Semi-Markov model with Generalized Weibull distribution for multistate data in kidney transplant recipients

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Plan

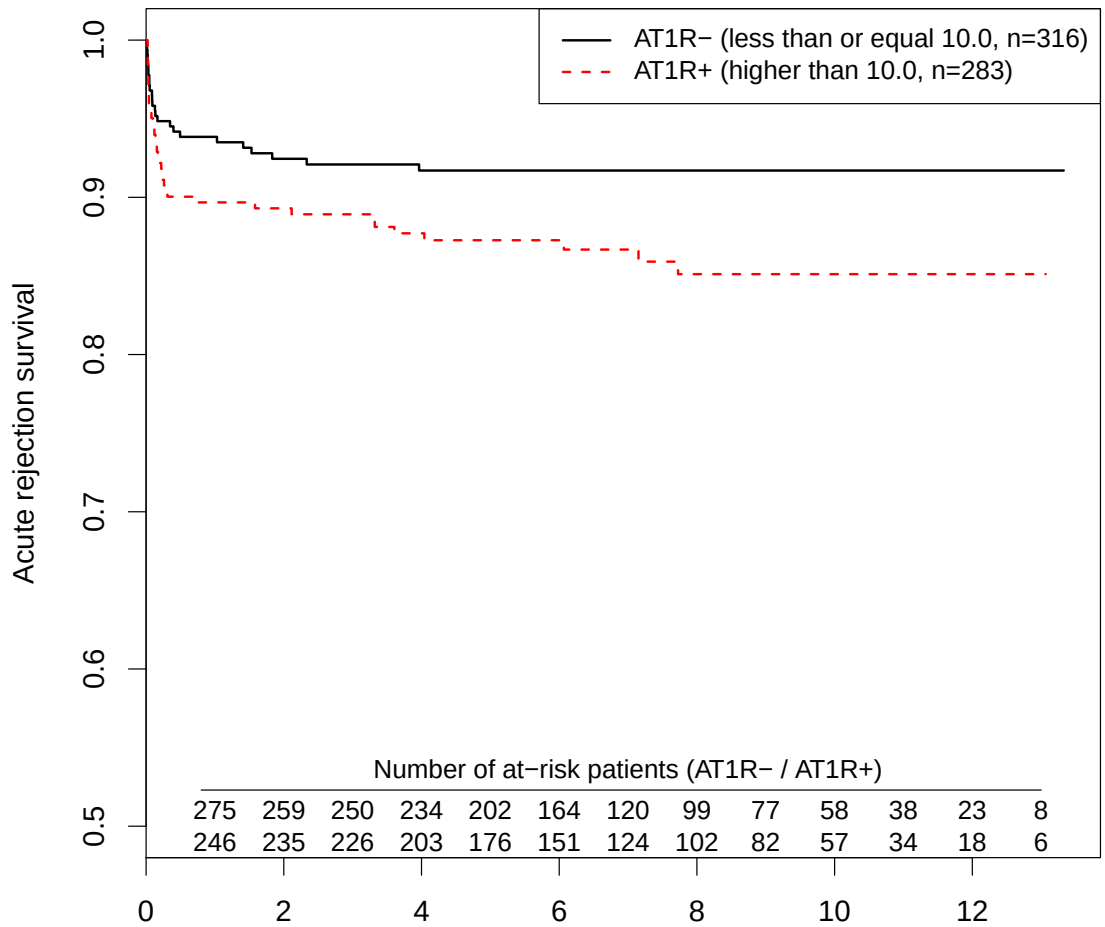
Angiotensin II Type 1 Receptor

- Angiotensin II Type 1 Receptor (AT_1R) = Non-HLA antigen
- Antibodies against AT_1R (AT_1R-Abs) found during acute rejection episode (ARE) in kidney transplants

$\Rightarrow$ Association between AT_1R-Abs and time to first ARE ?

