The modeling of the evolution of kidney transplant recipients

Applications to the DIVAT cohort

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Outline

Outline

Context (1)

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.

Context (2)

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.

Context (3)

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.

Cox-based results (1)

- DIVAT = Données Informatisées et VAlidées en Transplantation.
- Multicentric cohort with 5 French hospitals
  - Nantes, Paris Necker, Nancy, Toulouse, Montpellier.
- 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)

Hazard Ratio (p-value)	Patient/graft survival	Graft survival
Recipient age (> 55 vs ≤ 55 years)	1.58 (0.0001)	1.17 (0.1832)
Donor age (> 55 vs ≤ 55 years)	1.52 (0.0001)	1.40 (0.0055)
Cold ischemia time (>36 vs ≤ 36 hours) †		
Before 7 years of transplantation	1.14 (0.3895)	0.98 (0.9224)
After 7 years of transplantation	1.83 (0.0181)	2.68 (0.0011)
Recipient gender (male vs female)	0.94 (0.4512)	0.78 (0.0172)
Post-graft dialysis (yes vs no)	1.76 (0.0001)	1.88 (0.0001)
Acute rejection episode (yes vs no) ◊	1.76 (0.0001)	2.44 (0.0001)

◊ 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.

Cox-based results (3)

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.).

	Effectives	Percentages
Cancer	46	20.2%
Cardio-vascular cause	42	18.4%
Cerebro-vascular cause	12	5.3%
Gastro-intestinal cause	10	4.4%
Haemorrhage	18	7.9%
Infection	30	13.2%
Others	36	15.8%
Unknown/Missing	34	14.8%
TOTAL	228	100.0%

Table - Details about the cause of the 228 observed deaths

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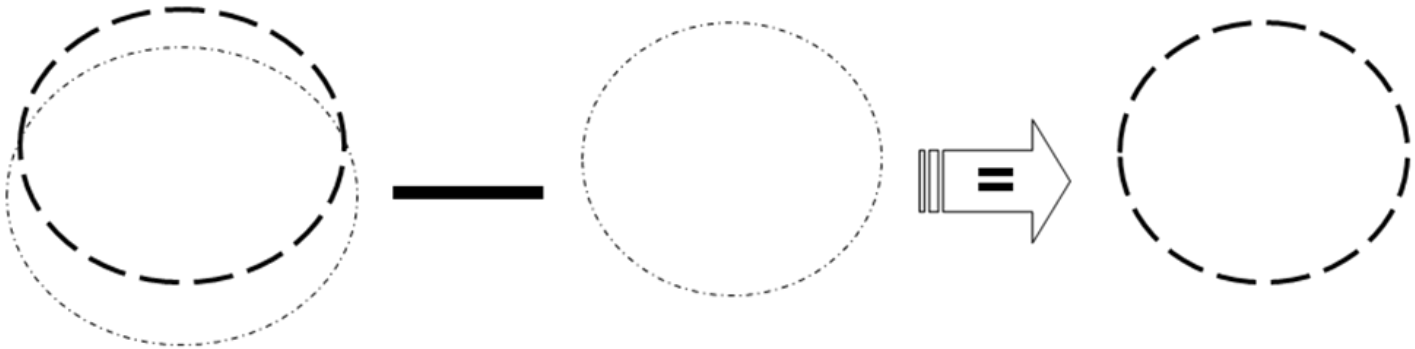
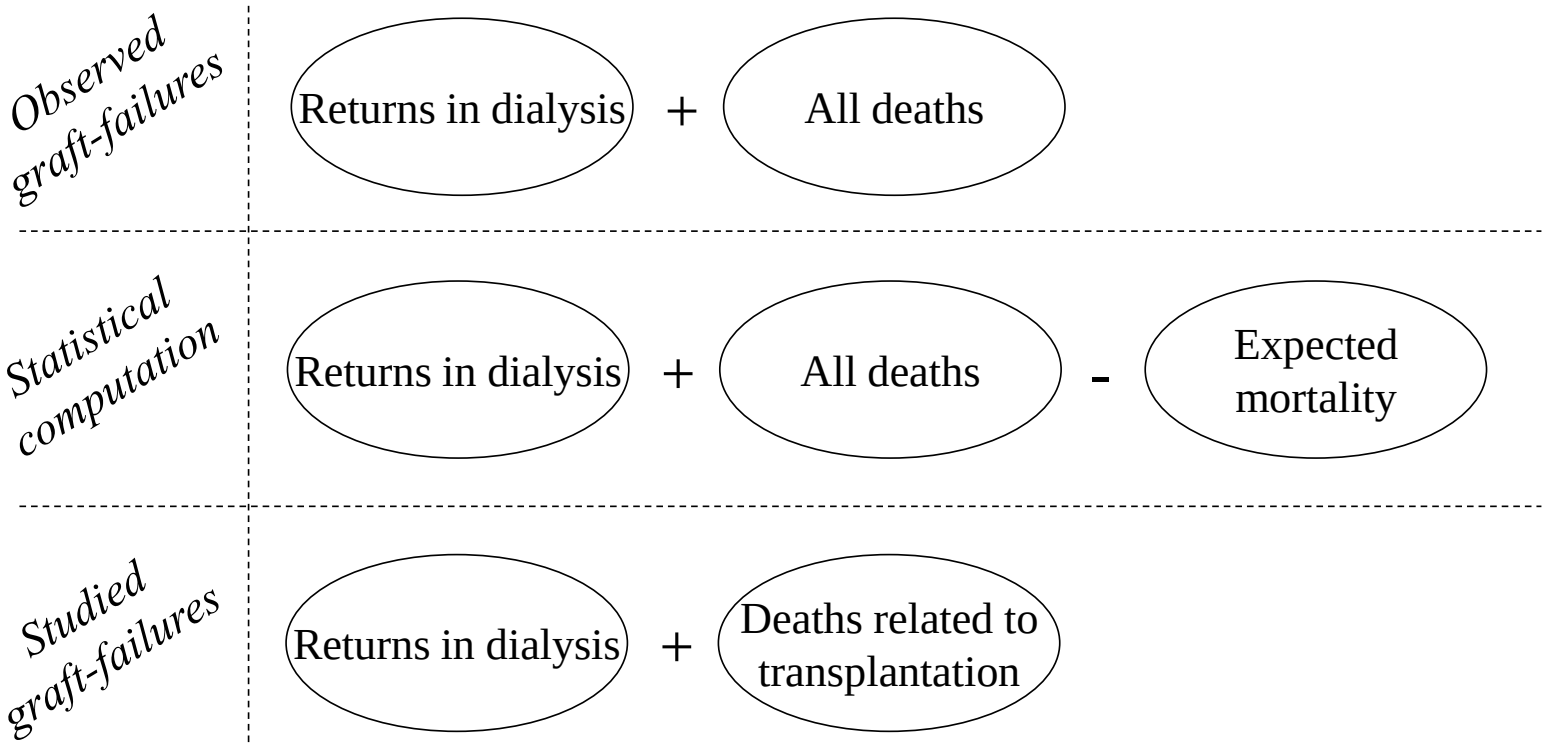
Principle of the method (1)

