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JOINT MODEL FOR LONGITUDINAL MARKER AND TIME-TO-EVENT IN PRESENCE OF COMPETING RISKS: APPLICATION ON CYSTIC FIBROSIS

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Key message

- Dynamic predictions in joint models depend on
 - The evolution of the longitudinal marker
 - Baseline characteristics of subjects

Questions

- What to choose as endpoint in prognostic models, a composite event or competing events?

Background

- Cystic Fibrosis (CF)
 - Incurable genetic disorder
 - Deterioration of lung function
 - Alternative of treatment: lung transplantation
- Management of CF
 - Monitoring of patients
 - Collection of markers of the disease
 - Forced Expiratory Volume in one Second (FEV₁)
- Anticipation of clinical events
 - Death
 - Lung transplantation

Objectives

- Provide dynamic individual prediction of clinical events (LT and death without LT)
- Identify different profile of CF evolution

Joint latent class model

The population

- is heterogeneous
- can be divided into a finite number of classes

In each class, subjects share

- similar mean profile of the marker (FEV_1)
- similar risk of event (death without LT or LT)

Specification of the joint model

Longitudinal Marker
FEV₁

$$Y_i(t_{ij}) | c_i, g = X_{2i}(t_{ij})^T \beta_{2ig} + X_{3i}(t_{ij})^T \beta_{3ig} + Z_i(t_{ij})^T b_{ig} + \epsilon_i(t_{ij})$$