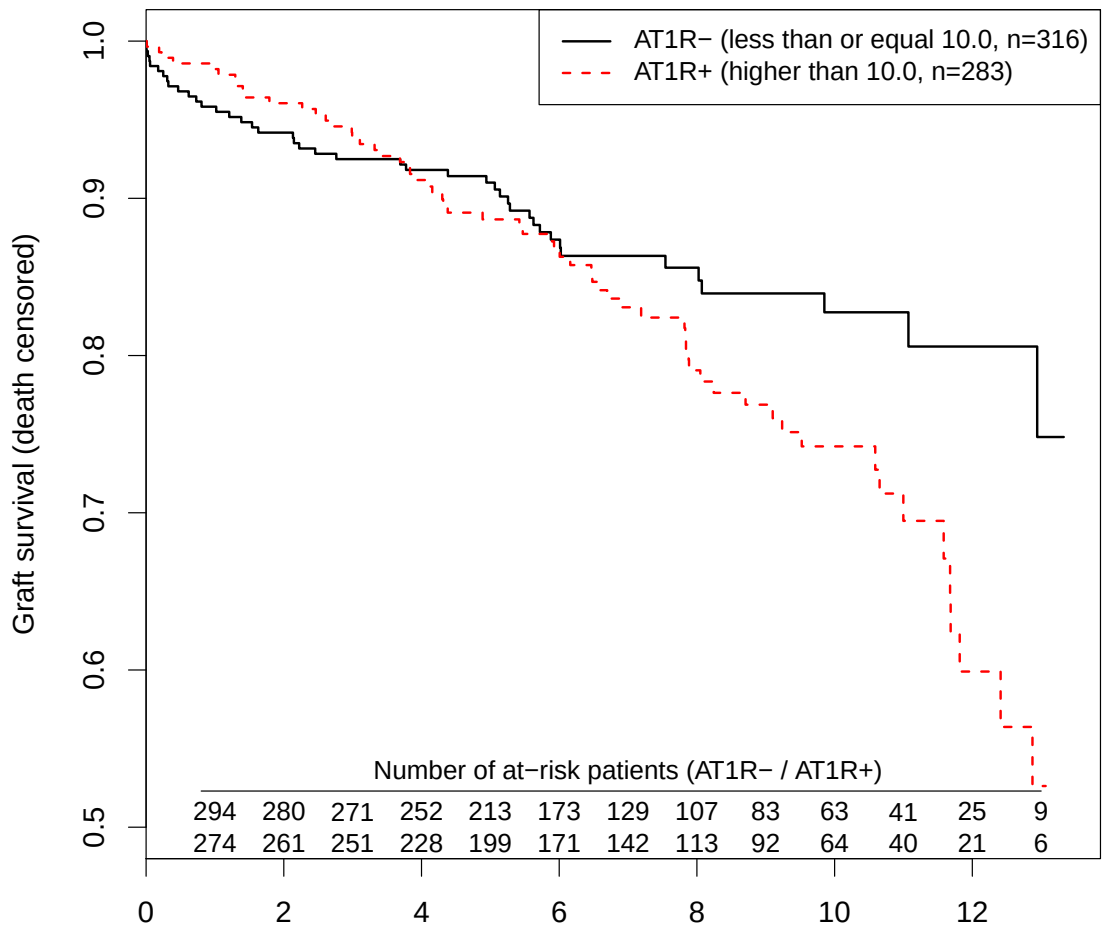
Pre-graft level of AT1R and Acute Rejection Episode

Higher frequency of ARE during the first months of the transplantation



Pre-graft level of AT1R and Return to dialysis

High pre-graft level of AT1R $\Rightarrow$ increased risk of return to dialysis after 3 years post-transplantation



Problematic

Raised Issue :

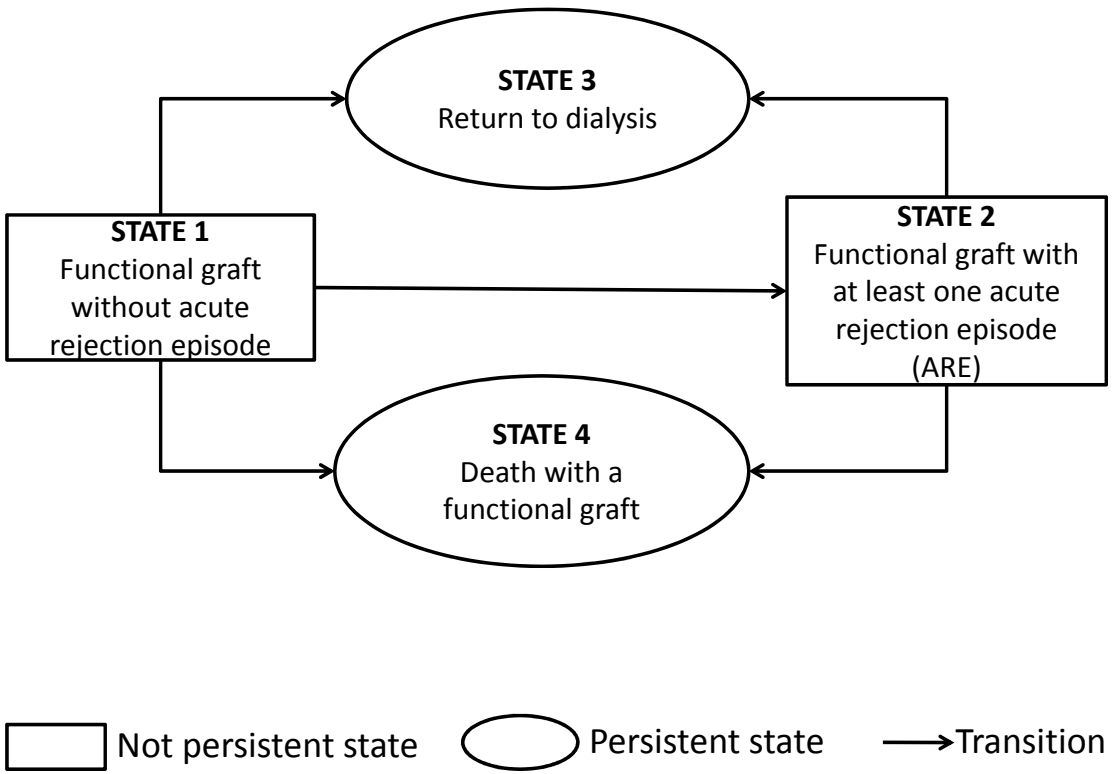
Delayed effect of AT1R for the risk of return to dialysis ?