- The traditional additive relative survival models:



Principle of the method (2)

- The adaptation in kidney 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)

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

$$\Longleftrightarrow$$

$$\Lambda_{ob}(t) = \Lambda^*(t) + \Lambda_{re}(t)$$

$$\Longleftrightarrow$$

$$S_{ob}(t) = S^*(t) \times S_{re}(t)$$

- 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]:

$$\lambda_{re}(t, z_{re}) = \underbrace{exp\left(\sum_{k=1}^{m} \kappa_k \mathbb{1}_{\tau_{k-1} \leq t < \tau_k}\right)}_{\lambda_0(t)} exp\left(\sum_{j=1}^{p} \beta_j z_{re,j}\right)$$

  - The baseline hazard function is a step function respecting the m intervals $[\tau_0, \tau_1[$, $[\tau_1, \tau_2[$, ..., $[\tau_{m-1}, \tau_m[$.
  - β_j are the regression parameters associated with the jth covariate $z_{re,j}$ ($j = 1, 2, ..., p$).
  - 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 ith patient with $\delta_i = 1$ if he/she has failed and 0 otherwise.
- z_i is the observed vector of all covariates for the ith 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:

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

$$\Longleftrightarrow$$

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

  - $\lambda^*(t_i, z_i^*)$ 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 $\geq$ 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

Application to DIVAT (2)

Hazard Ratio (p-value)	Patient/graft survival	Graft survival	Relative survival
Recipient age (> 55 vs ≤ 55 years)	1.58 (0.0001)	1.17 (0.1832)	1.38 (0.0041)
Donor age (> 55 vs ≤ 55 years)	1.52 (0.0001)	1.40 (0.0055)	1.53 (0.0001)
Cold ischemia time (>36 vs ≤ 36 hours) †			
Before 7 years of transplantation	1.14 (0.3895)	0.98 (0.9224)	1.19 (0.3002)
After 7 years of transplantation	1.83 (0.0181)	2.68 (0.0011)	1.79 (0.0371)
Recipient gender (male vs female)	0.94 (0.4512)	0.78 (0.0172)	0.82 (0.0367)
Post-graft dialysis (yes vs no)	1.76 (0.0001)	1.88 (0.0001)	1.89 (0.0001)
Acute rejection episode (yes vs no) ◊	1.76 (0.0001)	2.44 (0.0001)	1.94 (0.0001)

◊ 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

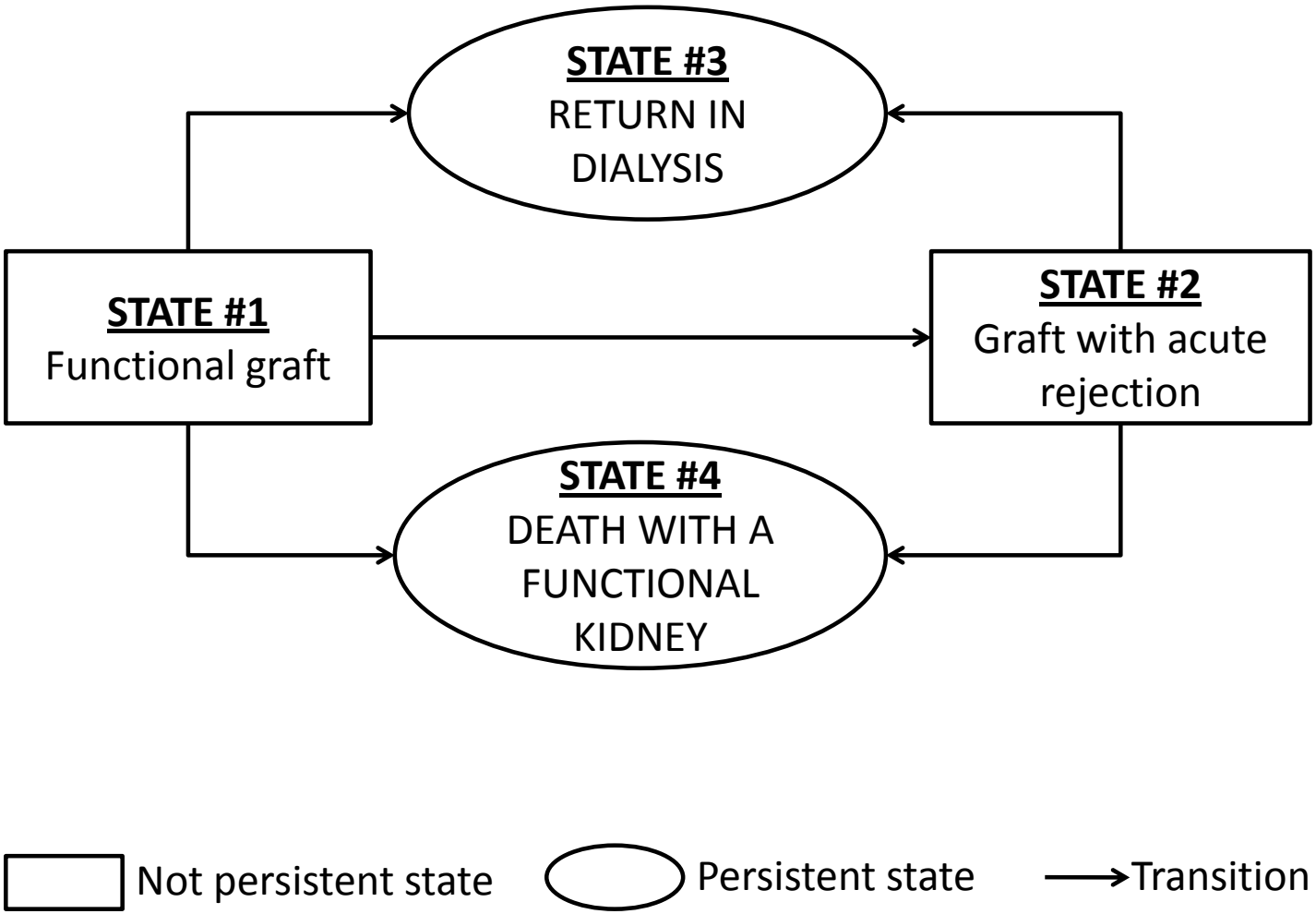
- The relative survival model can be used when cause-specific models are not adapted.
- The relative survival model is an objective synthesis between both usual models (graft or graft-patient survival).
- The interpretation of the model is simple (hazard ratio).
- Reduction of the heterogeneity between countries (the backgound mortality is removed).

