Assessing Risk Indicators in Clinical Practice with Joint Models of Longitudinal and Time-to-Event Data

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Outline

- **Introduction to Joint Models**
- **Recent Applications in Joint Models**
  - ▷ Shrinkage approach
  - ▷ Time-varying effects

Introduction to Joint Models

Introduction to Joint Models

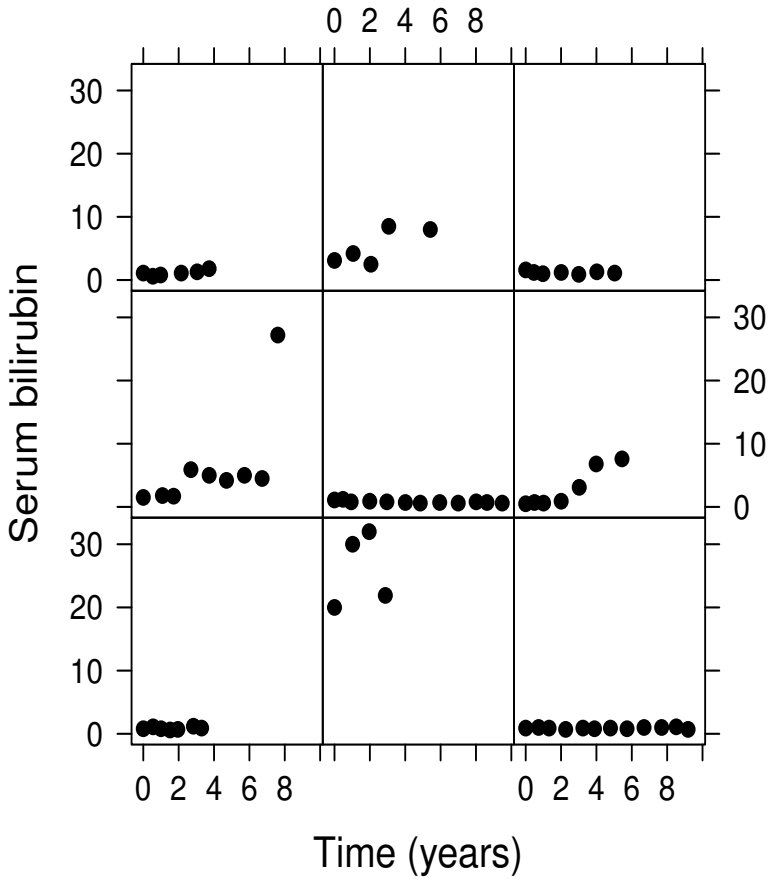
- Often in clinical studies multiple outcomes are collected

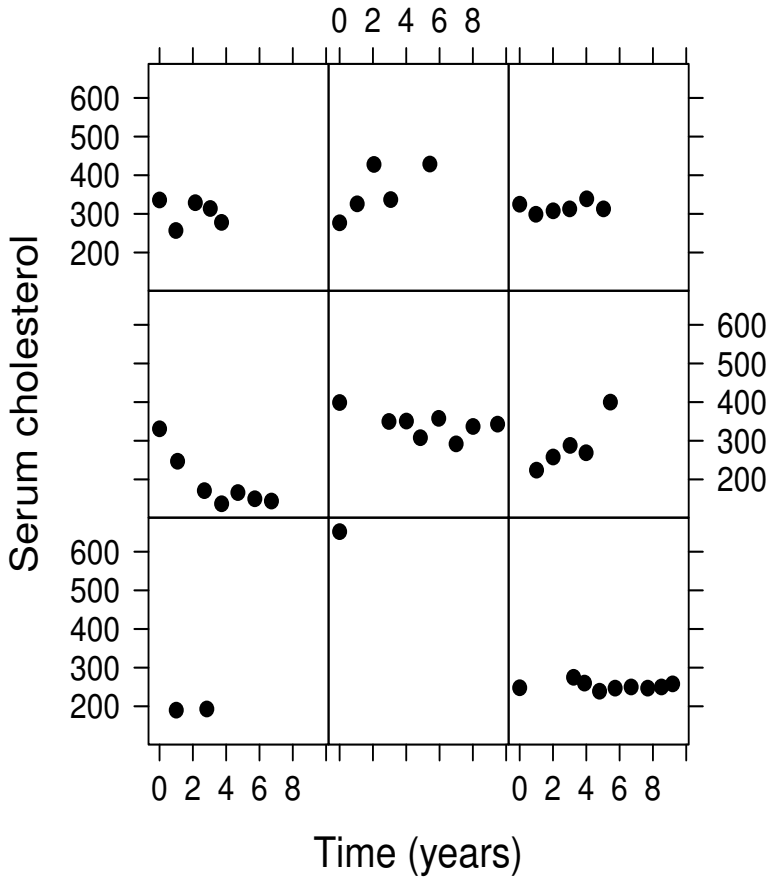
- Type of data
  - ▷ Longitudinal responses
  - ▷ Time-to-event data

Motivation - Data set 1

- 312 patients with primary **biliary cirrhosis**, a rare autoimmune liver disease, at Mayo Clinic
  - ▷ Patients were 50 years and older, 88% females and 50% D-penicil
  - ▷ Median number of visits per individual is 6
  - ▷ Longitudinal responses: **serum bilirubin** and **serum cholesterol** in mg/dl
  - ▷ Time-to-event response: time-to-**death** (45%)

Motivation - Data set 1 (con't)

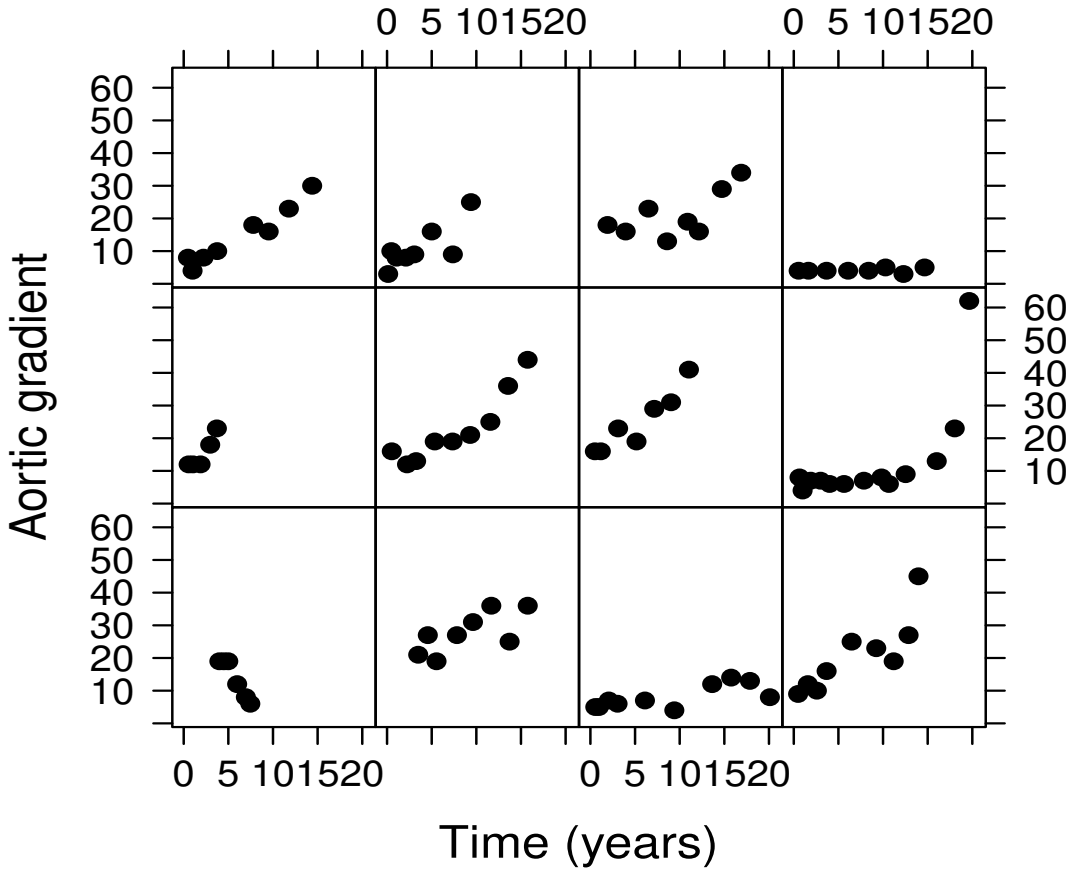




Motivation - Data set 2

- 286 patients who received **human tissue valve in aortic position** in Erasmus University Medical Center (Department of Cardio-Thoracic Surgery)
  - ▷ Patients were 16 years and older
  - ▷ Echo examinations scheduled at 6 months and 1 year postoperatively and biennially thereafter
  - ▷ Longitudinal response: **aortic gradient**
  - ▷ Time-to-event response: time-to-**death/reoperation** (54%)

Motivation - Data set 2 (con't)



Research Questions

- Are **serum bilirubin** and **serum cholesterol** both associated with **survival**?

- Is **aortic gradient** associated with the composite event **death/reoperation**?

  ▷ Could we improve death/reoperation predictions, if we incorporate all available longitudinal information?

How can use all available information?

Introduction to Joint Models (cont'd)

- Special features should be taken into account

Longitudinal data

▷ Correlation between measurements obtained from the same patients

▷ Biological variation of the outcome

▷ Unbalanced datasets

Survival data

▷ Censored data (partial information for the event times)

Jointly

▷ Association between all outcomes

Introduction to Joint Models (cont'd)

- Frequently used analysis
  - ▷ **Separate** analysis per outcome

    Mixed-effects models for the longitudinal outcomes

    Cox models for the time-to-event outcomes

  - ▷ Naive **joint** analysis

    Cox model using the last observation

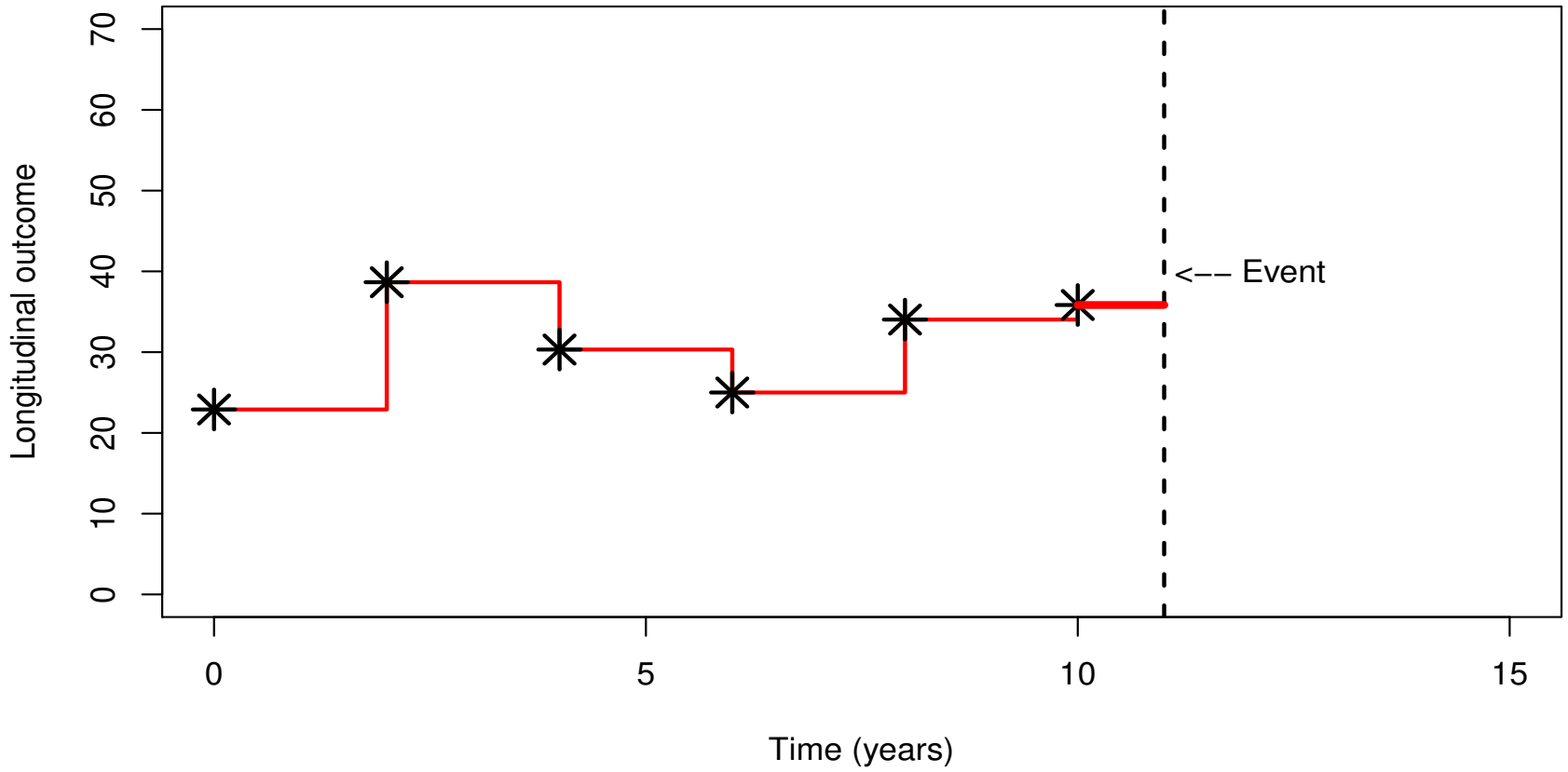
    Cox model using the mean or the slope of the repeated covariate

