The modeling of the evolution of kidney transplant recipients
Applications to the DIVAT cohort

Y. Foucher

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The modeling of the evolution of kidney transplant recipients

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  Cox-based results

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Collaborations
What is the terminal renal insufficiency?

- The chronic kidney disease is a reduction in the renal function.
- The end-stage is the terminal renal insufficiency.
- Two possible treatments:
  - Dialysis (hemodialysis or peritoneal dialysis)
  - Kidney transplantation
- The kidney transplantation is the preferred treatment regarding:
  - The quality of life
  - The long term survival
- The cost of a patient with a functional transplant is significantly lower in comparison with a patient treated by dialysis.
Objectives of clinical research

- To increase the kidney graft survival.
- A lot of papers are devoted to the analysis of the survival:
  - 21997 papers are referenced in PubMed with the keywords: survival + kidney + transplantation.

Problem

- The evolution of the transplanted patient is complex:
  - The acute rejection of the transplant
  - The return in dialysis (definitive rejection)
  - The death with a functional kidney
- Usual survival model may be not adapted.
- The Cox model is used to analyze a single time-to-event.
Guidelines for survival analysis in kidney transplantation

- Two Cox models are recommended for a single paper:
  1. **Graft survival**: time between the transplantation and the return in dialysis (death-censored approach).
  2. **Graft-Patient survival**: time between the transplantation and the first graft failure (return in dialysis or the death with a functional kidney)

- The acute rejection is analyzed as a time-dependent covariate.

Assumptions of these models

1. All the deaths are considered independent from the transplant.
   - False: Infections due to the post-operative complications.
2. All the deaths are considered related to the transplantation.
   - False: Car crash.
DIVAT = Données Informatisées et VAlidées en Transplantation.

Multicentric cohort with 5 French hospitals

Inclusion criteria:
  - Age at the graft $\geq$ 18 years
  - Only cadaveric donors
  - First and second transplantations

$\Rightarrow N = 4280$ individuals were included.
## Cox-based results (2)

<table>
<thead>
<tr>
<th>Hazard Ratio (p-value)</th>
<th>Patient/graft survival</th>
<th>Graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (&gt; 55 vs ≤ 55 years)</td>
<td>1.58 (0.0001)</td>
<td>1.17 (0.1832)</td>
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<td>1.40 (0.0055)</td>
</tr>
<tr>
<td>Cold ischemia time (&gt;36 vs ≤ 36 hours) †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 7 years of transplantation</td>
<td>1.14 (0.3895)</td>
<td>0.98 (0.9224)</td>
</tr>
<tr>
<td>After 7 years of transplantation</td>
<td>1.83 (0.0181)</td>
<td>2.68 (0.0011)</td>
</tr>
<tr>
<td>Recipient gender (male vs female)</td>
<td>0.94 (0.4512)</td>
<td>0.78 (0.0172)</td>
</tr>
<tr>
<td>Post-graft dialysis (yes vs no)</td>
<td>1.76 (0.0001)</td>
<td>1.88 (0.0001)</td>
</tr>
<tr>
<td>Acute rejection episode (yes vs no) †</td>
<td>1.76 (0.0001)</td>
<td>2.44 (0.0001)</td>
</tr>
</tbody>
</table>

◊ Included as a time dependant covariate.

† Because the proportionality of hazard is not respected for the cold ischemia time and for the analysis of graft survival (death-censored).

**Table** – Multivariate results of the three survival regressions.
Limitations of the approach

- Multiple models to analyze the kidney transplant recipients evolution.
- Necessity of a subjective interpretation to synthetize the results.
- Dependence of the censoring process and the time-to-event in the death-censored model.
- The acute rejection is an important step in the evolution of the disease
  - The evolution is different before and after this event.
  - What are the covariates associated with this event?
Cox-based results (4)

What about the use of a cause-specific model?

- The deaths not related to the transplantation are considered as right-censoring.
- The causality of the deaths is often unknown.
- For instance, a cancer can be due to:
  1. The immunosuppressive drugs after transplantation.
  2. Other risk factors (smoke, heredity, etc.).

