Introduction
Materials
Methods
Results
Discussion

The use of joint models for longitudinal and time-to-event data: an application on kidney transplantation

Marie-Cécile Fournier

EA4275 methodS for Patients-centered outcomes and HEalth ResEarch,
ITUN INSERM UMR1064, Nantes university

August, 25th 2016

Objectives of my talk

Introduction
Materials
Methods
Results
Discussion

1. To present an application of shared random effect multivariable joint model in renal transplantation

Eur J Epidemiol
DOI 10.1007/s10654-016-0121-2

CrossMark

CLINICAL EPIDEMIOLOGY

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

Marie-Cécile Fournier[1,2] · Yohann Foucher[1] · Paul Blanche[3] · Fanny Buron[4] · Magali Giral[2,5] · Etienne Dantan[1]

2. To discuss the usefulness and limits of such complex models in clinical applications

Context

Introduction
Materials
Methods
Results
Discussion

In chronic diseases:

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

Context

Introduction
Materials
Methods
Results
Discussion

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:

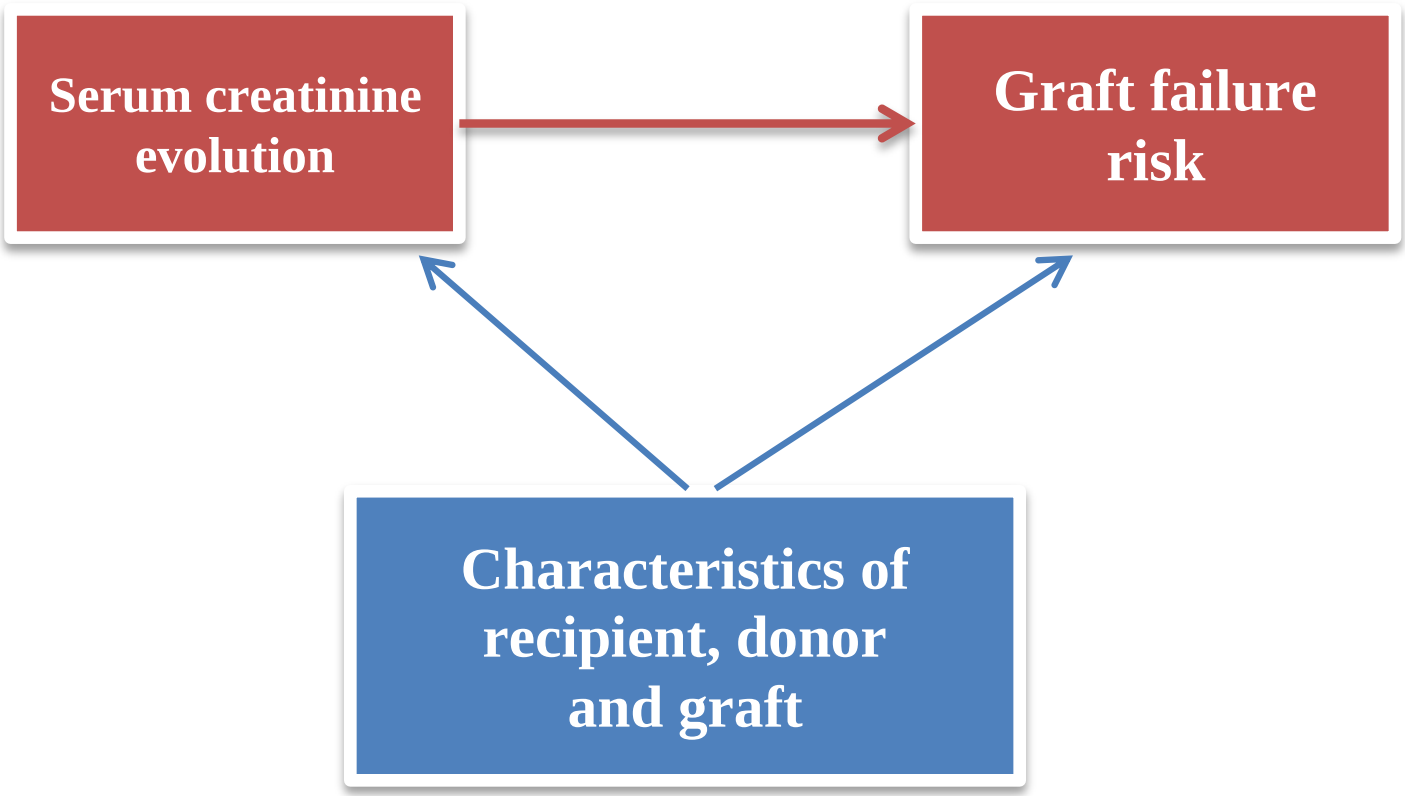
- **Serum creatinine** (SCr) is routinely measured during the follow-up
- 2 major events:
  - ☞ graft loss (return to dialysis or retransplantation)
  - ☞ death with a functioning graft
- **Graft failure** is a major clinical event of interest

