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A joint model for longitudinal and time-to-event data to better assess the specific role of donor and recipient factors on kidney transplantation outcomes

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Context

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In chronic diseases:

- **Longitudinal markers** allow to follow patient evolution → helpful to determine the most beneficial care
- Occurrence of **events** is overseen

In renal transplantation:

- **Serum creatinine** (SCr) is routinely measured during the follow-up
- **Graft failure** is a major clinical event of interest

It is well-known that:

↗ SCr is associated with ↗ graft failure risk

Methodological features

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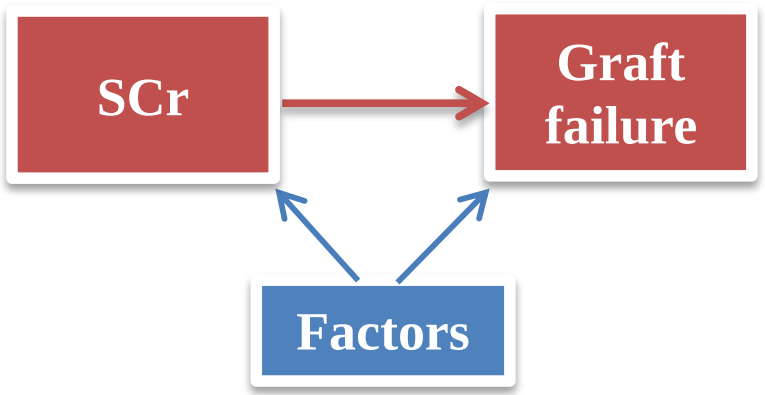

Separate analysis may lead to biased results:

- mixed models can't integrate informative censoring
  (Little & Rubin 2002, Rizopoulos 2012)
- time-dependent Cox model fails to correctly handle an endogeneous variable
  (Kalbfleisch 2002, Andrinopoulou 2012, Asar 2015)

☞ Joint models for longitudinal and time-to-event data take into account the **dependence** between both processes

Objective

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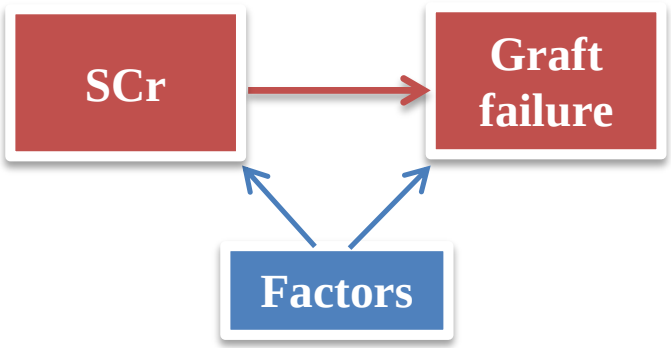
- To distinguish risk factors associations on each process (longitudinal / survival)

  ⇒ 3 types of associations considered:

  1. association on SCr evolution only
  2. association on graft failure risk only
  3. association on both SCr evolution and graft failure risk



- By using a joint model to simultaneously consider the 2 processes in a shared random framework *(Rizopoulos 2012)*

The DIVAT cohort
(www.divat.fr)

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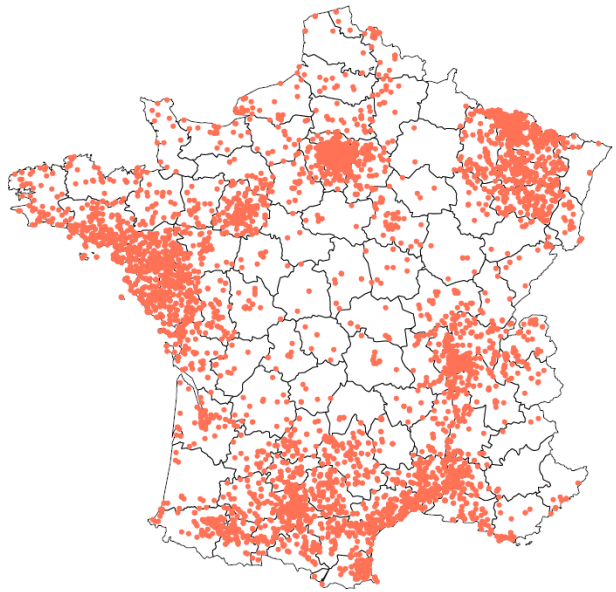
DIVAT: = Données Informatisées et VAlidées en Transplantation
⇒computerized and validated data in transplantation