<table>
<thead>
<tr>
<th>Cause</th>
<th>Effectives</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>46</td>
<td>20.2%</td>
</tr>
<tr>
<td>Cardio-vascular cause</td>
<td>42</td>
<td>18.4%</td>
</tr>
<tr>
<td>Cerebro-vascular cause</td>
<td>12</td>
<td>5.3%</td>
</tr>
<tr>
<td>Gastro-intestinal cause</td>
<td>10</td>
<td>4.4%</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>18</td>
<td>7.9%</td>
</tr>
<tr>
<td>Infection</td>
<td>30</td>
<td>13.2%</td>
</tr>
<tr>
<td>Others</td>
<td>36</td>
<td>15.8%</td>
</tr>
<tr>
<td>Unknown/Missing</td>
<td>34</td>
<td>14.8%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>228</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

**Table** - Details about the cause of the 228 observed deaths
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Principle of the method (1)

- The traditional additive relative survival models:

\[
\text{Global mortality (all the observed deaths)} - \text{Expected mortality (population life-tables)} = \text{Transplantation related mortality}
\]
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Principle of the method (2)

The adaptation in kidney transplantation:

- Observed graft-failures:
  - Returns in dialysis + All deaths

- Statistical computation:
  - Returns in dialysis + All deaths - Expected mortality

- Studied graft-failures:
  - Returns in dialysis + Deaths related to transplantation
Definition of the model (1)

- Let $t$ the time between the transplantation and the first failure (death or return in dialysis)

\[ \lambda_{ob}(t) = \lambda^*(t) + \lambda_{re}(t) \]

- $\lambda_{ob}(t)$ is the observed hazard function.
  - This is the global hazard of the observed cohort of patients.
  - All the observed failures are taking into account.

- $\lambda^*(t)$ is the expected hazard.
  - This hazard is given by lifetime tables of the reference population.
  - Its value is not estimated.

- $\lambda_{re}(t)$ is the hazard related to the disease.
  - This hazard is indirectly estimated from the observed and the expected hazard.
  - Its represents the excess of risk of the studied cohort compared to the reference population.
Definition of the model (2)

\[
\lambda_{ob}(t) = \lambda^*(t) + \lambda_{re}(t)
\]
\[\iff\]
\[
\Lambda_{ob}(t) = \Lambda^*(t) + \Lambda_{re}(t)
\]
\[\iff\]
\[
S_{ob}(t) = S^*(t) \times S_{re}(t)
\]

- Interpretation: The relative survival is the proportion of patients who have survived until time \(t\), if the disease would be the unique cause of failure.

- Introduction of covariates:

\[
\lambda_{ob}(t, z) = \lambda^*(t, z^*) + \lambda_{re}(t, z_{re})
\]

- \(z\) represents all the covariates taking into account in the model.
- \(z^*\) are the covariates associated with the expected failure rate.
- \(z_{re}\) are the factors associated with the relative risk of failure.
The model of Esteve (1)

- Esteve proposed a proportional hazard approach [2]:

\[
\lambda_{re}(t, z_{re}) = \exp\left(\sum_{k=1}^{m} \kappa_k 1_{\tau_{k-1} \leq t < \tau_k}\right) \exp\left(\sum_{j=1}^{p} \beta_j z_{re,j}\right)
\]

- The baseline hazard function is a step function respecting the \(m\) intervals \([\tau_0, \tau_1[, [\tau_1, \tau_2[, \ldots, [\tau_{m-1}, \tau_m[\). 
- \(\beta_j\) are the regression parameters associated with the \(j\)th covariate \(z_{re,j}\) (\(j = 1, 2, \ldots, p\)).
- Interpretation: \(HR_{z_{re,j}=1/0} = \exp(\beta_j)\). The group \(z_{re,j} = 1\) has \(\exp(\beta_j)\) more times risk to fail due to the disease compared to the group \(z_{re,j} = 0\).
The model of Esteve (2)

- Let a sample of \( N \) patients (\( i=1,2,..., N \)).
- \( t_i \) is the time-to-failure for the \( i \)th patient with \( \delta_i = 1 \) if he/she has failed and 0 otherwise.
- \( z_i \) is the observed vector of all covariates for the \( i \)th patient.
  - \( z_i^* \) for the variables associated with the expected survival.
  - \( z_{re,i} \) for the variables associated with the transplant-related survival.
- The logLikelihood:

\[
\log \ell = \sum_{i=1}^{N} \delta_i \log \left( \lambda_{ob}(t_i, z_i) \right) - \Lambda_{ob}(t_i, z_i)
\]

\[\iff\]

\[
\log \ell = \sum_{i=1}^{N} \delta_i \log(\lambda^*(t_i, z_i^*) + \lambda_{re}(t_i, z_{re,i})) - \Lambda^*(t_i, z_i^*) - \Lambda_{re}\left(t_i, z_{re,i}\right)
\]