Limitations of the model

- 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.

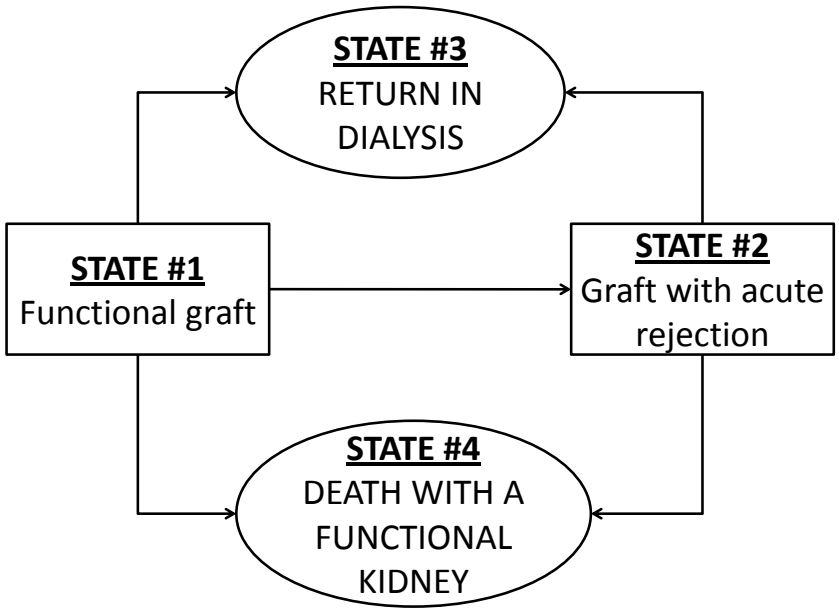
Outline

Definition of the multistate structure



SMM framework (1)

- Let the sample of size N, $h = 1, ..., N$.
- Let $X_h = \{X_{h,r}, r = 0, ..., m_h\}$ 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)

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

SMM framework (2)

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

$$\downarrow$$

Semi-Markov property

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

SMM framework (2)

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

$\downarrow$ *Semi-Markov property*

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

$P(A, B) = P(A|B)P(B)$

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

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P_{ij} : *Trajectory*

SMM framework (2)

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

$\downarrow$ *Semi-Markov property*

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

$P(A, B) = P(A|B)P(B)$

$$\underbrace{P(X_{h,r+1} = j | X_{h,r} = i)}_{P_{ij}\ :\ \textit{Trajectory}} \times \underbrace{P(D_{h,r} \leq x | X_{h,r+1} = j, X_{h,r} = i)}_{F_{ij}(x)\ :\ \textit{Waiting time distribution}}$$

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 $P_{ii} = 1$.

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 $P_{ii} = 1$.

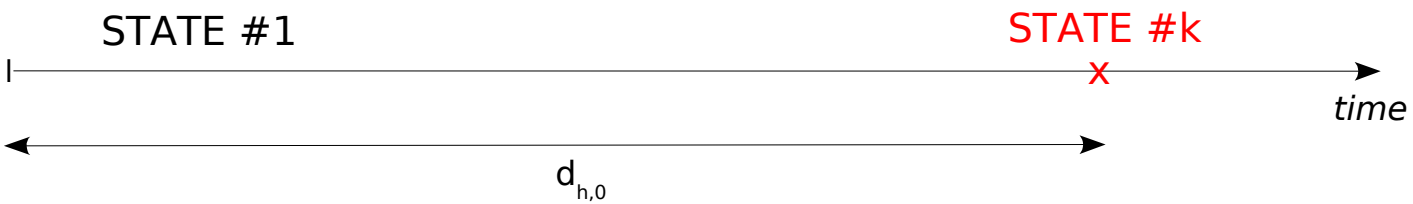
Distribution of waiting times

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

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

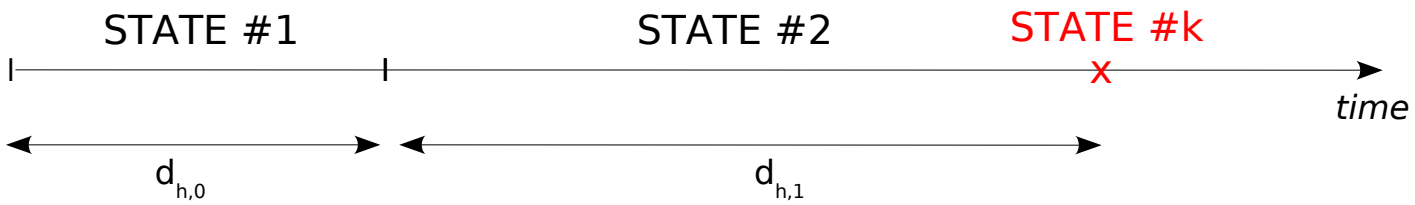


$$\begin{aligned} \ell_{h,1} &= \lim_{d \to 0} \left\{ P(d_{h,0} < D_{h,0} < d_{h,0} + d, X_{h,1} = k) \right\} \\ &= P(X_{h,1} = k | X_{h,0} = 1) \lim_{d \to 0} \left\{ P(d_{h,0} < D_{h,0} < d_{h,0} + d | X_{h,1} = k) \right\} \end{aligned}$$

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

Likelihood estimation (2)

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



$$\begin{aligned}
\ell_{h,2} &= \lim_{d \to 0} \Big\{ P(d_{h,0} < D_{h,0} < d_{h,0} + d, X_{h,1} = 2, \\
&\quad d_{h,1} < D_{h,1} < d_{h,1} + d, X_{h,2} = k) \Big\} \\
&= \lim_{d \to 0} \Big\{ P(d_{h,0} < D_{h,0} < d_{h,0} + d, X_{h,1} = 2) \\
&\quad \times P(d_{h,1} < D_{h,1} < d_{h,1} + d, X_{h,2} = k | X_{h,1} = 2) \Big\}
\end{aligned}$$

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

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 β_{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:

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

- Hazard functions can be $\bigcup -$ or $\bigcap -$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}

$$P_{1j} = \frac{exp(\alpha_{1j})}{\sum_{k=2}^{4} exp(\alpha_{1k})} \; \forall \alpha_{12}, \alpha_{13}, \alpha_{14} \in \Re$$

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

$$P_{2j} = \frac{exp(\alpha_{2j})}{exp(\alpha_{23}) + exp(\alpha_{24})} \; \forall \alpha_{23}, \alpha_{24} \in \Re$$