OR

Increased risk due to ARE ?

$\Rightarrow$ **Multistate model**

The different possible states for the patient



Plan

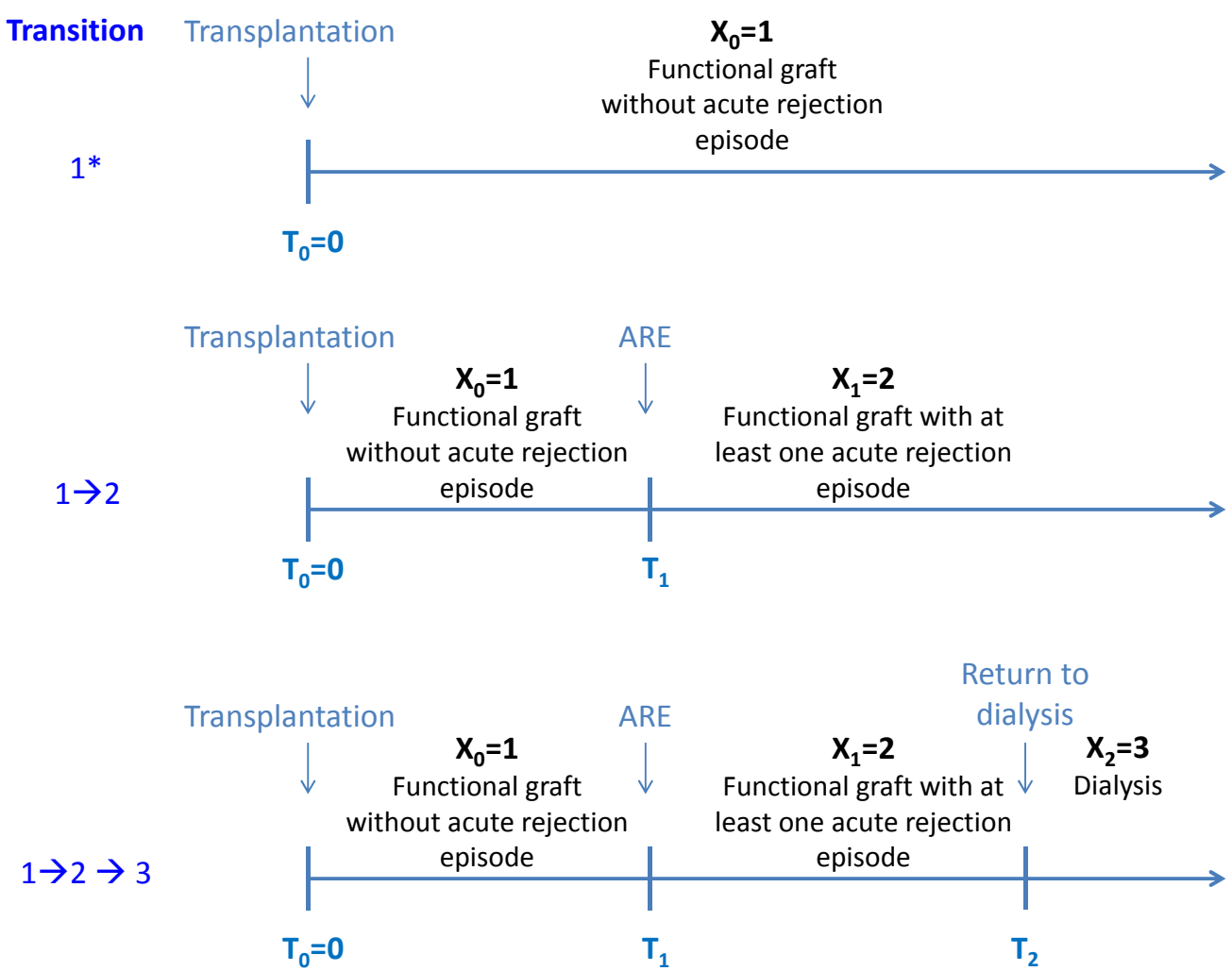
Interest

Next state to be visited + time of occurence will depend on :

- the present state
- **the time since entry of that state**

$\Rightarrow$ Adapted for time-to-event in Kidney Transplants

Notations



The Semi-Markovian process

Two characteristics of interest :

- **Transition probability** p_{ij}
  Probability that a patient in state i enters in state j on its next transition

  $\Rightarrow$ Probability to do a Trajectory

- **Instantaneous hazard rate** $\lambda_{ij}(d)$ of the sojourn time from state i to state j

  $\Rightarrow$ Speed of transition

Modelling of transition probabilities p_{ij}

Probability that a patient in state i enters in state j on its next transition :

$$p_{ij} = P(X_{m+1} = j | X_m = i) \text{ and } \sum_j p_{ij} = 1, \text{ for } ij \in \epsilon \qquad (1)$$

- Multinomial distributions + covariates

$$p_{ij}(W) = \frac{\exp(\gamma_{ij0} + \gamma'_{ij} W)}{\sum_r \exp(\gamma_{ir0} + \gamma'_{ir} W)}$$

  - r : possible states following the transient states i
  - W : covariate matrix
  - $\gamma_{ij} = \{\gamma_{ij1}, \gamma_{ij2}, ..., \gamma_{ijR}\}'$: vector of associated regression coefficients.