- \( \lambda^*(t_i, z_i^*) \) is obtained from lifetime tables
- \( \Lambda^*(t_i, z_i^*) = \sum_{u=0}^{t_i} \lambda^*(u, z_i^*) \)
Application to DIVAT (1)

- We performed the analysis on the same sample used in the introduction
  - Age at the graft ≥ 18 years
  - Only cadaveric donors
  - First and second transplantations
  - \( N = 4280 \) individuals were included

- We used the French lifetime tables to take into account the expected mortality according to age, gender and birthdates [6].
  - http://www.ined.fr/cdrom_vallin_mesle/contenu.htm

- The results were compared with both usual Cox models
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Application to DIVAT (2)

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<tr>
<th>Hazard Ratio (p-value)</th>
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<th>Relative survival</th>
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<td>1.17 (0.1832)</td>
<td>1.38 (0.0041)</td>
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<td>1.52 (0.0001)</td>
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<td>1.14 (0.3895)</td>
<td>0.98 (0.9224)</td>
<td>1.19 (0.3002)</td>
</tr>
<tr>
<td>After 7 years of transplantation</td>
<td>1.83 (0.0181)</td>
<td>2.68 (0.0011)</td>
<td>1.79 (0.0371)</td>
</tr>
<tr>
<td>Recipient gender (male vs female)</td>
<td>0.94 (0.4512)</td>
<td>0.78 (0.0172)</td>
<td>0.82 (0.0367)</td>
</tr>
<tr>
<td>Post-graft dialysis (yes vs no)</td>
<td>1.76 (0.0001)</td>
<td>1.88 (0.0001)</td>
<td>1.89 (0.0001)</td>
</tr>
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<td>Acute rejection episode (yes vs no)‡</td>
<td>1.76 (0.0001)</td>
<td>2.44 (0.0001)</td>
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† Included as a time dependant covariate.
‡ Because the proportionality of hazard is not respected for the cold ischemia time and for the analysis of graft survival (death-censored), the time dependent relationship is taken into account. The corresponding hazard ratio just concerns individuals after 7 years of transplantation.

**Table** – Multivariate results of the three survival regressions.
Conclusions and advantages of this approach

- The relative survival model can be used when cause-specific models are not adapted.
- The relative survival model is an objective synthesis between both usual models (graft or graft-patient survival).
- The interpretation of the model is simple (hazard ratio).
- Reduction of the heterogeneity between countries (the background mortality is removed).
The baseline hazard function is a piecewise function.
  - Giorgi et al. have proposed to use splines [5].
  - Lambert et al. have proposed to use fractional polynomials [3].
  - Pohar et al. proposed an EM algorithm in order to avoid the estimation of the baseline hazard function [4].

The effects of covariates are estimated regardless the type of failure: death or return in dialysis.

The acute rejection is analyzed as a covariate.

The reference population is the general population. However, a patient without kidney transplant is under dialysis.
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Definition of the multistate structure

STATE #1
Functional graft

STATE #2
Graft with acute rejection

STATE #3
RETURN IN DIALYSIS

STATE #4
DEATH WITH A FUNCTIONAL KIDNEY

Not persistent state

Persistent state

Transition
SMM framework (1)

- Let the sample of size \( N, h = 1, \ldots, N \).
- Let \( X_h = \{X_{h,r}, r = 0, \ldots, m_h\} \) the sequence of distinct states observed for \( h \)th individual.
  - The first state is the state #1, \( X_{h,1} = 1 \).
  - \( m_h \) is the number of transitions for the \( h \)th individual.
  - This sequence can be equal to: \( \{1\}, \{1, 2\}, \{1, 3\}, \{1, 4\}, \{1, 2, 3\} \), or \( \{1, 2, 4\} \).
- Let \( D_{h,r} \) the time spend in the state \( X_{h,r} \).
SMM framework (2)

\[ P(D_{h,r} \leq x, X_{h,r+1} = j | X_{h,0}, D_{h,0}, \ldots, X_{h,r} = i) \]
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SMM framework (2)

\[ P(D_{h,r} \leq x, X_{h,r+1} = j | X_{h,0}, D_{h,0}, \ldots, X_{h,r} = i) \]

\[ P(D_{h,r} \leq x, X_{h,r+1} = j | X_{h,r} = i) \]

