Joint Models with Multi-State Processes

G. Papageorgiou and D. Rizopoulos

Department of Biostatistics, Erasmus MC, Rotterdam, the Netherlands

November 16th, 2020

CISNET Prostate Annual Meeting

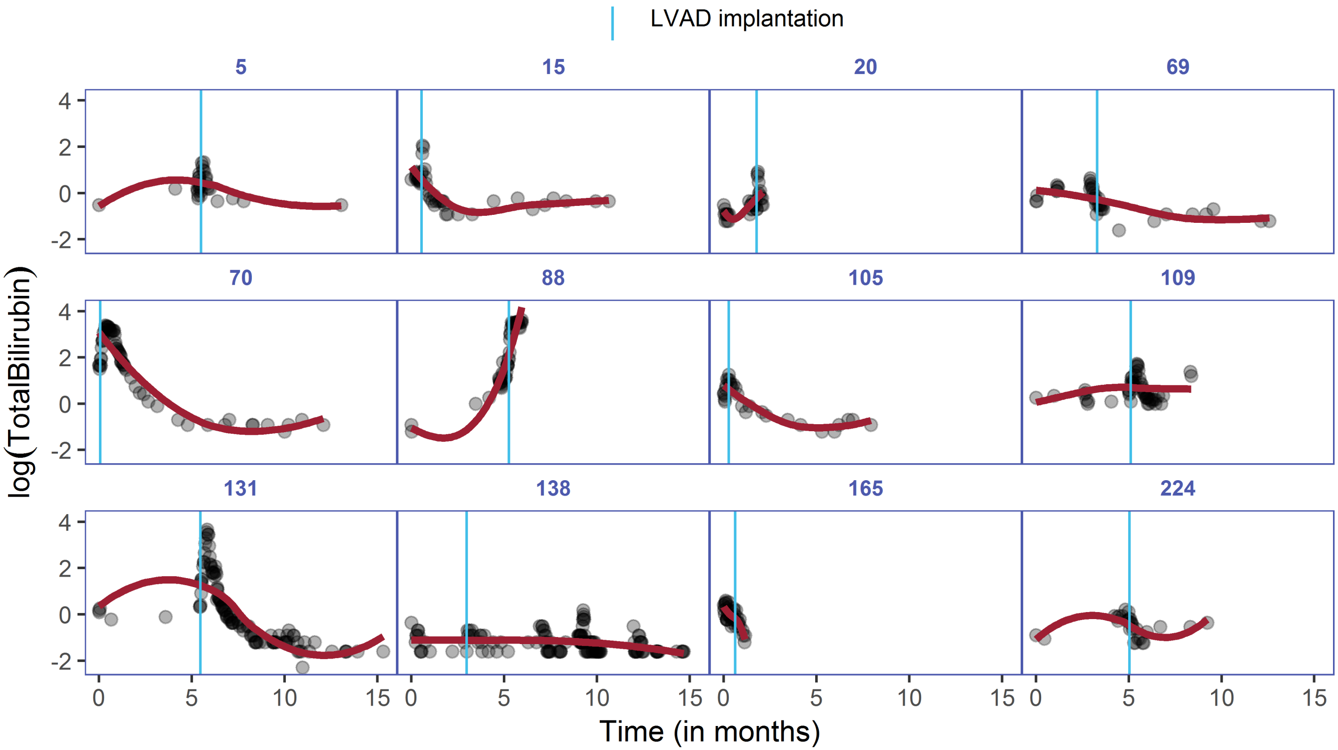
Motivation

- Outcomes in follow-up studies
- Multiple longitudinal responses:
  - biomarkers, blood values
- Times of transitions between states of interest:
  - relapse, clinical complications, death
- Intermediate events
  - (re)intervention