- $P_{23} + P_{14} = 1$
- We assumed by convention that $\alpha_{23} = 0$

Application to DIVAT (1)

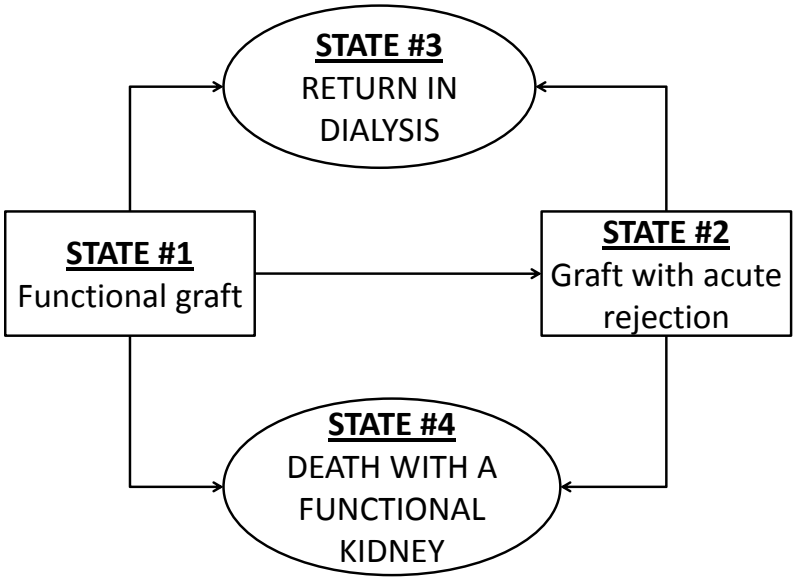
Inclusion criteria

- In order to obtain a homogeneous sample:
  - Transplantations after the 1st January 1996.
  - Age at the graft $\geq$ 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.

$\Rightarrow N = 2245$ individuals were included.

Application to DIVAT (2)

Description of the trajectories



Trajectory	Effective	Percent.
$X_h = \{1\}^*$	1636	72.9%
$X_h = \{1,2\}^*$	373	16.6%
$X_h = \{1,3\}$	107	4.8%
$X_h = \{1,4\}$	79	3.5%
$X_h = \{1,2,3\}$	39	1.7%
$X_h = \{1,2,4\}$	11	0.5%

* 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:

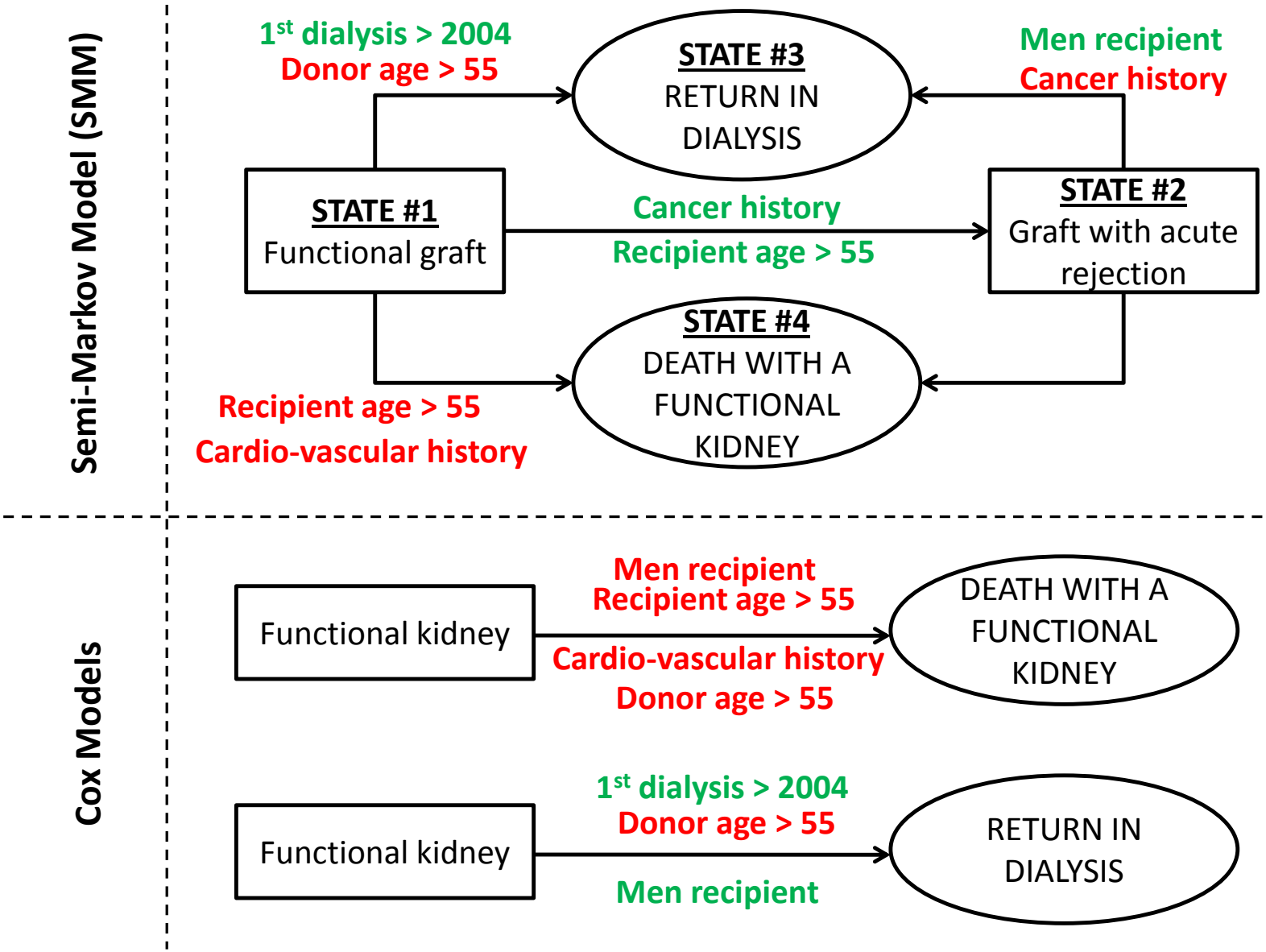
Parameters	Estmation	SD
$\log(\sigma_{12})$	-4.12	0.08
$\log(\nu_{12})$	1.88	0.27
$\log(\theta_{12})$	3.52	0.35
$\log(\sigma_{13})$	-5.95	0.00
$\log(\nu_{13})$	4.54	0.00
$\log(\theta_{13})$	8.97	0.39
$\log(\sigma_{14})$	5.37	2.49
$\log(\nu_{14})$	-0.53	0.17
$\log(\sigma_{23})$	3.21	0.51
$\log(\nu_{23})$	-0.43	0.15
$\log(\sigma_{24})$	0.79	0.91
α_{13}	0.76	0.43
α_{14}	-0.34	1.04
α_{24}	-3.12	0.62

