk factors for STR (the cumulative exposure to immunosuppressive drugs)
  - Clinicians should pay a particular attention to recipient age in second graft
- The adverse effect of older transplants was attenuated for STR
  - An indication bias with only high-quality donors proposed to STR?
  - A higher pre-graft non-HLA immunization in STR, explaining why graft failure is due to immunological phenomena rather than transplant quality?

REFERENCES

[1] PK Andersen, K Borch-Johnsen, T Deckert, A Green, P Hougaard, N Keiding, and S. Kreiner.
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