Motivation

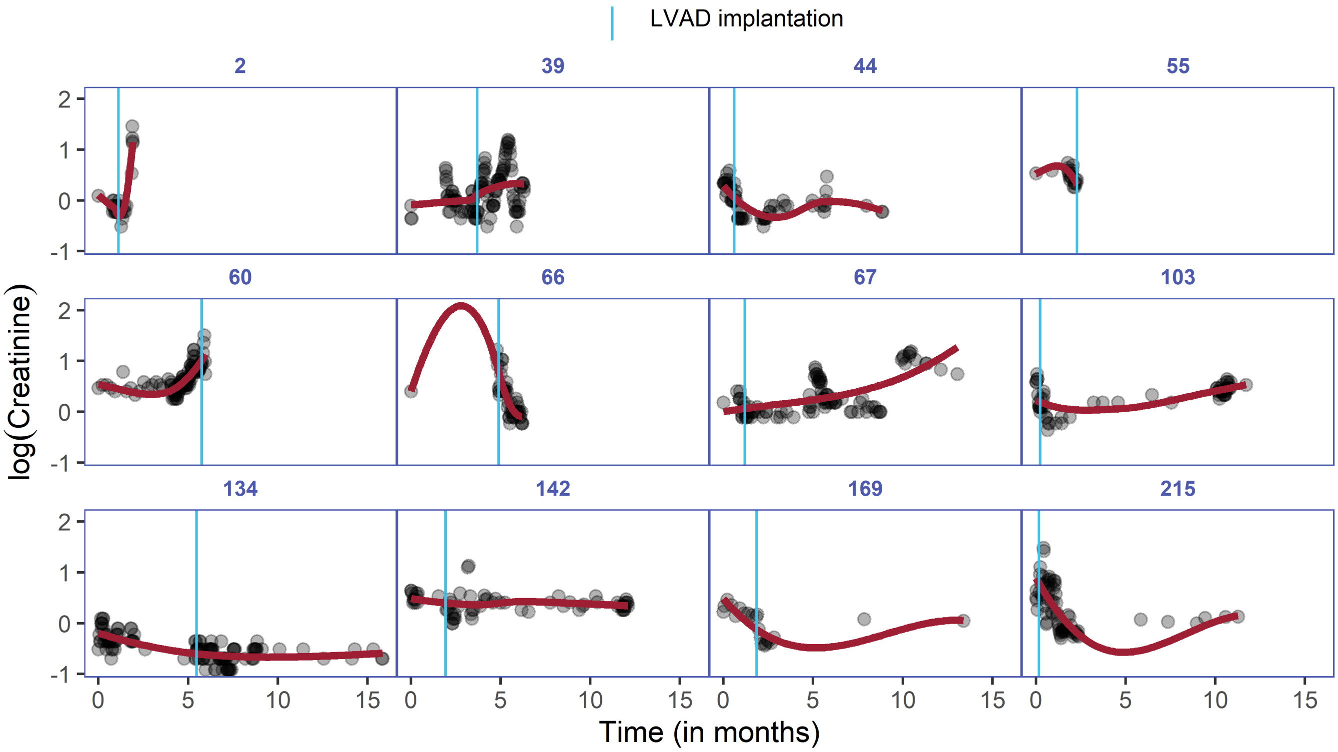
- **232** patients who were followed-up after heart failure
  - All patients received a **L**eft **V**entricular **A**ssist **D**evice during folow-up
- Longitudinal outcomes:
  - Total bilirubin (mg/dl)
  - Creatinine (mg/dl)
- Events of interest:
  - Complications: Thrombosis, Embolic Events, Dialysis
  - Transplantation/Death

Motivation

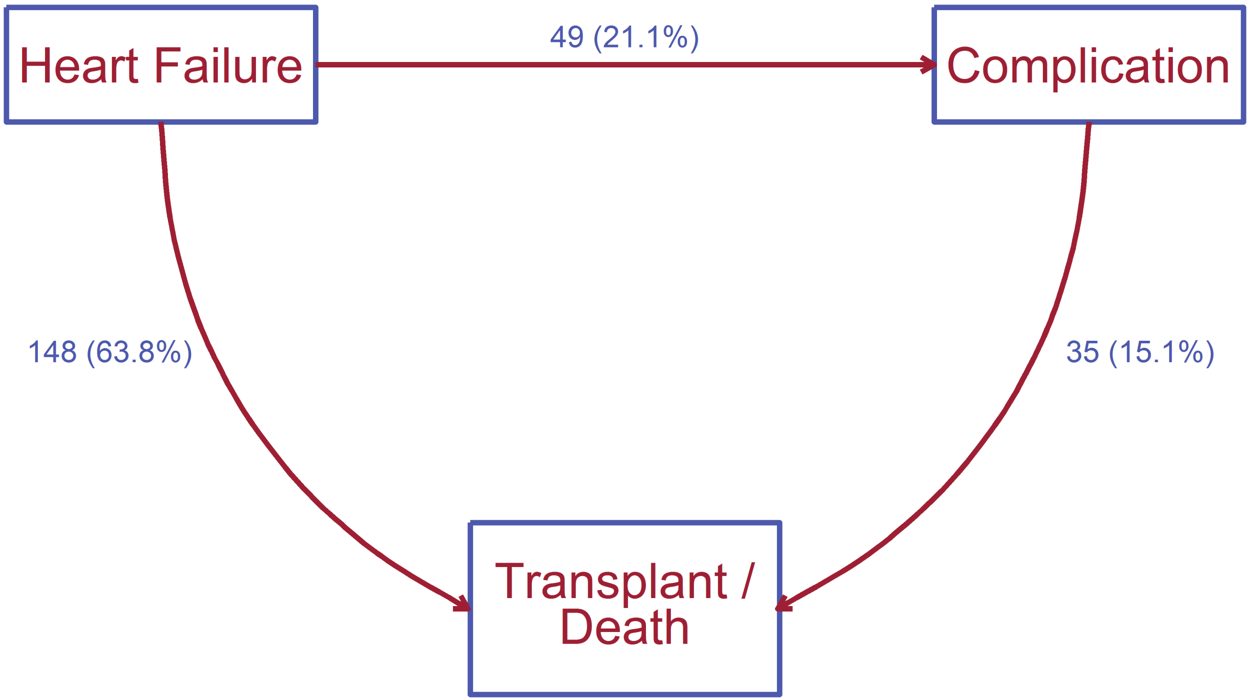


LVAD implantation
5
15
20
69
70
88
105
109
131
138
165
224
log(TotalBilirubin)
Time (in months)

Motivation


LVAD implantation
2
39
44
55
60
66
67
103
134
142
169
215
log(Creatinine)
Time (in months)
2
1
0
-1
0
5
10
15