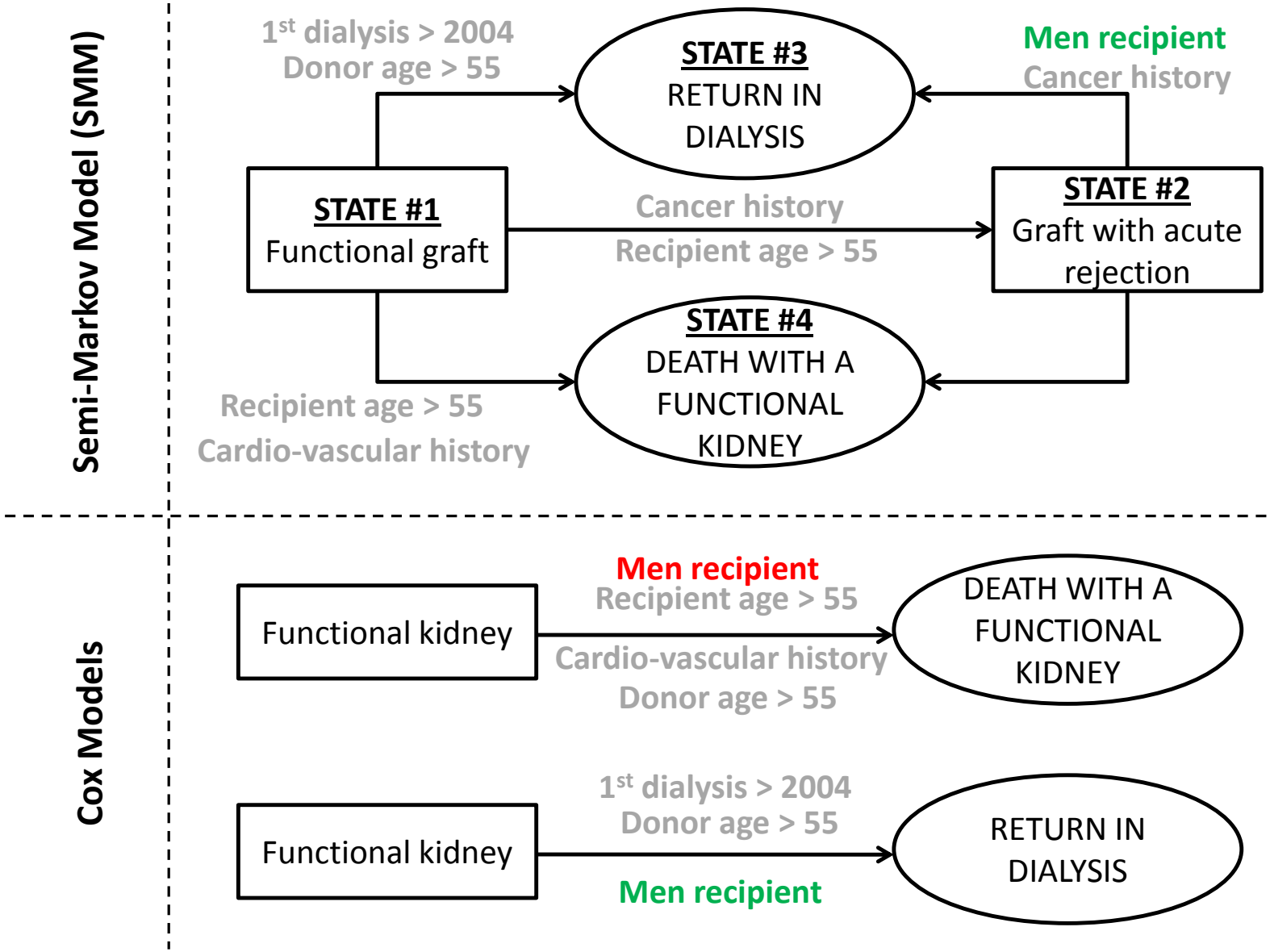
Application to DIVAT (4)