Semi-Markov property
SMM framework (2)

\[ P(D_{h,r} \leq x, X_{h,r+1} = j | X_{h,0}, D_{h,0}, \ldots, X_{h,r} = i) \]

\[ \downarrow \]

Semi-Markov property

\[ P(D_{h,r} \leq x, X_{h,r+1} = j | X_{h,r} = i) \]

\[ P(A, B) = P(A|B)P(B) \]

\[ P(X_{h,r+1} = j | X_{h,r} = i) \times P(D_{h,r} \leq x | X_{h,r+1} = j, X_{h,r} = i) \]
SMM framework (2)

\[ P(D_{h,r} \leq x, X_{h,r+1} = j | X_{h,0}, D_{h,0}, \ldots, X_{h,r} = i) \]

Semi-Markov property

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\[ P_{ij} : Trajectory \]
SMM framework (2)

\[ P(D_{h,r} \leq x, X_{h,r+1} = j | X_{h,0}, D_{h,0}, \ldots, X_{h,r} = i) \]

\[ \text{Semi-Markov property} \]

\[ P(D_{h,r} \leq x, X_{h,r+1} = j | X_{h,r} = i) \]

\[ P(A, B) = P(A|B)P(B) \]

\[ P(X_{h,r+1} = j | X_{h,r} = i) \times P(D_{h,r} \leq x | X_{h,r+1} = j, X_{h,r} = i) \]

\[ P_{ij} : \text{Trajectory} \quad F_{ij}(x) : \text{Waiting time distribution} \]
SMM framework (3)

Embedded Markov chain (trajectories)

\[ P_{ij} = P(X_{h,r+1} = j \mid X_{h,r} = i) \]

- If state \( i \) is not persistent then \( P_{ij} \geq 0 \) and \( P_{ii} = 0 \).
- If state \( i \) is persistent then \( P_{ij} = 0 \) and \( P_{ii} = 1 \).
SMM framework (3)

Embedded Markov chain (trajectories)

\[
P_{ij} = P(X_{h,r+1} = j | X_{h,r} = i)
\]

- If state \(i\) is not persistent then \(P_{ij} \geq 0\) and \(P_{ii} = 0\).
- If state \(i\) is persistent then \(P_{ij} = 0\) and \(P_{ii} = 1\).

Distribution of waiting times

\[
F_{ij}(d) = P(D_{h,r} \leq d | X_{h,r+1} = j, X_{h,r} = i)
\]

- The hazard function: \(\lambda_{ij}(d)\)
- The cumulative hazard function: \(\Lambda_{ij}(d) = \int_0^d \lambda_{ij}(u)du\)
- The survival function: \(S_{ij}(d) = 1 - F_{ij}(d) = \exp(-\Lambda_{ij}(d))\)
- The density probability function: \(f_{ij}(d) = \lambda_{ij}(d)S_{ij}(d)\)
Likelihood estimation (1)

Case #1: $X_h = \{1, k\} \forall k = 3, 4$

\[ \ell_{h,1} = \lim_{d \to 0} \left\{ P(d_{h,0} < D_{h,0} < d_{h,0} + d, X_{h,1} = k) \right\} \]

\[ = P(X_{h,1} = k | X_{h,0} = 1) \lim_{d \to 0} \left\{ P(d_{h,0} < D_{h,0} < d_{h,0} + d | X_{h,1} = k) \right\} \]

\[ \ell_{h,1} = P_{1k} f_{1k}(d_{h,0}) \]
Likelihood estimation (2)

- Case #2: $X_h = \{1, 2, k\}$ $\forall k = 3, 4$

$$\ell_{h,2} = \lim_{d \to 0} \left\{ P(d_{h,0} < D_{h,0} < d_{h,0} + d, X_{h,1} = 2, d_{h,1} < D_{h,1} < d_{h,1} + d, X_{h,2} = k) \right\}$$

$$= \lim_{d \to 0} \left\{ P(d_{h,0} < D_{h,0} < d_{h,0} + d, X_{h,1} = 2) \times P(d_{h,1} < D_{h,1} < d_{h,1} + d, X_{h,2} = k | X_{h,1} = 2) \right\}$$

$$\ell_{h,2} = P_{12} f_{12}(d_{h,0}) \times P_{2k} f_{2k}(d_{h,1})$$
Parameterization of the SMM (1)