- French observational and prospective cohort
- Kidney transplant recipients since 1990
- Data about donors, recipients, grafts and follow-up are recorded
- 8 centres / coordination: ITUN Nantes
- ~ 30% of kidney grafts
- ~ 800 grafts / year



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Inclusion criteria

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- Adult recipients
- Transplanted in Nantes, Paris-Necker, Lyon, Nancy, Toulouse or Montpellier
- Between 2000 and 2013
- For the first or second times
- From living or heart beating deceased donor
- alive with a functioning graft at 1-year post transplantation

n = 2749 patients

Materials
Kidney transplantation outcomes

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SCr evolution beyond 1-year post transplantation

Yearly recorded during the follow-up until an event
Measurement time: time elapsed since 1-year visit
Unit: μmol/L

Graft failure

First event occurring between return to dialysis or death with a functioning graft

Statistical analyses (1)
Shared random effect approach

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Submodels hypotheses are checked separetely:

- **Longitudinal process:**
  - logarithmic transformation of SCr values

⇒ residuals homoscedasticity & linear evolution assumption

  - 2 random effects included (baseline value and slope)
  - unstructured variance-covariance matrix

- **Survival process:**
  - no variable with time-dependent effect
  - categorization of some continuous variables

Quantitative variables are standardized (as recommended in *Rizopoulos 2012*)

Statistical analyses (2)
shared random effect approach

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- **Modeling strategy:**
  1. Specification is defined in a crude joint model:
     - baseline risk function type (Weibull)
     - dependence type (level and slope)
  2. Covariate selection:
     - univariate analyses (3 fixed effects/variable: on baseline log(SCr), on log(SCr) slope & on graft failure risk)
     - non significant effect removed in backward way (5%)
     - multivariate joint model: stepwise inclusion of significant variables

- **R software (3.0.1 version) with the JM package (1.3 version)** *(Rizopoulos 2010)*

Clinical interpretation of joint model parameters

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- Longitudinal process: results expressed as relative change
- Survival process: hazard ratios can be calculated in SCr units:
  - For an ↗ of 25 % of SCr:

$$\begin{aligned} \text{HR}_{1.25SCr \text{ vs } SCr} &= \frac{h_0(t)\exp(\gamma^T X + \alpha \log(1.25SCr))}{h_0(t)\exp(\gamma^T X + \alpha \log(SCr))} \\ &= \exp(\alpha \log(1.25)) \\ &= 1.25^{\alpha} \end{aligned}$$

Baseline characteristics
(n=2749 patients)

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	Missing	Estimations	IQR
Quantitative characteristics: mean ± SD			
Recipient age (years)	0	49.7 ± 13.6	[39.8 - 60.3]
Donor age (years)	1	50.7 ± 15.5	[41.1 - 61.9]
Categorical characteristics: N (%)			
Recipient men	0	1674 (60.9)	
Transplanted before 2008	0	1369 (49.8)	
Second transplantation	0	474 (17.2)	
History of diabetes	0	319 (11.6)	
History of cardiovascular diseases	0	933 (33.9)	
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)	
Acute rejection episode during the first year	0	591 (21.5)	

IQR: interquartile range ; SD: Standard Deviation ; BMI: Body Mass Index;

SCr: Serum Creatinine; HLA Human Leukocytes Antigen.