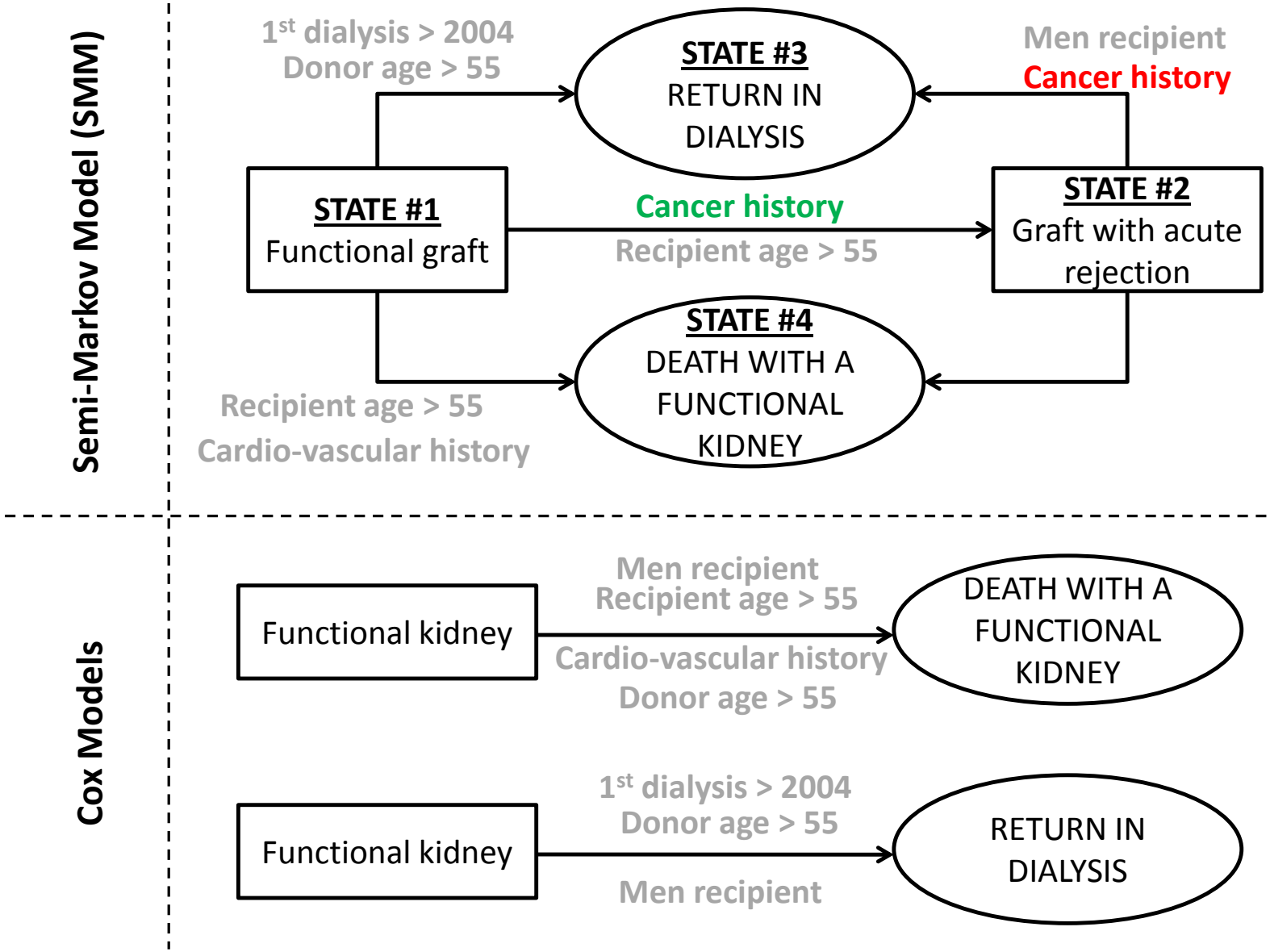
Multivariate Semi-Markov model

- Regression parameters:

	Coef.	SD	Wald	HR	pvalue
Transition 1 $\rightarrow$ 2					
Recipient age ($\geq$ 55 vs. $<$55 years)	-0.46	0.18	-2.61	0.62	0.0091
Cancer history (yes vs. no)	-0.89	0.40	-2.20	0.41	0.0278
Transition 1 $\rightarrow$ 3					
Donor age ($\geq$ 55 vs. $<$55 years)	0.67	0.21	3.17	1.96	0.0015
Year of first dialysis ($>$2004 vs. $\leq$2004)	-0.88	0.29	-2.99	0.41	0.0028
Transition 1 $\rightarrow$ 4					
Recipient age ($\geq$ 55 vs. $<$55 years)	1.44	0.38	3.83	4.22	0.0001
Cardio-vascular history (yes vs. no)	0.70	0.30	2.33	2.02	0.0198
Transition 2 $\rightarrow$ 3					
Recipient gender (Men vs. Women)	-1.09	0.34	-3.17	0.34	0.0015
Cancer history (yes vs. no)	1.73	0.54	3.22	5.66	0.0013







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.

Outline

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Cox-based results

The relative survival

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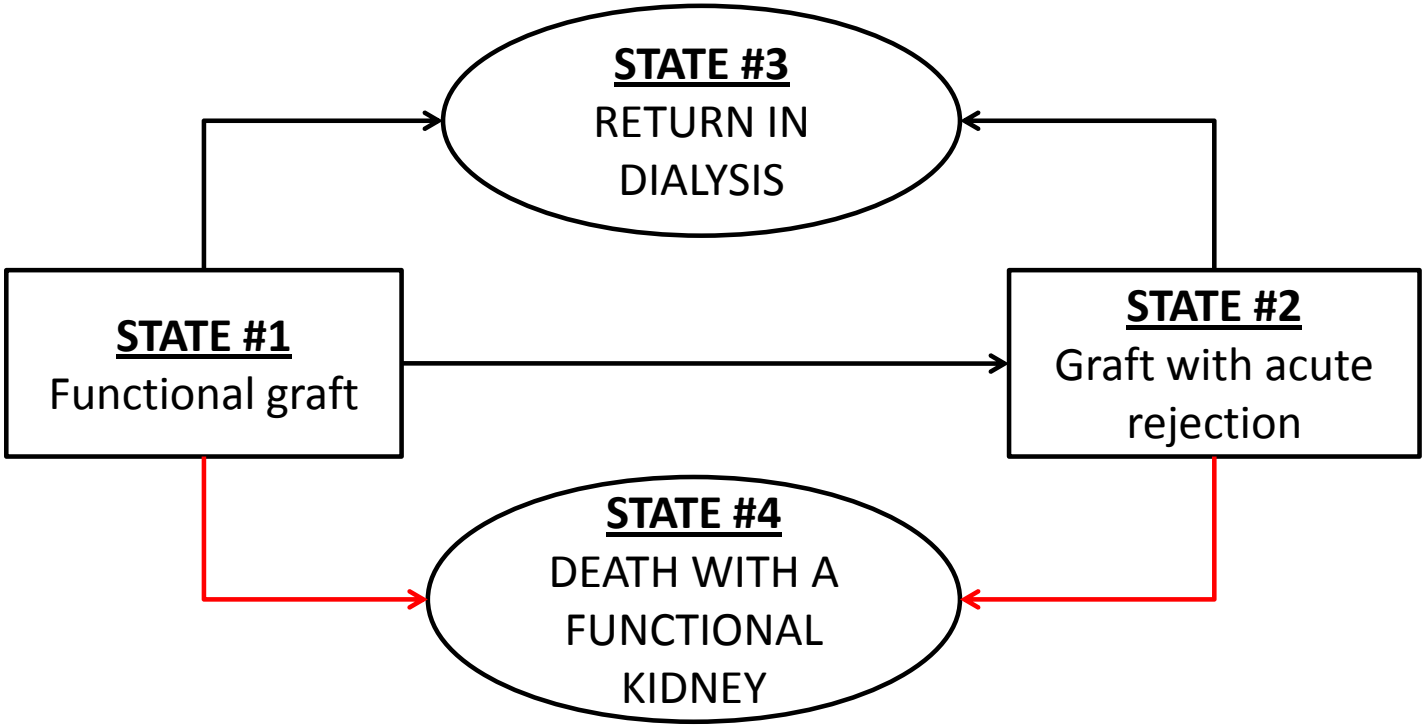
Collaborations

Principle of relative semi-Markov model (R-SMM)



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.
  - Δ_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:

$$
\begin{aligned}
S_{ob,14}(d_{h,0}) &= exp\left(- \int_0^{d_{h,0}} \left(\lambda^*(u+\Delta_h) + \lambda_{re,14}(u) \right) du \right) \\
&= exp\left(- \int_{\Delta_h}^{d_{h,0}+\Delta_h} \lambda^*(u) du \right) exp\left(- \int_0^{d_{h,0}} \lambda_{re,14}(u) du \right) \\
&= exp\left(- \Lambda^*(d_{h,0}+\Delta_h) + \Lambda^*(\Delta_h) \right) exp\left(- \Lambda_{re,14}(d_{h,0}) \right) \\
&= \frac{exp\left(- \Lambda^*(d_{h,0}+\Delta_h) \right)}{exp\left(- \Lambda^*(\Delta_h) \right)} exp\left(- \Lambda_{re,14}(d_{h,0}) \right)
\end{aligned}
$$