It is well-known that:

↗ SCr is associated with ↗ graft failure risk

Context

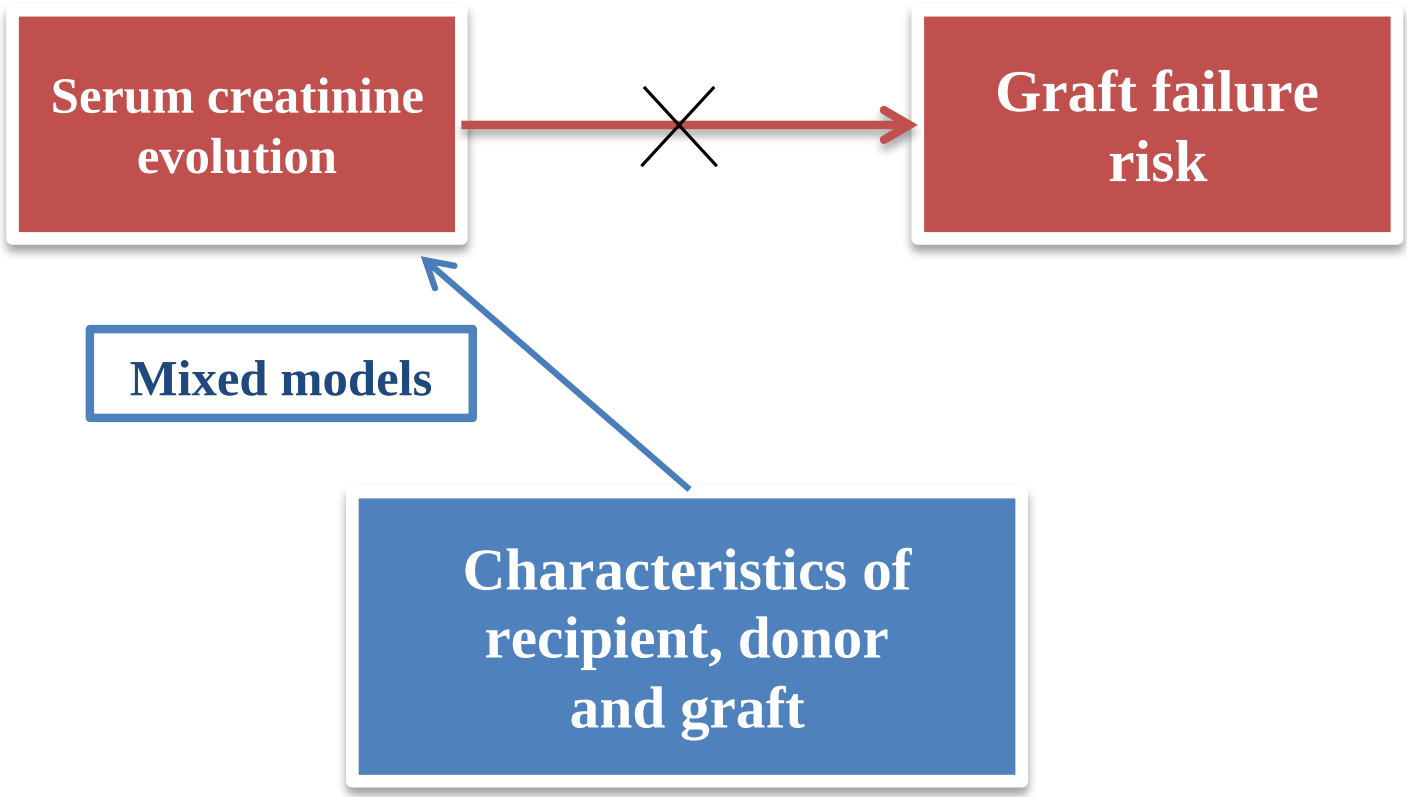
Introduction
Materials
Methods
Results
Discussion



