Stratified and personalised medicine using model-based recursive partitioning

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Joint work with Torsten Hothorn (UZH) and Achim Zeileis (UIBK), sponsored by SNF

What are *Stratified and Personalised Medicine*?

Stratified medicine:
Find subgroups of patients that differ with respect to their treatment effect. Estimate the treatment effect for each subgroup.

Personalised medicine:
Estimate a personalised treatment effect for each patient.

Pooled Resource Open-Access ALS Clinical Trials Database

PRO-ACT database[1]

- 23 phase 2 clinical trials
- Riluzole versus no treatment
- Primary endpoints of interest:
  - ALS Functional Rating Scale (ALSFRS)
  - Survival time

[1] https://nctu.partners.org/ProACT

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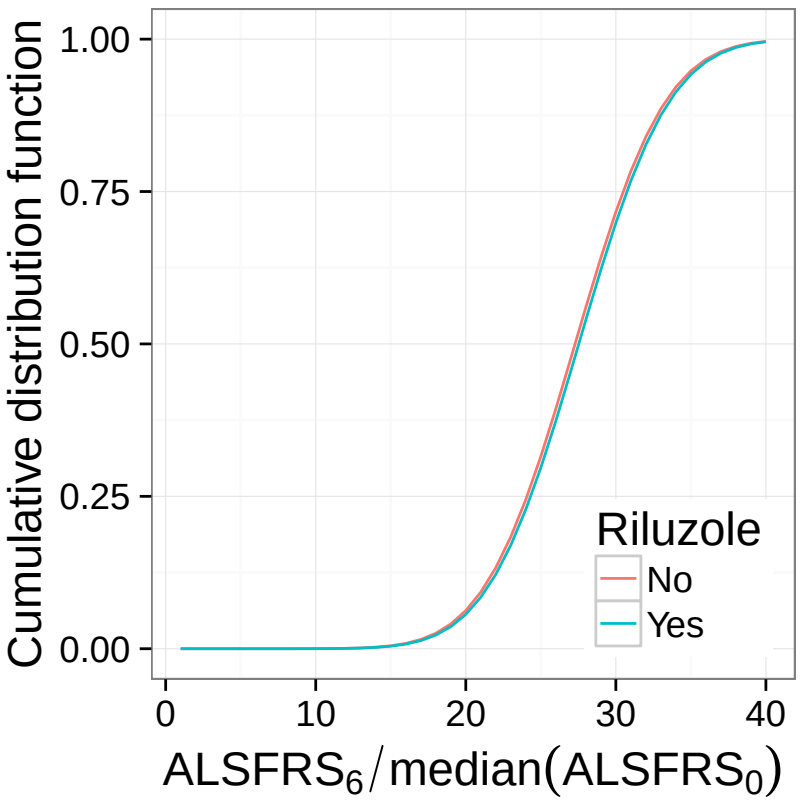
ALSFRS: Normal GLM with log link

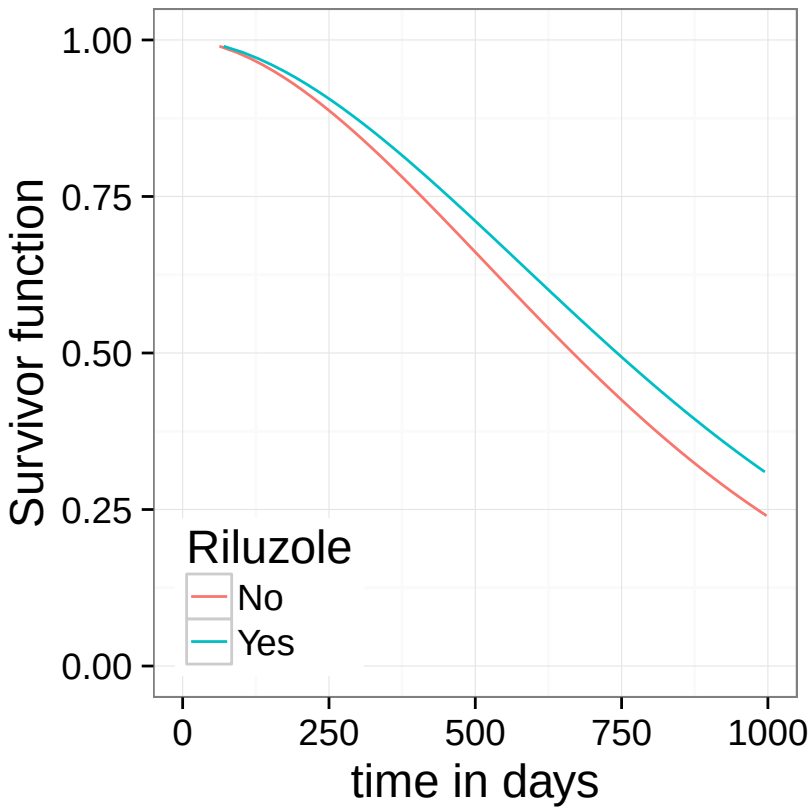
$$\mathbb{E}\left(\frac{\text{ALSFRS}_6}{\text{ALSFRS}_0}\middle| X = x\right) = \frac{\mathbb{E}(\text{ALSFRS}_6|X = x)}{\text{ALSFRS}_0} = \exp\{\alpha + \beta x_R\}$$