- Constraint $\sum_{i \neq j} p_{ij}(W) = 1 \Rightarrow$ reference transition ij_{ref}.

Transition probability p_{ij} & Interpretation

$$\text{If } AT_1R = \begin{cases} 1 & \text{si } AT_1R \geq 10 \\ 0 & \text{si } AT_1R < 10 \end{cases}$$

$$OR_{ij}^{AT_1R=1/AT_1R=0} = \exp(\gamma_{ij})$$

$\Rightarrow$ Risk to experience the event j as next event (after event i) relative to the

Risk to experience the referent event j_{ref} as next event for high values of AT_1R

Modelling of the sojourn time distributions $\lambda_{ij}(d)$

Instantaneous hazard rate $\lambda_{ij}(d)$ of the sojourn time from state i to state j :

$$\lambda_{ij}(d) = \lim_{\Delta d \to 0^+} \frac{P(d \leq T_{m+1} - T_m < d + \Delta d | T_{m+1} - T_m > d, \boldsymbol{X_{m+1} = j}, \boldsymbol{X_m = i})}{\Delta d} \tag{2}$$

- **Hazard function** from state i to state j at time d :

$$\lambda_{ij}(d|Z) = \lambda_{0,ij}(d) \exp(\beta'_{ij} Z)$$

where

- $Z = \{Z_1, Z_2, ..., Z_L\}'$: vector of L covariates
- $\beta_{ij} = \{\beta_{ij1}, \beta_{ij2}, ..., \beta_{ijL}\}'$: vector of associated regression coefficients
- $\lambda_{0,ij}(d)$: baseline hazard function

Instantaneous hazard rate λ_{ij} & Interpretation

$$\text{If } AT_1R = \begin{cases} 1 & \text{si } AT_1R \geq 10 \\ 0 & \text{si } AT_1R < 10 \end{cases}$$

$$HR_{ij}^{AT_1R=1/AT_1R=0}(d) = \exp(\beta_{ij})$$

$\Rightarrow$ Risk to do the trajectory ij quickly for high values of AT_1R

Instantaneous hazard rate of the semi-Markovian process

(1)+(2)

- $\Rightarrow$ Instantaneous joint probability of jumping towards the state j from state i, after a certain sojourn time d in this state i

$$\alpha_{ij}(d) = \lim_{\Delta d \to 0^+} \frac{P(d \leq T_{m+1} - T_m < d + \Delta d, \boldsymbol{X_{m+1} = j} | T_{m+1} - T_m > d, \boldsymbol{X_m = i})}{\Delta d}$$

- and :

$$\alpha_{ij}(d) = \frac{p_{ij} \lambda_{ij}(d) S_{ij}(d)}{\sum_{j : j \in \epsilon} p_{ij} S_{ij}(d)}$$

with $S_{ij}(d)$ the survival function from state i to state j

The likelihood function

- Likelihood for a sample H of subjects :

$$L = \prod_{h \in H} \prod_{ij \in \epsilon_h \cup \epsilon'_h} \left[p_{ij}(W_{ij}^h) f_{ij}(d_{ij} | Z_{ij}^h) \right]^{\delta_{\epsilon_h}} \left[\sum_{jr \in \epsilon'_h} p_{jr}(W_{jr}^h) S_{jr}(d_{jr} | Z_{jr}^h) \right]^{1-\delta_{\epsilon_h}}$$

  - **subject h who jumps from state i to state j** after a sojourn time d_{ij} in this state i given its covariates W_{ij}^h and Z_{ij}^h
  - **subject h right censored** in the state i after a sojourn time d_i in this state i given covariates W_i^h and Z_i^h

- $\lambda_{0,ij}(d)$: Parametric distribution
  $\Rightarrow$ Simple expression $\Rightarrow$ Easy computation to maximise likelihood

Model strategy

1. Parametric sojourn time distributions (Generalized Weibull, Weibull or Exponential)
2. AT_1R forced in the SMM on the transition probabilities and the transition intensities (with possible time-varying effect)
3. Stepwise selection for covariate adjustment (with possible time-varying effect)