☞ **Specific role of factors ?**

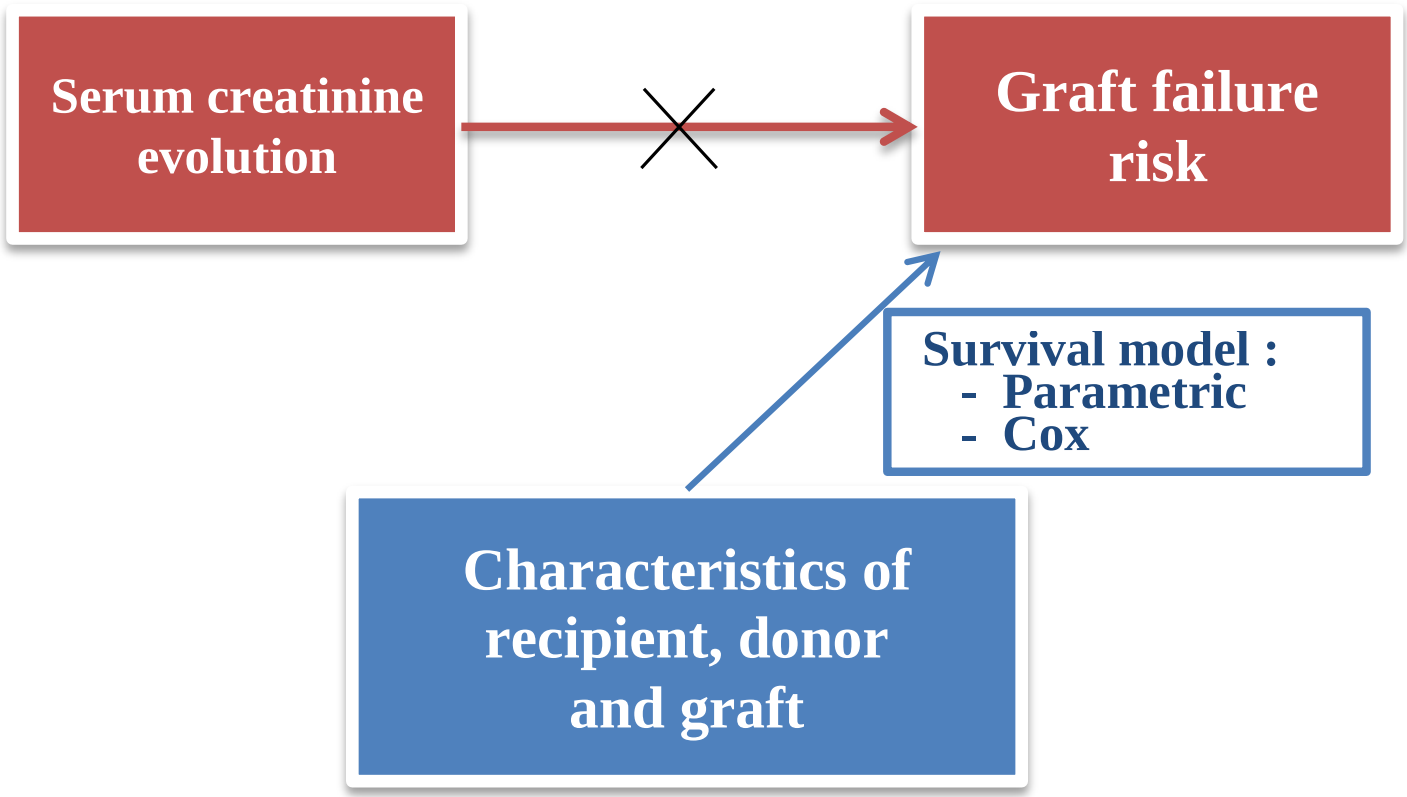
Context

Introduction
Materials
Methods
Results
Discussion