	estimate	2.5 %	97.5 %
α	−0.16	−0.17	−0.15
β	0.01	−0.01	0.02

Survival time: Weibull model

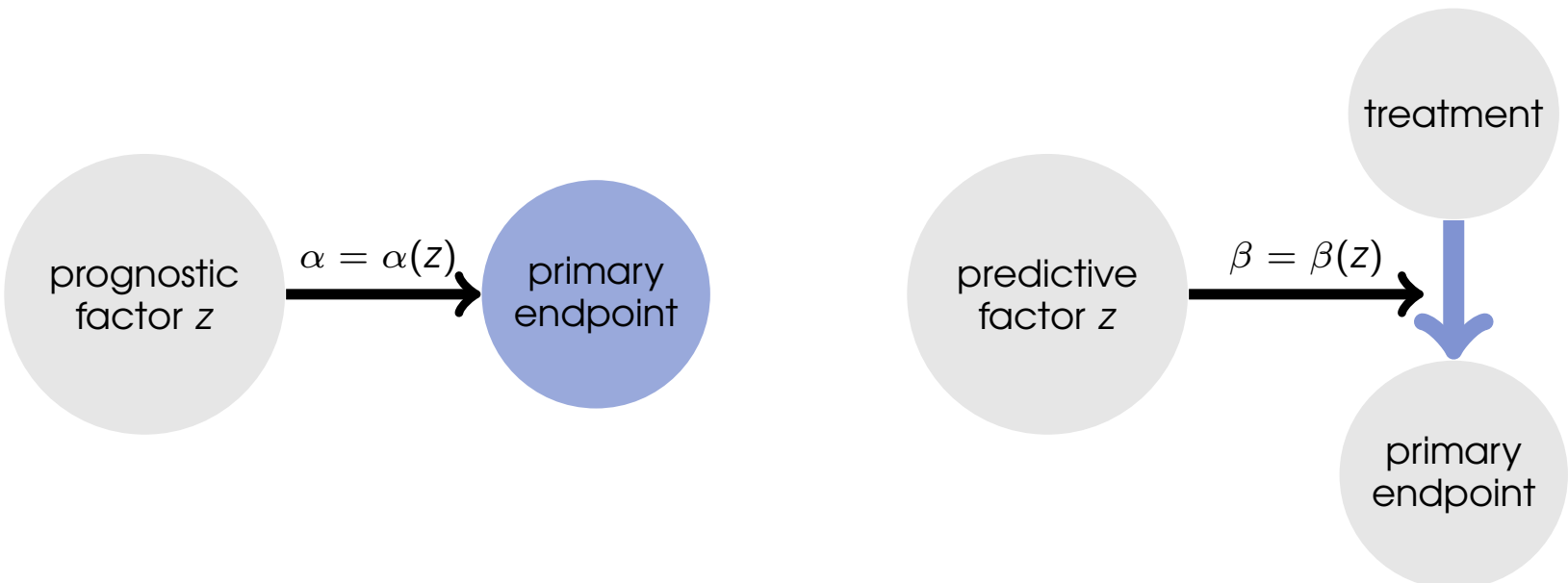
$$\mathbb{P}(Y \leq y | X = x) = F\left(\frac{\log(y) - \alpha_1 - \beta x_R}{\alpha_2}\right)$$



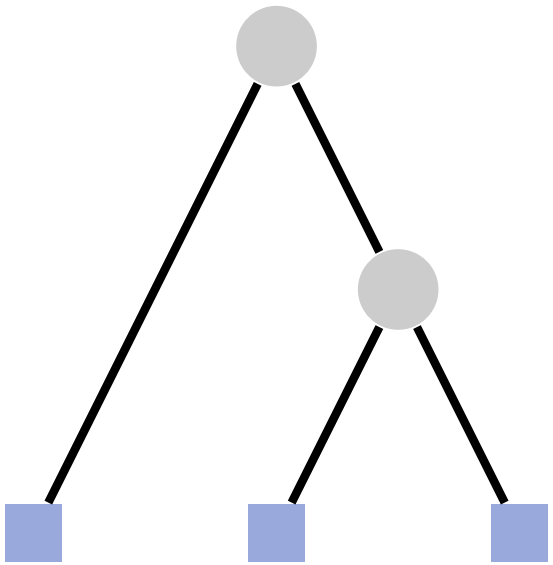
	estimate	2.5 %	97.5 %
α_1	6.71	6.64	6.77
β	0.11	0.03	0.18
$\log(\alpha_2)$	−0.58	−0.64	−0.53

Are there patients for whom Riluzole has a stronger effect?

Predictive and prognostic factors



Stratified medicine: Subgroup analyses



MOB Basics

MOB: Model-based recursive partitioning

Start with model $\mathcal{M}((Y, \mathbf{X}), \boldsymbol{\vartheta})$ with

$$\boldsymbol{\vartheta} = \begin{pmatrix} \boldsymbol{\alpha} \\ \boldsymbol{\beta} \end{pmatrix} \begin{array}{l} \text{intercept(s)} \\ \text{treatment effect} \end{array}$$

which fits data $(Y, \mathbf{X})$.

ALSFRS: Normal GLM with log link

$$\frac{\mathbb{E}(\text{ALSFRS}_6 | X = x)}{\text{ALSFRS}_0} = \exp\{\alpha + \beta x_R\}$$

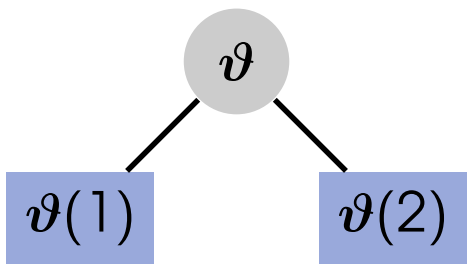
Survival time: Weibull model

$$\mathbb{P}(Y \leq y | X = x) = F\left(\frac{\log(y) - \alpha_1 - \beta x_R}{\alpha_2}\right)$$

MOB Basics

$\Rightarrow$ Find partitions of the data based on patient characteristics $\mathbf{Z} = (\mathbf{Z}_1, ..., \mathbf{Z}_J) \in \mathcal{Z}$ which differ with respect to the model parameters $\boldsymbol{\vartheta}$.

$\Rightarrow$ Fit separate models $\mathcal{M}((Y, \mathbf{X}), \boldsymbol{\vartheta}(b))$ in partitions.



How to find the Partitions?

