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

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Objectives of my talk

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

   ![CrossMark]
   
   *Bur J Epidemiol*

   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

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2. To discuss the usefulness and limits of such complex models in clinical applications
In chronic diseases:

- **Longitudinal markers** allow to follow patient evolution → helpful to determine the most beneficial care
- Occurrence of **events** is overseen
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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
Specific role of factors?
Characteristics of recipient, donor and graft

Mixed models

Graft failure risk

Serum creatinine evolution
Context

- Serum creatinine evolution
- Graft failure risk

Survival model:
- Parametric
- Cox

Characteristics of recipient, donor and graft
Characteristics of recipient, donor and graft

Serum creatinine evolution

Graft failure risk

Time dependent Cox model

! endogenous variable!
Joint model for longitudinal and time-to-event data
(Rizopoulos, Chapman & Hall 2012)
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
Submodel hypotheses are checked separately:

- **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*)
• **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)

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal process</th>
<th>Survival process</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RC in baseline 1-yr SCr</td>
<td>p-value</td>
</tr>
<tr>
<td>Current value of SCr (µmol/L), for 25% growth</td>
<td>-2.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current slope of log(SCr), for 25% growth</td>
<td>1.89</td>
<td>0.0097</td>
</tr>
<tr>
<td>Recipient age (for a 10 years increase)</td>
<td>-2.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recipient gender (male vs female)</td>
<td>7.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes histories (yes vs no)</td>
<td>0.0%</td>
<td>0.9866</td>
</tr>
<tr>
<td>Cardiovascular histories (yes vs no)</td>
<td>0.0%</td>
<td>0.9812</td>
</tr>
<tr>
<td>3-month SCr (for a 50 µmol/L increase)</td>
<td>8.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6-month SCr (for a 50 µmol/L increase)</td>
<td>18.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute rejection episode in 1st year (yes vs no)</td>
<td>5.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anticlass I immunization (+ vs -)</td>
<td>0.0%</td>
<td>0.2707</td>
</tr>
<tr>
<td>Rank of graft: second vs first</td>
<td>1.32</td>
<td>0.0381</td>
</tr>
<tr>
<td>Donor type (ref: living donor)</td>
<td>0.0773</td>
<td>0.0022</td>
</tr>
<tr>
<td>Cerebrovascular death</td>
<td>2.8</td>
<td>12.5%</td>
</tr>
<tr>
<td>Non cerebrovascular death</td>
<td>1.9</td>
<td>7.1%</td>
</tr>
<tr>
<td>Donor gender (male vs female)</td>
<td>0.83</td>
<td>0.0589</td>
</tr>
<tr>
<td>Donor age (for a 10 years increase)</td>
<td>5.8%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

RC: Relative Change; SCr: Serum Creatinine
Key message

Serum creatinine evolution

Risk factors associated to the marker
- Type of donor
- Donor age...

Risk factors associated to both processus
- Cardiovascular history
- Immunisation anti-HLA class I
- Acute rejection episode...

Graft failure risk

Risk factors associated to the event
- Graft rank...

Level and slope
**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