    Time-dependent Cox model

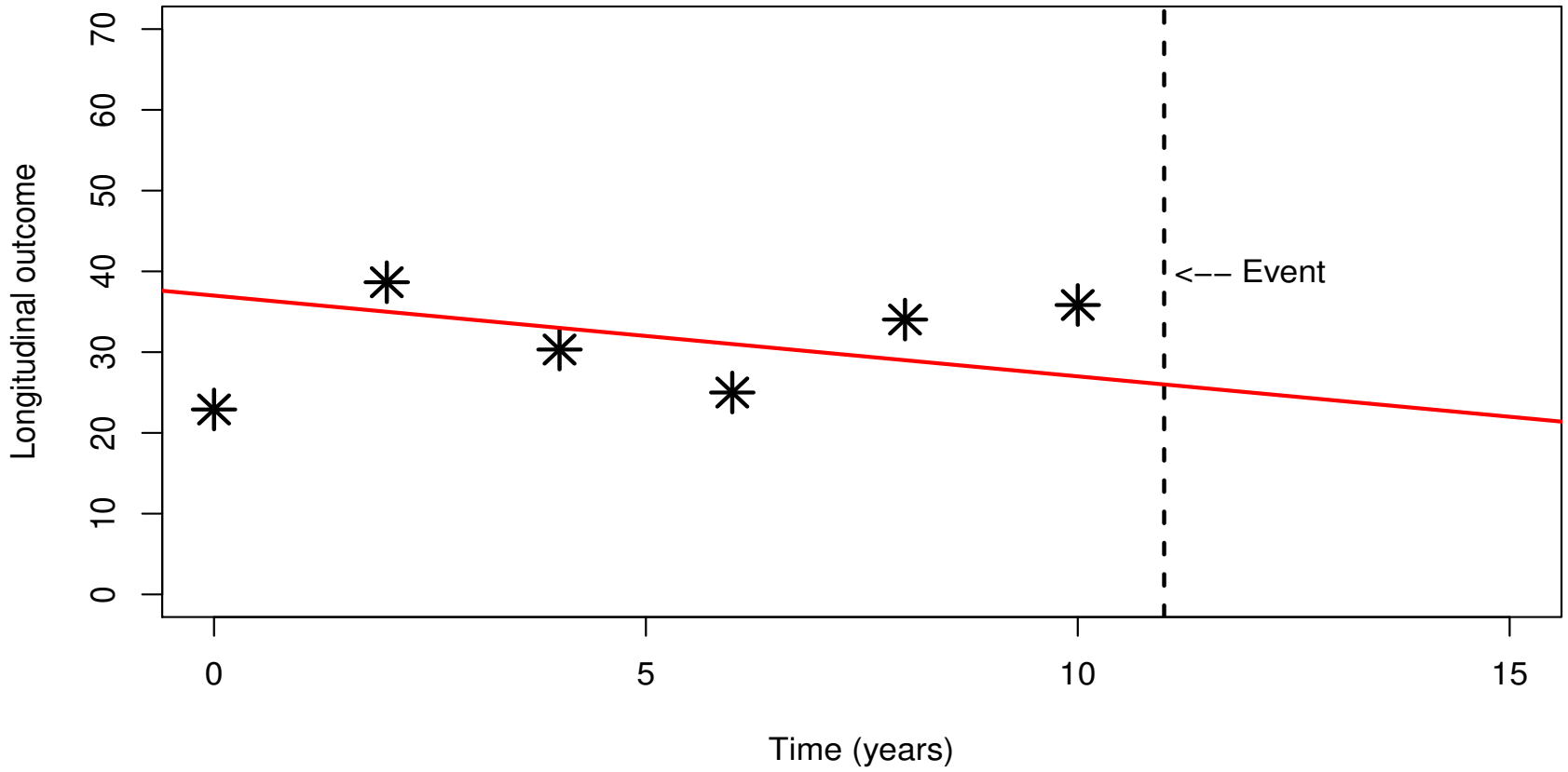
Introduction to Joint Models (cont'd)

- Time-dependent Cox models are suitable only for **exogenous** covariates, not got **endogenous**
  - ▷ A time-varying covariate is **exogenous** if its value at any time point t is not affected by an event occurring at an earlier time point $s < t$ (period of the year, enviromental variables)
  - ▷ On the other hand all covariates measured on the patient (e.g., biomarkers) are **endogenous**

Introduction to Joint Models (cont'd)



Introduction to Joint Models (cont'd)



Introduction to Joint Models (cont'd)

- **Step 1**

Let y_i represent the repeated measurements of an outcome for the i-th patient, $i = 1, \ldots, n$

Mixed-effects model:

$$y_i(t) = x_i^\top(t)\beta + z_i^\top(t)b_i + \epsilon_i(t) = \eta_i(t) + \epsilon_i(t),$$

$b_i \sim N(0, D)$ and $\epsilon_i(t) \sim N(0, \Sigma_i)$

where

- ▷ $x_i^\top(t)\beta$ denotes the fixed part
- ▷ $z_i^\top(t)b_i$ denotes the random part

Introduction to Joint Models (cont'd)

- **Step 2**

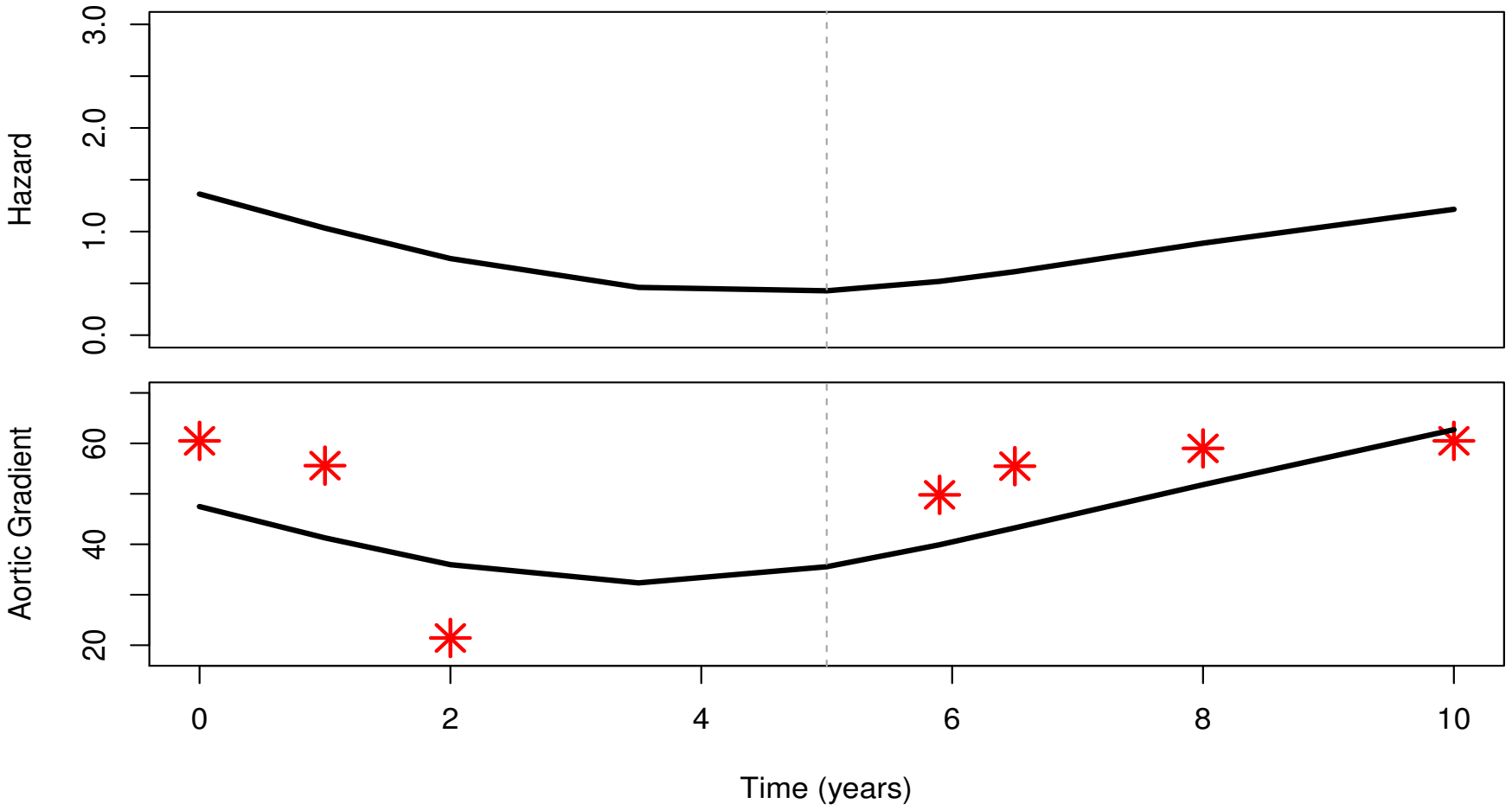
Cox model:

$$h_i(t) = h_0(t) \exp\{\gamma^\top \omega_i + \alpha \eta_i(t)\},$$

where

- ▷ $\gamma^\top \omega_i$ denotes the baseline covariates with their coefficients
- ▷ $\eta_i(t)$ denotes the value of the time-dependent covariate at time t
- ▷ α measures the association between the longitudinal outcome at time t and the hazard for an event at the same time point

Introduction to Joint Models (cont'd)



Recent Applications in Joint Models

Shrinkage Approach

Motivated by the biliary cirrhosis data:

- Longitudinal responses:
  - ▷ **serum bilirubin**
  - ▷ **serum cholesterol**
- Time-to-event response:
  - ▷ time-to-**death**

Andrinopoulou, E. R. and Rizopoulos, D. (2016). Bayesian shrinkage approach for a joint model of longitudinal and survival outcomes assuming different association structures. Statistics in Medicine, 35(26), 4813-4823.

Shrinkage Approach (cont'd)

- In the standard joint model we assume that the underying value of the longitudinal biomarker is associated with the survival outcome at a time point t

Is that option always correct?

Shrinkage Approach (cont'd)

- Inappropriate modelling of time-dependent covariates may result in surprising results

- **Example**: Cavender et al. (1992, J Am. Coll. Cardiol) conducted an analysis to test the effect of cigarette smoking on survival of patients who underwent coronary artery surgery
  - ▷ the estimated effect of current cigarette smoking was positive on survival although not significant (i.e. patient who smoked had higher probability of survival)
  - ▷ most of those who had died were smokers but many stopped smoking at the last follow-up before they died

Shrinkage Approach (cont'd)

We need to carefully consider which longitudinal outcomes and which functional forms we will include

- Let's investigate that ...

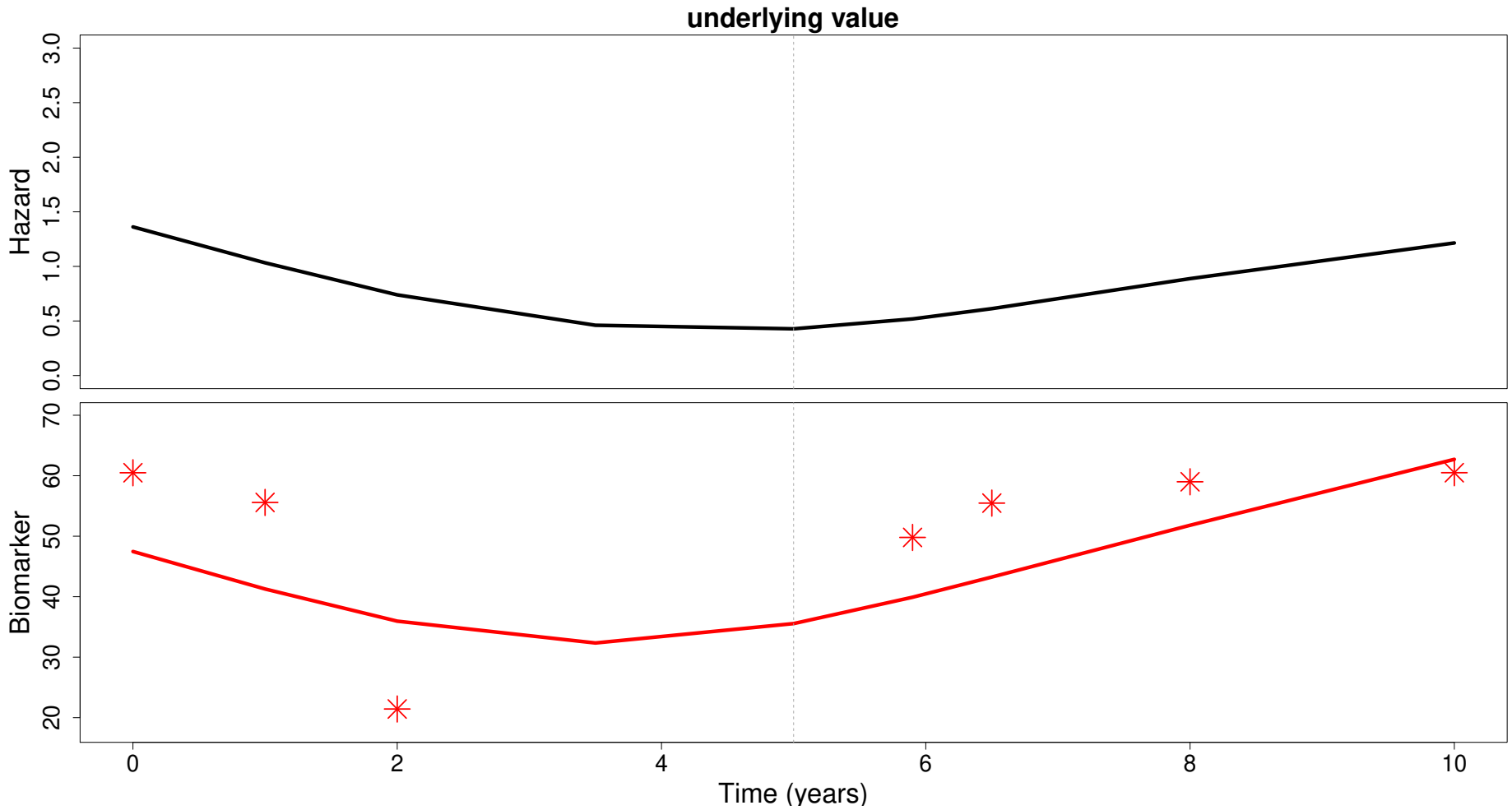
Shrinkage Approach (cont'd)