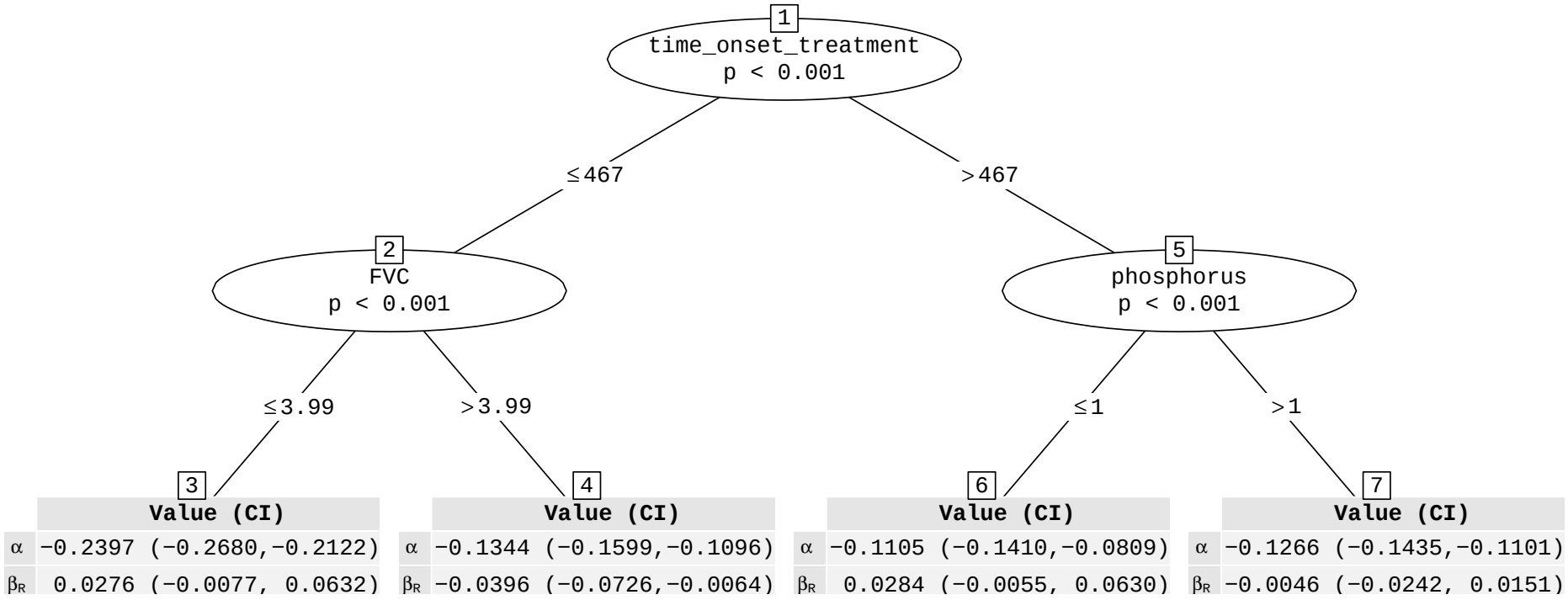
Test of independence between the **partial score functions** and each **patient characteristic**:

$$
\begin{aligned}
H_0^{\alpha,j}: \quad & \psi_\alpha((Y, \mathbf{X}), \hat{\boldsymbol{\vartheta}}) \quad \perp \quad \mathbf{Z}_j \\
H_0^{\beta,j}: \quad & \psi_\beta((Y, \mathbf{X}), \hat{\boldsymbol{\vartheta}}) \quad \perp \quad \mathbf{Z}_j, \quad j = 1, \ldots, J
\end{aligned}
$$

ψ_α, ψ_β partial derivatives of the log-likelihood with respect to $\boldsymbol{\alpha}/\boldsymbol{\beta}$.

- Partition if global p-value smaller than significance level
- Use as split variable the one with the smallest p-value

ALSFRS

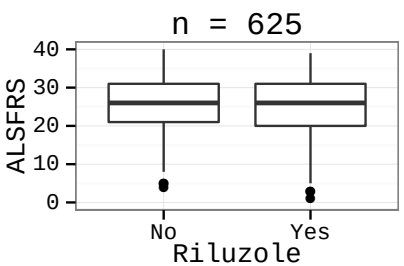


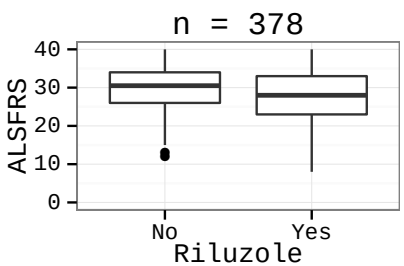
	Value (CI)
α	−0.2397 (−0.2680,−0.2122)
β_R	0.0276 (−0.0077, 0.0632)

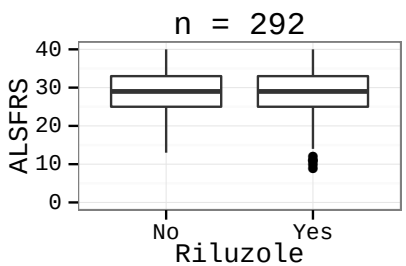
	Value (CI)
α	−0.1344 (−0.1599,−0.1096)
β_R	−0.0396 (−0.0726,−0.0064)

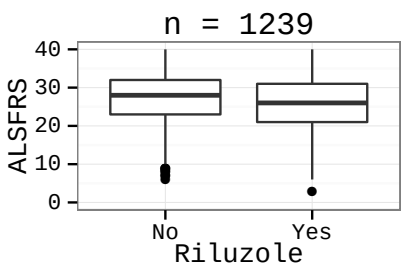
	Value (CI)
α	−0.1105 (−0.1410,−0.0809)
β_R	0.0284 (−0.0055, 0.0630)

	Value (CI)
α	−0.1266 (−0.1435,−0.1101)
β_R	−0.0046 (−0.0242, 0.0151)