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

Definition of the R-SMM (3)

- For the transition $2 \rightarrow 4$, we can perform similar developments:

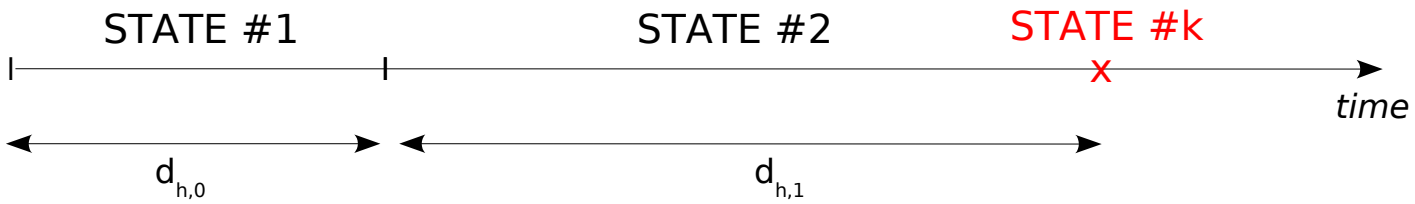
$$\lambda_{ob,24}(d_{h,1}) = \lambda^*(\Delta_h + d_{h,0} + d_{h,1}) + \lambda_{re,14}(d_{h,1})$$

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

- The individual contributions to the likelihood are similar but tacking into account the new definitions of the waiting time distribution before a death.

Definition of the R-SMM (4)

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



- 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:

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

Estimation of the expected survival in dialysis

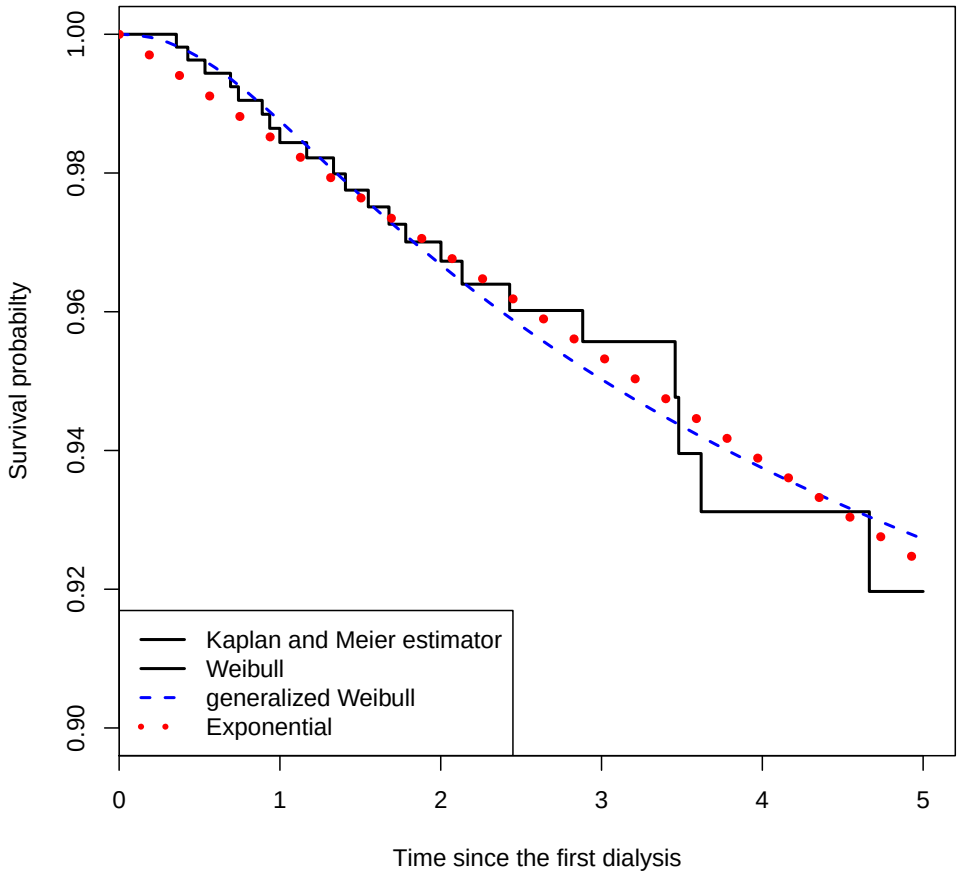
Available data

- 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



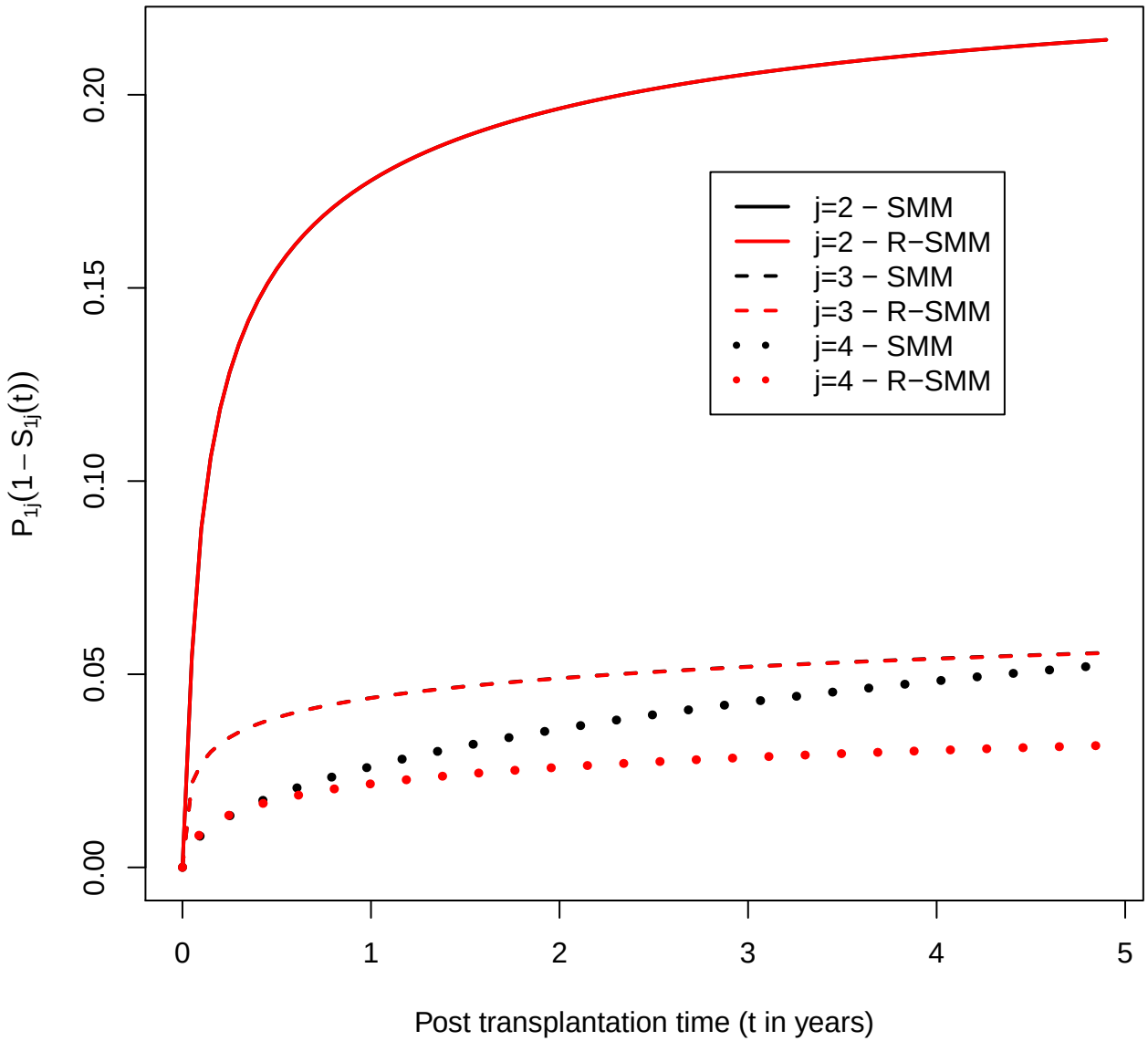
- Exponential distribution of the survival times.