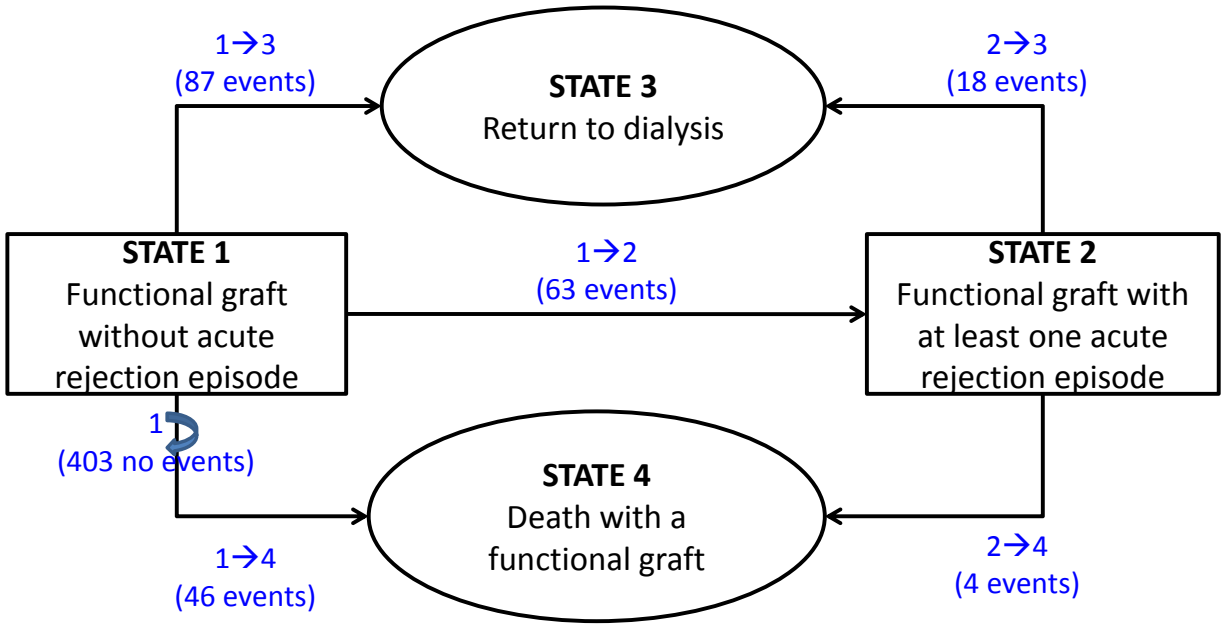
Generalized Weibull distribution

$$\lambda_{0,ij}(d) = \nu_{ij}\left(\frac{1}{\sigma_{ij}}\right)^{\nu_{ij}} d^{\nu_{ij}-1} \text{ ,with } \sigma_{ij} > 0 \text{ and } \nu_{ij} > 0$$

Plan

Frequency of the transitions observed

599 kidney transplant recipients
63 acute rejections/105 returns to dialysis/50 deaths

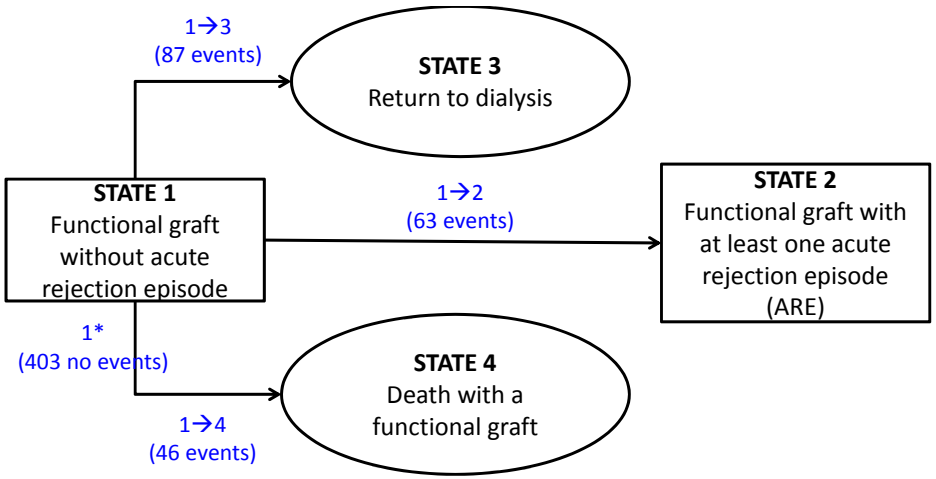


Multivariate SMM (N=575)