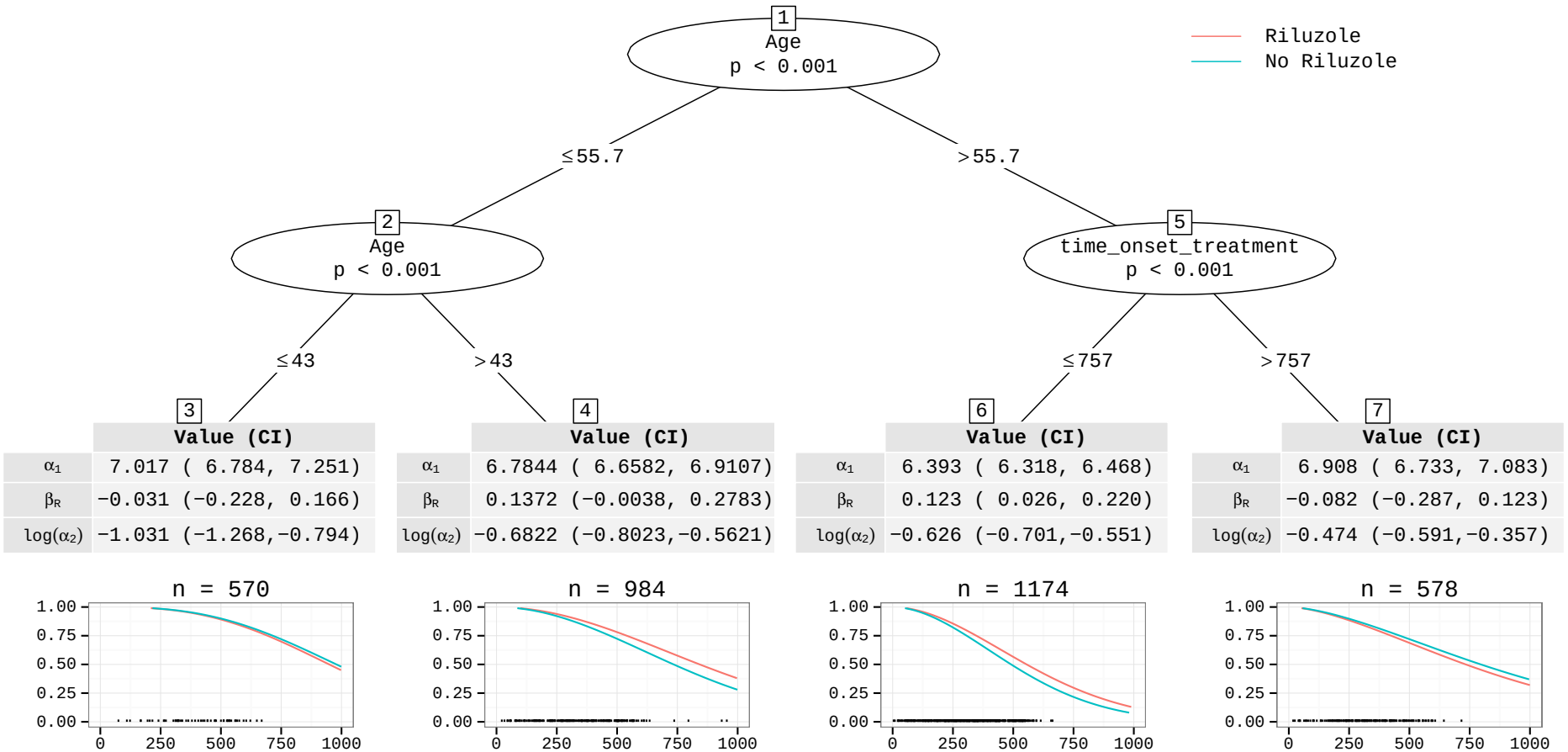








Survival time



	Value (CI)
α_1	7.017 (6.784, 7.251)
β_R	−0.031 (−0.228, 0.166)
$\log(\alpha_2)$	−1.031 (−1.268,−0.794)

	Value (CI)
α_1	6.7844 (6.6582, 6.9107)
β_R	0.1372 (−0.0038, 0.2783)
$\log(\alpha_2)$	−0.6822 (−0.8023,−0.5621)

	Value (CI)
α_1	6.393 (6.318, 6.468)
β_R	0.123 (0.026, 0.220)
$\log(\alpha_2)$	−0.626 (−0.701,−0.551)

	Value (CI)
α_1	6.908 (6.733, 7.083)
β_R	−0.082 (−0.287, 0.123)
$\log(\alpha_2)$	−0.474 (−0.591,−0.357)

Summary: MOB for stratified medicine

- Data-driven approach for subgroup analyses.
- Easy to understand and communicate.

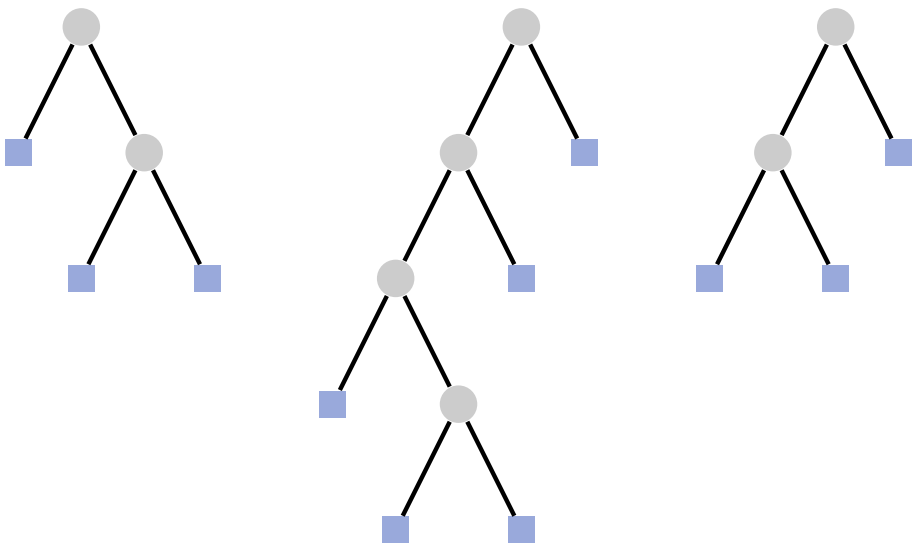
Extensions:

- Dose-response models
- Mixed models[2]
- PALM trees

[2] M. Fokkema, N. Smits, A. Zeileis, T. Hothorn, H. Kelderman. *Detecting treatment-subgroup interactions in clustered data with generalized linear mixed-effects model trees*. Working Papers in Economics and Statistics of the University of Innsbruck, 2015.