Follow-up description

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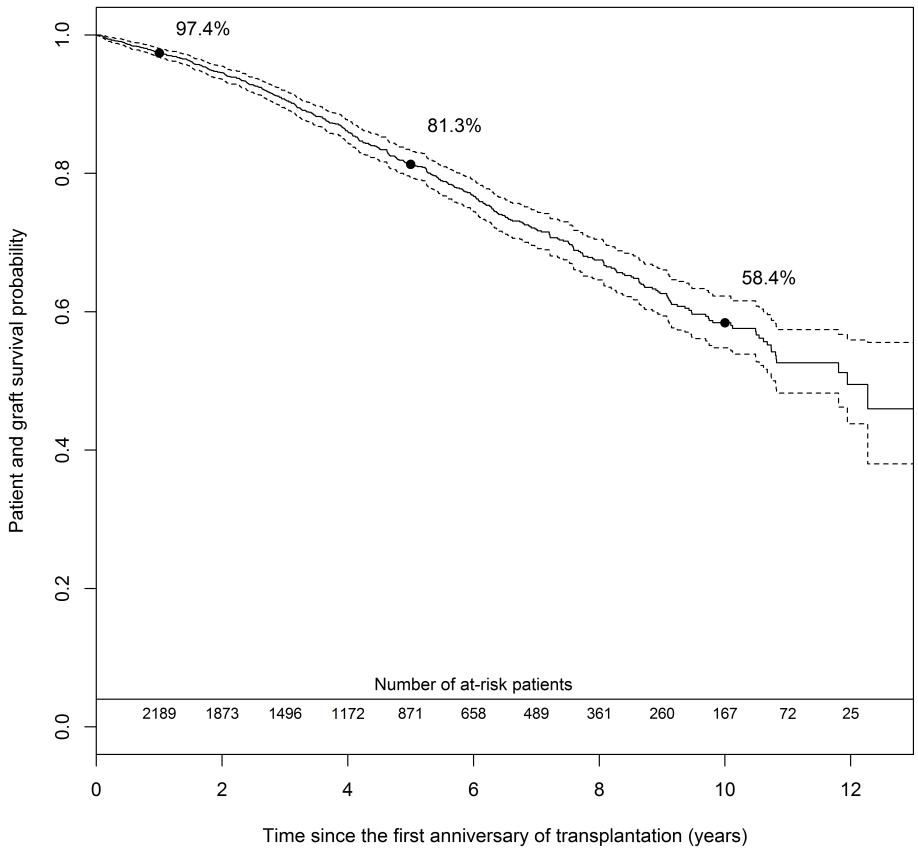

- 278 return to dialysis and 203 deaths were observed
- 12843 SCr measurements were recorded (4 / patients in median)

Multivariate joint model
(n=2584 patients)

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	Longitudinal process				Survival process	
	RC in 1-yr SCr	baseline *p*-value	**RC in 5-yr SCr**	slope *p*-value	**HR**	*p*-value
Current value of SCr (μmol/L), for 25% growth					1.93	<0.0001
Current slope of log(SCr), for +0.0082					1.03	0.0127
Recipient age (for a 10 years increase)	-1.9%	<0.0001	-5.4%	<0.0001	1.35	<0.0001
Recipient gender (male vs female)	7.3%	<0.0001	3.6%	0.0414		
Diabetes histories (yes vs no)			14.5%	<0.0001		
Cardiovascular histories (yes vs no)			4.1%	0.0365	1.39	0.0011
3-month SCr (for a 50 μmol/L increase)	8.3%	<0.0001			0.85	0.0050
6-month SCr (for a 50 μmol/L increase)	18.1%	<0.0001				
Acute rejection episode in 1st year (yes vs no)	5.5%	<0.0001			1.46	0.0011
Anticlass I immunization (+ vs -)			6.2%	0.0022	1.50	0.0006
Rank of graft: second vs first					1.33	0.0376
Donor type (ref: living donor)				0.0008		
Cerebrovascular death			10.0%			
Non cerebrovascular death			5.7%			
Donor gender (male vs female)					0.83	0.0593
Donor age (for a 10 years increase)	3.6%	<0.0001				

RC: Relative Change; SCr: Serum Creatinine

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Comparaison with independent modelisation

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1. Longitudinal part:
   - $\neq$ variables retained on the SCr evolution between linear mixed model and JM
2. Survival part:
   - $\neq$ variables retained between time-dependent cox model and JM
3. For common set of variables: coefficients or HR do not vary greatly
4. Benefit of JM = to test different specification for the dependence

Discussion

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- A better understanding of clinical pathway:
  - Inclusion of the **whole SCr trajectory** after 1-year post transplantation
  - Identification of **specific role** for factors in renal transplantation outcomes
  - Quantification and qualification of the dependence between both processes

- Some risk factors appear to be potentially important in the patient **monitoring**, in addition to SCr follow-up

Limitations and perspective

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Some limitations:

- SCr as a marker can be discussed
- no centers effect
- no distinction between graft loss and patient death
- time-consuming modelisation strategy

Perspective:

☞ to develop a dynamic prognostic score

References

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Thank you for your attention