Different parameterizations

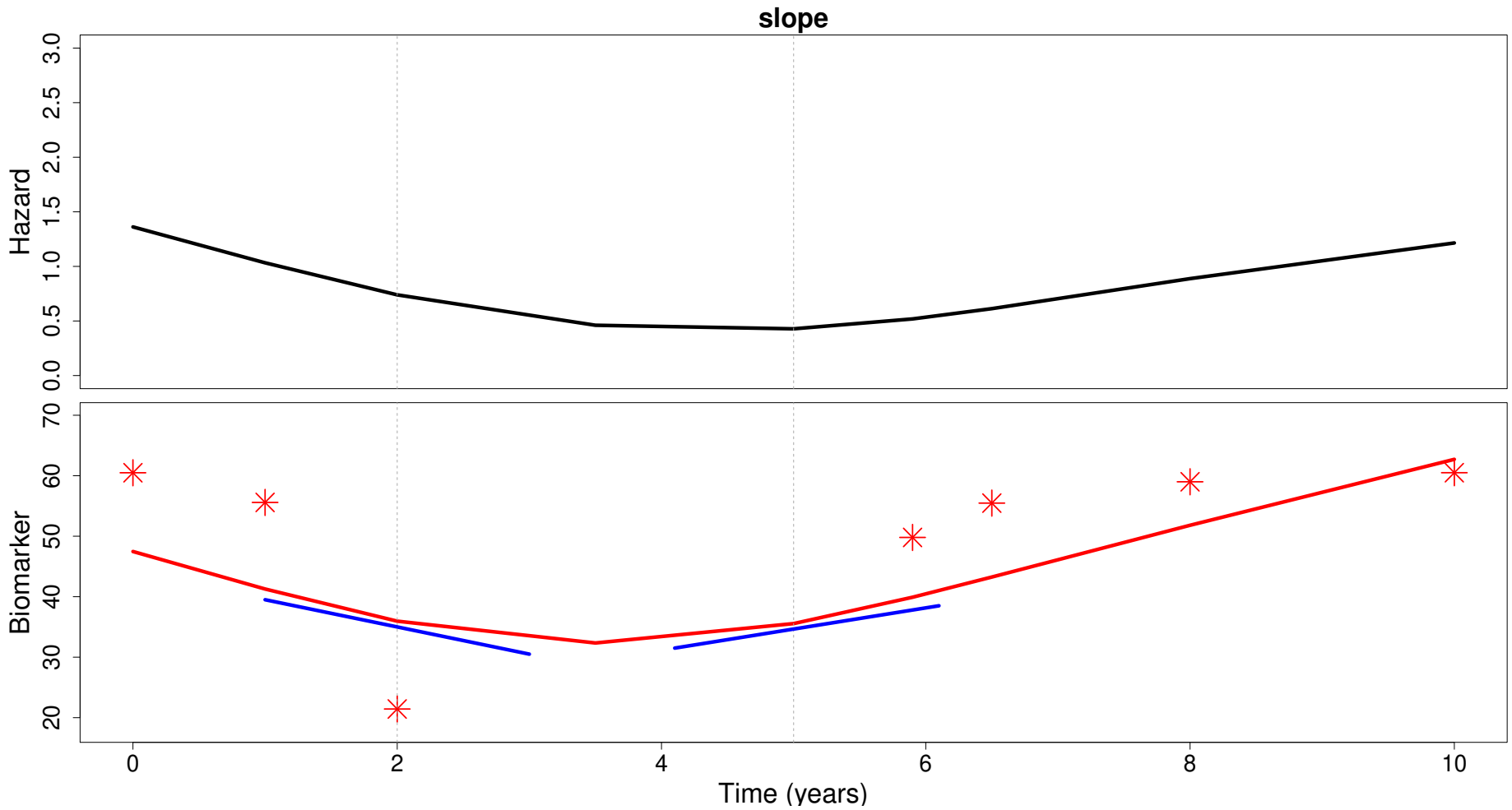
Let us assume $k = 1, \ldots, K$ longitudinal outcomes

$$
\begin{aligned}
M_1 : h_i(t) &= h_0(t) \exp\{\gamma^\top w_i + \sum_{k=1}^{K} \alpha_{k1} \eta_{ik}(t)\}, \\
M_2 : h_i(t) &= h_0(t) \exp\{\gamma^\top w_i + \sum_{k=1}^{K} \alpha_{k2} \eta'_{ik}(t)\}, \\
M_3 : h_i(t) &= h_0(t) \exp\{\gamma^\top w_i + \sum_{k=1}^{K} \alpha_{k3} \int_0^t \eta_{ik}(s) ds\} \\
&\vdots
\end{aligned}
$$

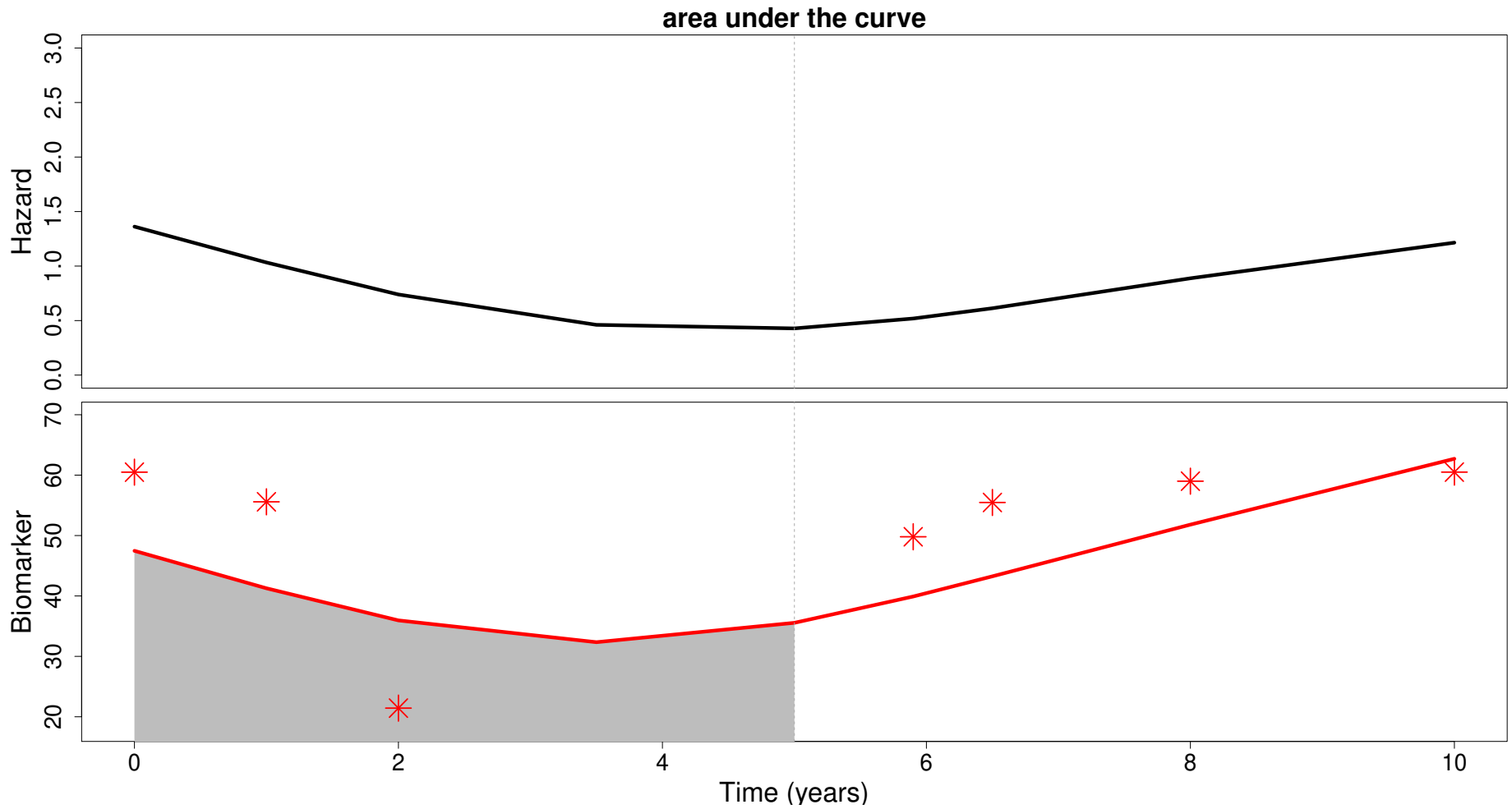
Shrinkage Approach (cont'd)



Shrinkage Approach (cont'd)



Shrinkage Approach (cont'd)



Shrinkage Approach (cont'd)

Extension of the standard JM

$$h_i(t) \;=\; h_0(t) \exp \left[\gamma^\top w_i + \sum_{k=1}^{K} \sum_{j=1}^{J} f_j\{\eta_{ik}(t), \alpha_{kj}\} \right],$$

where

- $i = 1, \ldots, n$ represents the patient,
- $k = 1, \ldots, K$ represents the longitudinal outcome
- $j = 1, \ldots, J$ represents the parameterization

Shrinkage Approach (cont'd)

For every longitudinal outcome which features are more predictive for survival?

$\Downarrow$

High dimensional model

$\Downarrow$

Variable selection problem

Shrinkage Approach (cont'd)

For every longitudinal outcome which features are more predictive for survival?

$\Downarrow$

High dimensional model

$\Downarrow$

Variable selection problem

$\Downarrow$

Penalties

Shrinkage Approach (cont'd)

- We employed a Bayesian approach and used Markov chain Monte Carlo (MCMC) methods to estimate the parameters of the proposed joint model

  ▷ Shrinkage priors for the association parametes

  ▷ Priors that give a high probability of being near 0

  Bayesian lasso

  Bayesian ridge

  Horseshoe

Shrinkage Approach (cont'd)

Bayesian lasso (BL):

- Bayesian variable selection for the joint model:

$$h_i(t) = h_0(t) \exp\left[\gamma^\top w_i + \sum_{k=1}^{K} \sum_{j=1}^{J} f_j\{\eta_{ik}(t), \alpha_{kj}\}\right]$$

$$\alpha_{kj} \mid \tau_{kj}^2 \sim N(0, \tau_{kj}^2)$$

$$\tau_{kj}^2 \sim exp(\lambda^2/2)$$

$$\lambda^2/2 \sim gamma(0.1, 0.1),$$

where λ is the shrinkage parameter

Shrinkage Approach (cont'd)

Bayesian lasso (BL):

- Bayesian variable selection for the joint model:

$$h_i(t) = h_0(t) \exp\left[\gamma^\top w_i + \sum_{k=1}^{K} \sum_{j=1}^{J} f_j\{\eta_{ik}(t), \alpha_{kj}\}\right]$$

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$$\lambda^2/2 \sim gamma(0.1, 0.1),$$

where λ is the shrinkage parameter

The Laplacian prior assigns more weight to regions near zero than the normal prior

Shrinkage Approach (cont'd)

Bayesian ridge (BR):

- Bayesian variable selection for the joint model:

$$h_i(t) = h_0(t) \exp\left[\gamma^\top w_i + \sum_{k=1}^{K}\sum_{j=1}^{J} f_j\{\eta_{ik}(t), \alpha_{kj}\}\right]$$

$$\alpha_{kj} \mid \tau^2_{kj} \sim N(0, \tau^2_{kj})$$

$$\tau^2_{kj} \sim Inv - gamma(\nu/2, (\nu/2)s^2)$$

$$1/\nu \sim dunif(0, 1)$$

$$s \sim dunif(0, 100),$$

where ν and s^2 represent the df and the scale

Shrinkage Approach (cont'd)

Bayesian ridge (BR):

- Bayesian variable selection for the joint model:

$$h_i(t) = h_0(t) \exp\left[\gamma^\top w_i + \sum_{k=1}^{K}\sum_{j=1}^{J} f_j\{\eta_{ik}(t), \alpha_{kj}\}\right]$$

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where ν and s^2 represent the df and the scale

Leads to a Student-t prior

Shrinkage Approach (cont'd)

Horseshoe (H):

- Bayesian variable selection for the joint model:

$$h_i(t) = h_0(t) \exp\left[\gamma^\top w_i + \sum_{k=1}^{K} \sum_{j=1}^{J} f_j\{\eta_{ik}(t), \alpha_{kj}\}\right]$$

$$\alpha_{kj} \mid \tau_{kj}^2 \sim N(0, \tau_{kj}^2)$$

$$\tau_{kj} \sim C^+(0, u)$$

$$u \sim C^+(0, 1),$$

where C^+ is the standard half Cauchy distribution

Shrinkage Approach (cont'd)

Horseshoe (H):

- Bayesian variable selection for the joint model:

$$h_i(t) = h_0(t) \exp\left[\gamma^\top w_i + \sum_{k=1}^{K}\sum_{j=1}^{J} f_j\{\eta_{ik}(t), \alpha_{kj}\}\right]$$

$$\alpha_{kj} \mid \tau_{kj}^2 \sim N(0, \tau_{kj}^2)$$

$$\tau_{kj} \sim C^+(0, u)$$

$$u \sim C^+(0, 1),$$

where C^+ is the standard half Cauchy distribution

Its tails allow strong signals to remain large (that is, un-shrunk) a posteriori
Its infinitely tall spike at the origin provides severe shrinkage for the 0 elements of α

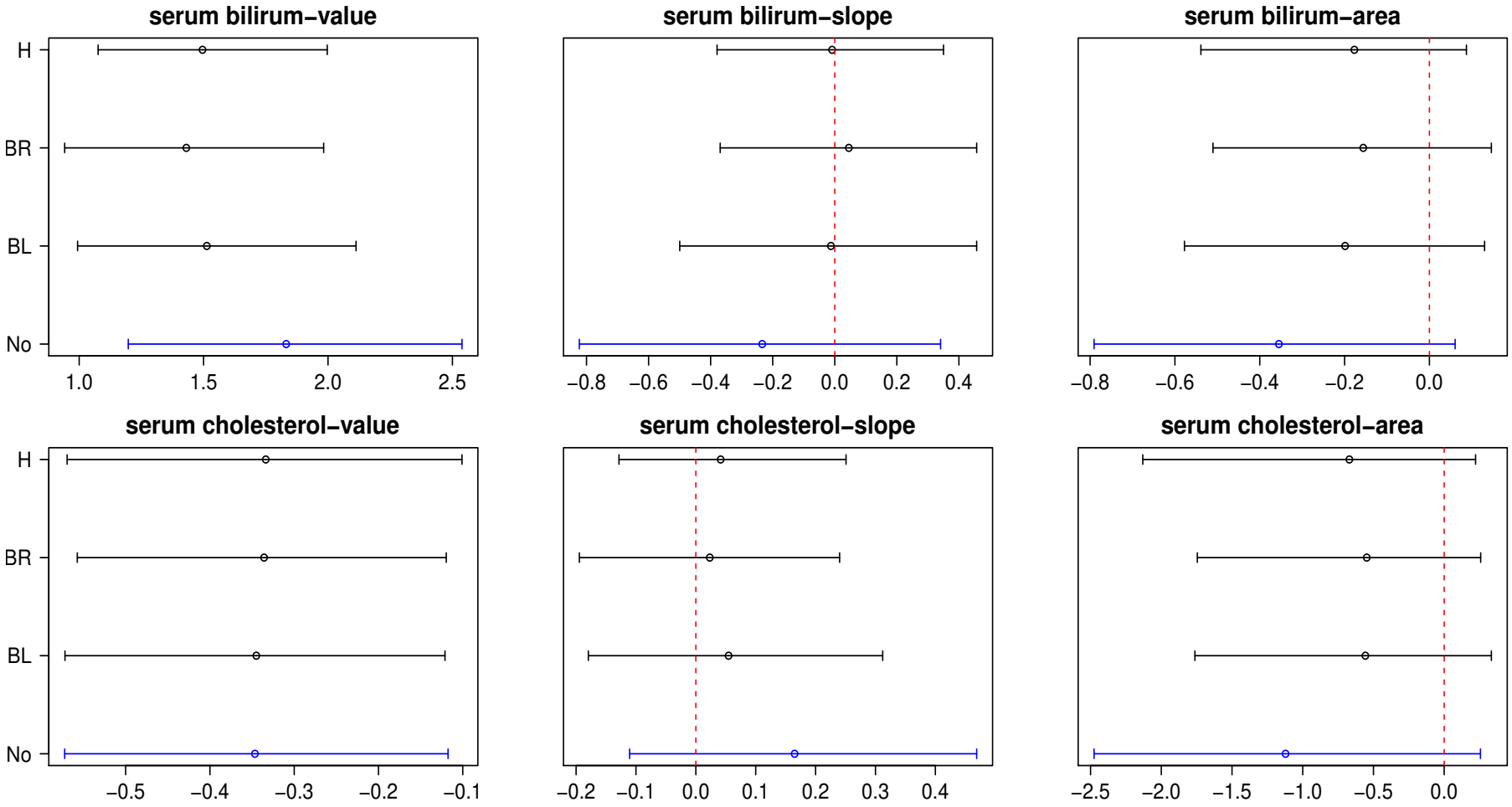
Shrinkage Approach (cont'd)

Analysis:

- **Longitudinal submodels** (Serum bilirubin and Serum cholesterol):
  - ▷ Fixed part: splines for time and gender
  - ▷ Random part: splines for time
- **Survival submodel** (Time-to-death):
  - ▷ underlying value, slope and the area under the curve for serum bilirubin and serum cholesterol
  - ▷ age and gender

Shrinkage Approach (cont'd)

Results:



Time-Varying Effects

Motivated by the heart data:

- Longitudinal response:
  - ▷ **aortic gradient**
- Time-to-event response:
  - ▷ time-to-**death/reoperation**

Andrinopoulou, E. R., Eilers, P. H., Takkenberg, J. J. and Rizopoulos, D. (2017). Improved dynamic predictions from joint models of longitudinal and survival data with time-varying effects using P-splines. Biometrics, doi: 10.1111/biom.12814.