Proportional hazard assumption

- Let \( Z_{ij} \) the transition-specific vector of covariates \((\forall ij = 12, 13, 14, 23, 24)\).
- Let \( \beta_{ij} \) the vector of regression parameters associated with \( Z_{ij} \).
  \[
  \lambda_{ij}(d, z_{ij}) = \lambda_{0,ij}(d) \exp(\beta_{ij} z_{ij})
  \]
- \( \lambda_{0,ij}() \) is the baseline hazard function of the transition \( ij \).
- \( HR_{ij} = \exp(\beta_{ij}) \) represents the hazard ratio of the transition \( ij \).
- Interpretation: The group \( Z_{ij} = 1 \) has \( HR_{ij} \) times more risk to jump from the state \( i \), given that the following state is \( j \).
Parameterization of the SMM (2)

Parametric baseline hazard function

► We used the generalized Weibull distribution:

$$\lambda_{0,ij}(d) = \frac{1}{\theta} \left( 1 + \left( \frac{d}{\sigma} \right)^{\nu} \right)^{(1/\theta)-1} \frac{\nu}{\sigma} \left( \frac{d}{\sigma} \right)^{\nu-1}$$

with $\theta$, $\nu$ and $\sigma > 0$.

► Hazard functions can be $\cup$ – or $\cap$ – shaped.

► If $\theta = 1$, we obtain the Weibull distribution.

► If $\theta = \nu = 1$, we obtain the Exponential distribution.

► The Likelihood Ratio Statistic can be used.
Parameterization of the SMM (3)

**Multinomial logistic regression to model** $P_{ij}$

\[
P_{ij} = \frac{\exp(\alpha_{1j})}{\sum_{k=2}^{4} \exp(\alpha_{1k})} \quad \forall \alpha_{12}, \alpha_{13}, \alpha_{14} \in \mathbb{R}
\]

- $\sum_{k=2}^{4} P_{1k} = 1$
- We assumed by convention that $\alpha_{12} = 0$

\[
P_{2j} = \frac{\exp(\alpha_{2j})}{\exp(\alpha_{23}) + \exp(\alpha_{24})} \quad \forall \alpha_{23}, \alpha_{24} \in \mathbb{R}
\]

- $P_{23} + P_{14} = 1$
- We assumed by convention that $\alpha_{23} = 0$
Application to DIVAT (1)

Inclusion criteria

- In order to obtain a homogeneous sample:
  - Transplantations after the 1st January 1996.
  - Age at the graft ≥ 18 years.
  - Only cadaveric donors.
  - First transplantations.

- In order to compare the results with the next relative Semi-Markov model:
  - Less than 5 years in dialysis before the graft.
  - With at least one pre-graft dialysis.
  - End of follow-up at 5 years after the first dialysis.

⇒ $N = 2245$ individuals were included.
Application to DIVAT (2)

Description of the trajectories

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<thead>
<tr>
<th>Trajectory</th>
<th>Effective</th>
<th>Percent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_h = {1}$*</td>
<td>1636</td>
<td>72.9%</td>
</tr>
<tr>
<td>$X_h = {1, 2}$*</td>
<td>373</td>
<td>16.6%</td>
</tr>
<tr>
<td>$X_h = {1, 3}$</td>
<td>107</td>
<td>4.8%</td>
</tr>
<tr>
<td>$X_h = {1, 4}$</td>
<td>79</td>
<td>3.5%</td>
</tr>
<tr>
<td>$X_h = {1, 2, 3}$</td>
<td>39</td>
<td>1.7%</td>
</tr>
<tr>
<td>$X_h = {1, 2, 4}$</td>
<td>11</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

* Right-censoring trajectories.
Application to DIVAT (3)