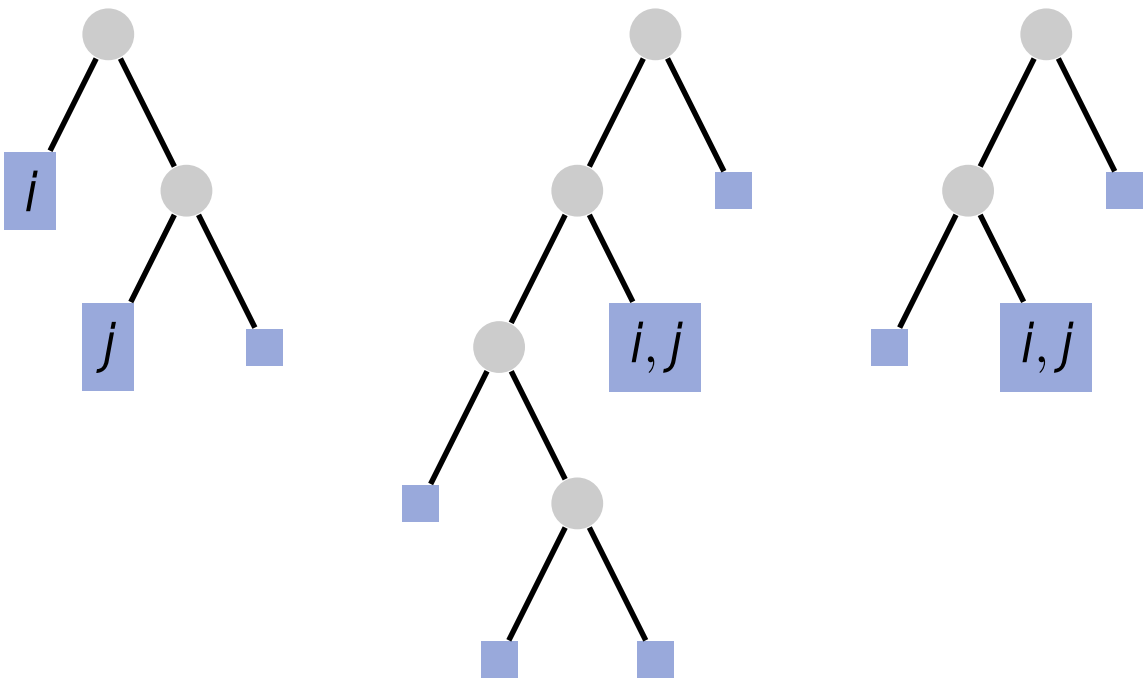
Personalised medicine: Individual treatment effect prediction

Maybe subgroups are still not good enough
$\Rightarrow$ Personalised treatment effects through model-based random forests



Personalised models

Compute similarity (-weights) of patient *i* to each patient *j* in the training data:
How often are *i* and *j* assigned to the same subgroup?