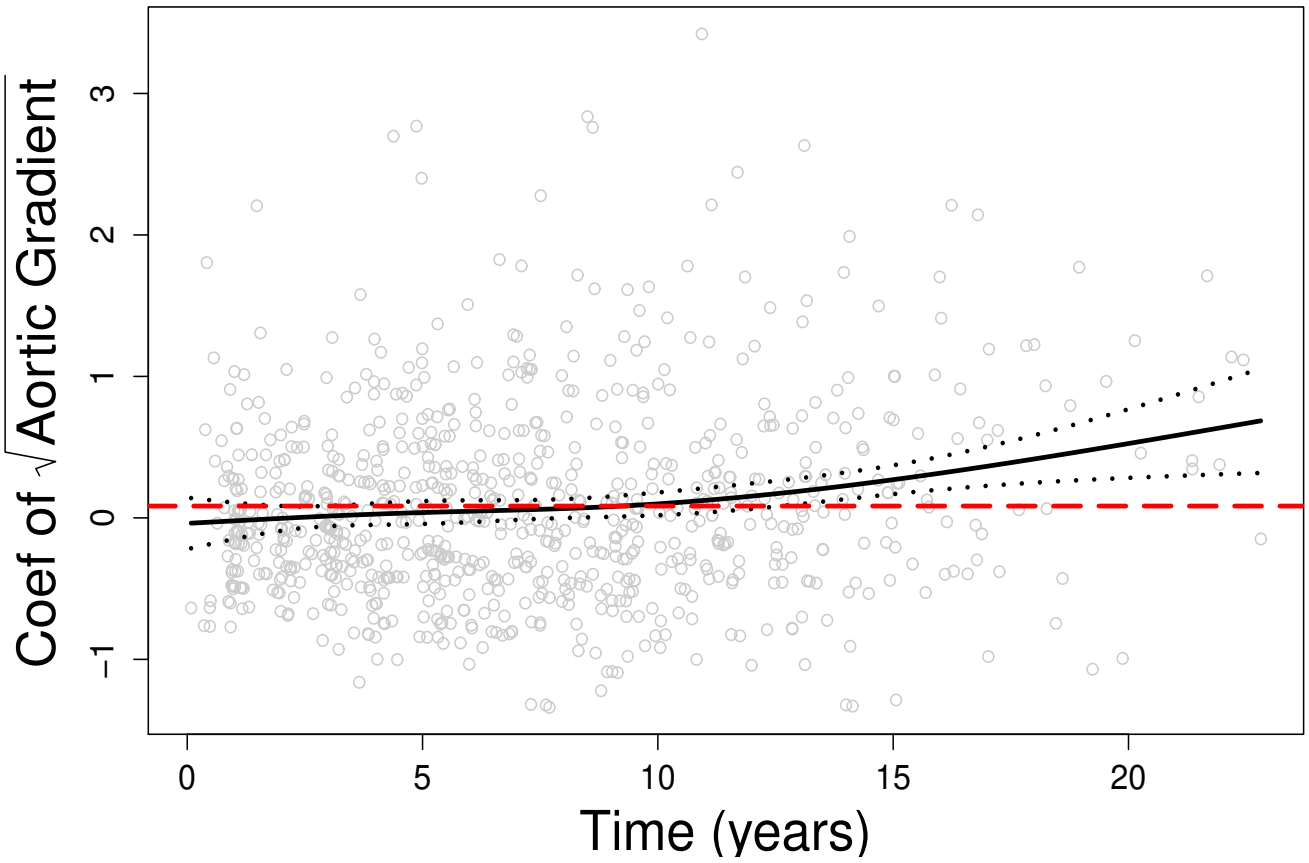
Time-Varying Effects (cont'd)

- Standard joint models assume a constant regression coefficient for the effect of the covariates.

  ▷ when treatment is initiated, the strength of the association between the longitudinal and survival outcomes may also change

Time-Varying Effects (cont'd)

Proportional hazard assumption - Time dependent Cox model



Time-Varying Effects (cont'd)

A time-varying coefficient joint model

Time-Varying Effects (cont'd)

Specifically,

$$h_i(t) \;=\; h_0(t)\exp[\gamma^\top w_i + f_j\{\eta_i(t), \lambda_j(t)\}],$$

where

- w_i is a vector of baseline covariates with a corresponding vector of regression coefficients γ
- $f_j\{\eta_i(t), \lambda_j(t_i)\}$ is the form of association (j = 1, . . . , J) between the longitudinal and the survival outcomes $\rightarrow$ **underlying value, slope or area under the curve**

Time-Varying Effects (cont'd)

- We consider estimation of the function $\lambda_j(t)$ using the regression P-spline method, where

$$\lambda_j(t) = \sum_{\ell=1}^{L} \alpha_{j\ell} B_\ell(t, \nu),$$

where

  - $\alpha_{j\ell}$ is a set of parameters that capture the strength of association between the longitudinal and survival outcomes

  - $B_\ell(t_i, \nu)$ denotes the q-th basis function of a B-spline with knots $\nu_1, \ldots, \nu_Q$

- The idea behind the P-spline method is to assume a high number of knots and penalize the coefficients to tackle the problem of the large number or parameters

Time-Varying Effects (cont'd)

- We employ a Bayesian approach and use Markov chain Monte Carlo (MCMC) methods to estimate the parameters of the proposed joint model

- The penalty from the frequentist penalized likelihood translates into a prior distribution
  In particular,

$$\begin{aligned} \alpha_j \mid \tau_\alpha &\sim N(0, M_\alpha \tau_\alpha^2), \\ \tau_\alpha^2 &\sim Inv - gamma(1, 0.005), \end{aligned}$$

  where M_α is the penalty matrix. Specifically, we assume a second-order penalty.

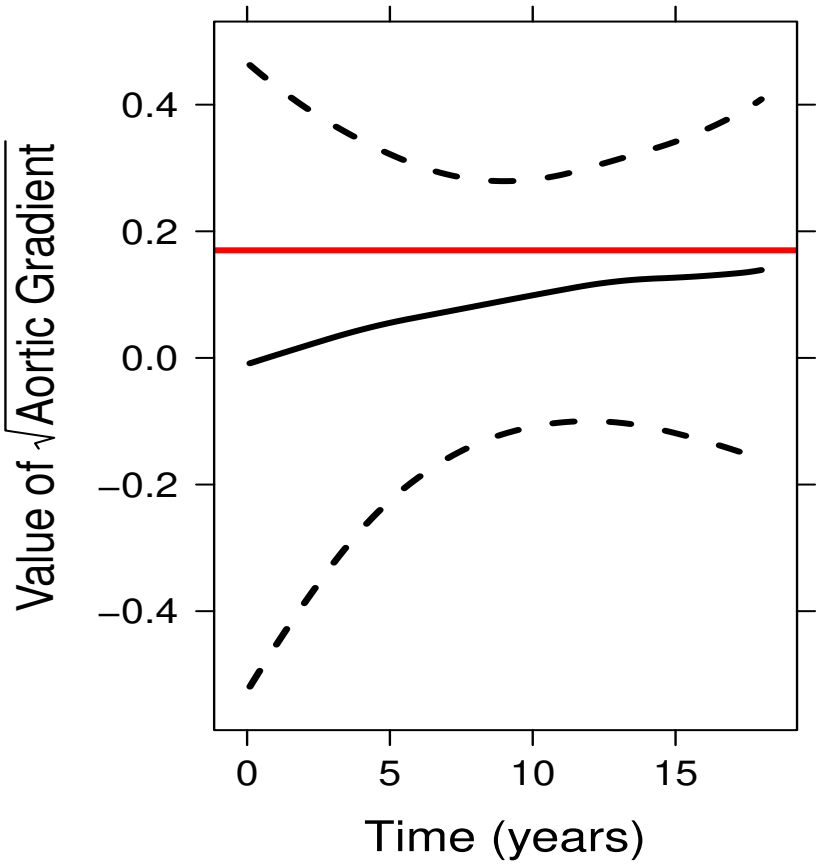
Time-Varying Effects (cont'd)

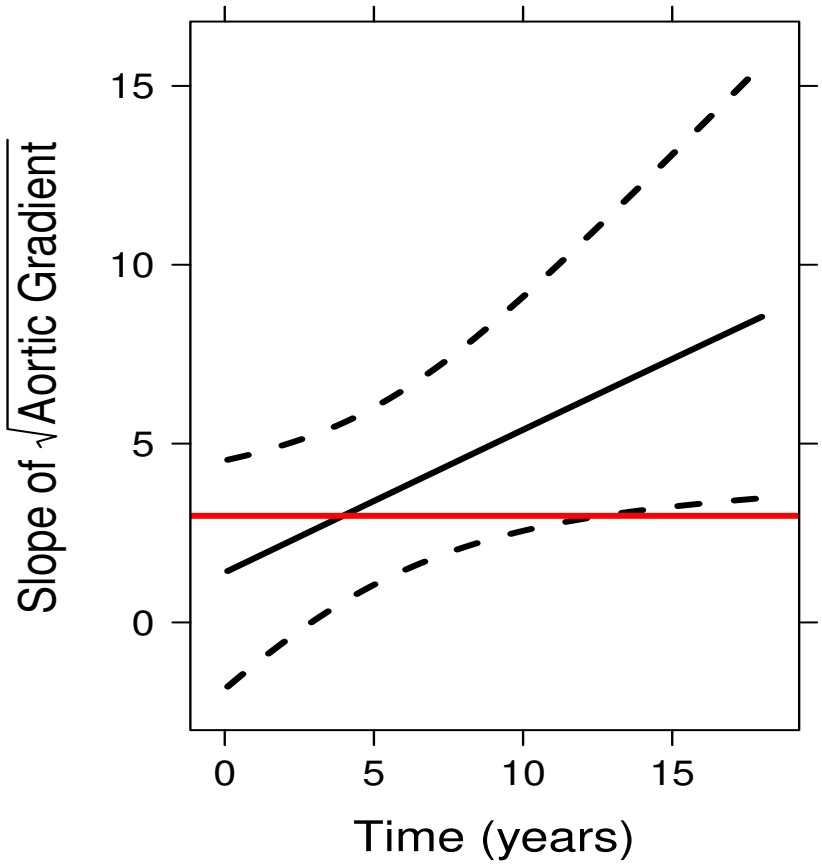
Analysis:

- **Longitudinal submodel** (Aortic gradient):
  - ▷ Fixed part: splines for time and gender
  - ▷ Random part: splines for time
- **Survival submodel** (Time-to-death/reoperation):
  - ▷ value and slope of aortic gradient
  - ▷ gender

Time-Varying Effects (cont'd)

Results:





Time-Varying Effects (cont'd)

A prognostic model is needed!