Multivariate Semi-Markov model

- $\ell = -1532.682$

- Parameters associated with the baseline hazard functions and the multinomial logistic regressions:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimation</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\log(\sigma_{12})$</td>
<td>-4.12</td>
<td>0.08</td>
</tr>
<tr>
<td>$\log(\nu_{12})$</td>
<td>1.88</td>
<td>0.27</td>
</tr>
<tr>
<td>$\log(\theta_{12})$</td>
<td>3.52</td>
<td>0.35</td>
</tr>
<tr>
<td>$\log(\sigma_{13})$</td>
<td>-5.95</td>
<td>0.00</td>
</tr>
<tr>
<td>$\log(\nu_{13})$</td>
<td>4.54</td>
<td>0.00</td>
</tr>
<tr>
<td>$\log(\theta_{13})$</td>
<td>8.97</td>
<td>0.39</td>
</tr>
<tr>
<td>$\log(\sigma_{14})$</td>
<td>5.37</td>
<td>2.49</td>
</tr>
<tr>
<td>$\log(\nu_{14})$</td>
<td>-0.53</td>
<td>0.17</td>
</tr>
<tr>
<td>$\log(\sigma_{23})$</td>
<td>3.21</td>
<td>0.51</td>
</tr>
<tr>
<td>$\log(\nu_{23})$</td>
<td>-0.43</td>
<td>0.15</td>
</tr>
<tr>
<td>$\log(\sigma_{24})$</td>
<td>0.79</td>
<td>0.91</td>
</tr>
<tr>
<td>$\alpha_{13}$</td>
<td>0.76</td>
<td>0.43</td>
</tr>
<tr>
<td>$\alpha_{14}$</td>
<td>-0.34</td>
<td>1.04</td>
</tr>
<tr>
<td>$\alpha_{24}$</td>
<td>-3.12</td>
<td>0.62</td>
</tr>
</tbody>
</table>
## Application to DIVAT (4)

### Multivariate Semi-Markov model

- **Regression parameters:**

<table>
<thead>
<tr>
<th>Transition</th>
<th>Coef.</th>
<th>SD</th>
<th>Wald</th>
<th>HR</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transition 1 → 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient age (≥ 55 vs. &lt;55 years)</td>
<td>-0.46</td>
<td>0.18</td>
<td>-2.61</td>
<td>0.62</td>
<td>0.0091</td>
</tr>
<tr>
<td>Cancer history (yes vs. no)</td>
<td>-0.89</td>
<td>0.40</td>
<td>-2.20</td>
<td>0.41</td>
<td>0.0278</td>
</tr>
<tr>
<td><strong>Transition 1 → 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor age (≥ 55 vs. &lt;55 years)</td>
<td>0.67</td>
<td>0.21</td>
<td>3.17</td>
<td>1.96</td>
<td>0.0015</td>
</tr>
<tr>
<td>Year of first dialysis (&gt;2004 vs. ≤2004)</td>
<td>-0.88</td>
<td>0.29</td>
<td>-2.99</td>
<td>0.41</td>
<td>0.0028</td>
</tr>
<tr>
<td><strong>Transition 1 → 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient age (≥ 55 vs. &lt;55 years)</td>
<td>1.44</td>
<td>0.38</td>
<td>3.83</td>
<td>4.22</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cardio-vascular history (yes vs. no)</td>
<td>0.70</td>
<td>0.30</td>
<td>2.33</td>
<td>2.02</td>
<td>0.0198</td>
</tr>
<tr>
<td><strong>Transition 2 → 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient gender (Men vs. Women)</td>
<td>-1.09</td>
<td>0.34</td>
<td>-3.17</td>
<td>0.34</td>
<td>0.0015</td>
</tr>
<tr>
<td>Cancer history (yes vs. no)</td>
<td>1.73</td>
<td>0.54</td>
<td>3.22</td>
<td>5.66</td>
<td>0.0013</td>
</tr>
</tbody>
</table>
The modeling of the evolution of kidney transplant recipients

Y. Foucher

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STATE #1
Functional graft

STATE #2
Graft with acute rejection

STATE #3
RETURN IN DIALYSIS

STATE #4
DEATH WITH A FUNCTIONAL KIDNEY

Recipient age > 55
Cardio-vascular history

Recipient age > 55

Recipient age > 55

1st dialysis > 2004

Donor age > 55

Men recipient
Cancer history

Cancer history

Donor age > 55

1st dialysis > 2004

Donor age > 55

Men recipient

FUNCTIONAL KIDNEY

FUNCTIONAL KIDNEY

FUNCTIONAL KIDNEY

RETURN IN DIALYSIS
Discussions

Conclusions

- SMM is more adapted than Cox modeling:
  - In opposition with the usual graft survival analysis, the independence of the censoring is more realistic.
  - The covariate effects are transition specific: different factor effects for the mortality and for the return in dialysis.
  - The acute rejection is analyzed as a real health state.