Motivation



Heart Failure
49 (21.1%)
Complication
148 (63.8%)
35 (15.1%)
Transplant / Death

Research Goals

- Investigate the association between the longitudinal and multi-state processes
    - Functional form of the association for **each transition**
    - Strength of the association for **each transition**
    - Selection of the association structure for **each transition**

- Investigate the impact of LVAD on the evolution of the markers

Methods

Multivariate generalized linear mixed-effects submodel:

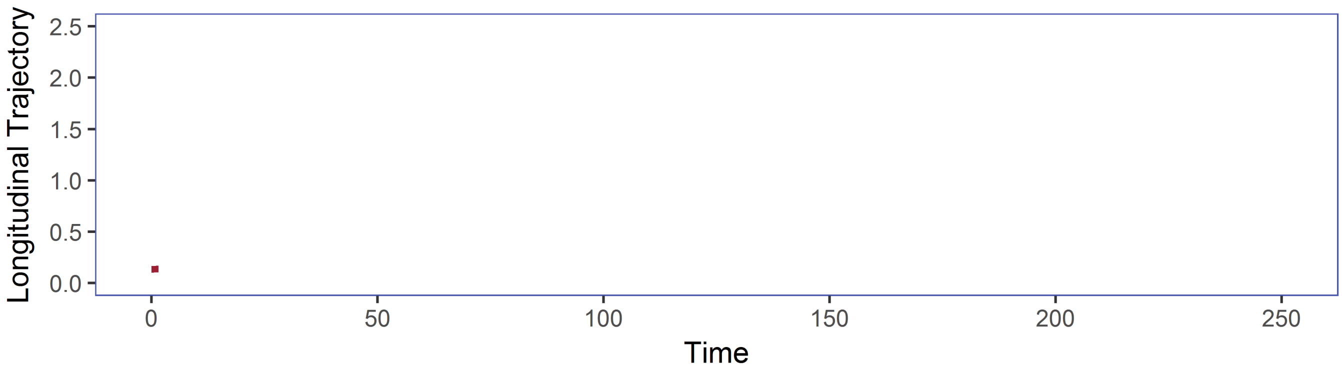
$$g_k \left[E\{y_{ki}(t) \mid b_{ki}\} \right] = \eta_{ki}(t) = \begin{cases} x_{ki}^\top(t)\,\beta_k + z_{ki}^\top(t)\,b_{ki}, & 0 < t < \rho_i \\ x_{ki}^\top(t)\,\beta_k + z_{ki}^\top(t)\,b_{ki} + \tilde{x}_{ki}^\top(t_{i+})\,\tilde{\beta}_k + \tilde{z}_{ki}^\top(t_{i+})\,\tilde{b}_{ki}, & t \geq \rho_i, \end{cases}$$

- y_{ki}: repeated measurements of the k^{th} outcome for the i^{th} subject
- $b^\top = \left(b_{1i}, \dots, b_{Ki}, \tilde{b}_{1i}, \dots, \tilde{b}_{Ki}\right)^\top \sim \mathcal{N}(0, D)$
- ρ_i: time of occurrence of the intermediate event
- $t_{i+} = \max(0, t_{ki} - \rho_i)$: time relative to the occurrence of the intermediate event

Methods

$$\eta_{ki}(t) = \begin{cases} x_{ki}^\top(t)\,\beta_k + z_{ki}^\top(t)\,b_{ki}, & 0 < t < \rho_i \\ x_{ki}^\top(t)\,\beta_k + z_{ki}^\top(t)\,b_{ki} + \tilde{x}_{ki}^\top(t_{i+})\,\tilde{\beta}_k + \tilde{z}_{ki}^\top(t_{i+})\,\tilde{b}_{ki}, & t \geq \rho_i, \end{cases}$$

- $\tilde{x}_{ki}^\top(t)\,\tilde{\beta}_k + \tilde{z}_{ki}^\top(t)\,\tilde{b}_{ki}$: May be any function of t_{i+}



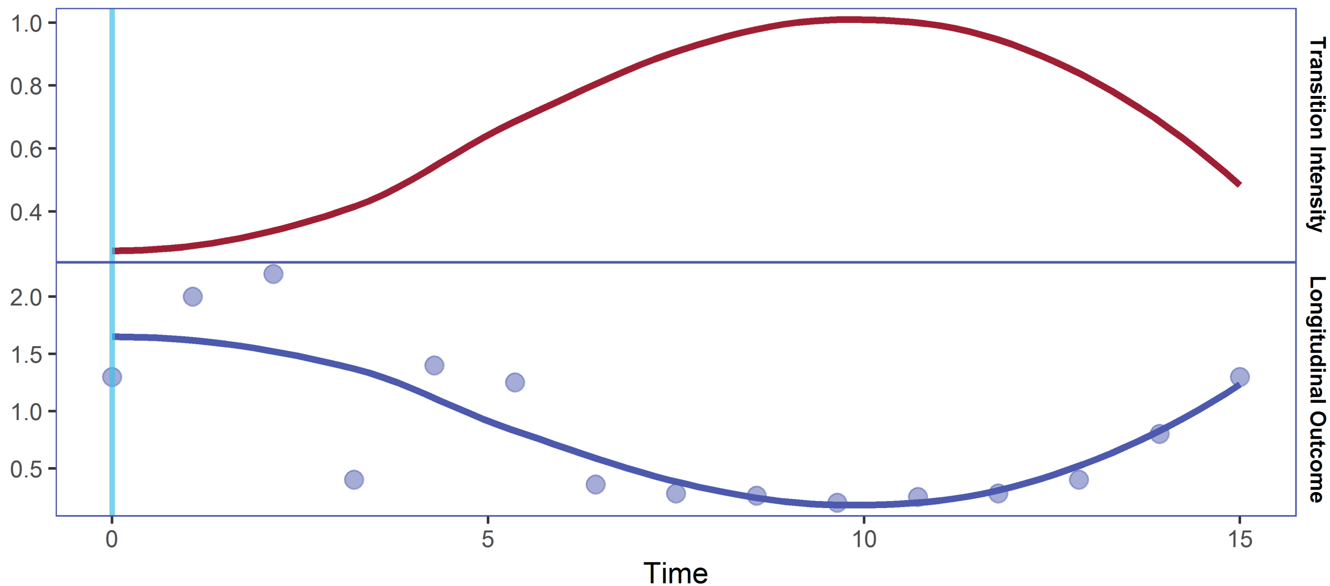
Multi-state submodel:

- $S = \{1, \dots, M\}$: state space
- $T_i = \left(T_{i1}, \dots, T_{im_i}\right)^\top$: vector of observed times for the i^{th} subject
- $\delta_i = \left(\delta_{i1}, \dots, \delta_{im_i}\right)^\top$: vector of observed transition indicators for the i^{th} subject

$$\lambda_{hl}^{i}(t) = \begin{cases} \lambda_{hl,0}(t) \exp\left[W_{hl,i}^{S\,\top} \gamma_{hl} + \sum_{k=1}^{K} \sum_{j=1}^{J} f_j\left\{\eta_{ki}(t), \alpha_{kj}\right\}\right], & 0 < t < \rho_i, \\ \lambda_{hl,0}(t) \exp\left[W_{hl,i}^{S\,\top} \gamma_{hl} + \sum_{k=1}^{K} \sum_{j=1}^{J} f_j\left\{\eta_{ki}(t), \alpha_{kj}\right\}\right], & t \geq \rho_i. \end{cases}$$

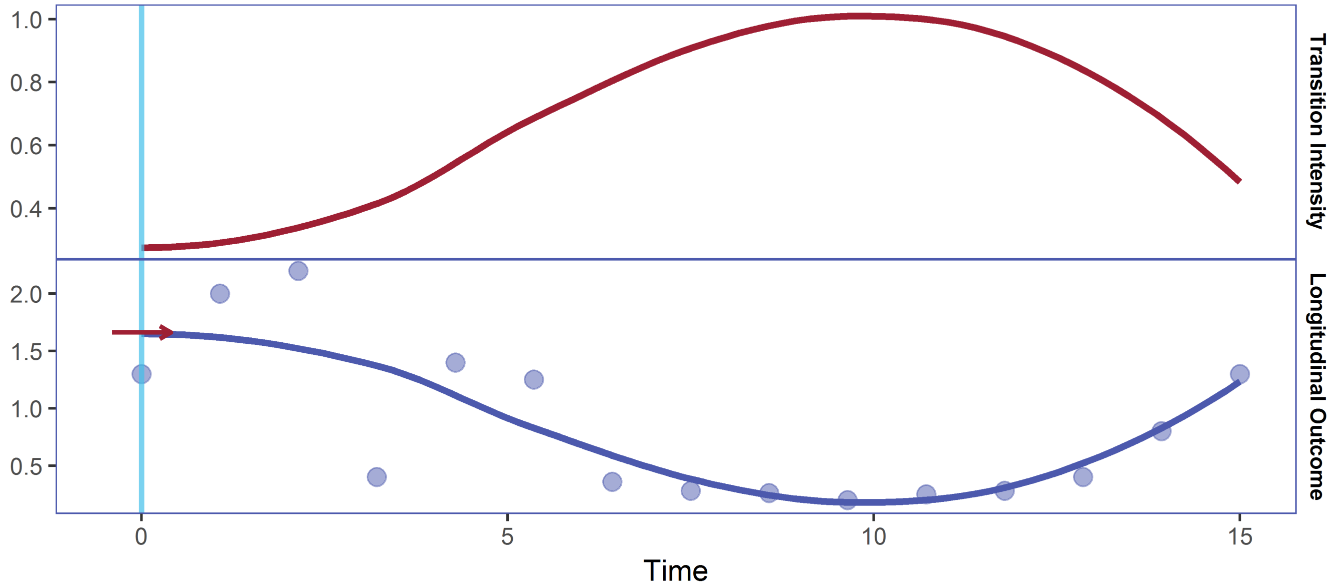
Association Structures

Current value: $f_j\left\{\eta_{ki}(t), \alpha_{kj}\right\} = \eta_{ki}(t) \cdot \alpha_{kj}$