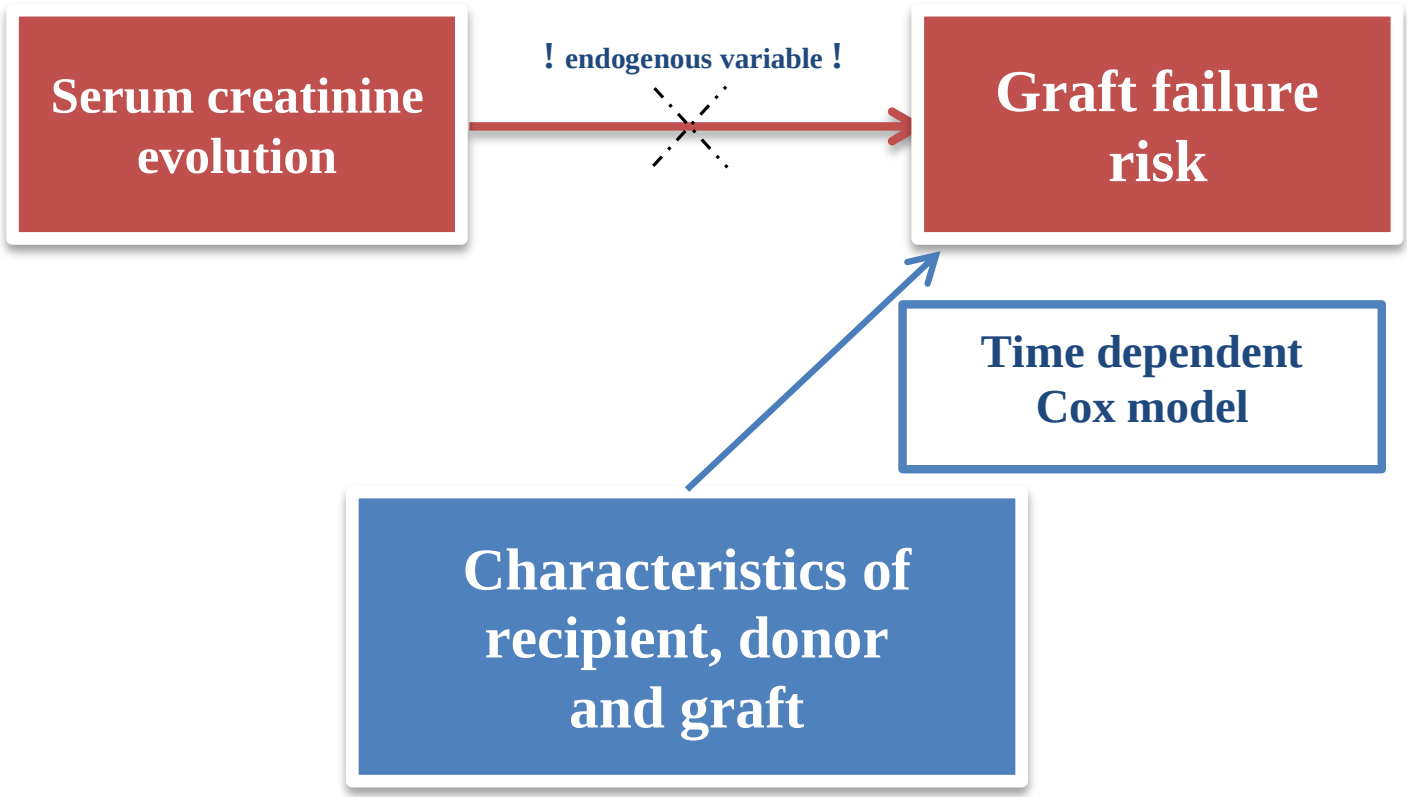
Context

Introduction
Materials
Methods
Results
Discussion



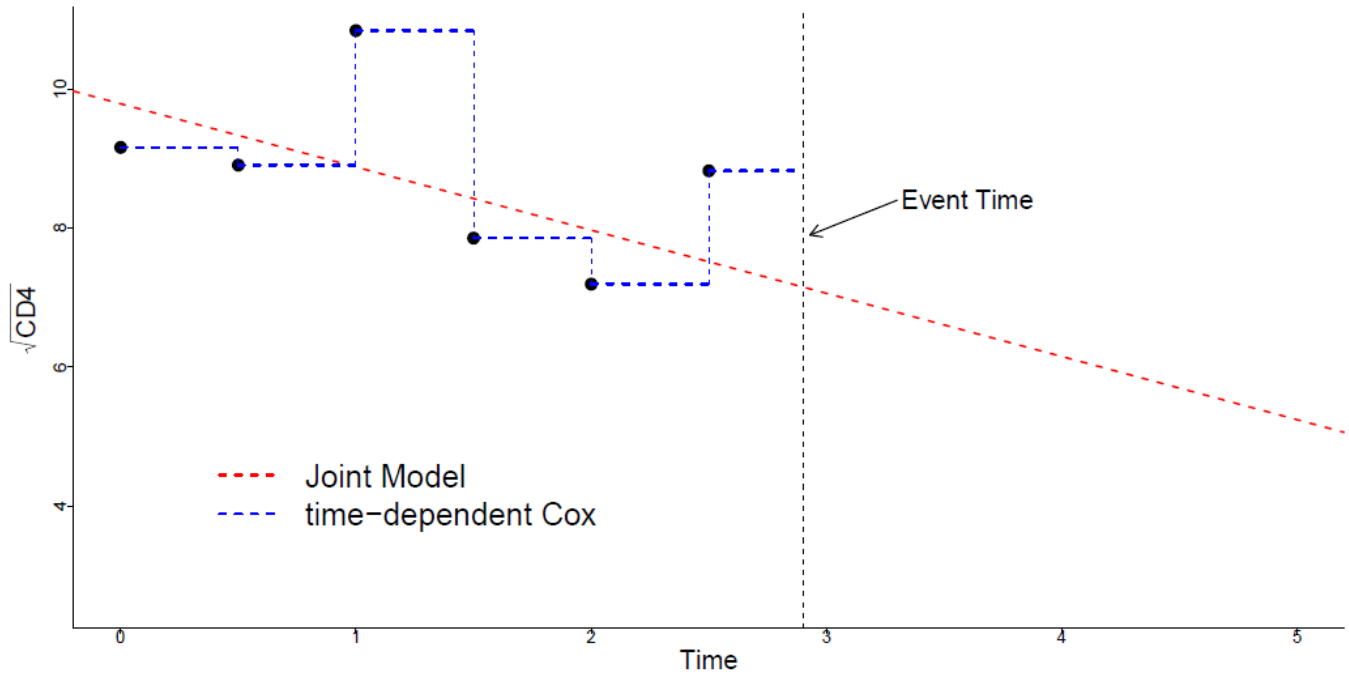
Context

Introduction