Problem

- The SMM does not only deal with the death related to the transplantation.
- Cause-specific approach always impossible
- To our knowledge, no multi-state model with relative survival exists.
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Principle of relative semi-Markov model (R-SMM)

**STATE #1**
Functional graft

**STATE #2**
Graft with acute rejection

**STATE #3**
RETURN IN DIALYSIS

**STATE #4**
DEATH WITH A FUNCTIONAL KIDNEY

Principle: to distinguish the expected mortality (in dialysis) from the related-transplantation mortality

Not persistent state

Persistent state

Transition
Definition of the R-SMM (1)

Common points with the SMM

- The embedded Markov Chain, $P_{ij} \forall ij = 12, 13, 14, 23, 24$.
- The waiting time distributions $F_{ij}(t)$ for transitions $ij \forall j \neq 4$.

Differences with the SMM

- For the transition $1 \rightarrow 4$, let the observed hazard for the $h$th individual equals to:

$$\lambda_{ob,14}(d_{h,0}) = \lambda^*(d_{h,0} + \Delta_h) + \lambda_{re,14}(d_{h,0})$$

- $d_{h,0}$ is the waiting time in the state 1.
- $\Delta_h$ is the time between the first dialysis and the transplantation.
- $\lambda_{ob,14}(.)$ is the observed hazard.
- $\lambda^*(.)$ is the expected mortality hazard.
- $\lambda_{re,14}(.)$ is the related-transplantation hazard.
Definition of the R-SMM (2)

The survival function is deduced as follow:

\[
S_{ob,14}(d_h,0) = \exp\left(-\int_0^{d_h,0} \left(\lambda^*(u + \Delta_h) + \lambda_{re,14}(u)\right) du\right)
\]

\[
= \exp\left(-\int_{\Delta_h}^{d_h,0+\Delta_h} \lambda^*(u) du\right) \exp\left(-\int_0^{d_h,0} \lambda_{re,14}(u) du\right)
\]

\[
= \exp\left(-\Lambda^*(d_h,0 + \Delta_h) + \Lambda^*(\Delta_h)\right) \exp\left(-\Lambda_{re,14}(d_h,0)\right)
\]

\[
= \frac{\exp\left(-\Lambda^*(d_h,0 + \Delta_h)\right)}{\exp\left(-\Lambda^*(\Delta_h)\right)} \exp\left(-\Lambda_{re,14}(d_h,0)\right)
\]

\[
S_{ob,14}(d_h,0) = S_{re,14}(d_h,0) \times S^*(d_h,0 + \Delta_h)/S^*(\Delta_h)
\]
Definition of the R-SMM (3)

- For the transition 2 → 4, we can perform similar developments:

\[ \lambda_{ob,24}(d_{h,1}) = \lambda^*(\Delta_h + d_{h,0} + d_{h,1}) + \lambda_{re,14}(d_{h,1}) \]

\[ S_{ob,14}(d_{h,1}) = S_{re,14}(d_{h,0}) \times S^*(\Delta_h + d_{h,0} + d_{h,1}) / S^*(\Delta_h + d_{h,0}) \]

- The individual contributions to the likelihood are similar but taking into account the new definitions of the waiting time distribution before a death.
Definition of the R-SMM (4)

- Example: $X_h = \{1, 2, 4\}$

![Diagram showing states and transitions](image)

- We defined for SMM the following individual contribution:

$$\ell_{h,2} = P_{12} f_{12}(d_{h,0}) \times P_{2k} f_{2k}(d_{h,1})$$

- For the R-SMM, we obtained:

$$\ell_{h,2} = P_{12} f_{12}(d_{h,0}) \times P_{2k} \left\{ \lambda^*(\Delta_h + d_{h,0} + d_{h,1}) + \lambda_{re,14}(d_{h,1}) \right\}$$

$$\times S_{re,14}(d_{h,0}) \times S^*(\Delta_h + d_{h,0} + d_{h,1}) / S^*(\Delta_h + d_{h,0})$$
Estimation of the expected survival in dialysis

Available data

- Data from the network REIN (Réseau Epidémiologie et Information en Néphrologie).
- Maximum follow-up equals 5 years:
  - We also have reduced the follow-up of transplanted patients.
- 2 French areas: Languedoc-Roussillon and Ile-de-France.
- Only patients on the waiting list.
- No previous kidney transplantation.
- \( N = 717 \) individuals were included.

