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

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**Introduction**

**Kidney transplantation**

**Definition of the graft failure**

- **END-STAGE RENAL DISEASE**
  - Patient death with a functioning graft
  - = Patient-and-graft survival

- **KIDNEY GRAFT**
  - Patient death after return to dialysis
  - = Censoring

**DIALYSIS**

- Patient death with a functioning graft
Objective

⇒ Are risk factors associated with graft failure comparable between first and second grafts?
Limits of classical survival models

- Test of interaction between each covariate and graft rank
- Only covariates common to first and second grafts

**Figure 1:** Clinical trajectory before second graft.
Relative survival models

**Classical approach**
- Additive-regression model for relative survival (Estève et al. Stat in Med 1990)
  - Endpoint = mortality related to chronic diseases
  - The expected mortality is based on general population

**Proposed approach**
- **Multiplicative**-regression model for relative survival (Andersen et al. Stat in Med 1989)
  - Endpoint = **graft failure** (return to dialysis or patient death)
  - The expected graft failure hazard is **estimated** in a control group (first graft)
Inclusion criteria

French DIVAT database

- Centers: Nantes, Necker, Nancy, Toulouse, Montpellier, Lyon
- Adult recipients
- Transplanted from 1996 to 2010
- Under mycophenolate mofetil and steroids at transplantation

Group of interest

566 second transplant recipients (STR)

Control group

2206 first transplant recipients (FTR)
Multiplicative-regression models for relative survival

- The hazard function

\[ h^{(o)}(t_i, z_i) = h^{(e)}(t_i, z^{(e)}_i) h^{(r)}(t_i, z^{(r)}_i) \]

**Observed** hazard function in the STR group

\[ z_i = \text{covariates associated with the observed hazard} \]

**Expected** hazard function in the FTR group

\[ z^{(e)}_i = \text{subset of } z_i, \text{ associated with the expected hazard} \]

**Relative** hazard function in the STR group

\[ z^{(r)}_i = \text{subset of } z_i, \text{ associated with the relative hazard} \]

**STEP 1**

**STEP 2**
**Methods**

**Expected hazard**

**STEP 1:**

**Estimation of the expected hazard function (N\(\text{(e)}\) = 2206 FTR)**

- Parametric model and proportional hazards assumption

\[
h^{(e)}(t_i, z_{i_j}^{(e)}) = h_0^{(e)}(t_i) \exp\left(\sum_{j=1}^{p^{(e)}} \beta_j^{(e)} z_{i_j}^{(e)}\right)
\]

- \(h_0^{(e)}(t_i)\) is a piecewise function

- Maximum-likelihood estimation

\[
\log \mathcal{L} = \sum_{i=1}^{N^{(e)}} \left\{ \delta_i \log(h^{(e)}(t_i, z_{i_j}^{(e)})) - H^{(e)}(t_i, z_{i_j}^{(e)}) \right\}
\]

with \(\delta_i = 1\) if the graft failure is observed

\(\delta_i = 0\) if the event is right-censored
Methods

Relative hazard

STEP 2 :

Estimation of the relative hazard function \((N^{(r)} = 566 \text{ STR})\)

- Parametric model and proportional hazards assumption

\[
h^{(r)}(t_i, z_i^{(r)}) = h_0^{(r)}(t_i) \exp\left(\sum_{j=1}^{p^{(r)}} \beta_j^{(r)} z_{i,j}^{(r)}\right)
\]

- \(h_0^{(r)}(t_i)\) is a piecewise function

- Maximum-likelihood estimation

\[
\log L = \sum_{i=1}^{N^{(o)}} \left\{ \delta_i \log(h^{(o)}(t_i, z_i)) - H^{(o)}(t_i, z_i) \right\}
\]

\[
h^{(e)}(t_i, z_i^{(e)}) h^{(r)}(t_i, z_i^{(r)}) \int_0^{t_i} h^{(e)}(u, z_i^{(e)}) h^{(r)}(u, z_i^{(r)}) \, du
\]
Methods