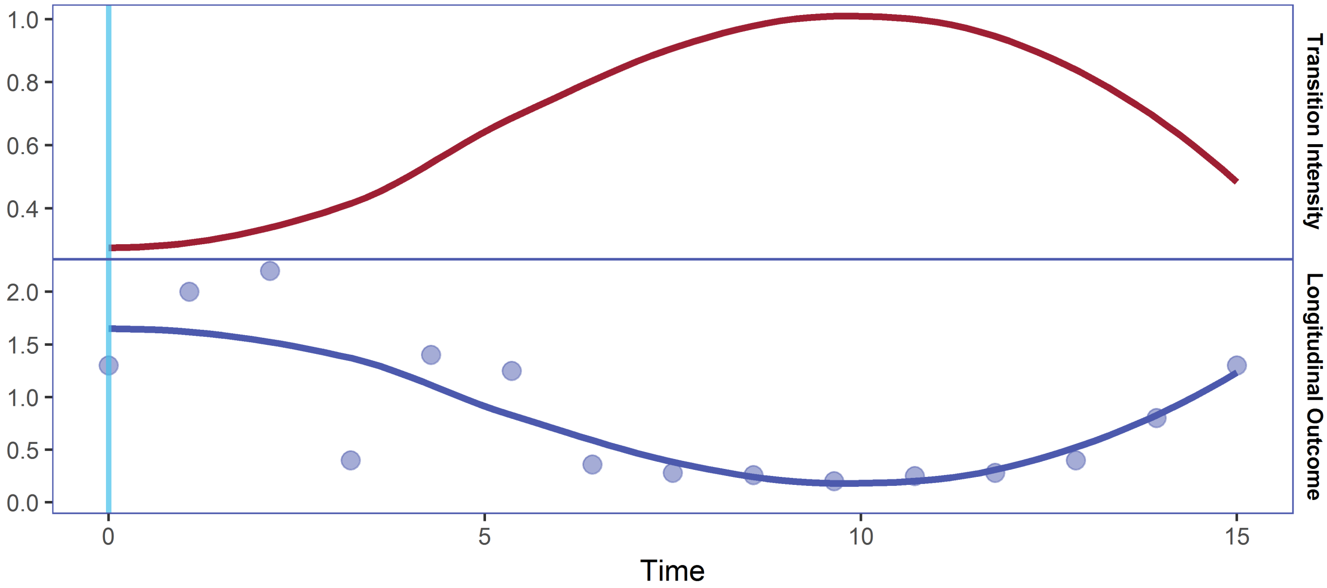
Association Structures

$$\text{Current slope: } f_j\left\{\eta_{ki}(t), \alpha_{kj}\right\} = \frac{d}{dt}\eta_{ki}(t) \cdot \alpha_{kj}$$



Association Structures

$$\text{Cumulative effect: } f_j\left\{\eta_{ki}(t), \alpha_{kj}\right\} = \int_0^t \eta_{ki}(s)\, ds \cdot \alpha_{kj}$$



Feature Selection

- Which features of the longitudinal outcomes are associated with transition intensities?

$$\#\text{Biomarkers} \times \#\text{Features} \times \#\text{Transitions}$$

- High dimensional parameter space
- (Potentially) high correlation among features from the same biomarker
- Feature selection $\rightarrow$ difficult

Bayesian Shrinkage

- Shrinkage priors for variable selection
- Priors that shrink towards zero:
  - Bayesian ridge
  - Bayesian horseshoe
  - Bayesian lasso
  - ...
- E.R. Andrinopoulou and D. Rizopoulos (2016) investigated the performance of local shrinkage priors

Bayesian Shrinkage

- Global-local priors:
  - $\alpha_{jk} \mid \tau^2_{jk}, \lambda^2 \sim \mathcal{N}\left(0, \tau^2_{jk}\lambda^2\right)$
  - τ^2_{jk}: Local shrinkage
  - λ^2: Global shrinkage

Bayesian Shrinkage

- Global-local horseshoe prior
  - Double inverse-gamma prior leads to $C^+(0, 1)$

$$
\begin{aligned}
\alpha_{jk} \mid \tau_{jk}^2, \lambda^2 &\sim \mathcal{N}\left(0, \tau_{jk}^2 \lambda^2\right)\\
\tau_{jk}^2 \mid \nu_{jk}^2 &\sim \mathcal{IG}\left(\frac{1}{2}, \frac{1}{\nu_{jk}}\right)\\
\lambda^2 \mid \xi &\sim \mathcal{IG}\left(\frac{1}{2}, \frac{1}{\xi}\right)\\
\nu_{1k}, \ldots, \nu_{JK}, \xi &\sim \mathcal{IG}\left(\frac{1}{2}, 1\right)
\end{aligned}
$$

- **Properties:**
  - Strong spike that leads to severe shrinkage near 0
  - Narrow tails that allow strong signals to remain strong