Measuring Predictive Performance

- Discrimination
  - ▷ how well can the longitudinal biomarker(s) discriminate between subject of low and high risk for the event
- Calibration
  - ▷ how well can the longitudinal biomarker(s) accurately predict future events

Time-Varying Effects (cont'd)

- We assume the following setting
  - ▷ using the available longitudinal data up to time t, $\tilde{y}_l(t) = \{y_l(s), 0 \leq s < t\}$
  - ▷ we are interested in events in the medically relevant interval $(t, t + \Delta t]$

- Based on the fitted joint model and for a particular threshold value $c = [0; 1]$, we can term a subject as a case if

$$\pi_l(t + \Delta t \mid t) \leq c$$

Time-Varying Effects (cont'd)

- Following, we can define

  ▷ sensitivity:

$$Pr\{\pi_l(t + \Delta t \mid t) \leq c \mid T_l^* \in (t, t + \Delta t]\},$$

  ▷ specificity:

$$Pr\{\pi_l(t + \Delta t \mid t) > c \mid T_l^* > t + \Delta t\},$$

where T_l^* denotes the observed failure time for the l-th patient

Time-Varying Effects (cont'd)

- **Discrimination**: For a randomly chosen pair of subjects (l_1, l_2) the discriminative capability of the assumed model can be assessed by the area under the receiver operating characteristic curve (AUC)

$$AUC(t + \Delta t \mid t) = Pr[\pi_{l_1}(t + \Delta t \mid t) < \pi_{l_2}(t + \Delta t \mid t) \mid \{T^*_{l_1} \in (t, t + \Delta t]\} \cap \{T^*_{l_2} > t + \Delta t\}]$$

Time-Varying Effects (cont'd)

- Estimation of $\mathsf{AUC}(t + \Delta t \mid t)$:

$$\widehat{\mathsf{AUC}}(t + \Delta t \mid t) = \sum_{w=1}^{4} \widehat{\mathsf{AUC}}_w(t + \Delta t \mid t),$$

Time-Varying Effects (cont'd)

- $AUC_1(t, \Delta t)$ refers to the pairs of subjects who can be compared,

$$\Omega^{(1)}_{l_1 l_2}(t) = [\{T_{l_1} \in (t, t + \Delta t]\} \cap \{\delta_{l_1} = 1\}] \cap \{T_{l_2} > t + \Delta t\},$$

where $\delta_l = 0, 1$ denotes the event indicator for the l-th patient

Time-Varying Effects (cont'd)

- $AUC_1(t, \Delta t)$ refers to the pairs of subjects who can be compared,

$$\Omega^{(1)}_{l_1 l_2}(t) = [\{T_{l_1} \in (t, t + \Delta t]\} \cap \{\delta_{l_1} = 1\}] \cap \{T_{l_2} > t + \Delta t\},$$

where $\delta = 0, 1$ denotes the event indicator

$$\widehat{\mathsf{AUC}}_1(t + \Delta t \mid t) = \frac{\sum_{l_1=1}^{n} \sum_{l_2=1; l_2 \neq l_1}^{n} I\{\hat{\pi}_{l_1}(t, \Delta t) < \hat{\pi}_{l_2}(t, \Delta t)\} \times I\{\Omega^{(w)}_{l_1 l_2}(t)\}}{\sum_{l_1=1}^{n} \sum_{l_2=1; l_2 \neq l_1}^{n} I\{\Omega^{(w)}_{l_1 l_2}(t)\}}$$

Time-Varying Effects (cont'd)

- $AUC_w(t, \Delta t)$, where $w = 2, \ldots, 4$, refer to the pairs of subjects who due to censoring cannot be compared,

$$\Omega^{(2)}_{l_1 l_2}(t) = [\{T_{l_1} \in (t, t + \Delta t]\} \cap \{\delta_{l_1} = 0\}] \cap \{T_{l_2} > t + \Delta t\},$$
$$\Omega^{(3)}_{l_1 l_2}(t) = [\{T_{l_1} \in (t, t + \Delta t]\} \cap \{\delta_{l_1} = 1\}] \cap [\{T_{l_1} < T_{l_2} \leq t + \Delta t\} \cap \{\delta_{l_2} = 0\}],$$
$$\Omega^{(4)}_{l_1 l_2}(t) = [\{T_{l_1} \in (t, t + \Delta t]\} \cap \{\delta_{l_1} = 0\}] \cap [\{T_{l_1} < T_{l_2} \leq t + \Delta t\} \cap \{\delta_{l_2} = 0\}]$$

Time-Varying Effects (cont'd)

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$$\Omega^{(4)}_{l_1 l_2}(t) = [\{T_{l_1} \in (t, t + \Delta t]\} \cap \{\delta_{l_1} = 0\}] \cap [\{T_{l_1} < T_{l_2} \leq t + \Delta t\} \cap \{\delta_{l_2} = 0\}]$$

where

$$\widehat{\mathsf{AUC}}_w(t + \Delta t \mid t) = \frac{\sum_{l_1=1}^{n} \sum_{l_2=1; l_2 \neq l_1}^{n} I\{\hat{\pi}_{l_1}(t, \Delta t) < \hat{\pi}_{l_2}(t, \Delta t)\} \times I\{\Omega^{(w)}_{l_1 l_2}(t)\} \times \hat{K}_w}{\sum_{l_1=1}^{n} \sum_{l_2=1; l_2 \neq l_1}^{n} I\{\Omega^{(w)}_{l_1 l_2}(t)\} \times \hat{K}_w}$$

and $\hat{K}_w$ are weights

Time-Varying Effects (cont'd)

- **Calibration**: The expected error of prediction has the form

$$PE(t + \Delta t \mid t) = E[L\{N_i(t + \Delta t) - \pi(t + \Delta t \mid t)\}]$$

where

  - ▷ $N_i(t) = I(T_i^* > t)$ is the event status at time t
  - ▷ $L(.)$ denotes a loss function, such as the absolute or square loss

Time-Varying Effects (cont'd)

- An estimator for $PE(u \mid t)$ that accounts for censoring:

$$\hat{PE}(t+\Delta t \mid t) = \{\mathcal{R}(t)\}^{-1} \sum_{i:T_i \geq t} I(T_i > t+\Delta t) L\{1 - \hat{\pi}(t+\Delta t \mid t)\} +$$
$$\delta_i I(T_i < t+\Delta t) L\{0 - \hat{\pi}(t+\Delta t \mid t)\} +$$
$$+(1-\delta_i) I(T_i < t+\Delta t) \Big[\hat{\pi}(t+\Delta t \mid T_i) L\{1 - \hat{\pi}(t+\Delta t \mid t)\} +$$
$$\{1 - \hat{\pi}(t+\Delta t \mid T_i)\} L\{0 - \hat{\pi}(t+\Delta t \mid t)\}\Big]$$

  where

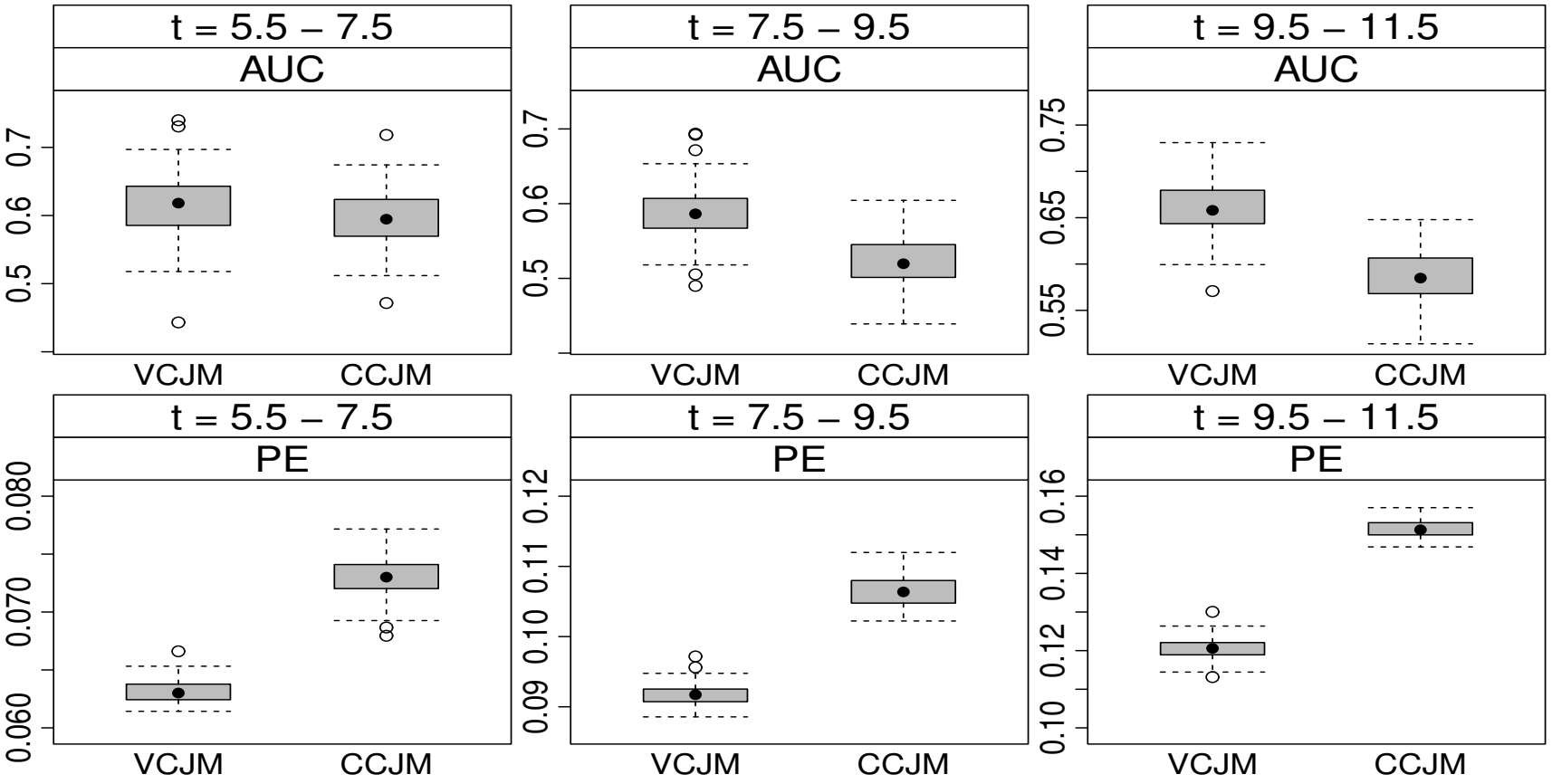
  - ▷ $\mathcal{R}(t)$ denotes the number of subjects at risk at t
  - ▷ red part: subjects still alive at $t+\Delta t$
  - ▷ blue part: subjects who died before $t+\Delta t$
  - ▷ purple part: subject censored before $t+\Delta t$

Time-Varying Effects (cont'd)

- We compared the VCJM with the CCJM based on the AUC$(t + \Delta t \mid t)$ and $PE(t + \Delta t \mid t)$
  - ▷ Internal validation procedure
  - ▷ 5-fold cross-validation
  - ▷ Prediction window: $t = 5.5, 7.5, 9.5$ and $\Delta t = 2$
  - ▷ 100 times

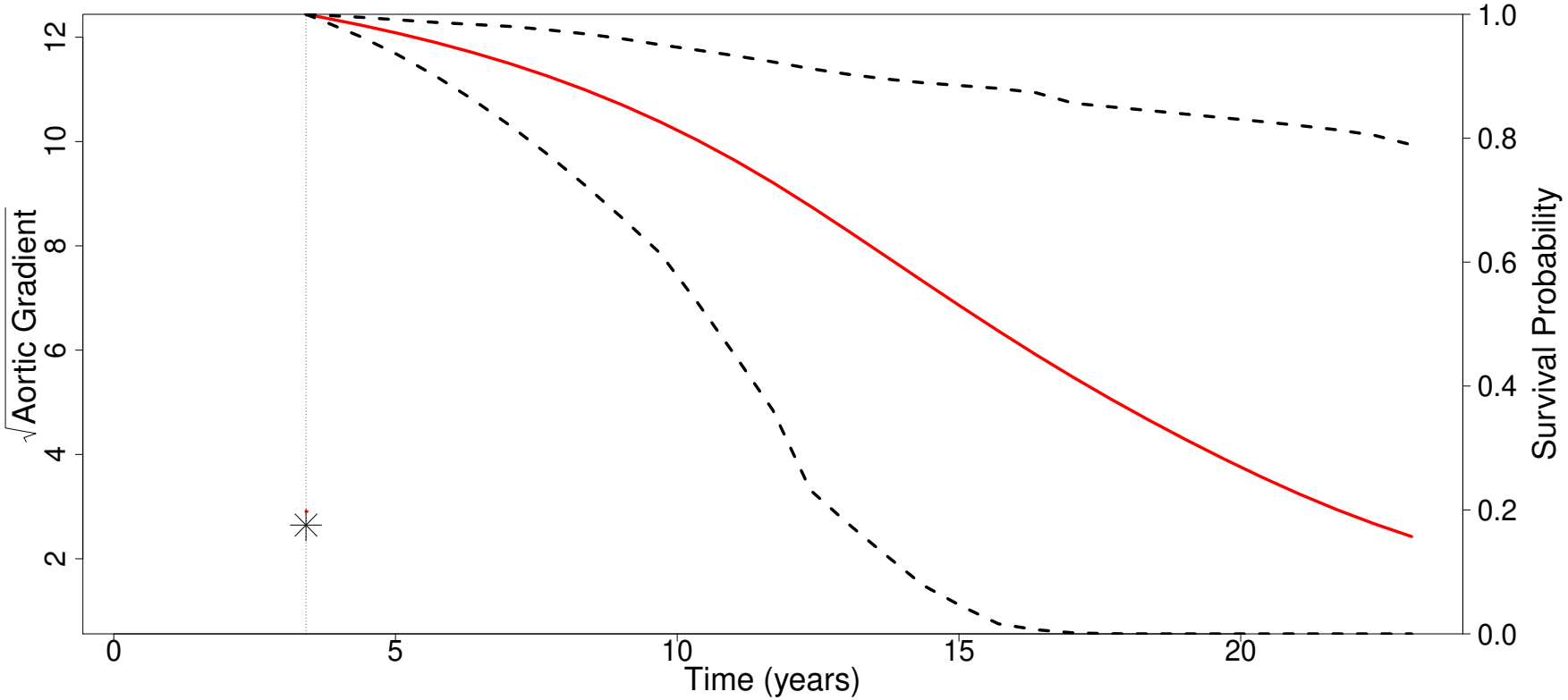
Time-Varying Effects (cont'd)

Results:



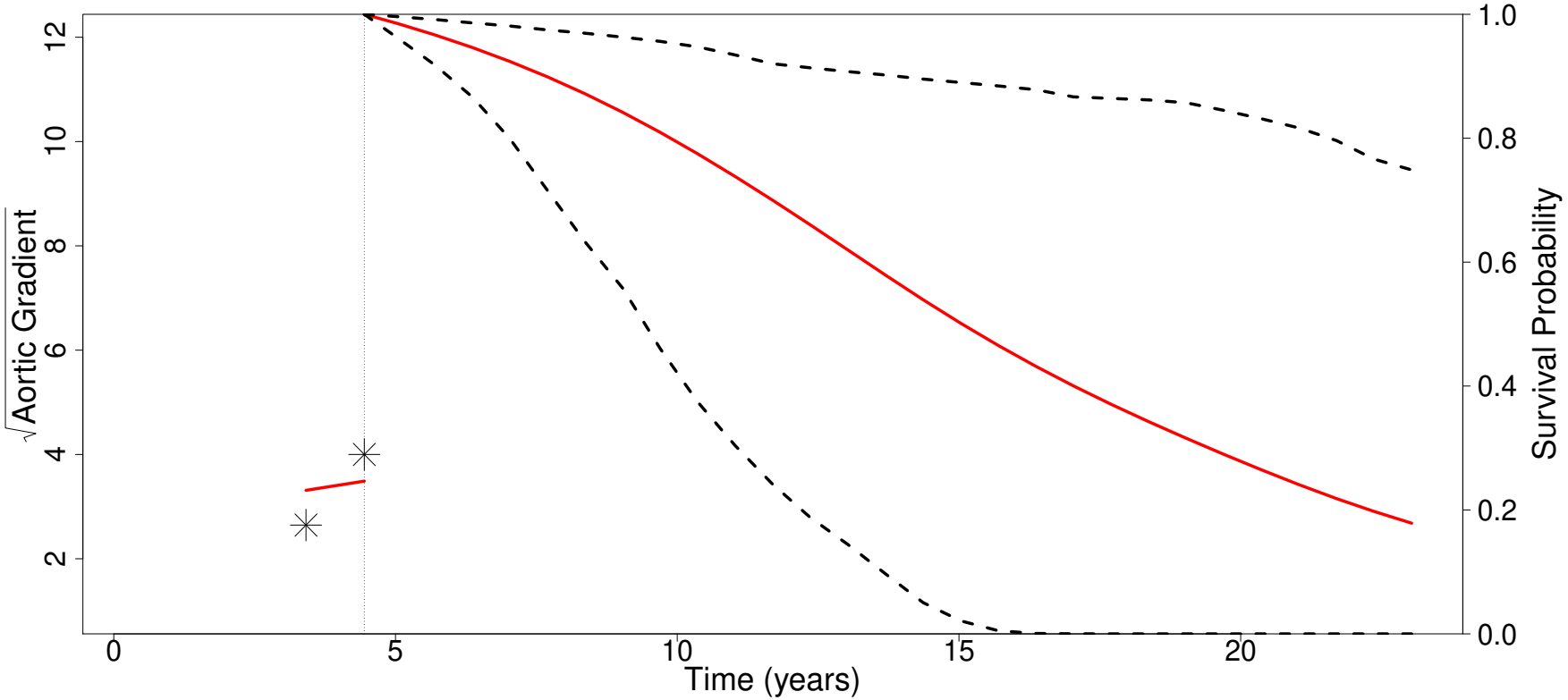
Time-Varying Effects (cont'd)