Materials
Methods
Results
Discussion



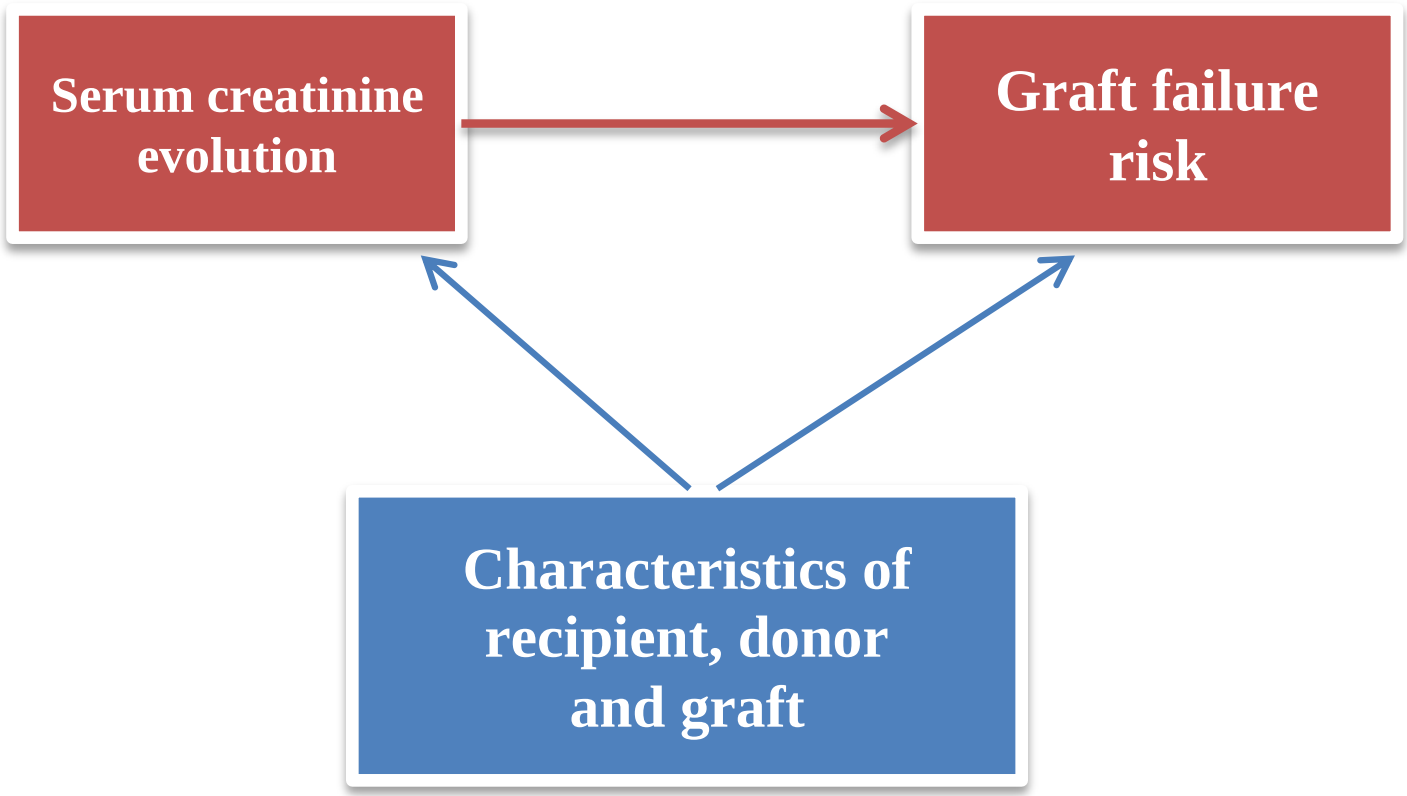
Context

Introduction
Materials
Methods
Results
Discussion



Context

Introduction
Materials
Methods
Results
Discussion



☞ **Joint model for longitudinal and time-to-event data**
(Rizopoulos, Chapman & Hall 2012)