Expected survival in dialysis

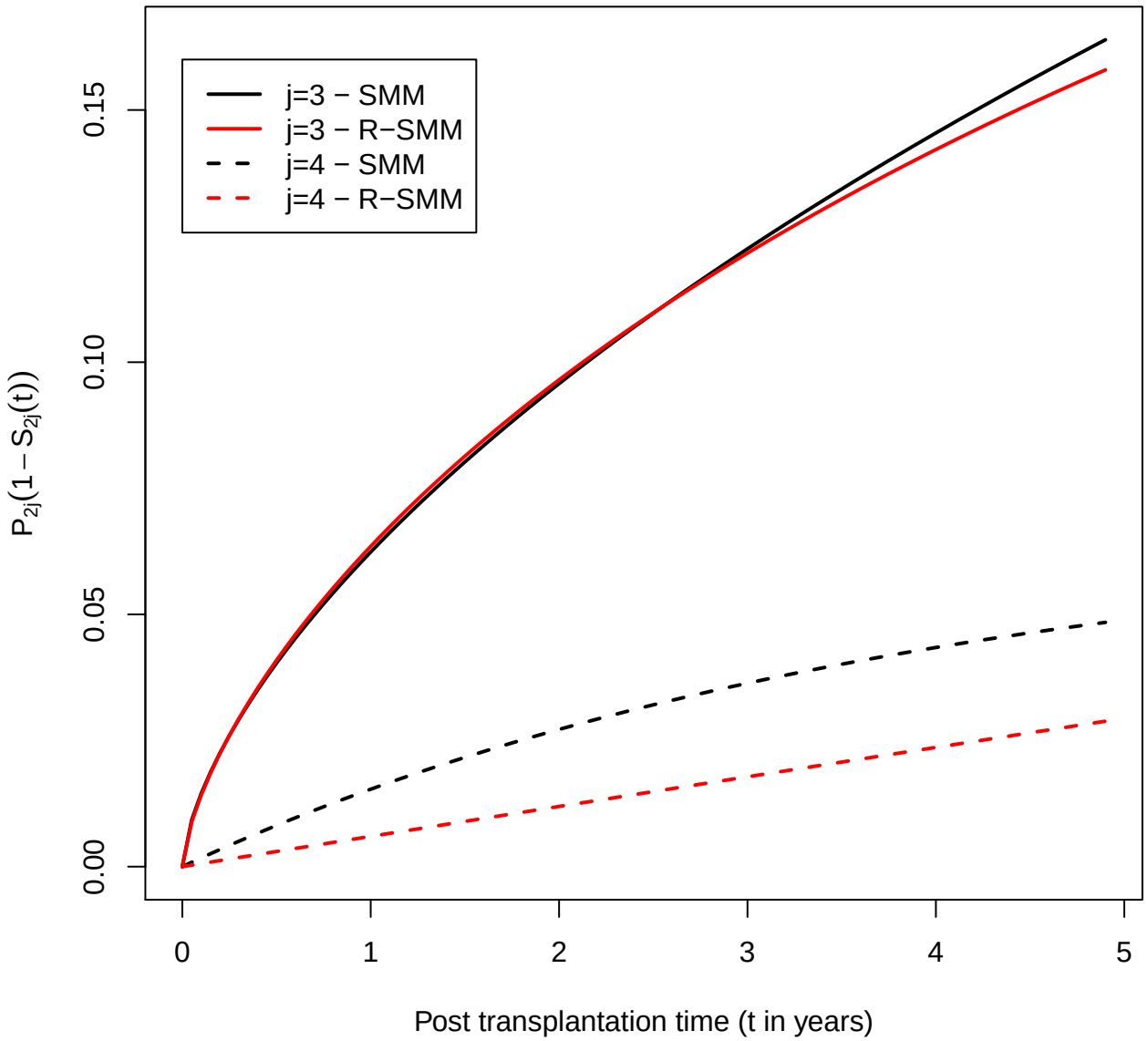
- Results from the multivariate parametric PH model

	HR	pvalue
Recipient gender (Men vs. Women)	1.23	0.6500
Recipient age ($\geq$ 55 vs. $<$55 years)	5.74	0.0003
Diabetic history (yes vs. no)	3.47	0.0047
Dialysis method (peritoneal vs. hemodialysis)	4.40	0.0028
Year of first dialysis ($>$2004 vs. $\leq$2004)	1.45	0.5062

SMM and R-SMM without covariates (1)



SMM and R-SMM without covariates (2)



Regression coefficients of the Multivariate R-SMM

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

- $\ell = -1752.272$.
- Covariates associated with the transition $1 \rightarrow 4$ 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 $\longrightarrow$ 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.

Outline

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Methods

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The relative semi-Markov model (R-SMM)

Methods

Results

Discussions

References

Collaborations

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- Nantes University, ITERT:
  - P. Rigouin, A. Akl, K. Launay, M. Giral
- 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)