Dynamic predictions - **Patient 1**:



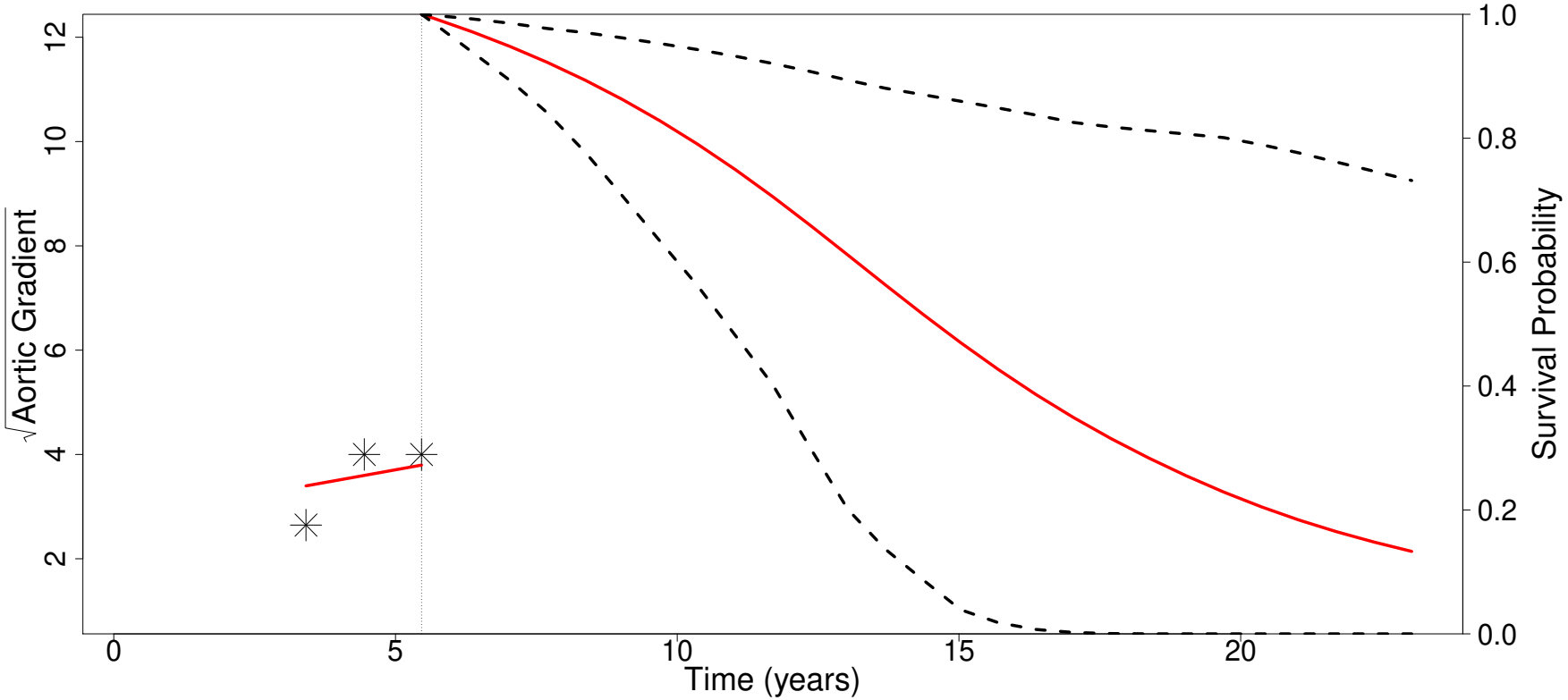
Time-Varying Effects (cont'd)

Dynamic predictions - Patient 1:



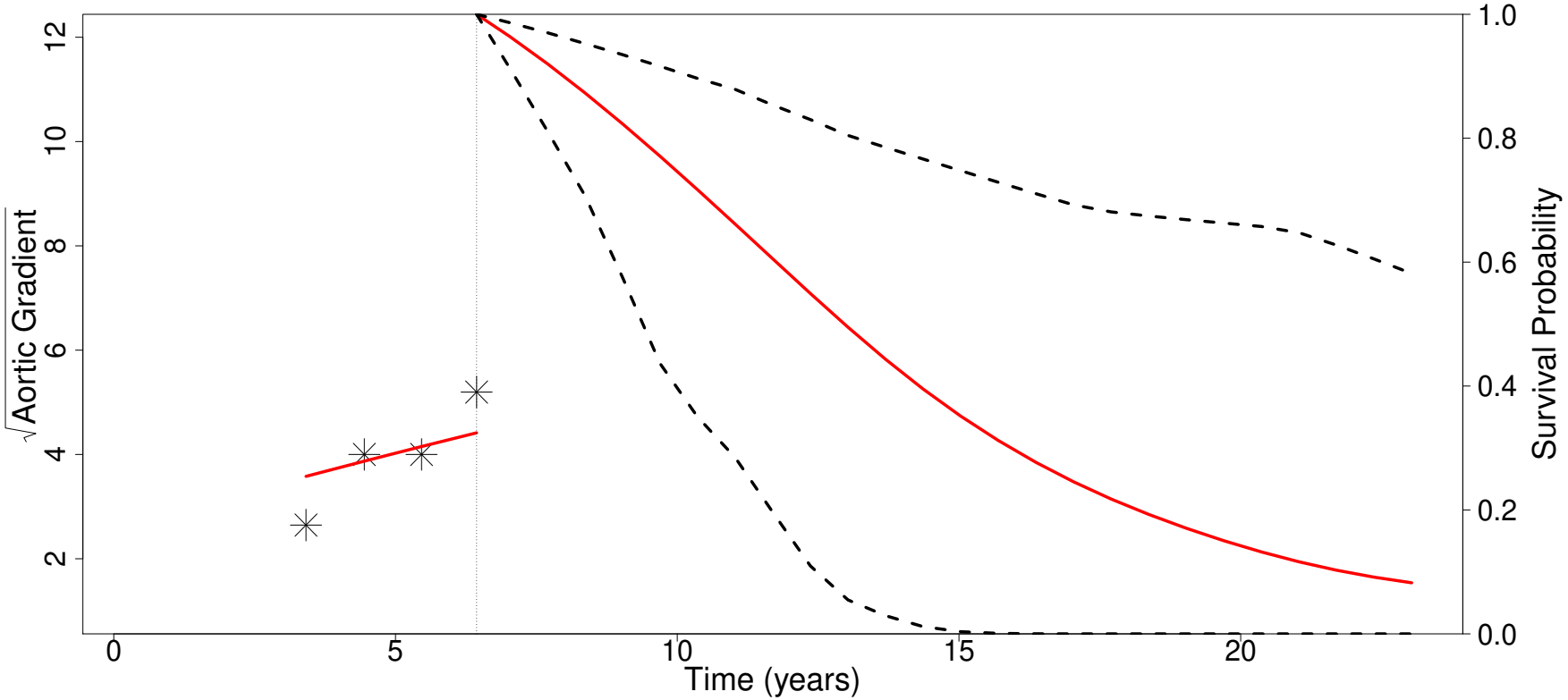
Time-Varying Effects (cont'd)

Dynamic predictions - **Patient 1**:



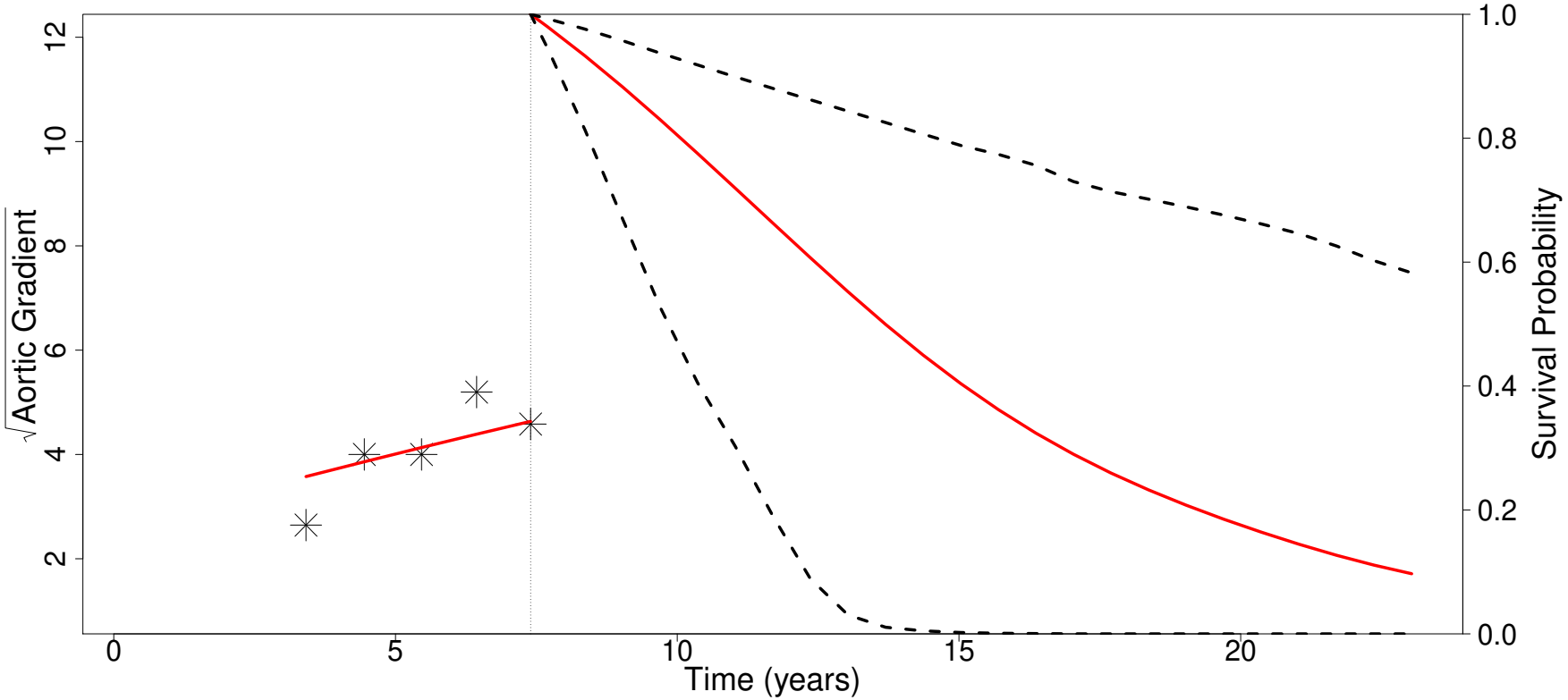
Time-Varying Effects (cont'd)

Dynamic predictions - **Patient 1**:



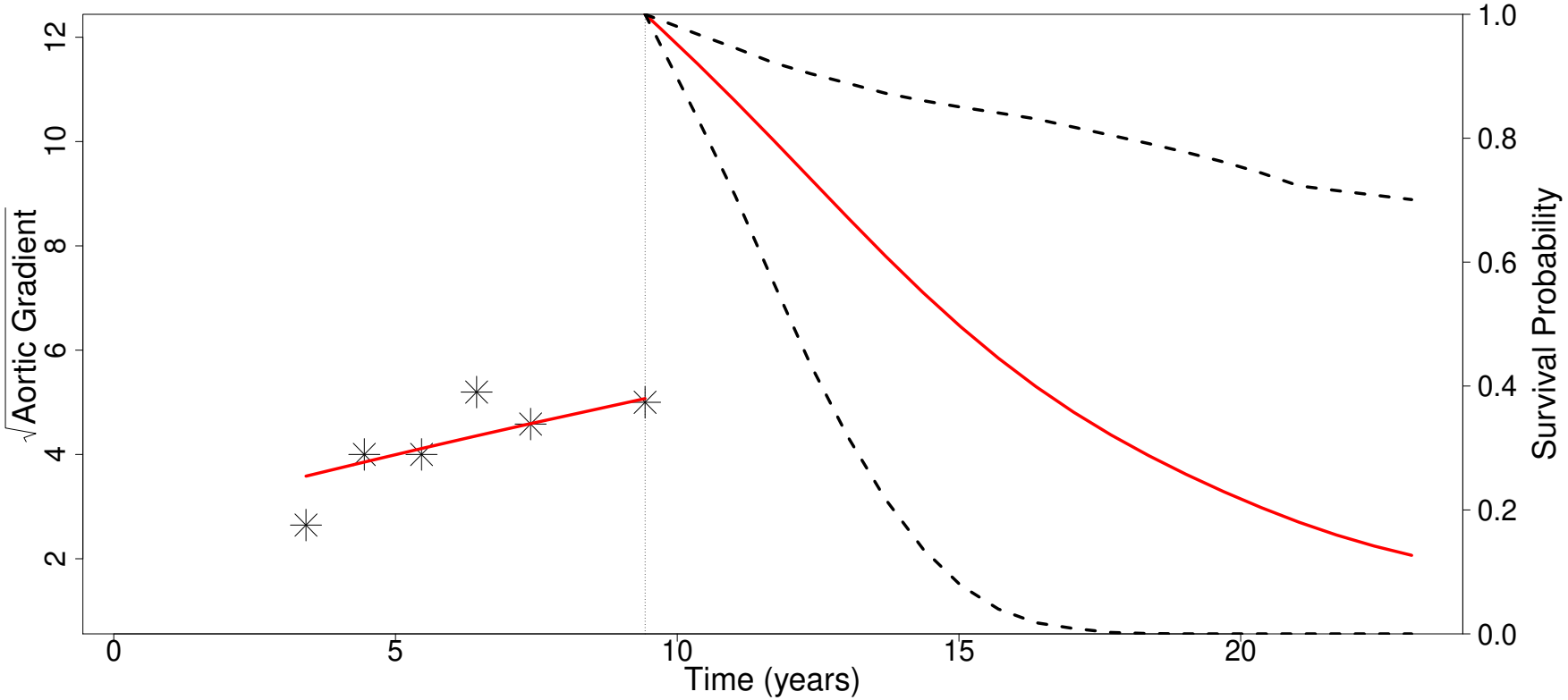
Time-Varying Effects (cont'd)