Data

Introduction
Materials
Methods
Results
Discussion

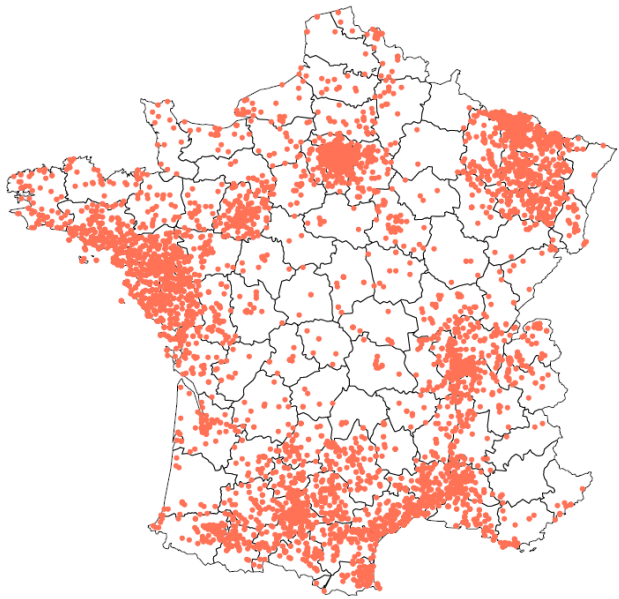
The DIVAT cohort (www.divat.fr):

= Données Informatisées et VAlidées en Transplantation

⇒computerized and validated data in transplantation

French observational and prospective cohort

- 2749 Kidney recipients
- Transplanted between 2000 and 2014
- SCr measurements: yearly recorded
  - 4 SCr measurements / patient were recorded in median
- Event: Graft failure
  - 481 events observed
  - Median follow-up time: 4 years



Distribution of patients included in the DIVAT cohort according to their home town in 2010

Statistical analyses
Shared random effect approach

Introduction
Materials
Methods
Results
Discussion

Submodel hypotheses are checked separetely:

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

⇒ for the linearity and homoscedasticity of the residuals

  - 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
shared random effect approach

Introduction
Materials
Methods
Results
Discussion

- **Modeling strategy:**
  1. Specification is defined in a crude joint model:
     - baseline risk function type (Weibull)
     - dependence type (level and slope)
  2. Covariate selection:
     - univariable 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%)
     - multivariable joint model: stepwise inclusion of significant variables

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

Multivariable joint model
(n=2584 patients)

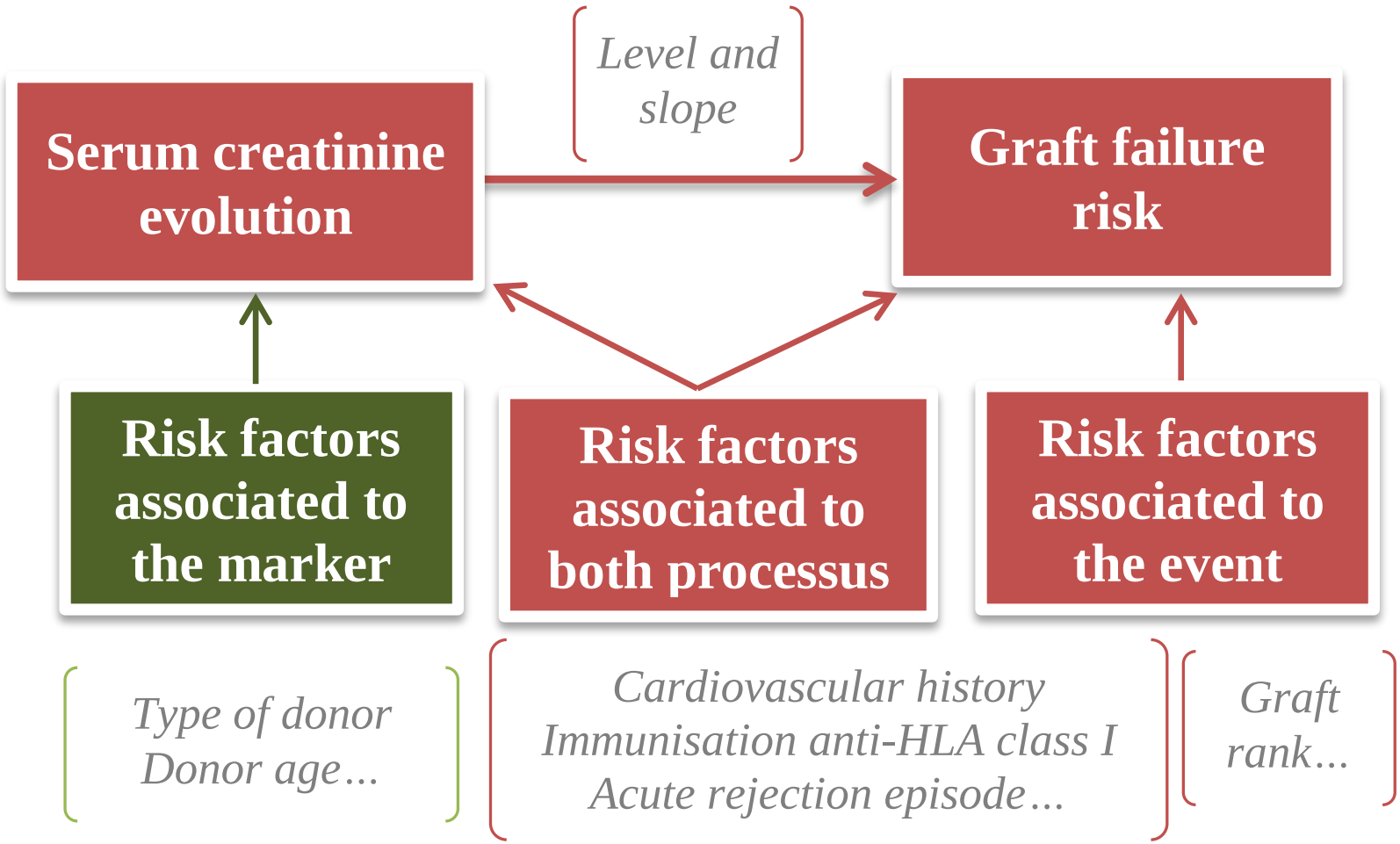
Introduction
Materials
Methods
Results
Discussion

