

Joint Models with Multi-State Processes

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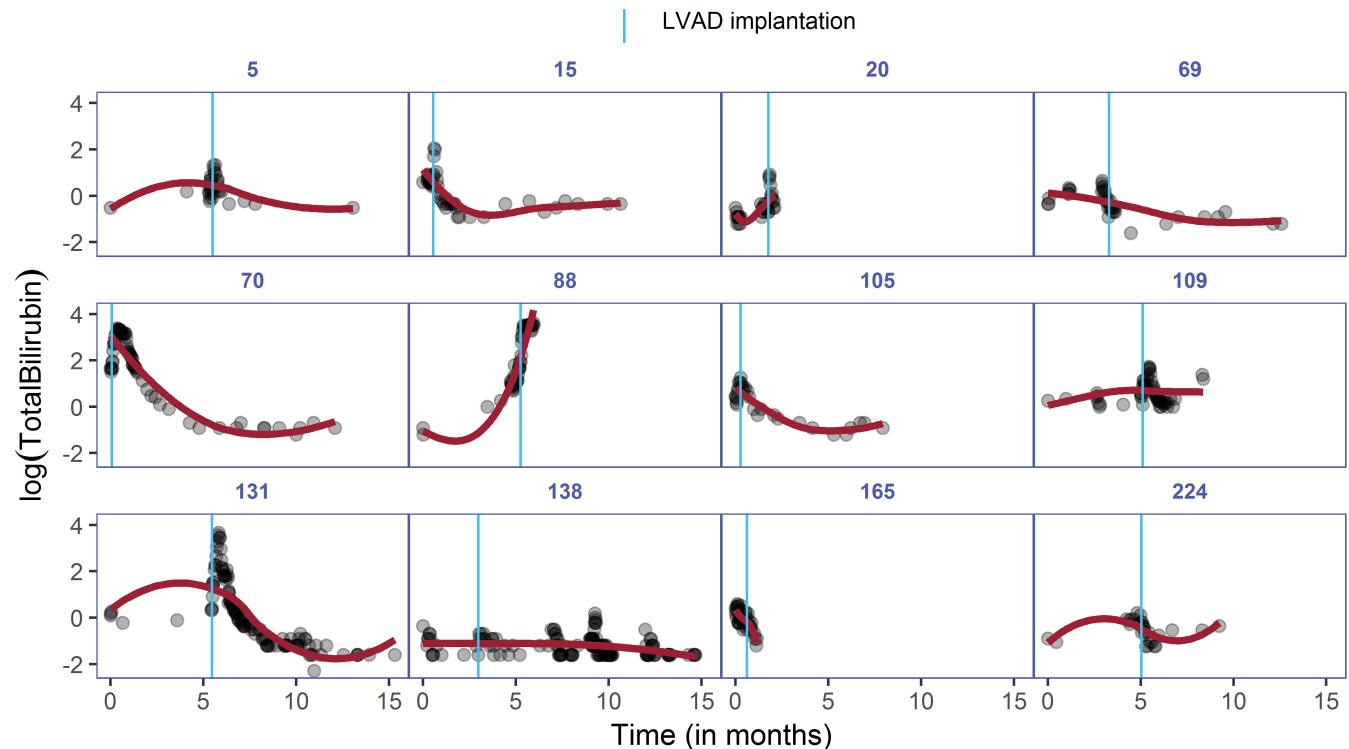
Motivation