Coefficient	Estimate	SE	Wald	exp(Est)	95%CI	p.value
Intercept						
γ_{13}	1.91	0.27	7.04	6.74	[3.97-11.44]	0.0000
γ_{14}	0.90	0.40	2.27	2.46	[1.13-5.4]	0.0230
γ_{24}	-0.05	0.56	-0.08	0.95	[0.32-2.86]	0.9337
Transition probabilities						
γ_{13} AT1R	-1.41	0.54	-2.62	0.24	[0.08-0.7]	0.0088
γ_{14} AT1R	-1.74	0.50	-3.45	0.18	[0.07-0.47]	0.0006
γ_{13} AgeR>55	-0.52	0.43	-1.22	0.59	[0.25-1.38]	0.2233
γ_{14} AgeR>55	1.67	0.43	3.90	5.30	[2.28-12.3]	0.0001
Transition intensities						
$\log(\sigma_{12})$	-4.12	0.19	-22.08	0.02	[0.01-0.02]	0.0000
$\log(\nu_{12})$	1.66	0.45	3.68	5.28	[2.18-12.75]	0.0002
$\log(\theta_{12})$	2.99	0.50	5.95	19.95	[7.49-53.15]	0.0000
β_{12} AT1R, t<4 months	-1.16	0.44	-2.65	0.31	[0.13-0.74]	0.0081
β_{12} AT1R, t≥4 months	-2.70	0.65	-4.16	0.07	[0.02-0.24]	0.0000
β_{12} IncompABDR>5	1.16	0.48	2.41	3.19	[1.24-8.17]	0.0161
$\log(\sigma_{13})$	3.58	0.33	10.74	35.73	[18.71-68.22]	0.0000
$\log(\nu_{13})$	0.26	0.14	1.83	1.29	[0.98-1.7]	0.0673
β_{13} AT1R t<3 years	0.10	0.49	0.21	1.11	[0.43-2.9]	0.8298
β_{13} AT1R t≥3 years	0.86	0.43	2.02	2.37	[1.02-5.5]	0.0430
β_{13} AgeR>55	1.90	0.48	3.99	6.72	[2.62-17.21]	0.0001
β_{13} PRA.T>25	0.49	0.38	1.30	1.64	[0.78-3.45]	0.1928
$\log(\sigma_{14})$	3.68	0.23	15.80	39.49	[25.16-61.98]	0.0000
β_{14} PRA.B>25	0.94	0.44	2.12	2.56	[1.08-6.08]	0.0341
$\log(\sigma_{23})$	3.43	0.85	4.04	30.85	[5.83-163.23]	0.0001
β_{23} AT1R	1.38	0.75	1.83	3.98	[0.91-17.29]	0.0672
β_{23} AgeD>55	1.71	0.65	2.62	5.54	[1.55-19.8]	0.0087
$\log(\sigma_{24})$	4.03	0.56	7.23	56.03	[18.7-167.93]	0.0000

N=575 (24 patients were excluded because of missing data)
t : time since graft transplantation (years)
AT1R : pre-graft level of angiotensin II type 1 receptor greater or equal to 10
$\sigma_{ij}, \nu_{ij}, \theta_{ij}$: parameters of the Weibull distribution

Transition probabilities (first event)

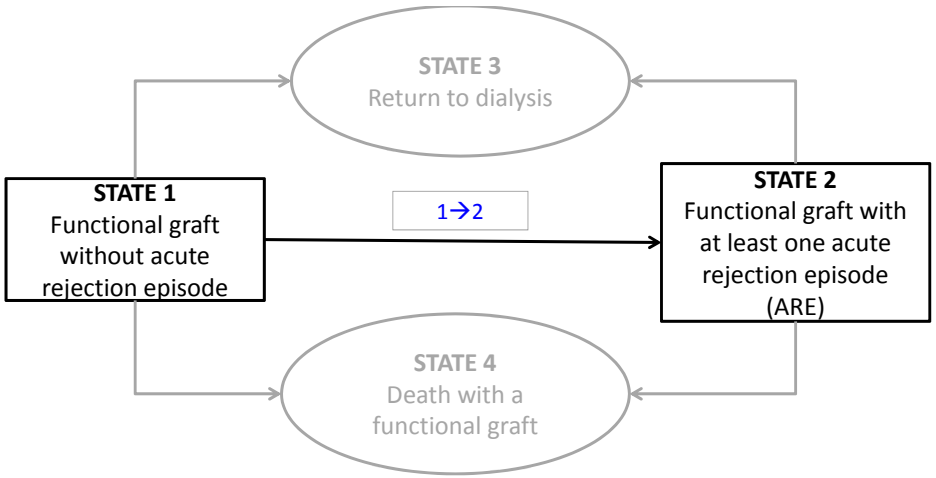


Coefficient	Estimate	SE	Wald	OR	95%CI	p.value
Transition probabilities						
γ_{13} AT1R	-1.41	0.54	-2.62	0.24	[0.08-0.7]	0.0088
γ_{14} AT1R	-1.74	0.50	-3.45	0.18	[0.07-0.47]	0.0006
...						

$\gamma_{12} = 0$, *ARE : reference level*

- Significant association between pre-graft level of AT1R and first trajectory
- High pre-graft level of AT1R was associated to a increased risk to do an ARE after transplantation.