Dynamic predictions - Patient 1:



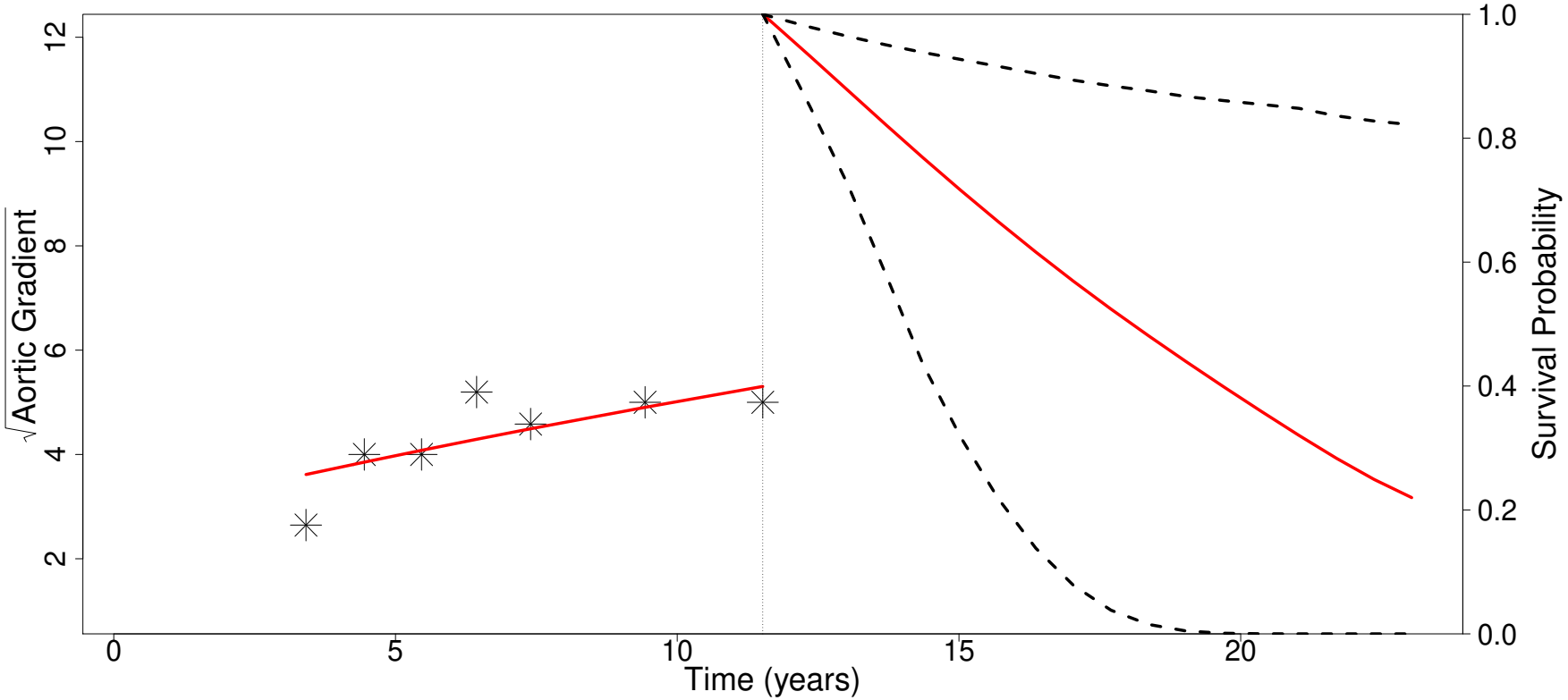
Time-Varying Effects (cont'd)

Dynamic predictions - **Patient 1**:



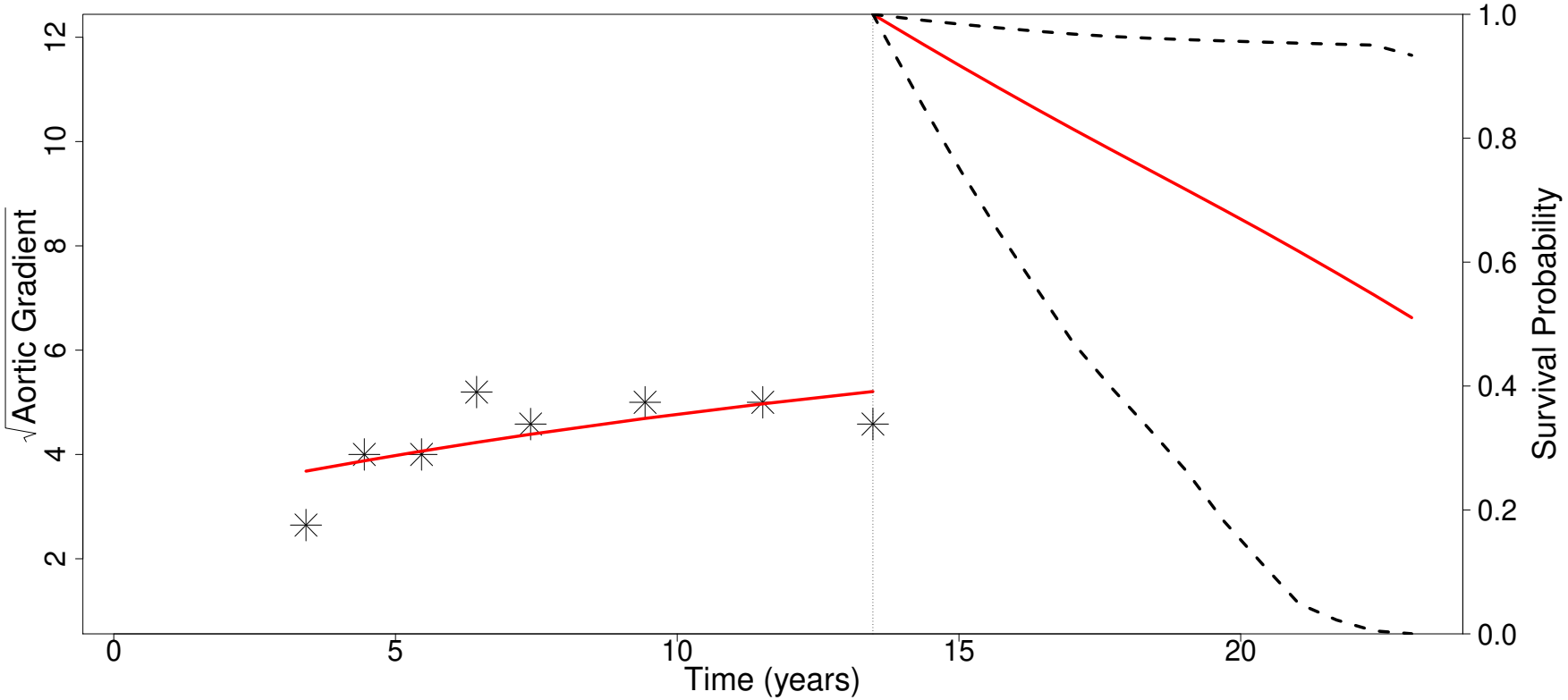
Time-Varying Effects (cont'd)

Dynamic predictions - Patient 1:



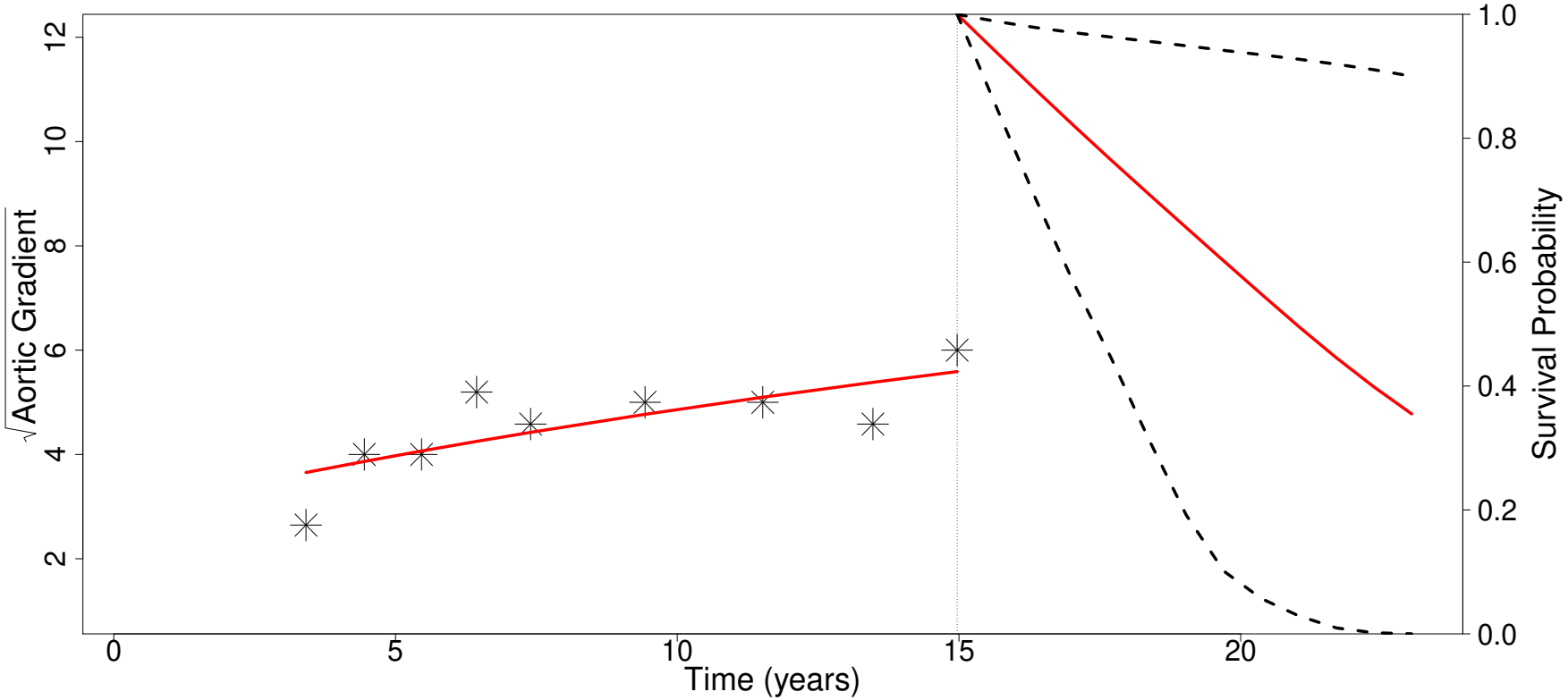
Time-Varying Effects (cont'd)

Dynamic predictions - **Patient 1**:



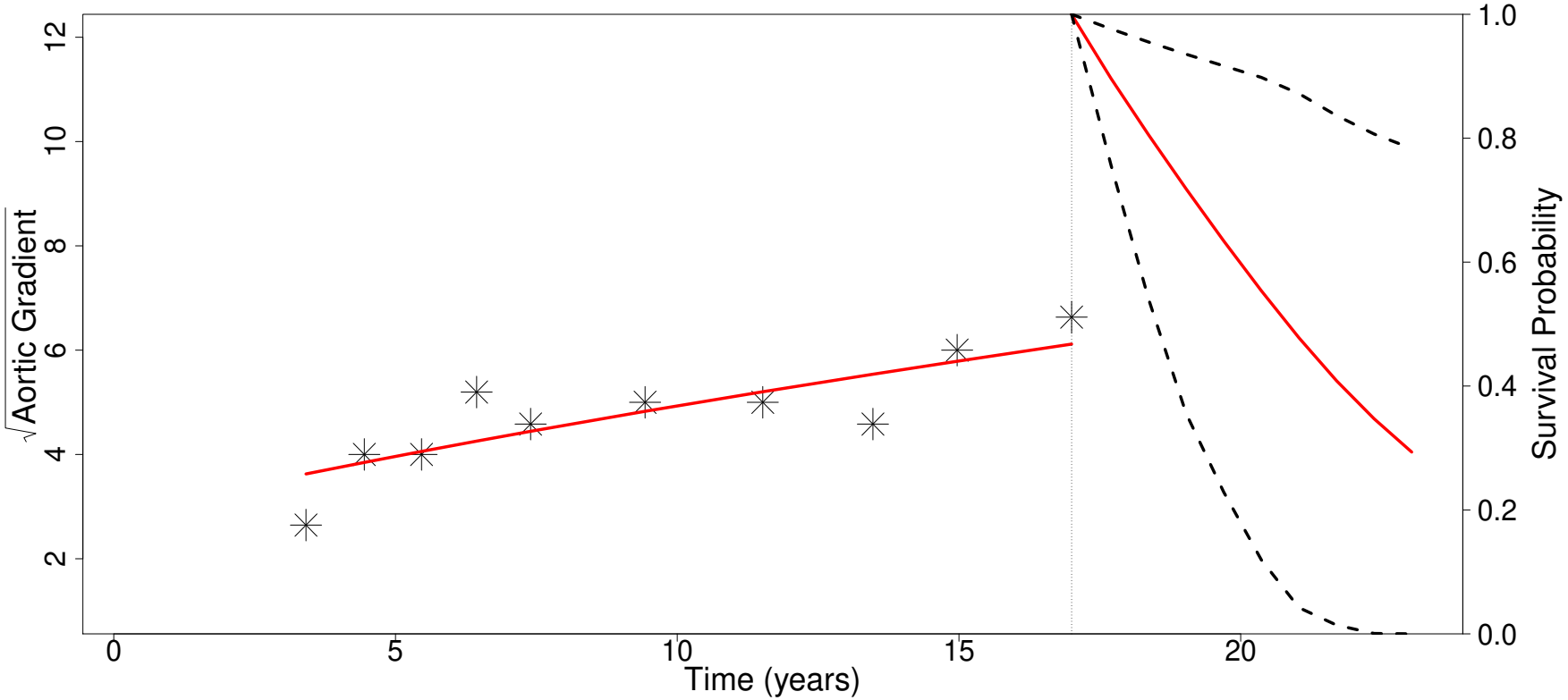
Time-Varying Effects (cont'd)