- 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

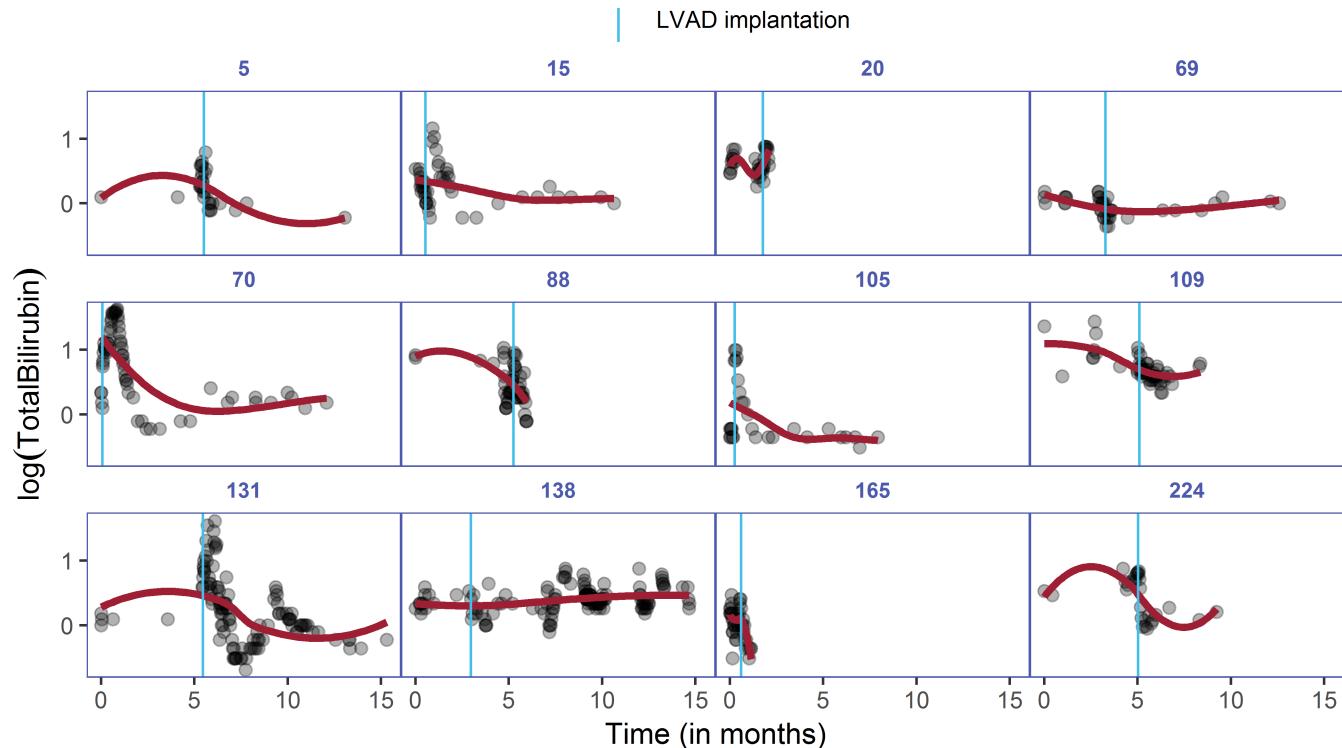
Motivation

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

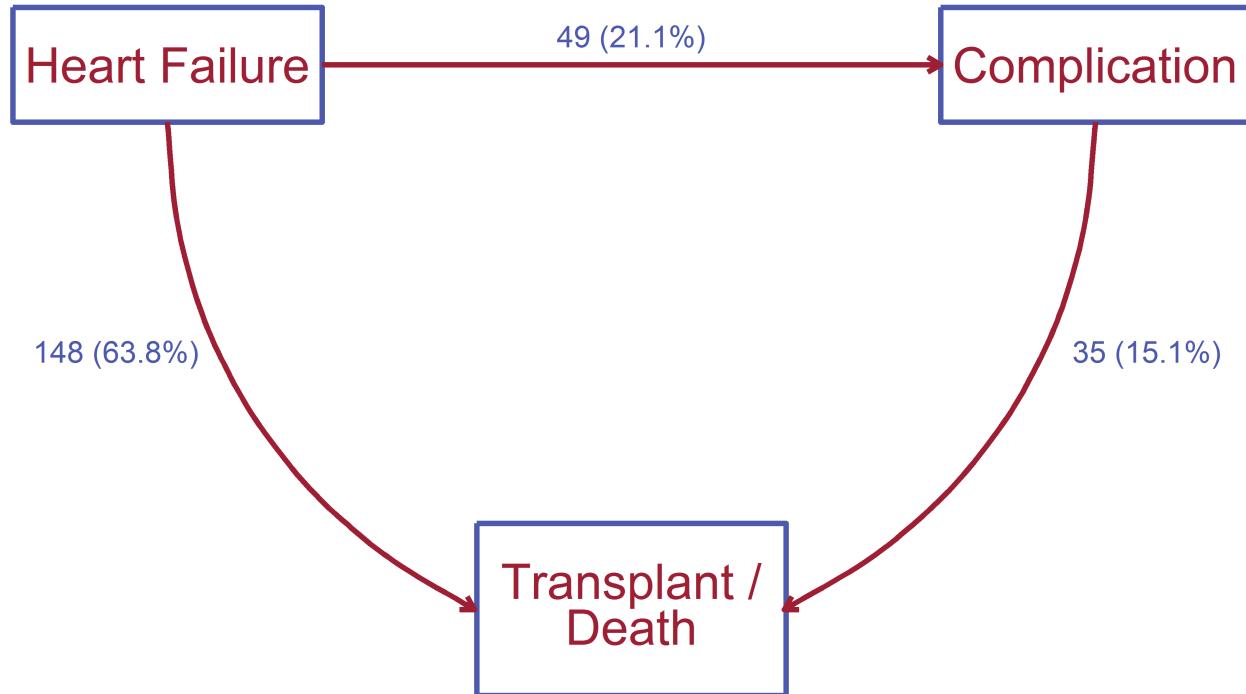
Motivation



Motivation



Motivation



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:

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

- y_{ki} : repeated measurements of the k^{th} outcome for the i^{th} subject
- $b^\top = (b_{1i}, \dots, b_{Ki}, \tilde{b}_{1i}, \dots, \tilde{b}_{Ki})^\top \sim \mathcal{N}(0, D)$
- 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

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

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

Methods

Multi-state submodel:

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

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



Association Structures

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

Association Structures

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

Association Structures

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?

#Biomarkers \times #Features \times #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

- Local priors:

- $\alpha_{jk} \mid \tau_{jk}^2 \sim \mathcal{N}(0, \tau_{jk}^2)$

- τ_{jk}^2 : Local shrinkage

- Global-local priors:

- $\alpha_{jk} \mid \tau_{jk}^2, \lambda^2 \sim \mathcal{N}(0, \tau_{jk}^2 \lambda^2)$

- τ_{jk}^2 : Local shrinkage

- λ^2 : Global shrinkage

Bayesian Shrinkage

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

$$\alpha_{jk} \mid \tau_{jk}^2, \lambda^2 \sim \mathcal{N}\left(0, \tau_{jk}^2 \lambda^2\right)$$

$$\tau_{jk}^2 \mid \nu_{jk}^2 \sim \mathcal{IG}\left(\frac{1}{2}, \frac{1}{\nu_{jk}}\right)$$

$$\lambda^2 \mid \xi \sim \mathcal{IG}\left(\frac{1}{2}, \frac{1}{\xi}\right)$$

$$\nu_{1k}, \dots, \nu_{JK}, \xi \sim \mathcal{IG}\left(\frac{1}{2}, 1\right)$$

- **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

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

- **Properties:**

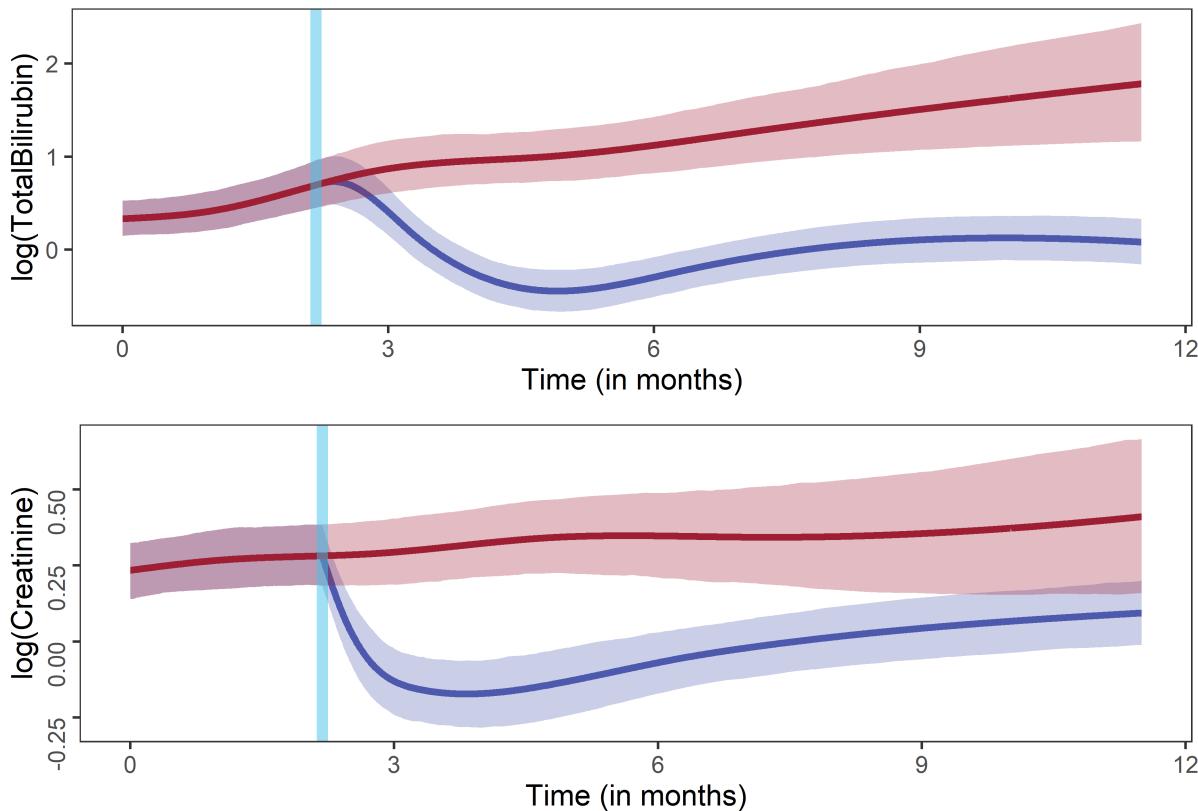
- Less shrinkage near 0
- Heavier tails than horseshoe