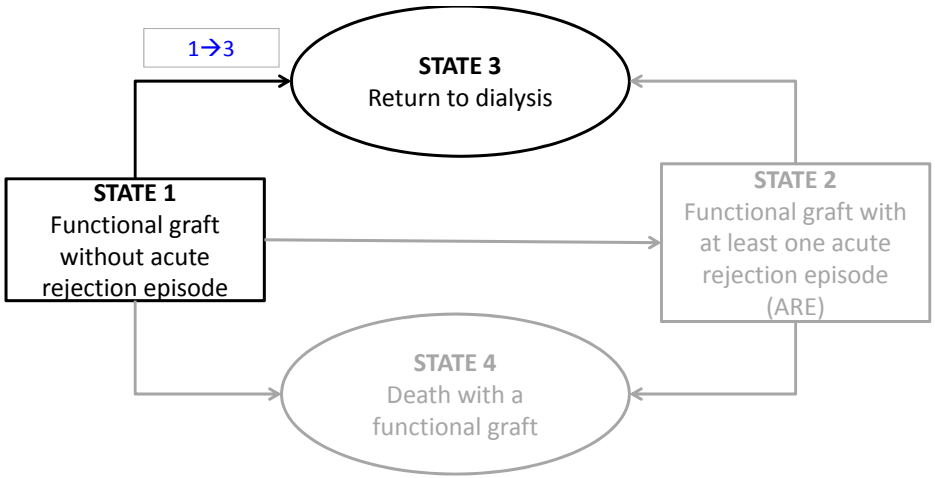
Transition 1 → 2



Coefficient	Estimate	SE	Wald	HR	95%CI	p.value
Transition intensities						
β_{12} AT1R, t<4 months	-1.16	0.44	-2.65	0.31	[0.13-0.74]	0.0081
β_{12} AT1R, t≥4 months	-2.70	0.65	-4.16	0.07	[0.02-0.24]	0.0000
...						

- Patients who had an ARE had a decreased risk to do it quickly (increase of time to ARE) with high values of AT1R.

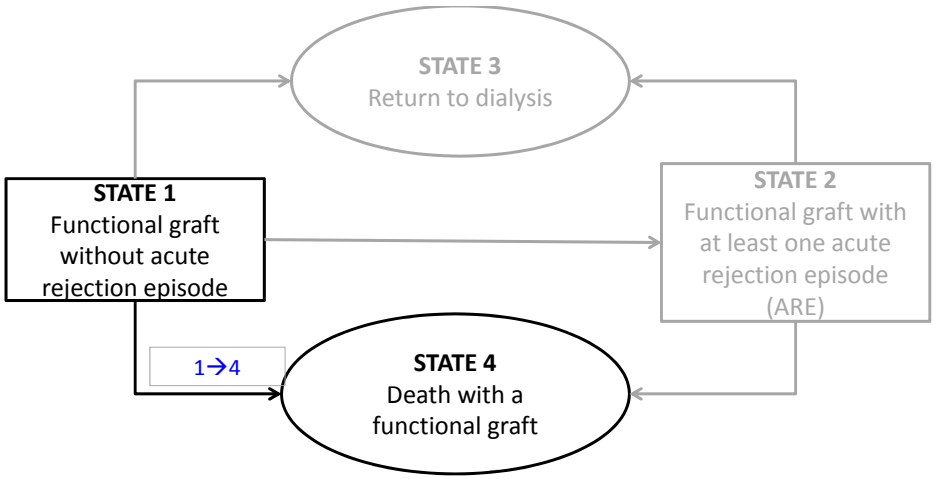
Transition 1 → 3



Coefficient	Estimate	SE	Wald	HR	95%CI	p.value
Transition intensities						
β_{13} AT1R t<3 years	0.10	0.49	0.21	1.11	[0.43-2.9]	0.8298
β_{13} AT1R t≥3 years	0.86	0.43	2.02	2.37	[1.02-5.5]	0.0430
...						

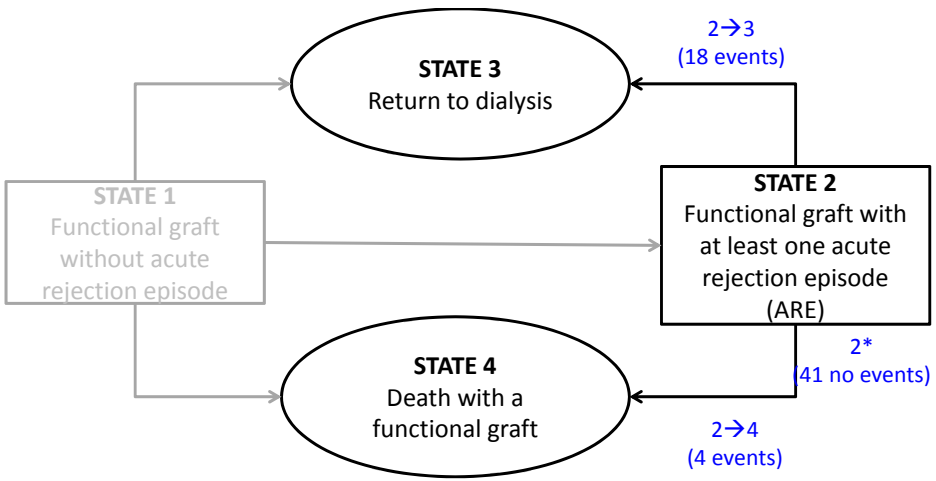
- The pre-graft level of AT1R seemed to not influence the time-to-return directly to dialysis in the 3 years following the transplantation
- Patients who returned to dialysis directly after transplantation had a faster time-to-return to dialysis after three years post-transplantation with an high pre-graft level of AT1R.