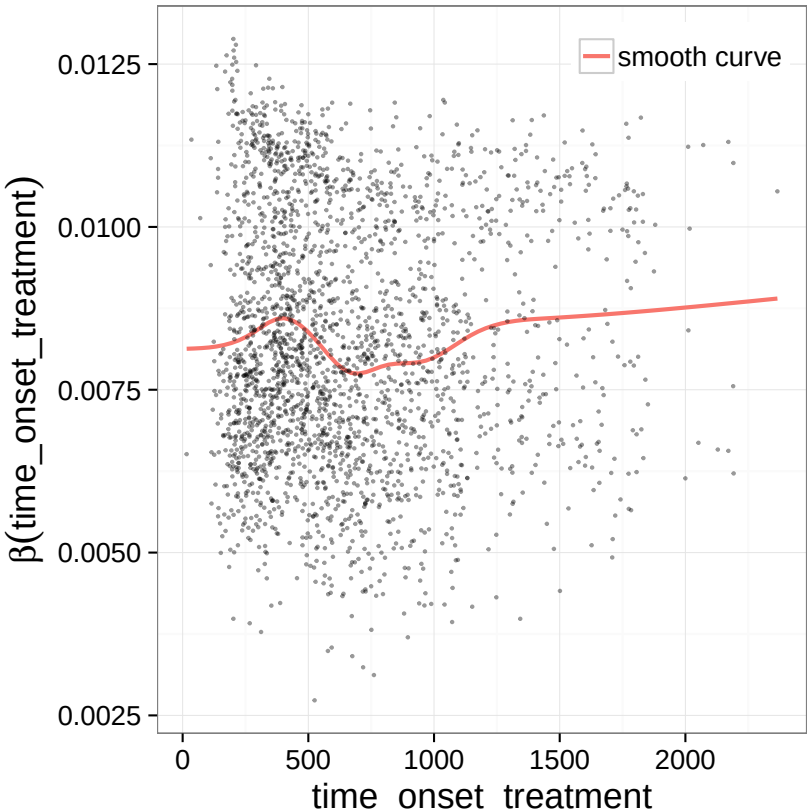


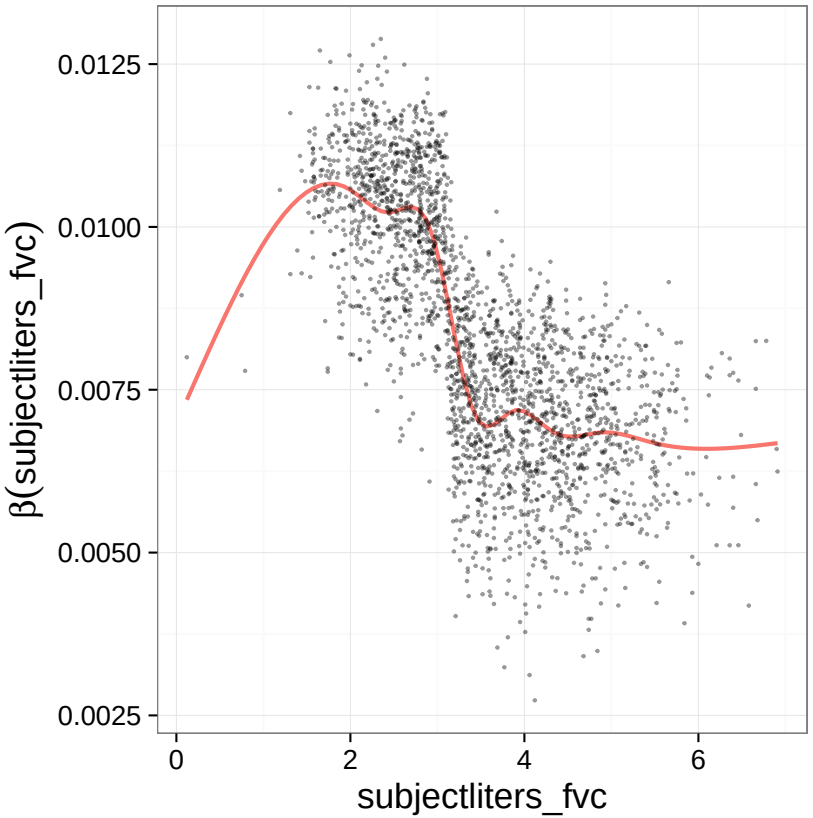
$\Rightarrow$ 2 times

Personalised models

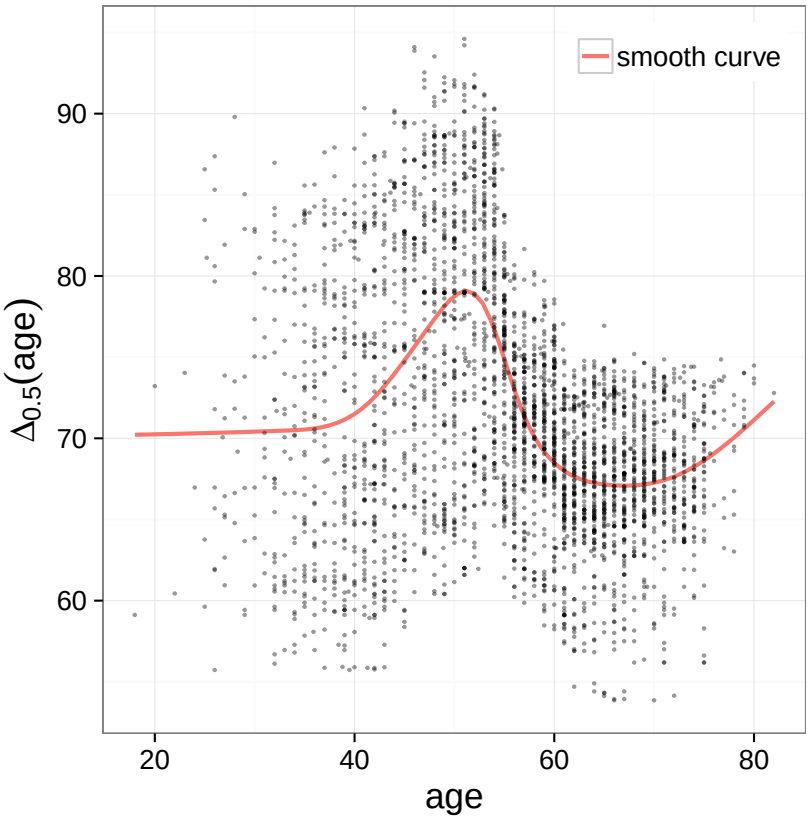
Compute the model using the weighted training data.
$\rightarrow$ *observation j enters 2 times in model for patient i.*

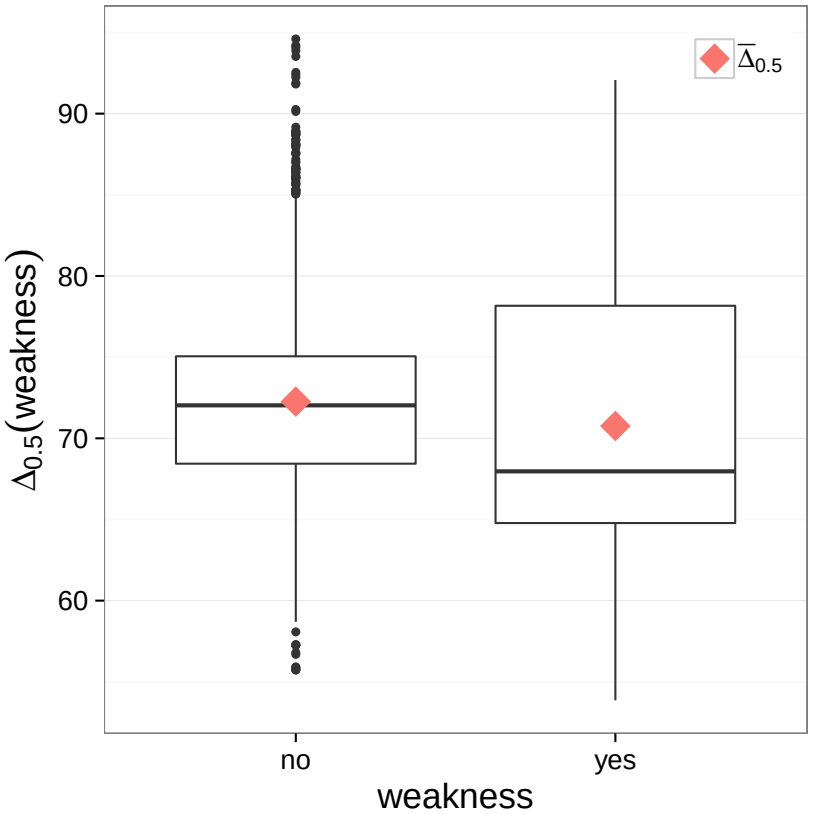
ALSFRS


smooth curve
β(time_onset_treatment)
0.0125
0.0100
0.0075
0.0050
0.0025
0
500
1000
1500
2000
time_onset_treatment


β(subjectliters_fvc)
0.0125
0.0100
0.0075
0.0050
0.0025
0
2
4
6
subjectliters_fvc