Analysis

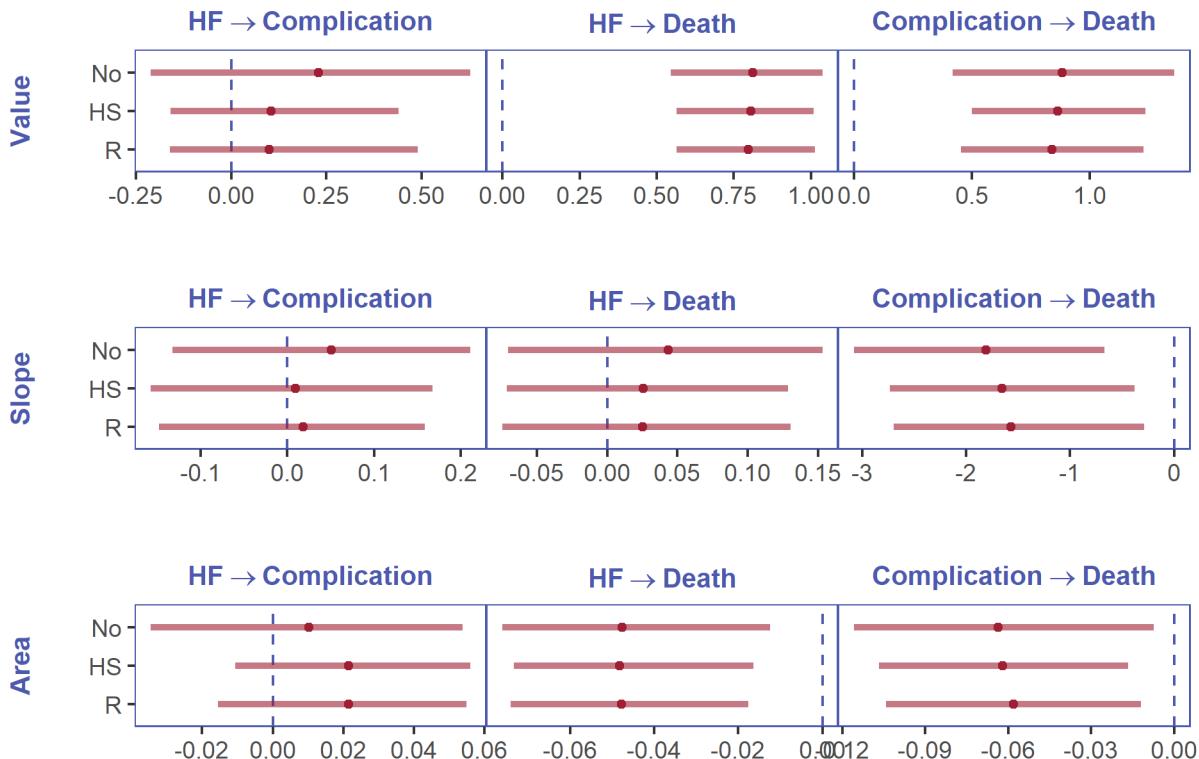
- **Longitudinal submodels:**

- **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**

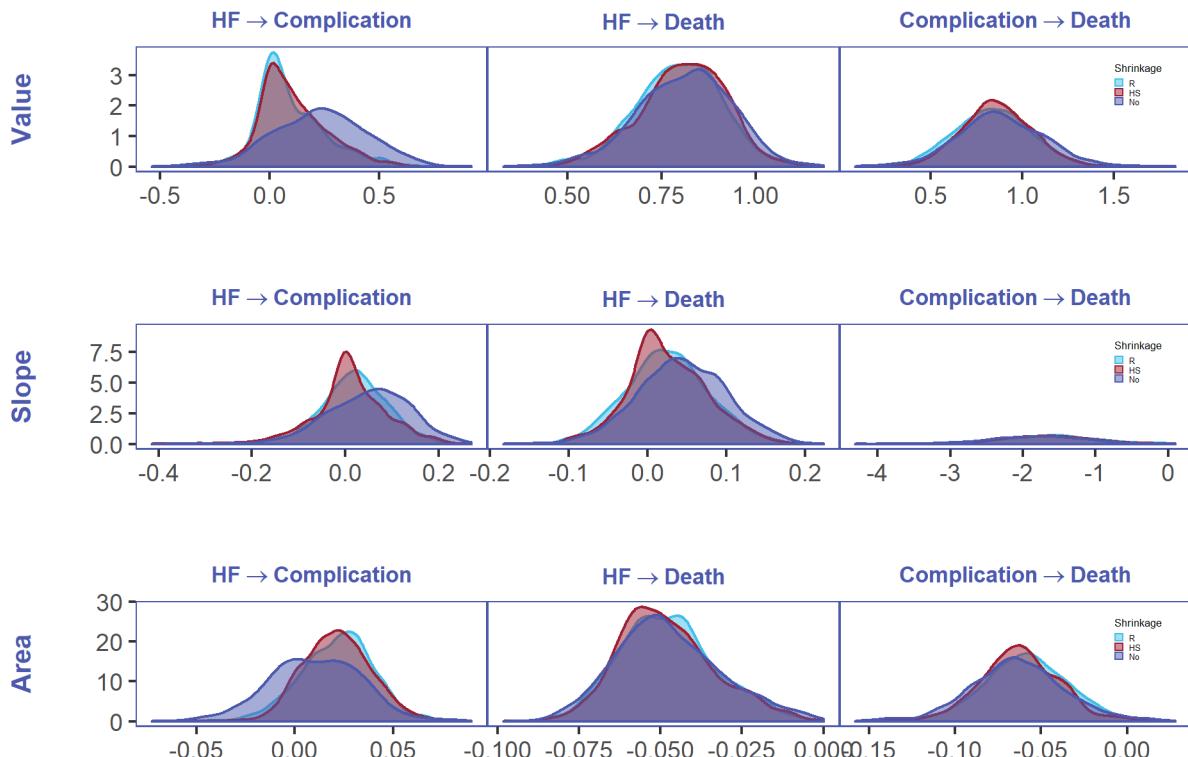