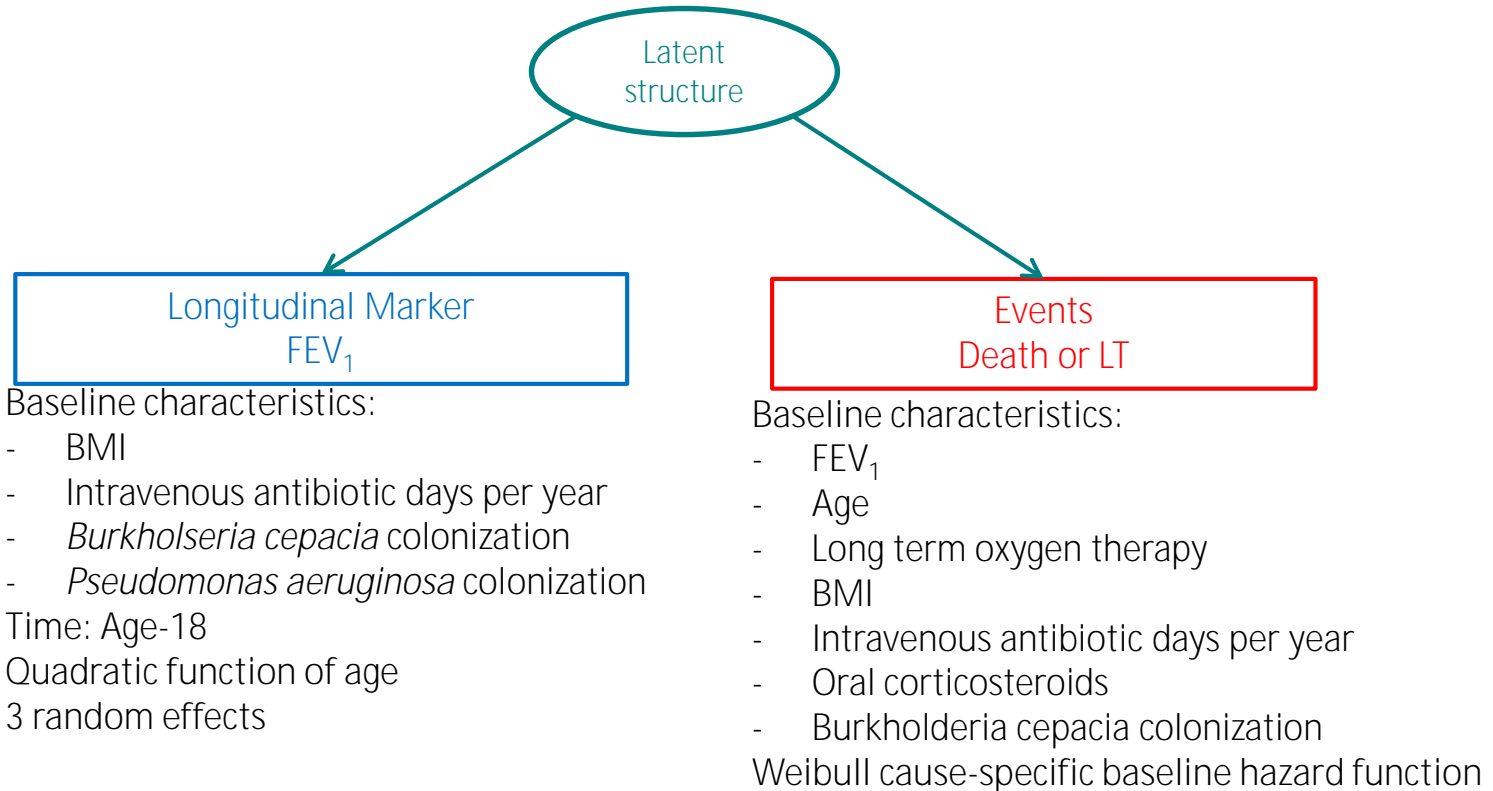
Events
Death or LT

$$h_k(t | c_i, g) = h_{0kg}(t; g) \exp(X_{4i}(t)^T \beta_{4ig} + X_{5i}(t)^T \beta_{5ig})$$

Probability of belonging to class g

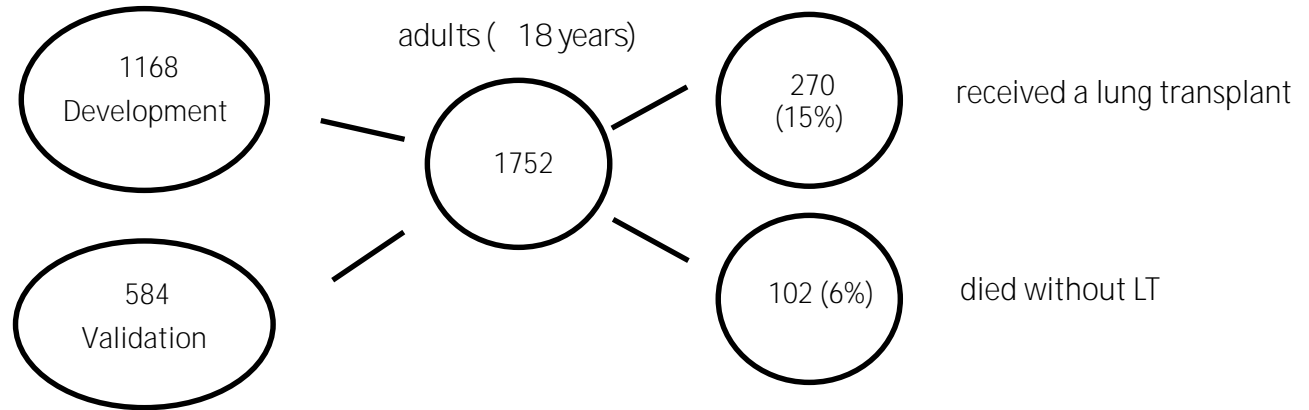
$$P(c_i = g | X_{1i}) = \frac{e^{\beta_{0g} + X_{1i}^T \beta_{1g}}}{\sum_{l=1}^G e^{\beta_{0l} + X_{1i}^T \beta_{1l}}}$$

Specification of the joint model



Data

- The French CF Registry (25 years of follow-up)
- Follow-up period: 2007-2013
- Median of FEV₁ measures 7 (IQR: 1 – 7)