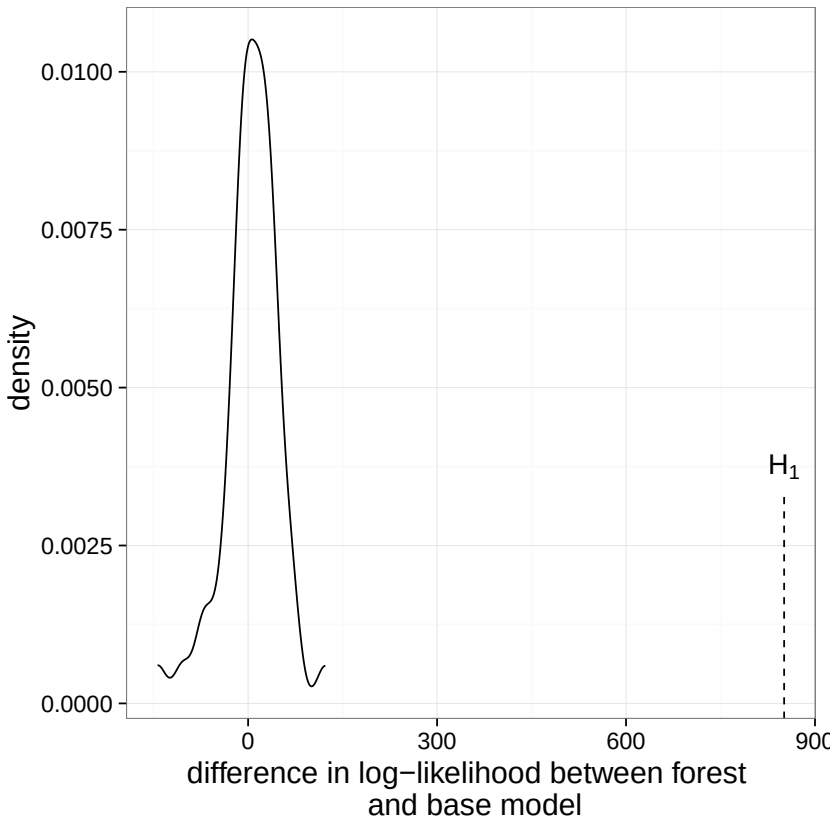
Survival time

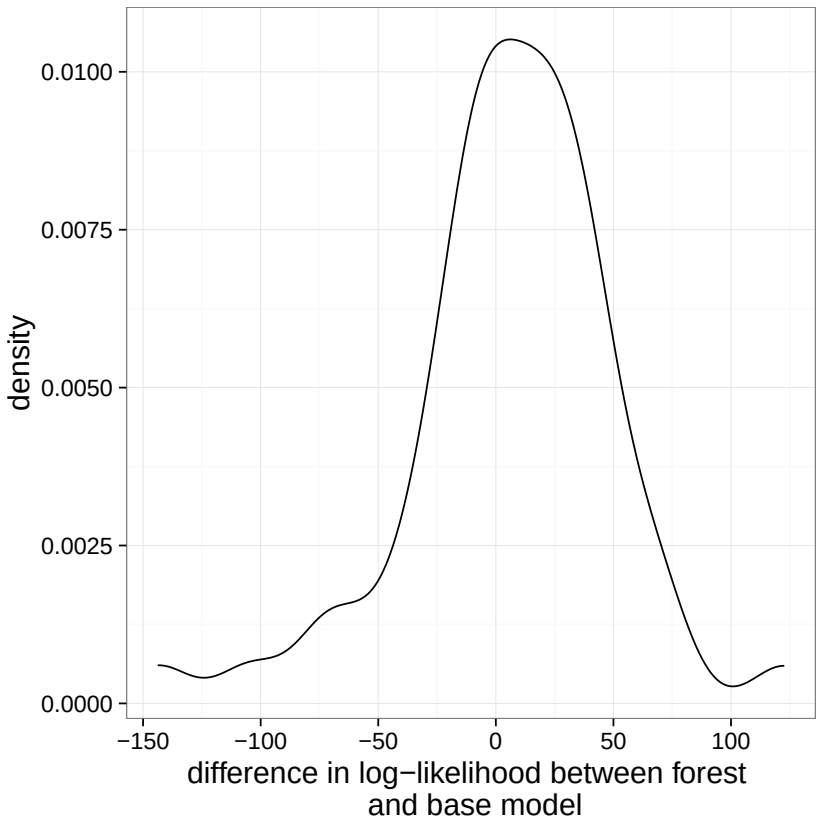




Is the overall treatment effect good enough?

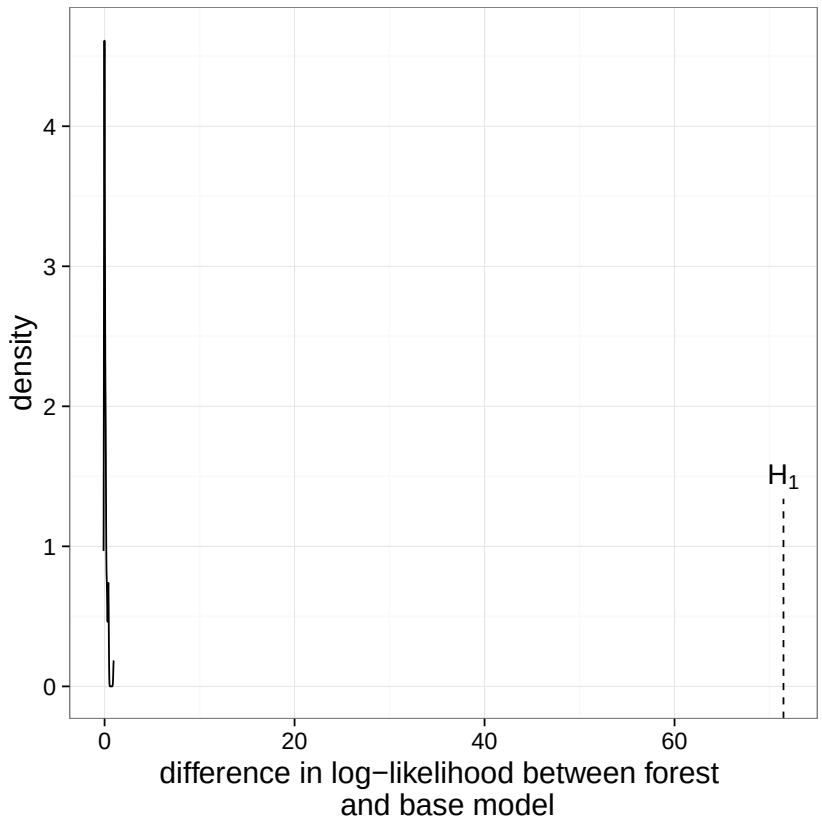
ALSFRS H_0 : Intercept and treatment effect are the same for all patients.