Results



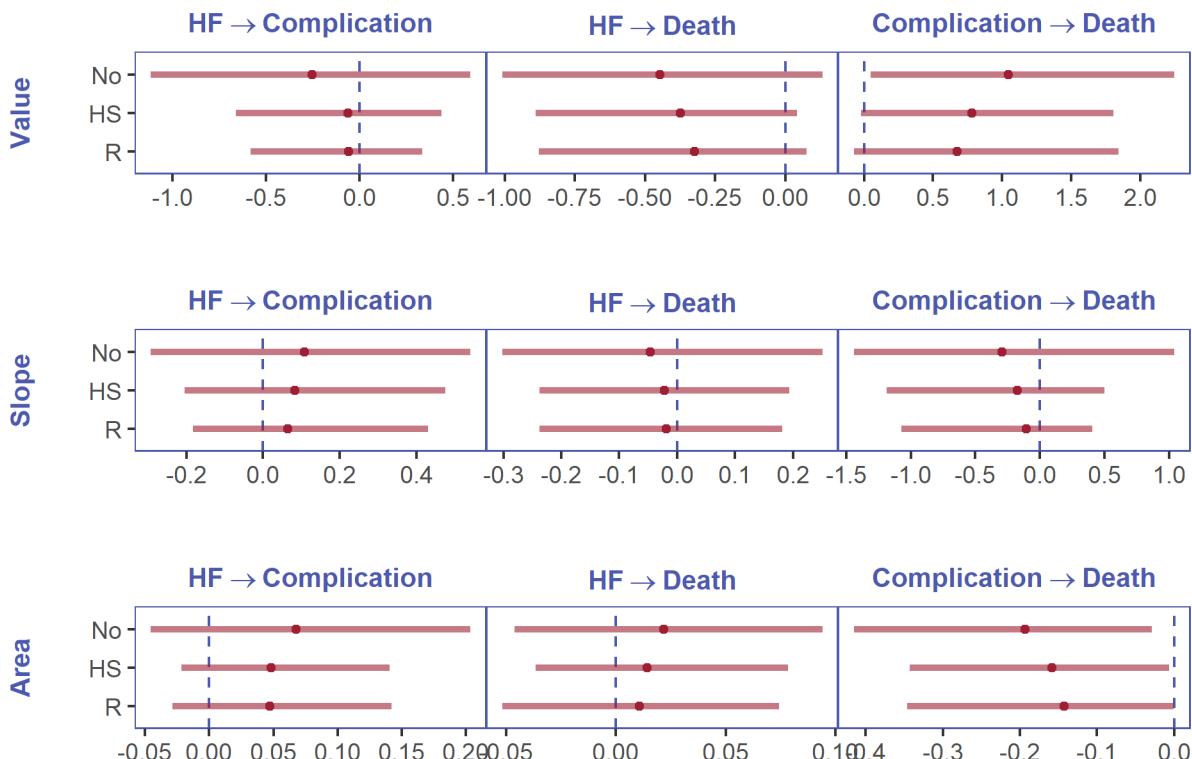
Results: Bilirubin



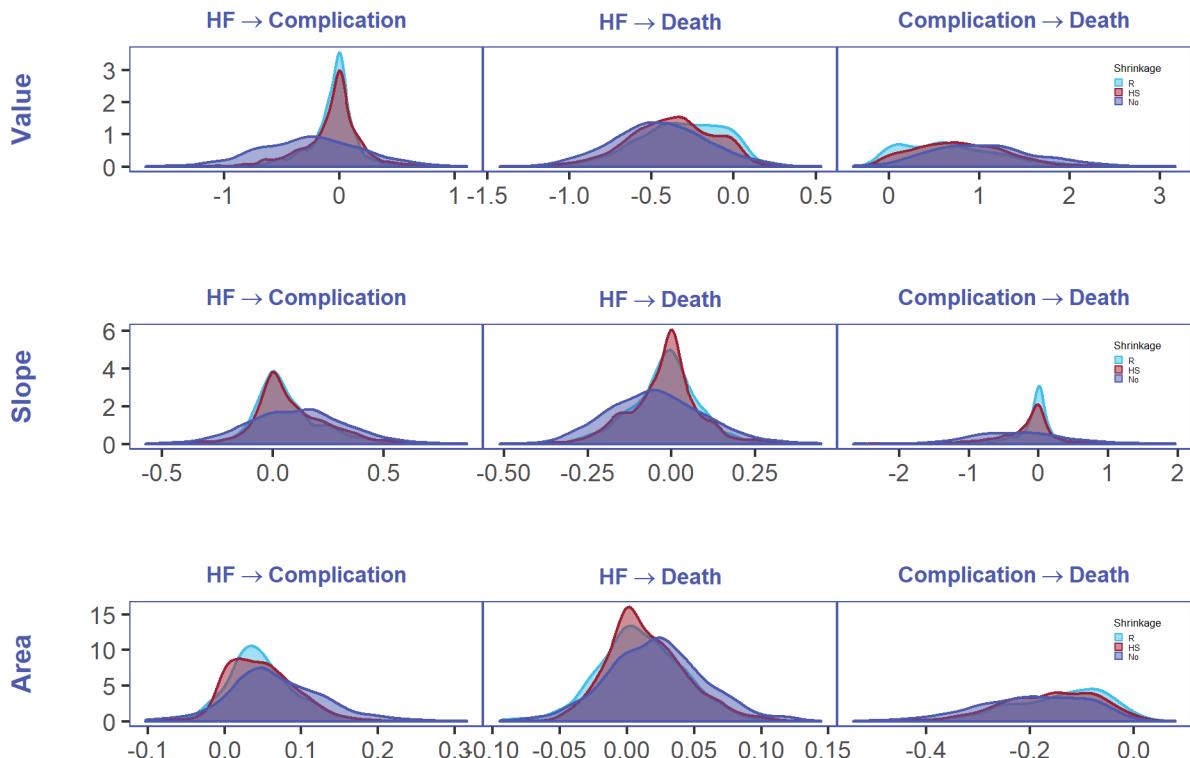
Results: Bilirubin



Results: Creatinine



Results: Creatinine



Software Implementation



Thank you

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 <https://github.com/drizopoulos>

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