Modeling assumptions

- Time between the first transplantation and the death.
- Transplanted-patient were transplanted.
- Parametric PH model with generalized Weibull distribution
- Age, Gender and year of first dialysis were kept in the model.
Expected survival in dialysis

- Exponential distribution of the survival times.
### Expected survival in dialysis

- **Results from the multivariate parametric PH model**

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient gender (Men vs. Women)</td>
<td>1.23</td>
<td>0.6500</td>
</tr>
<tr>
<td>Recipient age (≥ 55 vs. &lt;55 years)</td>
<td>5.74</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diabetic history (yes vs. no)</td>
<td>3.47</td>
<td>0.0047</td>
</tr>
<tr>
<td>Dialysis method (peritoneal vs. hemodialysis)</td>
<td>4.40</td>
<td>0.0028</td>
</tr>
<tr>
<td>Year of first dialysis (&gt;2004 vs. ≤2004)</td>
<td>1.45</td>
<td>0.5062</td>
</tr>
</tbody>
</table>
SMM and R-SMM without covariates (1)
SMM and R-SMM without covariates (2)

Post transplantation time (t in years)

$P_{2}(1-S_{2}(t))$

- $j=3$ – SMM
- $j=3$ – R-SMM
- $j=4$ – SMM
- $j=4$ – R-SMM
Regression coefficients of the Multivariate R-SMM

<table>
<thead>
<tr>
<th>Transition 1 → 2</th>
<th>Coef.</th>
<th>SD</th>
<th>Wald</th>
<th>HR</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (≥ 55 vs. &lt;55 years)</td>
<td>-0.38</td>
<td>0.17</td>
<td>-2.25</td>
<td>0.68</td>
<td>0.0246</td>
</tr>
<tr>
<td>Cancer history (yes vs. no)</td>
<td>-0.85</td>
<td>0.37</td>
<td>-2.29</td>
<td>0.43</td>
<td>0.0219</td>
</tr>
<tr>
<td>Transition 1 → 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor age (≥ 55 vs. &lt;55 years)</td>
<td>0.76</td>
<td>0.20</td>
<td>3.79</td>
<td>2.14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Year of first dialysis (&gt;2004 vs. ≤2004)</td>
<td>-0.63</td>
<td>0.24</td>
<td>-2.58</td>
<td>0.53</td>
<td>0.0100</td>
</tr>
<tr>
<td>Transition 1 → 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient age (≥ 55 vs. &lt;55 years)</td>
<td>1.33</td>
<td>0.33</td>
<td>4.05</td>
<td>3.78</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cardio-vascular history (yes vs. no)</td>
<td>0.59</td>
<td>0.30</td>
<td>2.00</td>
<td>1.80</td>
<td>0.0460</td>
</tr>
<tr>
<td>Transition 2 → 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient gender (Men vs. Women)</td>
<td>-2.17</td>
<td>0.45</td>
<td>-4.80</td>
<td>0.11</td>
<td>0.0000</td>
</tr>
<tr>
<td>Recurrent initial disease (yes vs. no)</td>
<td>1.16</td>
<td>0.42</td>
<td>2.74</td>
<td>3.18</td>
<td>0.0062</td>
</tr>
<tr>
<td>Year of first dialysis (&gt;2004 vs. ≤2004)</td>
<td>-1.51</td>
<td>0.53</td>
<td>-2.86</td>
<td>0.22</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

▶ $\ell = -1752.272$.

▶ Covariates associated with the transition 1 → 4 in the SMM:
  ▶ Recipient age: HR = 4.20
  ▶ Cardio-vascular history: HR = 2.02
Discussion

- We demonstrated the possibility of taking into account the expected mortality in SMM.

- The results are preliminary.

- A lot of limitations have to be underlined:
  - The follow-up is short, but the mortality is a long-term process.
  - The sample size is low according to the high percentage of censoring (n=11 for the transitions 2 → 4).
    - The same analysis will be performed with 4 others French areas (REIN) and with 2 other transplantation hospitals (DIVAT).
  - The quality and the definition of the collected data may be different between DIVAT and REIN.
  - The history of other disease (cardiovascular, cancer, etc.) is collected at two different times.
  - The assumptions of the R-SMM has to be validated (PH assumption and Semi-Markov assumption):
    - Adaptation of the goodness-of-fit analysis proposed by Foucher et al. [1].
  - The parametric distribution of the baseline hazard functions of waiting times.
  - We have only present the additive version, but the multiplicative R-SMM was also developed.
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Collaborations

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The DIVAT network:
  M. Kessler (Nancy), C. Legendre (Paris Necker), L. Rostaing (Toulouse), G. Mourad (Montpellier)

The REIN network:
  P. Landais (Paris Necker), C. Elie (Paris Necker), Y. Duny (IURC), JP. Daurès (IURC)