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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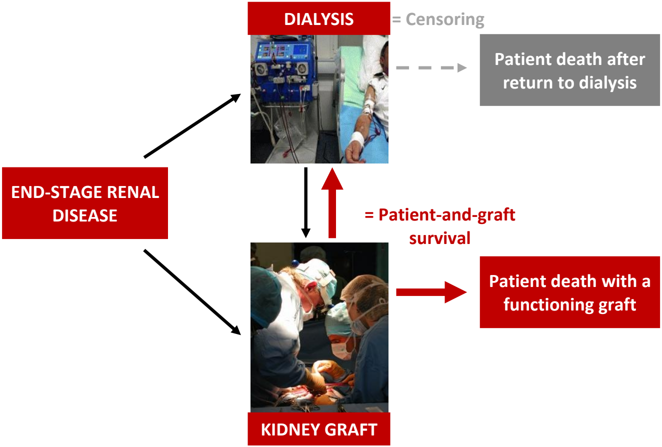
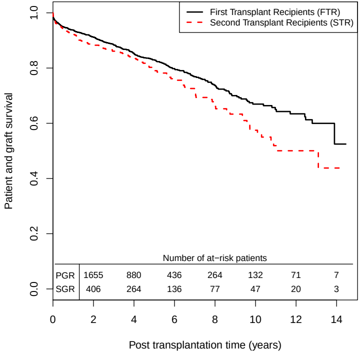
Definition of the graft failure



Close patient-and-graft survival between first and second 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

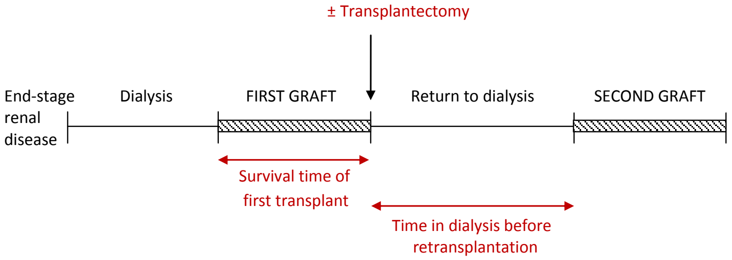


FIGURE 1: Clinical trajectory before second graft.

Introduction

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)

Materials

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)

Methods

General model applied to STR

Multiplicative-regression models for relative survival

- The hazard function

$$h^{(o)}(t_i, z_i) = h^{(e)}(t_i, z_i^{(e)})\ h^{(r)}(t_i, z_i^{(r)})$$

↙ ↓ ↘

Observed hazard function in the STR group

z_i = covariates associated with the observed hazard

Expected hazard function in the FTR group

$z_i^{(e)}$ = subset of z_i, associated with the expected hazard

STEP 1

Relative hazard function in the STR group

$z_i^{(r)}$ = subset of z_i, associated with the relative hazard

STEP 2

STEP 1 :

Estimation of the expected hazard function ($N^{(e)}$ = 2206 FTR)

- Parametric model and proportional hazards assumption

$$h^{(e)}(t_i, z_i^{(e)}) = h_0^{(e)}(t_i)\ exp(\sum_{j=1}^{p^{(e)}} \beta_j^{(e)} z_{i,j}^{(e)})$$

- $h_0^{(e)}(t_i)$ is a piecewise function
- Maximum-likelihood estimation

$$log\mathcal{L} = \sum_{i=1}^{N^{(e)}} \{\delta_i log(h^{(e)}(t_i, z_i^{(e)})) - H^{(e)}(t_i, z_i^{(e)})\}$$

with δ_i = 1 if the graft failure is observed
δ_i = 0 if the event is right-censored

Methods

Relative hazard

STEP 2 :

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

- Parametric model and proportional hazards assumption

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

- $h_0^{(r)}(t_i)$ is a piecewise function
- Maximum-likelihood estimation

$$log\mathcal{L} = \sum_{i=1}^{N^{(o)}} \{\delta_i log(h^{(o)}(t_i, z_i)) - H^{(o)}(t_i, z_i)\}$$

$$h^{(e)}(t_i, z_i^{(e)})\ h^{(r)}(t_i, z_i^{(r)}) \qquad \int_0^{t_i} h^{(e)}(u, z_i^{(e)})\ h^{(r)}(u, z_i^{(r)})\,\mathrm{d}u$$

Methods

Interpretation of the regression coefficient

CASE 1 :