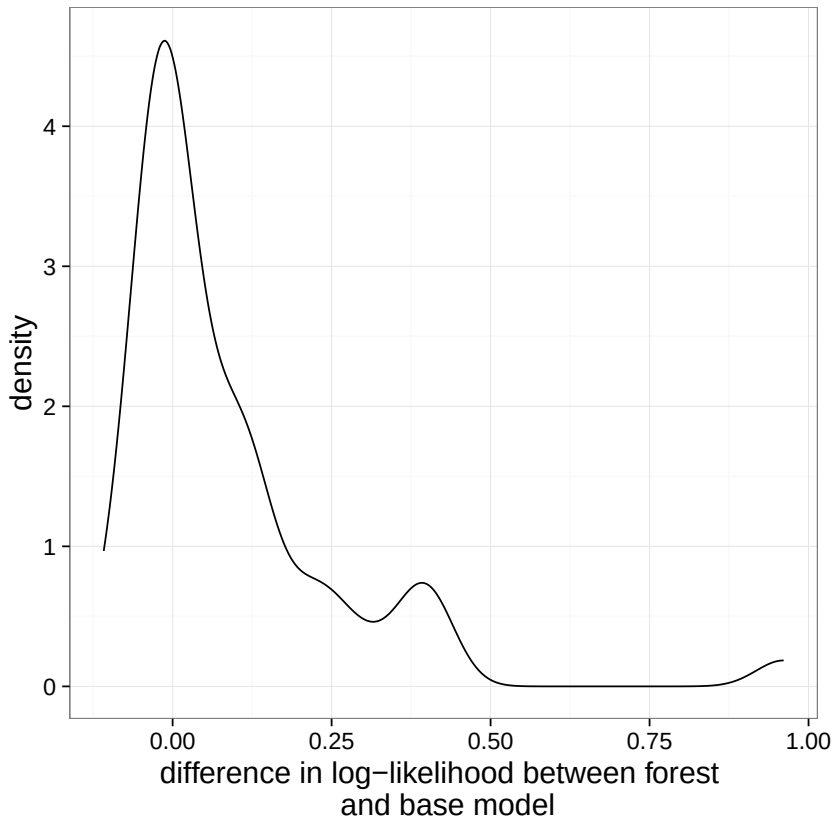




Is the overall treatment effect good enough?

Survival time H_0 : Baseline hazard and treatment effect are the same for all patients.





Summary

- Sound theoretical foundation for stratified and personalised medicine.
- Data-driven.

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But

- Results of secondary analysis need to be confirmed in independent trials.

Literature

- H. Seibold, A. Zeileis, T. Hothorn
  Model-based Recursive Partitioning for Subgroup Analyses
  International Journal of Biostatistics, 2016.

- H. Seibold, A. Zeileis, T. Hothorn
  Individual Treatment Effect Prediction for ALS Patients
  ArXiv e-prints, 2016.

Variable importance

1. Tree log-likelihood
   - Select the out-of-bag data $\mathcal{L}_t^c$ and determine the subgroup to which each observation i belongs.
   - Compute the log-likelihood contribution of each observation $i \in \mathcal{L}_t^c$ based on the respective model in the subgroup.
   - Compute the out-of-bag log-likelihood as the sum of the contributions

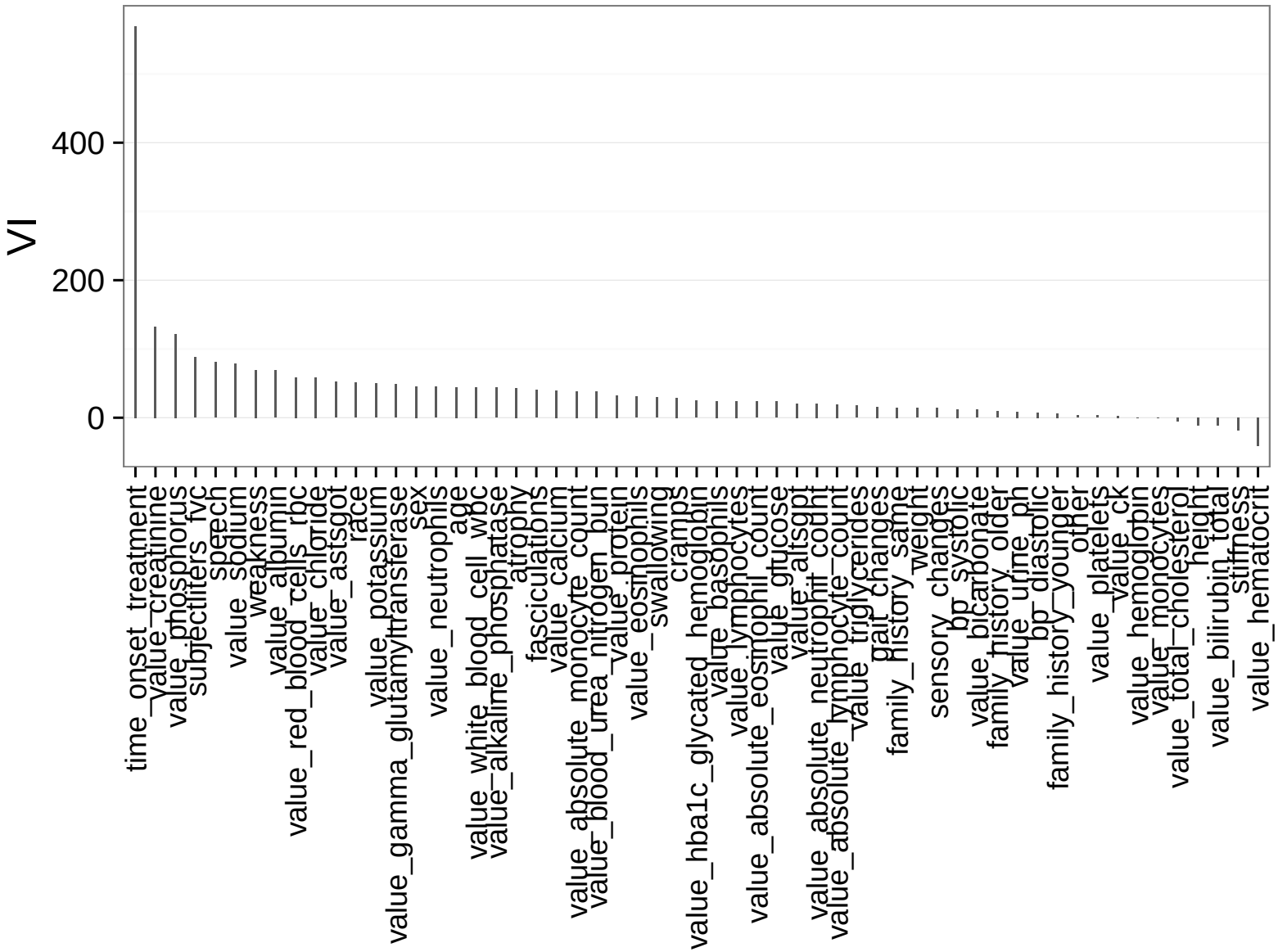
$$l_t = \sum_{i \in \mathcal{L}_t^c} l((y, \mathbf{x})_i, \hat{\vartheta}(\mathbf{z}_i)).$$

2. Variable importance

$$\text{VI}_j = \frac{1}{T} \sum_{t=1}^{T} \left[l_t - l_t^{(j)} \right]$$

$l_t^{(j)}$ log-likelihood with variable j permuted.

Variable importance: ALSFRS



Variable importance: Survival time