Identified latent classes

Class 3: 325 (28%) subjects

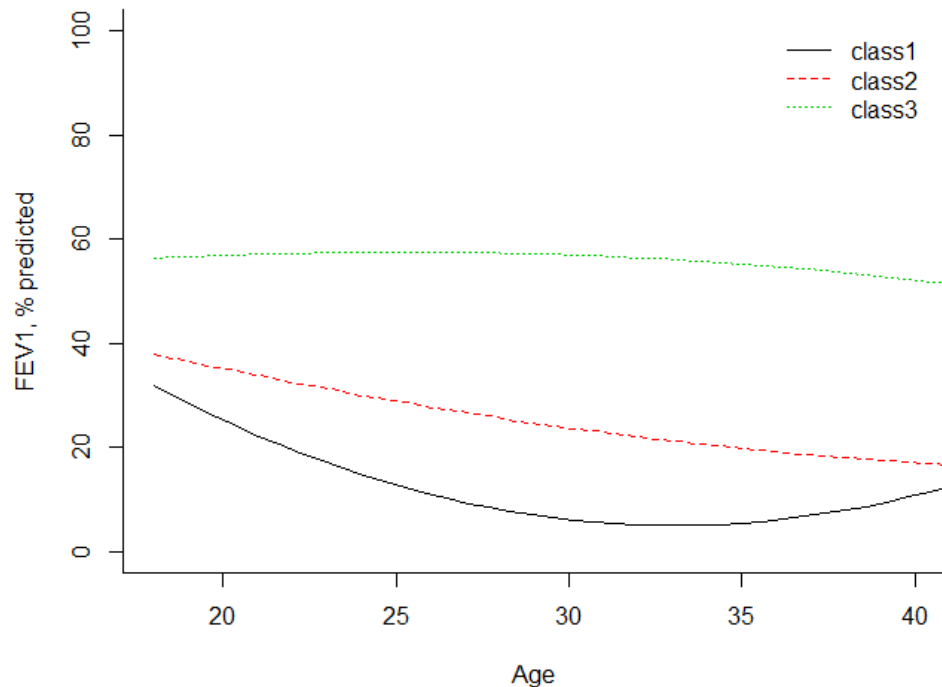
0.3% LT and 2% death

Class 2: 642 (55%) subjects

9% LT and 4% death

Class 1: 201 (17%) subjects

58% LT and 16% death



Class-specific mean predicted trajectories of FEV₁

Identified latent classes

Class 3: 325 (28%) subjects

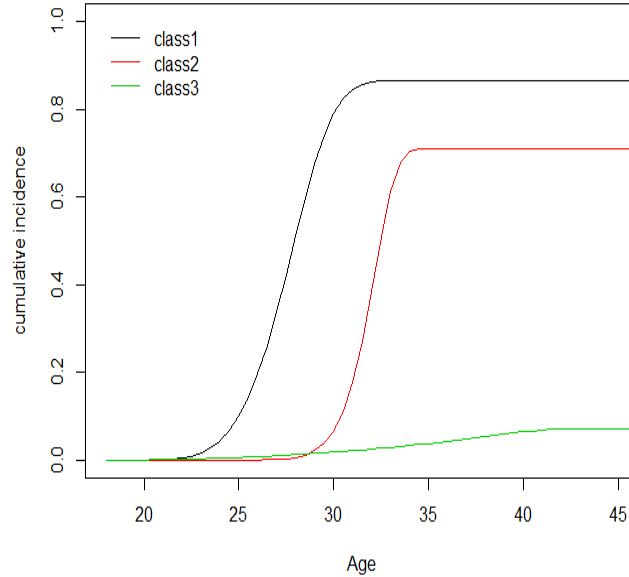
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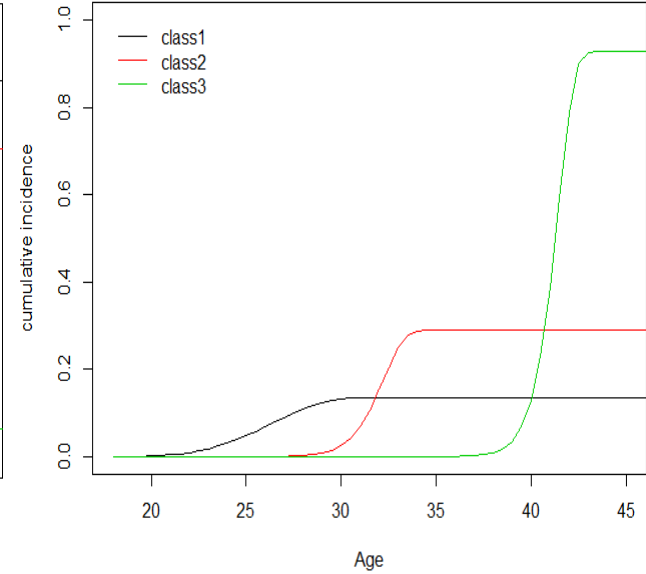
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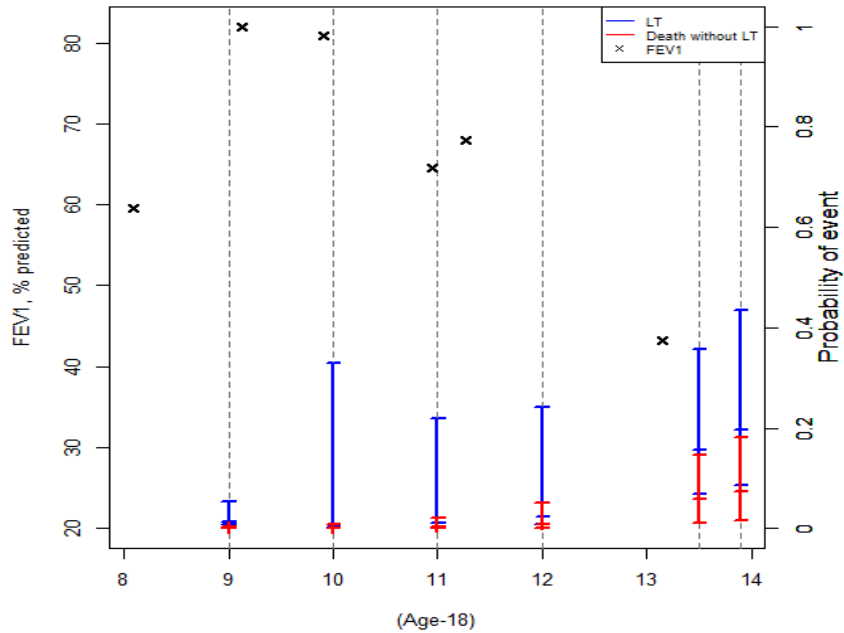
Lung transplantation