	Longitudinal process				Survival process	
	RC in baseline		RC in slope			
	1-yr SCr	*p*-value	5-yr SCr	*p*-value	HR	*p*-value
Current value of SCr (μmol/L), for 25% growth					1.92	<0.0001
Current slope of log(SCr), for 25% growth					1.89	0.0097
Recipient age (for a 10 years increase)	-2.0%	<0.0001	-5.6%	<0.0001	1.35	<0.0001
Recipient gender (male vs female)	7.7%	<0.0001	4.0%	0.0392		
Diabetes histories (yes vs no)	0.0%	0.9866	14.5%	<0.0001		
Cardiovascular histories (yes vs no)	0.0%	0.9812	4.1%	0.0371	1.39	0.0011
3-month SCr (for a 50 μmol/L increase)	8.1%	<0.0001	8.1%	<0.0001	0.84	0.0062
6-month SCr (for a 50 μmol/L increase)	18.0%	<0.0001	18.0%	<0.0001		
Acute rejection episode in 1st year (yes vs no)	5.7%	<0.0001			1.46	0.0010
Anticlass I immunization (+ vs -)	0.0%	0.2707	6.7%	0.0036	1.50	0.0006
Rank of graft: second vs first					1.32	0.0381
Donor type (ref: living donor)		0.0773		0.0022		
Cerebrovascular death	2.8		12.5%			
Non cerebrovascular death	1.9		7.1%			
Donor gender (male vs female)					0.83	0.0589
Donor age (for a 10 years increase)	5.8%	<0.0001	5.8%	<0.0001		

RC: Relative Change; SCr: Serum Creatinine

Key message

Introduction
Materials
Methods
Results
Discussion



Discussion

Introduction
Materials
Methods
Results
Discussion

- Joint models are interested
  - allow to account for the dynamic evolution of the SCr and the informative censoring process...
  - well for endogenous variable
  - for their epidemiological view of chronic disease evolution

but they are limited:

- time-consuming ++
- with several step (h_0, dependance)
- surprisingly, not really different than mixed model + time-dependent cox model in our application

How can we do to improve their use in clinical trials ?

Thank you for your attention