

INTRODUCTION

- ▶ **Serum creatinine** is the simplest biomarker routinely measured to manage kidney transplant recipient
- ▶ **Kidney graft failure (return to dialysis or death with a functioning graft)** is usually preceded by an increase of serum creatinine.
- ▶ Risk factors of graft failure are well described (*Pascual 2002 ; Debout 2014*) but their **own etiological associations** are not well known.
Hypothesis: Some factors are correlated with
 - ▷ serum creatinine increase, leading to graft loss
 - ▷ graft failure without changes of serum creatinine in the follow-up
 - ▷ both serum creatinine changes in the follow-up and graft failure risk, independently of serum creatinine evolution

OBJECTIVE

To investigate the **etiological role** of recipient, donor and transplant characteristics **on creatinine changes within the follow-up and/or graft failure risk**.

MATERIALS AND METHODS

- ▶ **Study population** - Transplanted patients were selected from the French prospective DIVAT cohort (www.divat.fr) as follows:
 - ▷ Adult recipients from living or heart beating deceased donors
 - ▷ Transplanted for the first or second time between 2000 and 2013
 - ▷ Maintained under Tacrolimus and MMF
 - ▷ Alive with a functioning graft at 1-year post transplantation
- ▶ **Kidney transplantation outcomes**
 - ▷ Longitudinal process: **serum creatinine** ($\mu\text{mol/L}$) measurements yearly recorded until the graft failure.
 - ▷ Survival process: graft failure (first event between **return to dialysis** and **death** with a functioning graft).
- ▶ **Statistical analyses** - We proposed a **joint model for longitudinal and time-to-event data** (*Rizopoulos 2012*) allowing correctly modelize each process, quantify their relationship and avoid the possible bias observed when Cox model or mixed model are used separately (*Asar 2015*)

RESULTS

▶ Patient sample description (N=2749)

	Missing data	mean \pm SD
Recipient age (years)	0	49.7 \pm 13.6
Recipient Body Mass Index (kg/m ²)	10	24.0 \pm 4.2
Donor age (years)	1	50.7 \pm 15.5
Cold ischemia time (hours)	10	17.8 \pm 9.8
3-months serum creatinine ($\mu\text{mol/L}$)	38	138.3 \pm 53.4
6-months serum creatinine ($\mu\text{mol/L}$)	75	136.6 \pm 53.2

RESULTS

	Missing data	n (%)
Recipient men	0	1674 (60.9)
Second transplantation	0	474 (17.2)
History of diabetes	0	319 (11.6)
History of hypertension	0	2272 (82.6)
History of cardiovascular diseases	0	933 (33.9)
History of dyslipidemia	0	860 (31.3)
History of cancer	0	228 (8.3)
Human Leukocytes Antigen incompatibility ABDR (>4)	7	350 (12.8)
Positive anticlass I immunisation	66	876 (32.6)
Positive anticlass II immunisation	87	792 (29.8)
Donor men	8	1545 (56.4)
Status	6	
Living donor		418 (15.2)
Cerebrovascular donor death		1309 (47.7)
Non cerebrovascular donor death		1016 (37.1)
Delayed graft function	15	714 (26.1)
Acute rejection episode during the first year	0	591 (21.5)

▶ Follow-up description

Return to dialysis: 278 ; death with a functioning graft: 205
12843 measurements of serum creatinine (median of 4 values/patient).

▶ Results of the joint model

Variables	Association with serum creatinine at				Graft failure risk	
	1-year		5-years		hazard ratio	p-value
	relative \neq (%)	p-value	relative \neq (%)	p-value		
<i>Level of serum creatinine ($\mu\text{mol/L}$, for 25% higher)</i>					2.14	<0.0001
Recipient gender (male vs female)	7	<0.0001	7	<0.0001		
Donor age (for 10 years higher)	4	<0.0001	4	<0.0001		
Serum creatinine at 3 months (for 50 $\mu\text{mol/L}$ higher)	7	<0.0001	7	<0.0001		
History of diabetes (yes vs no)	0		15	<0.0001		
Cold ischemia time (for 10 h higher)	0		2	0.0267		
Serum creatinine at 6 months (for 50 $\mu\text{mol/L}$ higher)	16	<0.0001	16	<0.0001	0.78	<0.0001
Recipient age (for 10 years older)	-2	<0.0001	-5	<0.0001	1.35	<0.0001
Immunisation anti-HLA class I (+ vs -)	0		7	0.0008	1.46	0.0013
Acute rejection episode < 1 year (yes vs no)	6	<0.0001	-5	0.0348	1.43	0.0017
History of cardiovascular diseases (yes vs no)	0		0		1.37	0.0016
Graft rank (second vs first)	0		0		1.41	0.0118

INTERPRETATION

- ▶ Variables in **gray** are only associated with serum creatinine changes.
 - ▷ Patients who received a kidney from a ten years older donor has a serum creatinine 4% higher compared to another patient.
 - ▷ Patients with history of diabetes have a stronger increase of serum creatinine during the follow up. After 5 years, their serum creatinine level is 15% higher compared to patients without history of diabetes.
- ▶ These variables are indirectly associated to graft failure, throughout the serum creatinine changes. A patient with a **creatinine level higher than 25% compared to another patient** at the same time, whenever the time of follow-up has **2 fold higher risk of graft failure** (HR=2.14).

INTERPRETATION

- ▶ **Direct** associations with graft failure risk are identified in **red**.
 - ▷ For instance, patients with history of cardiovascular disease have the same level of serum creatinine during the follow up but they are at higher risk of graft failure compared to patients without cardiovascular history (HR=1.37).
- ▶ Some variables are associated independently with **both** the serum creatinine changes and the graft failure risk (in **blue**).
 - ▷ Ex: Immunized patients have a serum creatinine 7% higher compared to non immunized patients after 5 years. However, after adjustment on serum creatinine changes, immunized patients are still at higher risk of graft failure compared to non immunized patients (HR=1.46).

CONCLUSION

- ▶ **This suitable model enhances the clinical message respecting methodological concepts.**
 - ▷ The whole serum creatinine trajectory is considered.
 - ▷ Graft failure risk is adjusted on serum creatinine change.
 - ▷ Serum creatinine changes and graft failure risk relationship is quantified.
- ▶ **Biological knowledge allows causality \Rightarrow etiological role**
 - ▷ *Debout et al. (2014)*: cold ischemia time (CIT) = graft failure risk factor. Our study: CIT \Rightarrow \nearrow serum creatinine \Rightarrow graft failure.
- ▶ Physicians should pay a particular attention such to elderly or immunized recipients, second transplant, patients with history of cardiovascular disease, those for which an acute rejection was occurred. For these patients, **the isolated monitoring of serum creatinine (adjusted) did not appear useful to evaluate the risk of graft failure.**

REFERENCES

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