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

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

CASE 2 :

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

$$HR^{(o)}_{z_1=1/z_1=0} = \frac{h_0^{(e)}(t_i) \; exp(\sum_{j=1}^{p^{(e)}} \beta_j^{(e)} z_{i,j}^{(e)}) \;\; h_0^{(r)}(t_i) \, exp(\sum_{j=1}^{p^{(r)}} \beta_j^{(r)} z_{i,j}^{(r)})}{h_0^{(e)}(t_i) exp(\sum_{j=2}^{p^{(e)}} \beta_j^{(e)} z_{i,j}^{(e)}) \;\; h_0^{(r)}(t_i) exp(\sum_{j=2}^{p^{(r)}} \beta_j^{(r)} z_{i,j}^{(r)})}$$

$$= exp(\beta_1^{(e)}) \; exp(\beta_1^{(r)})$$

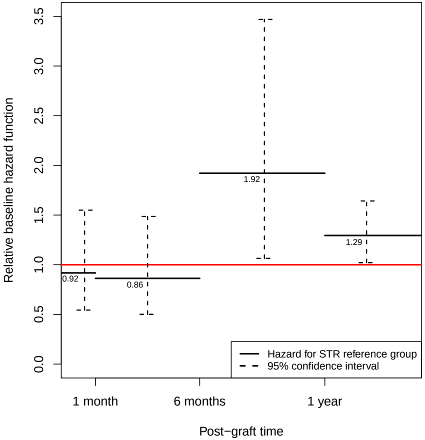
Methods

Covariates tested in the relative hazard

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

Results

Relative baseline hazard function ⇔ $\mathbf{z}^{(r)} = 0$



Results

Hazard ratio obtained from the mutivariate model

Final multivariate model

Covariates	Expected (FTR)	Relative (STR)	Observed (STR)	95% CI	p value
Transplant period (< 2005/≥2005)	1.37	1.27	-	0.83 - 1.95	0.2604
Recipient gender (male / female)	1.19	0.68	-	0.45 - 1.02	0.0645
Recipient age (≥55 years/<55 years)	1.55	1.61	-	1.03 - 2.52	0.0387
Donor age (≥55 years/<55 years)	1.37	0.59	-	0.37 - 0.95	0.0294
Type of donor (deceased/living)	2.91	0.33	-	0.12 - 0.91	0.0332
Donor gender (male / female)	-	-	1.57	1.01 - 2.45	0.0443
Retransplant time (>3 years/≤3 years)	-	-	2.06	1.33 - 3.20	0.0012

xxx = forced covariates

Results

Hazard ratio obtained from the mutivariate model

CASE 1 : $z_1^{(r)} \notin z_j^{(e)}$

Covariates	Expected (FTR)	Relative (STR)	Observed (STR)	95% CI	p value
Transplant period (< 2005/≥2005)	1.37	1.27	-	0.83 - 1.95	0.2604
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Retransplant time (>3 years/≤3 years)	-	-	2.06	1.33 - 3.20	**0.0012**

xxx = forced covariates

⇑

$HR^{(o)} = exp(\beta_1^{(r)})$

Results

Hazard ratio obtained from the mutivariate model

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

Covariates	Expected (FTR)	Relative (STR)	Observed (STR)	95% CI	p value
Transplant period (< 2005/≥2005)	1.37	1.27	-	0.83 - 1.95	0.2604
Recipient gender (male / female)	1.19	0.68	-	0.45 - 1.02	0.0645
Recipient age (≥55 years/<55 years)	1.55	1.61	2.50	1.03 - 2.52	**0.0387**
Donor age (≥55 years/<55 years)	1.37	0.59	0.81	0.37 - 0.95	**0.0294**
Type of donor (deceased/living)	2.91	0.33	0.96	0.12 - 0.91	**0.0332**
Donor gender (male / female)	-	-	1.57	1.01 - 2.45	0.0443
Retransplant time (>3 years/≤3 years)	-	-	2.06	1.33 - 3.20	0.0012

xxx = forced covariates

⇑

$$HR^{(o)} = exp(\beta_1^{(e)})\ exp(\beta_1^{(r)})$$

Conclusion

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

$\Rightarrow$ A Monte-Carlo approach is in process

$\Rightarrow$ A more flexible model for instance with spline functions

$\Rightarrow$ A generalisation with time-dependent covariates

Thank you for your attention !

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Of note

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