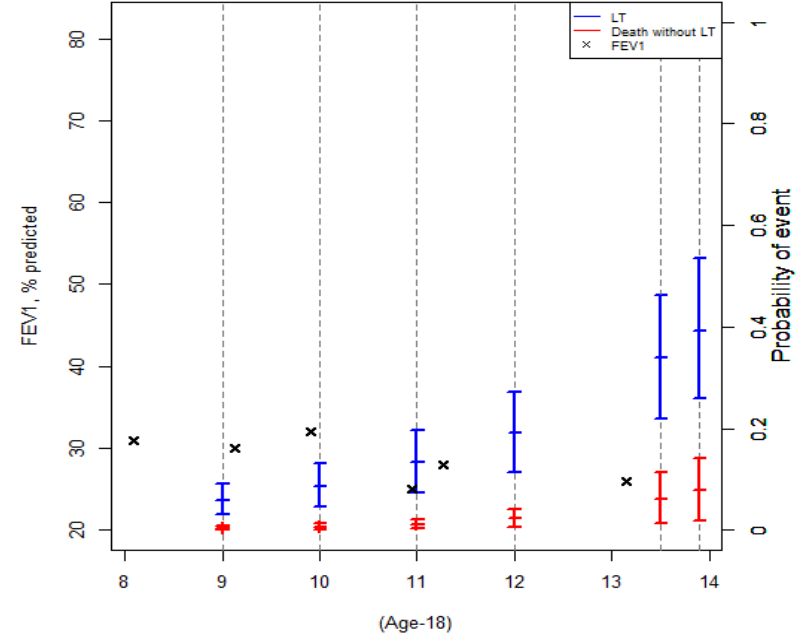
Death without LT

Class-specific cumulative incidence

Dynamic predictions (1)



Subject A



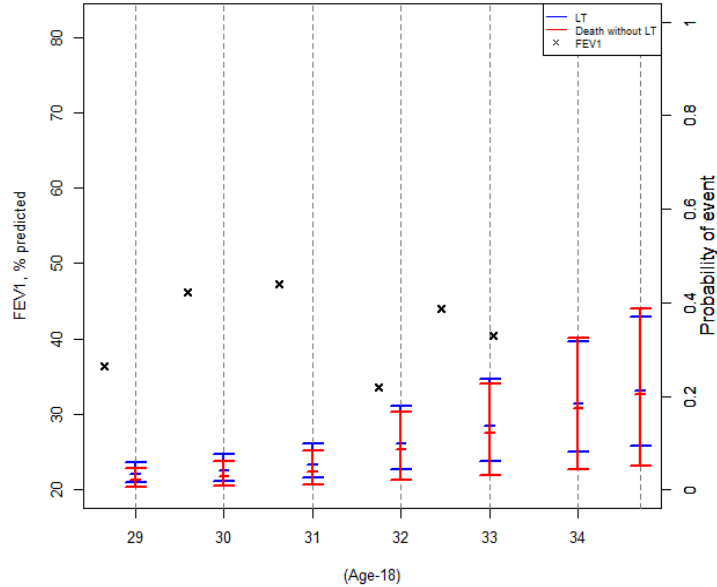
Subject B

Same baseline characteristics for subjects A and B, but different evolution of FEV₁