Bayesian Shrinkage

- Global-local ridge prior

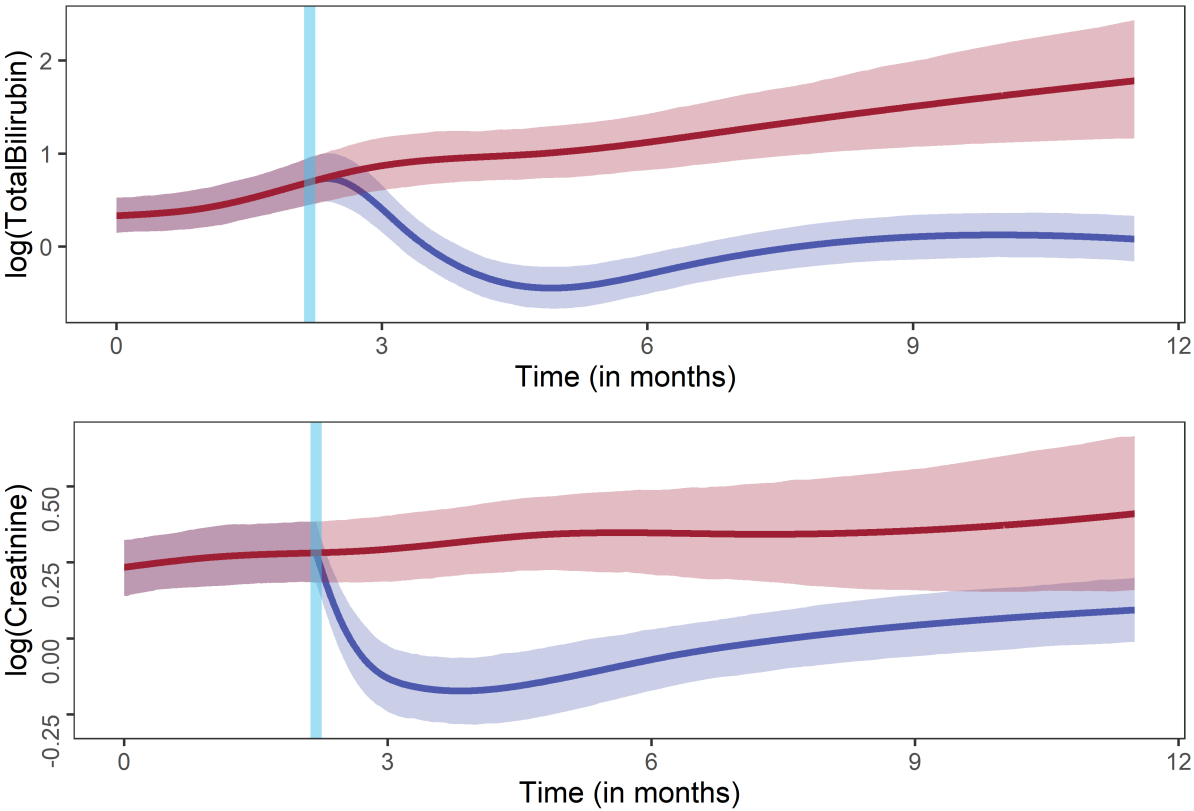
$$
\begin{aligned}
\alpha_{jk} \mid \tau_{jk}^2, \lambda^2 &\sim \mathcal{N}\left(0, \tau_{jk}^2 \lambda^2\right)\\
\tau_{jk}^2 &\sim \mathcal{IG}\left(\tfrac{1}{2}, 1\right)\\
\lambda^2 &\sim \mathcal{IG}\left(\tfrac{1}{2}, 1\right)
\end{aligned}
$$

- **Properties:**
  - Less shrinkage near 0
  - Heavier tails than horseshoe

Analysis

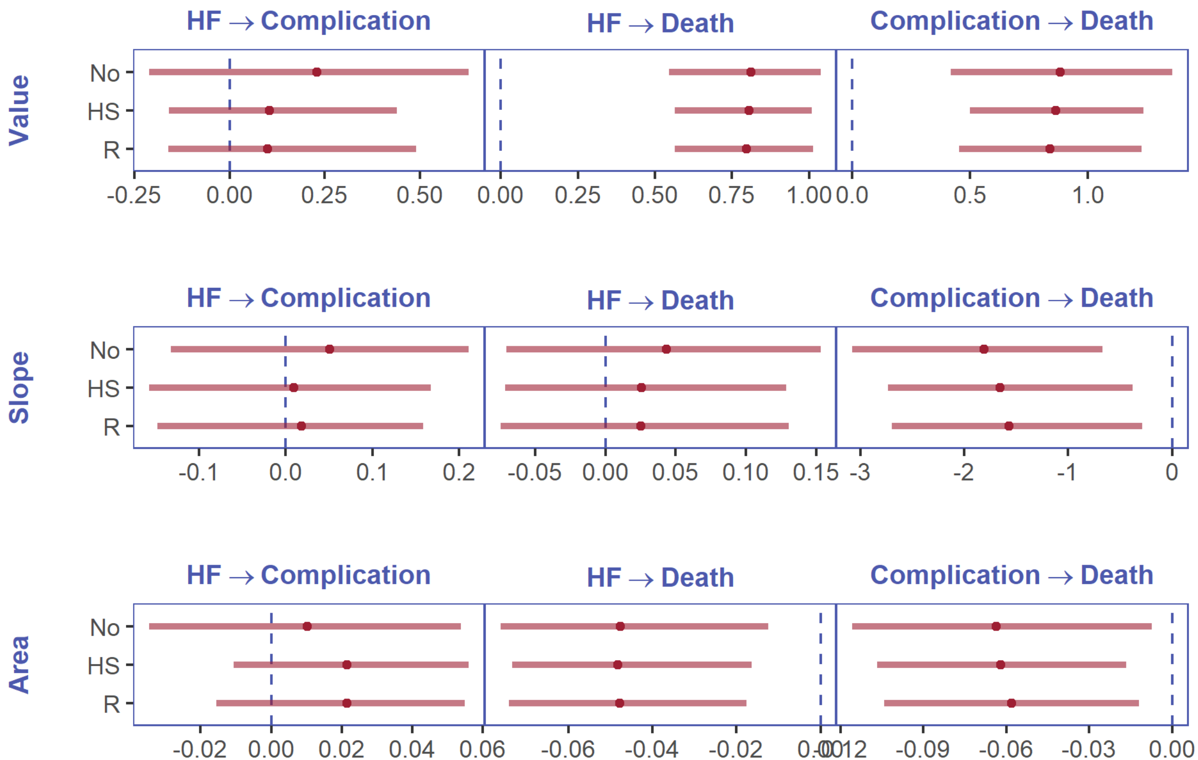
- **Longitudinal submodels:**
  - **Fixed-effects**: natural cubic splines for time and time relative to **LVAD** implantation, adjusted for BMI, age, sex and etiology
  - **Random-effects**: natural cubic splines for time and time relative to **LVAD** implantation
- **Multi-state submodel:**
  - **State-specific covariates**: BMI, age, sex and etiology
  - **Markers' features**: value, slope and cumulative effect association with **each transition**