Interpretation of the regression coefficient

CASE 1 :

For $z_1^{(r)} \notin z_j^{(e)} \implies \exp(\beta_1^{(r)}) = \text{hazard ratio}$

$$HR_{z_1=1/z_1=0}^{(o)} = \frac{h^{(e)}(t_i, z_i^{(e)}) \cdot h_0^{(r)}(t_i) \exp(\sum_{j=1}^{p^{(r)}} \beta_j^{(r)} z_{i,j}^{(r)})}{h^{(e)}(t_i, z_i^{(e)}) \cdot h_0^{(r)}(t_i) \exp(\sum_{j=2}^{p^{(r)}} \beta_j^{(r)} z_{i,j}^{(r)})} = \exp(\beta_1^{(r)})$$

CASE 2 :

For $z_1^{(r)} \in z_j^{(e)} \implies \exp(\beta_1^{(r)}) = \text{weighting factor of HR}$

$$HR_{z_1=1/z_1=0}^{(o)} = \frac{h^{(e)}(t_i) \exp(\sum_{j=1}^{p^{(e)}} \beta_j^{(e)} z_{i,j}^{(e)}) \cdot h_0^{(r)}(t_i) \exp(\sum_{j=1}^{p^{(r)}} \beta_j^{(r)} z_{i,j}^{(r)})}{h^{(e)}(t_i) \exp(\sum_{j=2}^{p^{(e)}} \beta_j^{(e)} z_{i,j}^{(e)}) \cdot h_0^{(r)}(t_i) \exp(\sum_{j=2}^{p^{(r)}} \beta_j^{(r)} z_{i,j}^{(r)})} = \exp(\beta_1^{(e)}) \exp(\beta_1^{(r)})$$
## Methods

### Covariates tested in the relative hazard

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Included in $z_j^{(e)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age ($\geq 55$ years / $&lt; 55$ years)</td>
<td>✓</td>
</tr>
<tr>
<td>Recipient gender (male / female)</td>
<td>✓</td>
</tr>
<tr>
<td>Causal nephropathy (recurrent / non recurrent)</td>
<td>✓</td>
</tr>
<tr>
<td>History of comorbidities (positive / negative)</td>
<td>✓</td>
</tr>
<tr>
<td>Body mass index ($\geq 30$ kg.m$^{-2}$ / $&lt; 30$ kg.m$^{-2}$)</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-class I or II PRA (positive / negative)</td>
<td>✓</td>
</tr>
<tr>
<td>Dialysis prior transplantation (positive / negative)</td>
<td>✓</td>
</tr>
<tr>
<td>Recipient EBV or CMV serology (positive / négative)</td>
<td></td>
</tr>
<tr>
<td>Type of donor (deceased donor / living donor)</td>
<td>✓</td>
</tr>
<tr>
<td>Donor age ($\geq 55$ years / $&lt; 55$ years)</td>
<td>✓</td>
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<td>Donor EBV serology (positive / négative)</td>
<td>✓</td>
</tr>
<tr>
<td>Donor gender (male / female)</td>
<td>✓</td>
</tr>
<tr>
<td>Cause of donor death (cerebro-vascular / other)</td>
<td>✓</td>
</tr>
<tr>
<td>Donor serum creatinine ($\geq 133$ µmol/l / $&lt; 133$ µmol/l)</td>
<td>✓</td>
</tr>
<tr>
<td>Donor CMV serology (positive / négative)</td>
<td></td>
</tr>
<tr>
<td>Transplantation period ($&lt; 2005$ / $\geq 2005$)</td>
<td>✓</td>
</tr>
<tr>
<td>Number of HLA-A-B-DR mismatches ($&gt; 4$ / $\leq 4$)</td>
<td>✓</td>
</tr>
<tr>
<td>Induction therapy (depleting / non depleting)</td>
<td>✓</td>
</tr>
<tr>
<td>Cold ischemia time ($\geq 24h$ / $&lt; 24h$)</td>
<td>✓</td>
</tr>
<tr>
<td>Survival time of the first transplant ($&lt; 1$ year / $\geq 1$ year)</td>
<td></td>
</tr>
<tr>
<td>Time before retransplantation ($&gt; 3$ years / $\leq 3$ years)</td>
<td></td>
</tr>
<tr>
<td>First graft transplantectomy (positive / négative)</td>
<td></td>
</tr>
</tbody>
</table>
Results