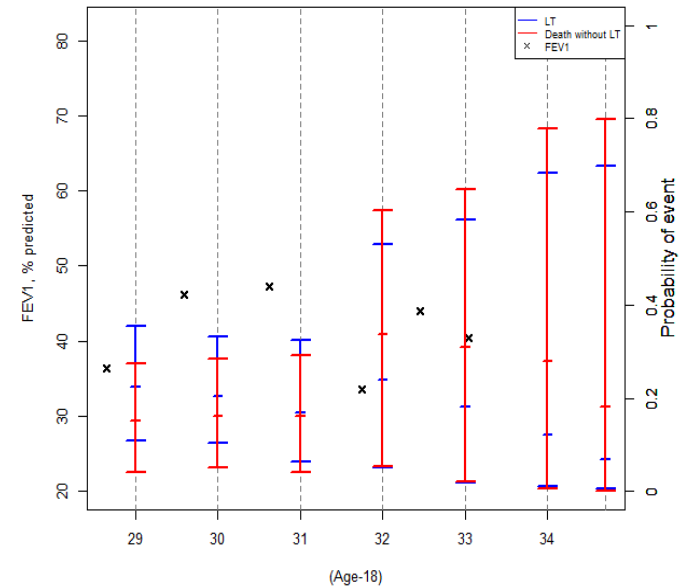
Gender: Female
BMI: 21 Kg/m²
Number of intravenous antibiotic courses: 30

Age: 26 years old
CFTR genotype: F508del/F508del
P. aeruginosa colonization

Dynamic predictions (2)



Subject C



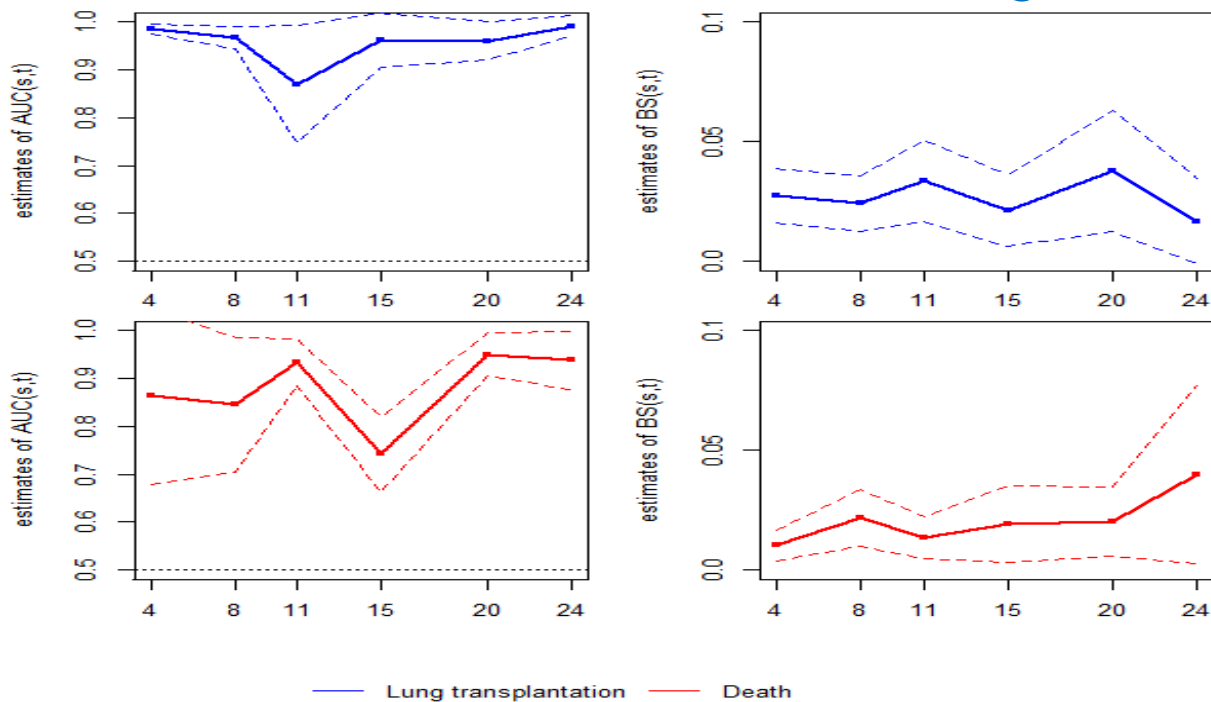
Subject D

Same evolution of FEV₁ for subject C and subject D, but different characteristics at baseline

Gender: Male
Age: 46 years old
BMI: 21 Kg/m²
CFTR genotype: F508del/F508del
Number of intravenous antibiotic courses: 1
P. aeruginosa colonization

Gender: Male
Age: 46 years old
BMI: 20 Kg/m²
CFTR genotype: F508del/F508del
Number of intravenous antibiotic courses: 5
P. aeruginosa colonization
Oral corticosteroids
Long term oxygen therapy

Predictive accuracy



Good discriminative ability for both LT and death without LT

Conclusion

- 3 profiles of evolution of CF
- Good predictive accuracy
- Identification of patients requiring a LT
- Comparison with the composite event