Results

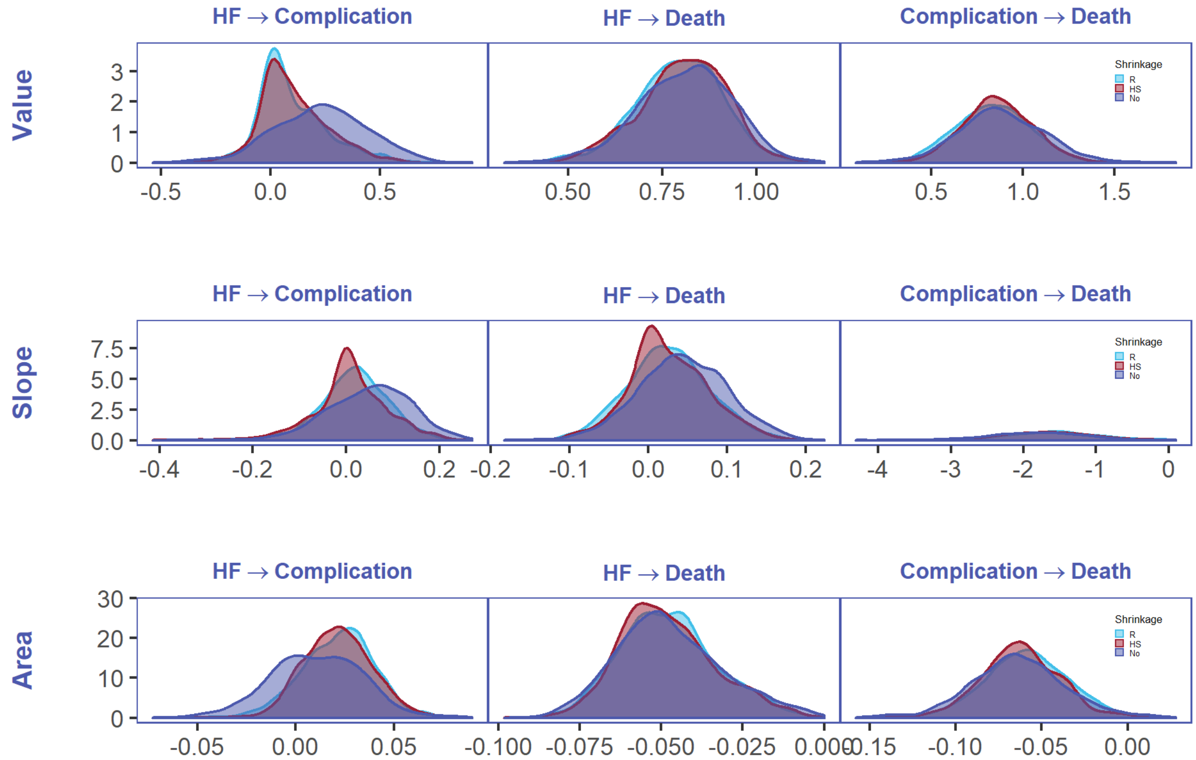


log(TotalBilirubin)
2
1
0
0
3
6
9
12
Time (in months)
log(Creatinine)
0.50
0.25
0.00
-0.25
0
3
6
9
12
Time (in months)