Relative baseline hazard function $\leftrightarrow z^{(r)} = 0$
### Results

Hazard ratio obtained from the multivariate model

#### Final multivariate model

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Expected (FTR)</th>
<th>Relative (STR)</th>
<th>Observed (STR)</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant period (&lt; 2005/≥2005)</td>
<td>1.37</td>
<td>1.27</td>
<td>-</td>
<td>0.83 - 1.95</td>
<td>0.2604</td>
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<tr>
<td>Recipient gender (male / female)</td>
<td>1.19</td>
<td>0.68</td>
<td>-</td>
<td>0.45 - 1.02</td>
<td>0.0645</td>
</tr>
<tr>
<td>Recipient age (≥55 years/&lt;55 years)</td>
<td>1.55</td>
<td>1.61</td>
<td>-</td>
<td>1.03 - 2.52</td>
<td>0.0387</td>
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<td>Donor age (≥55 years/&lt;55 years)</td>
<td>1.37</td>
<td>0.59</td>
<td>-</td>
<td>0.37 - 0.95</td>
<td>0.0294</td>
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<tr>
<td>Type of donor (deceased/living)</td>
<td>2.91</td>
<td>0.33</td>
<td>-</td>
<td>0.12 - 0.91</td>
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<tr>
<td>Donor gender (male / female)</td>
<td>-</td>
<td>-</td>
<td>1.57</td>
<td>1.01 - 2.45</td>
<td>0.0443</td>
</tr>
<tr>
<td>Retransplant time (&gt;3 years/≤3 years)</td>
<td>-</td>
<td>-</td>
<td>2.06</td>
<td>1.33 - 3.20</td>
<td>0.0012</td>
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*xxx = forced covariates*
### Results

Hazard ratio obtained from the multivariate model

#### CASE 1: $z_{1(r)} \neq z_{j(e)}$

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$xxx = \text{forced covariates}$

$$\text{HR}^{(o)} = \exp(\beta_{1(r)})$$
### Results

**Hazard ratio obtained from the multivariate model**

**CASE 2 :** $z_1^{(r)} \in z_j^{(e)}$

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**xxx** = forced covariates

\[
HR^{(o)} = \exp(\beta_1^{(e)}) \exp(\beta_1^{(r)})
\]
Clinical conclusions

- A particular attention to recipient age for clinical practice when faced a second transplantation should be paid

- A selection bias? Only transplants from "good quality" donors are proposed for STR when the donor is aged or deceased.

- An early effect of immunisation? The immunisation might take over the effect of other factors (donor age and donor type) for STR.

Statistical conclusion

- No necessity to test interactions between covariates and graft rank
- Possibility to take into account specific covariates for interest groups
Limits and prospects

**Limits**

- Parameters of the expected hazard function (STEP 1) were afterwards considered as constant when used for the estimation of the relative hazard (STEP 2).
- Proportional hazard model with a piecewise baseline function were chosen for the estimation of both baseline hazards functions.
- Only time-invariant covariates were included in the model.

⇒ A Monte-Carlo approach is in process.

⇒ A more flexible model for instance with spline functions.

⇒ A generalisation with time-dependent covariates.
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  - Marine Lorent, PhD Student in Biostatistics
  - Florence Gillaizeau, PhD Student in Biostatistics
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  - Florent Leborgne, Trainee in Biostatistics

Of note

- This presentation will be available online : http ://www.divat.fr/en