Transition 1 → 4



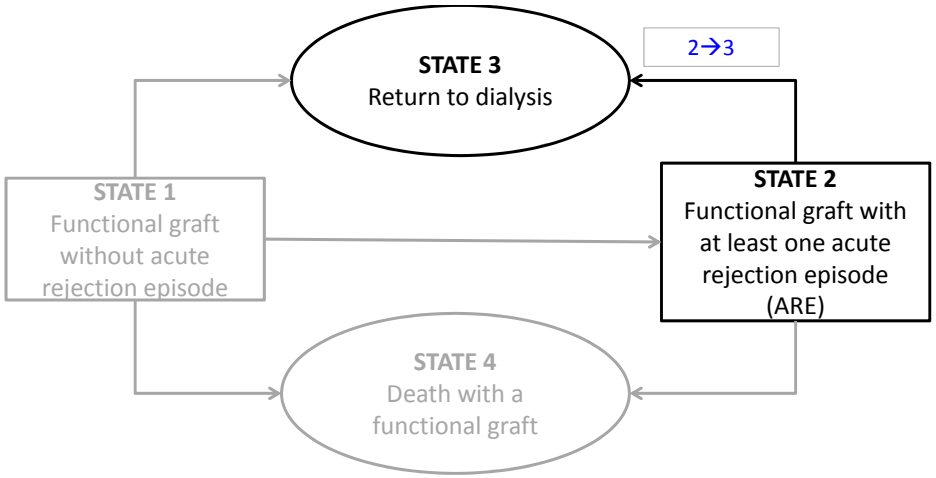
- Association between the pre-graft level of AT1R and time to death was not significant
  $\Rightarrow$ Not included in the model.

Transition probabilities (second event)



- No covariate candidate for the transition probabilities p_{23}, p_{24} (few events).

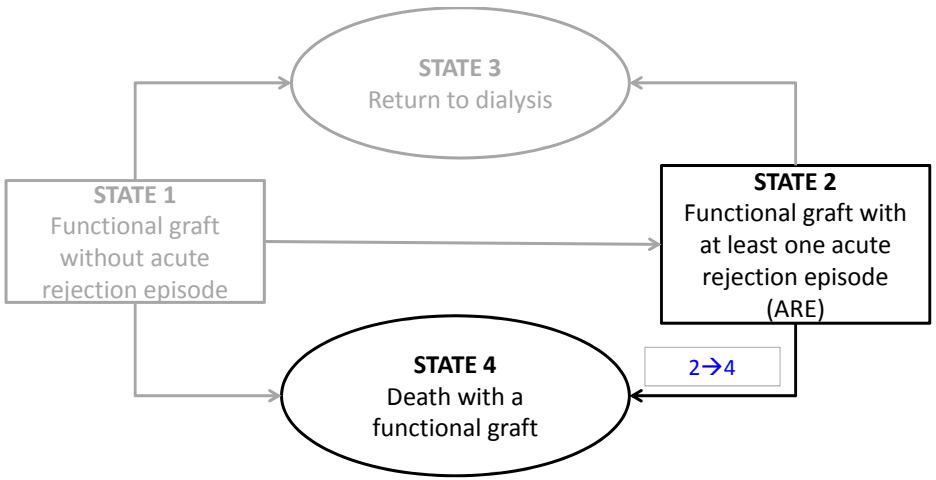
Transition 2 → 3



Coefficient	Estimate	SE	Wald	HR	95%CI	p.value
Transition intensities						
β_{23} AT1R	1.38	0.75	1.83	3.98	[0.91-17.29]	0.0672
...						

- After an ARE, patients who returned to dialysis tended to have a faster time-to-return to dialysis with high level of AT1R.

Transition 2 → 4



- No covariate candidate for the transition intensity $\lambda_{24}(d)$ (few events).

Plan

Multistate Models

- Overcome the limits of traditional survival models
- Parametric distributions $\Rightarrow$ Likelihood simple & easy computable
- Interpretation
  - Probability of trajectory (OR_{ij}^{γ})
  - Speed/Waiting time in a state (HR_{ij}^{β})

  $\Rightarrow$ Combination : Hazard ratio from the transition intensity of the Semi-Markov Model α_{ij} ($HR_{ij}^{\beta,\gamma}(d)$)

Future

- Hazard ratio from the transition intensity of the Semi-Markov Model with the time since graft transplantation ($HR_{ij}^{\beta,\gamma}(t)$) ?
- Study other biomarkers in the complete cohort DIVAT

Merci de votre attention !

Affiliations & Remerciements

Affiliations

- Institut de transplantation urologie-néphrologie (Itun), *INSERM UMR 1064, CHU de Nantes*
- Equipe d'Accueil 4275 Biostatistique, recherche clinique et mesures subjectives en santé, *Université de Nantes*

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