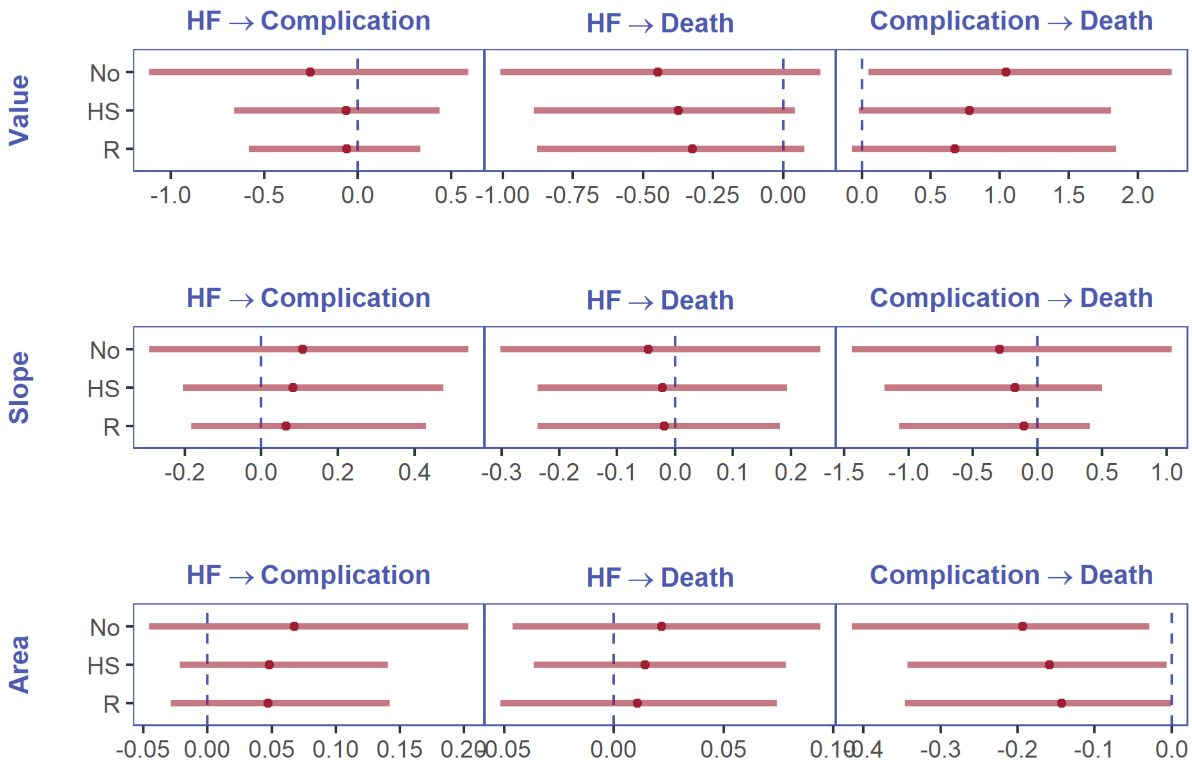
Results: Bilirubin



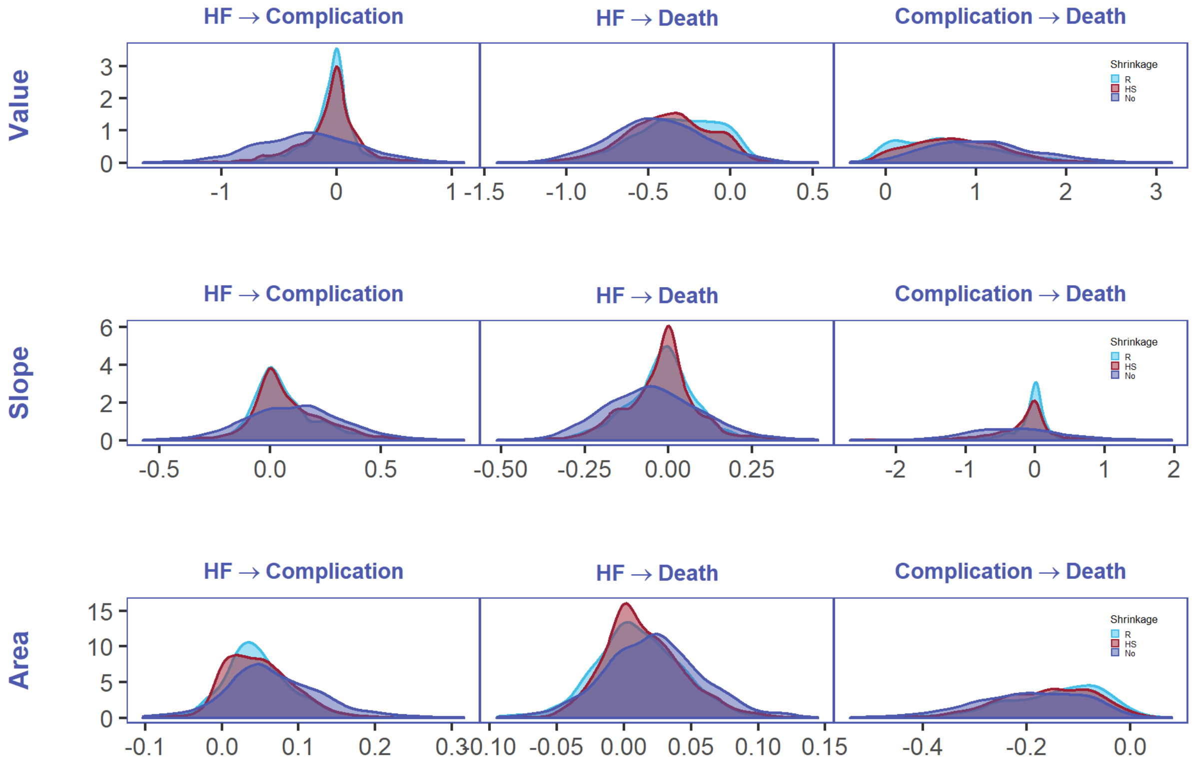
Results: Bilirubin



Results: Creatinine



Results: Creatinine



Thank you

@drizopoulos

https://github.com/drizopoulos

d.rizopoulos@erasmusmc.nl

http://www.drizopoulos.com/