Dynamic predictions - **Patient 1**:



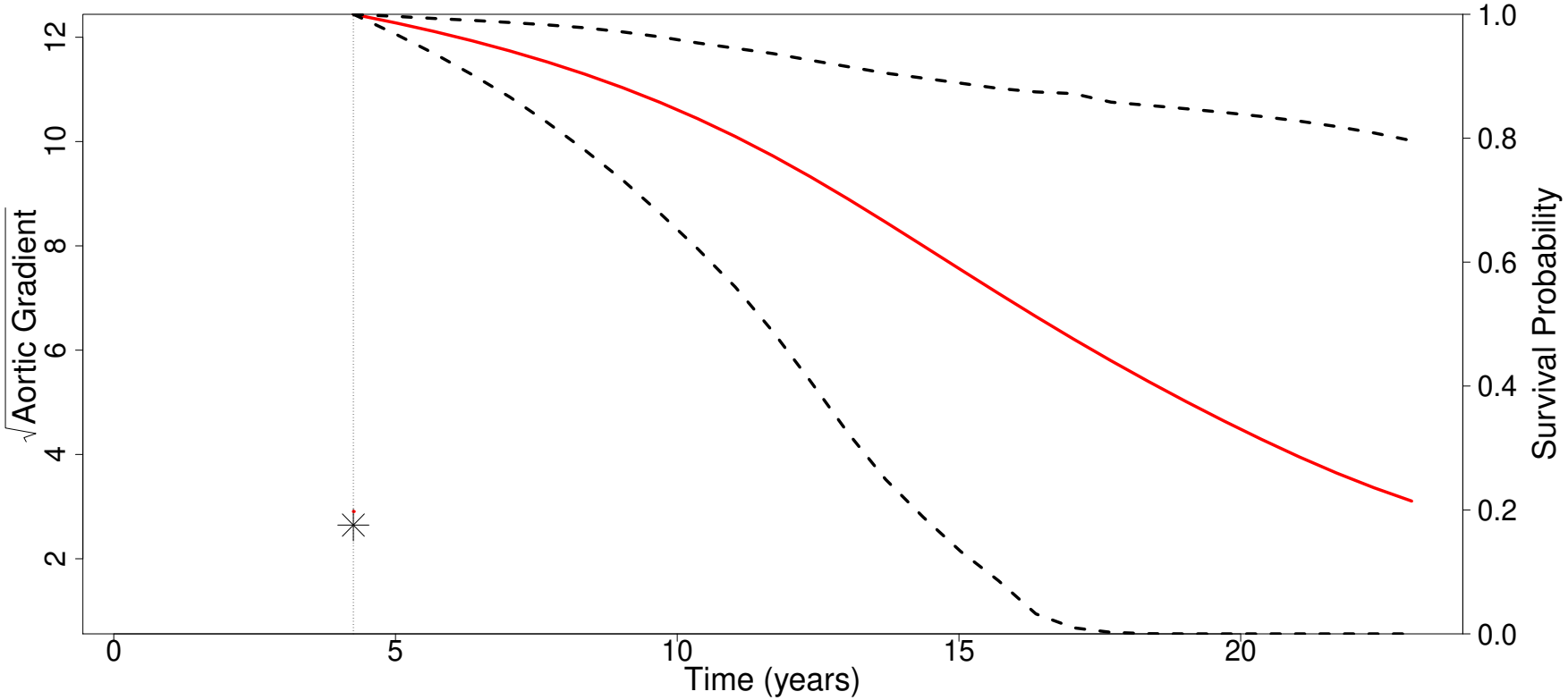
Time-Varying Effects (cont'd)

Dynamic predictions - **Patient 1**:



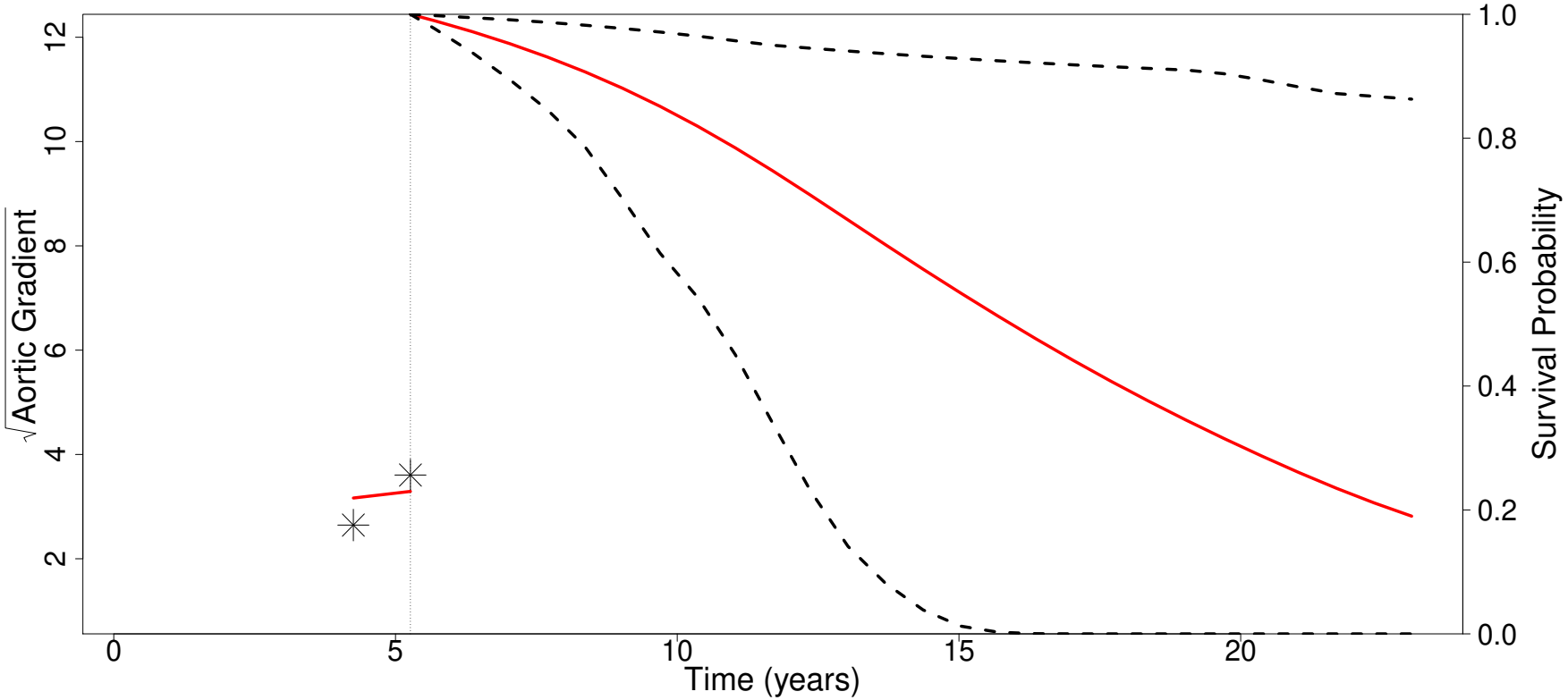
Time-Varying Effects (cont'd)

Dynamic predictions - Patient 2:



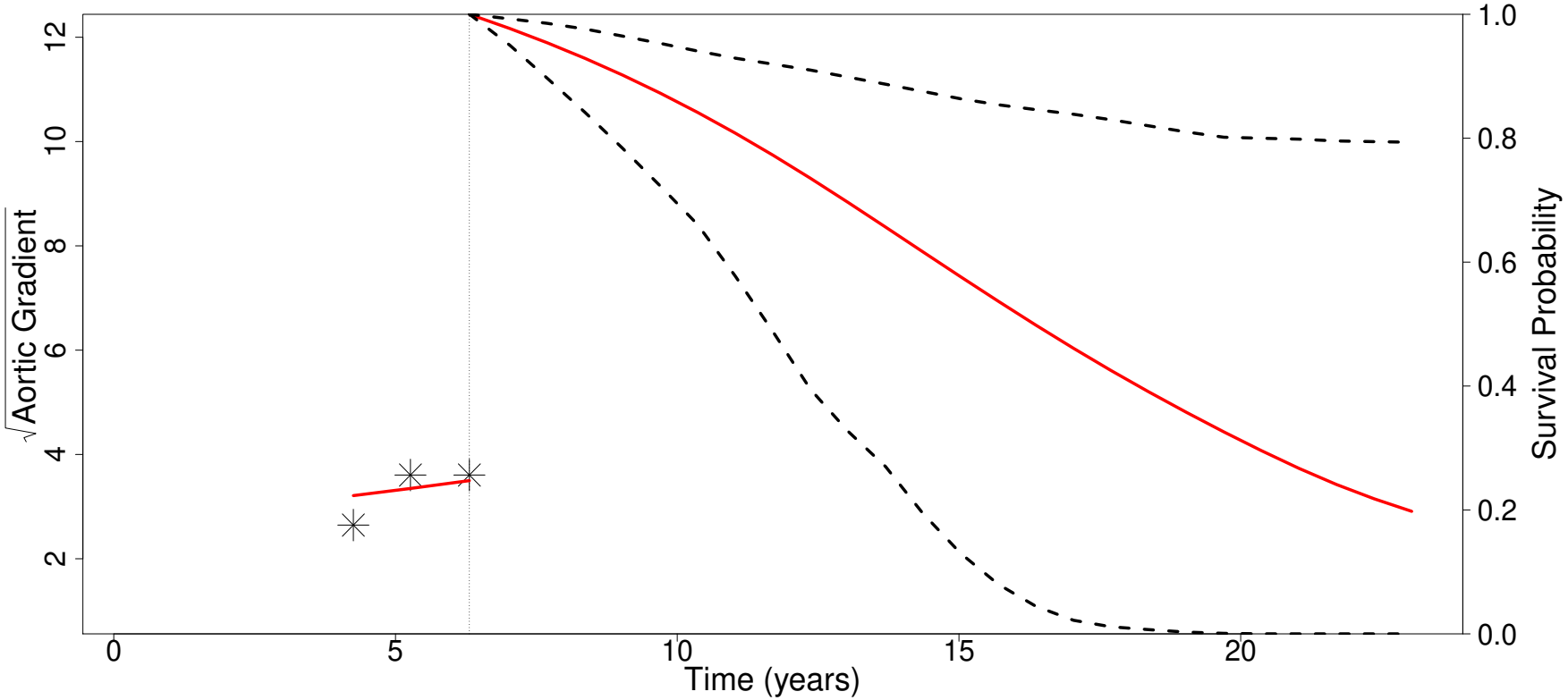
Time-Varying Effects (cont'd)

Dynamic predictions - Patient 2:



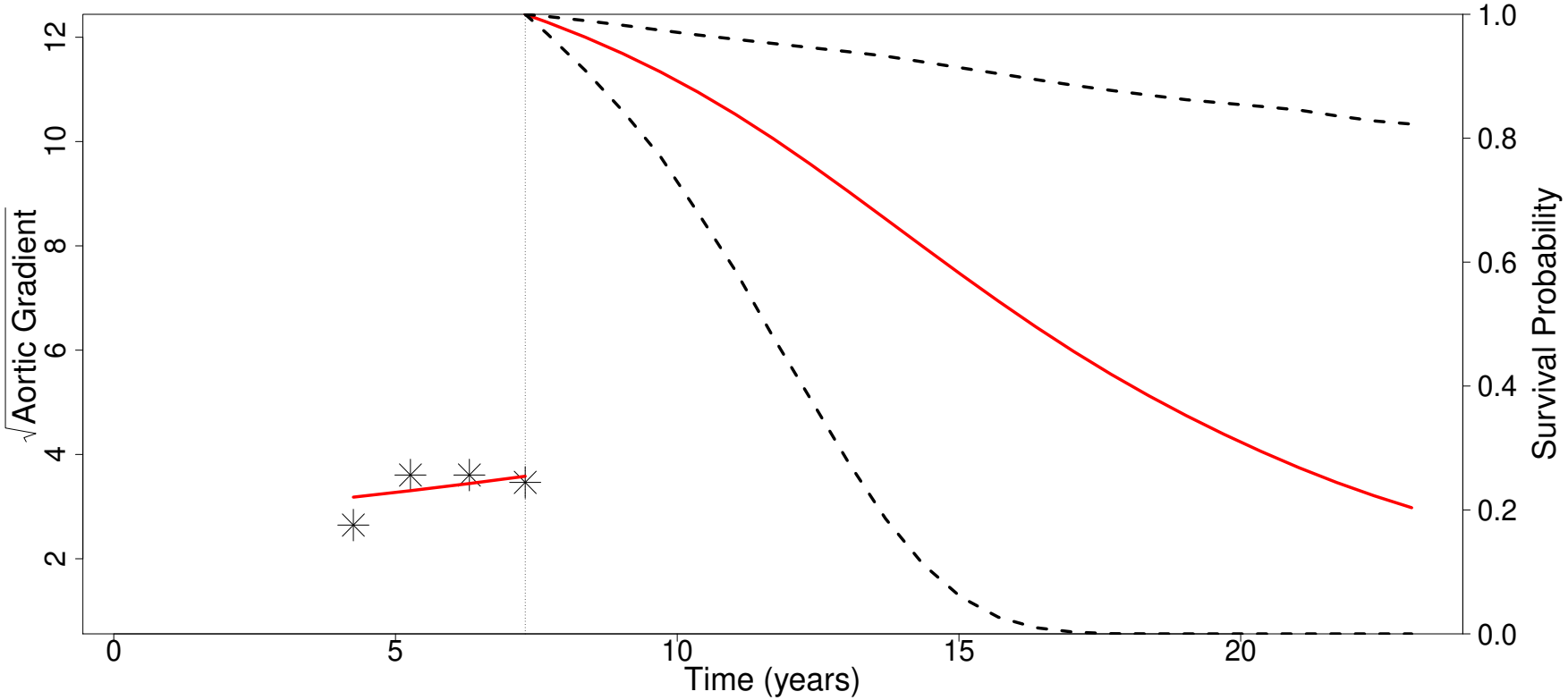
Time-Varying Effects (cont'd)

Dynamic predictions - Patient 2:



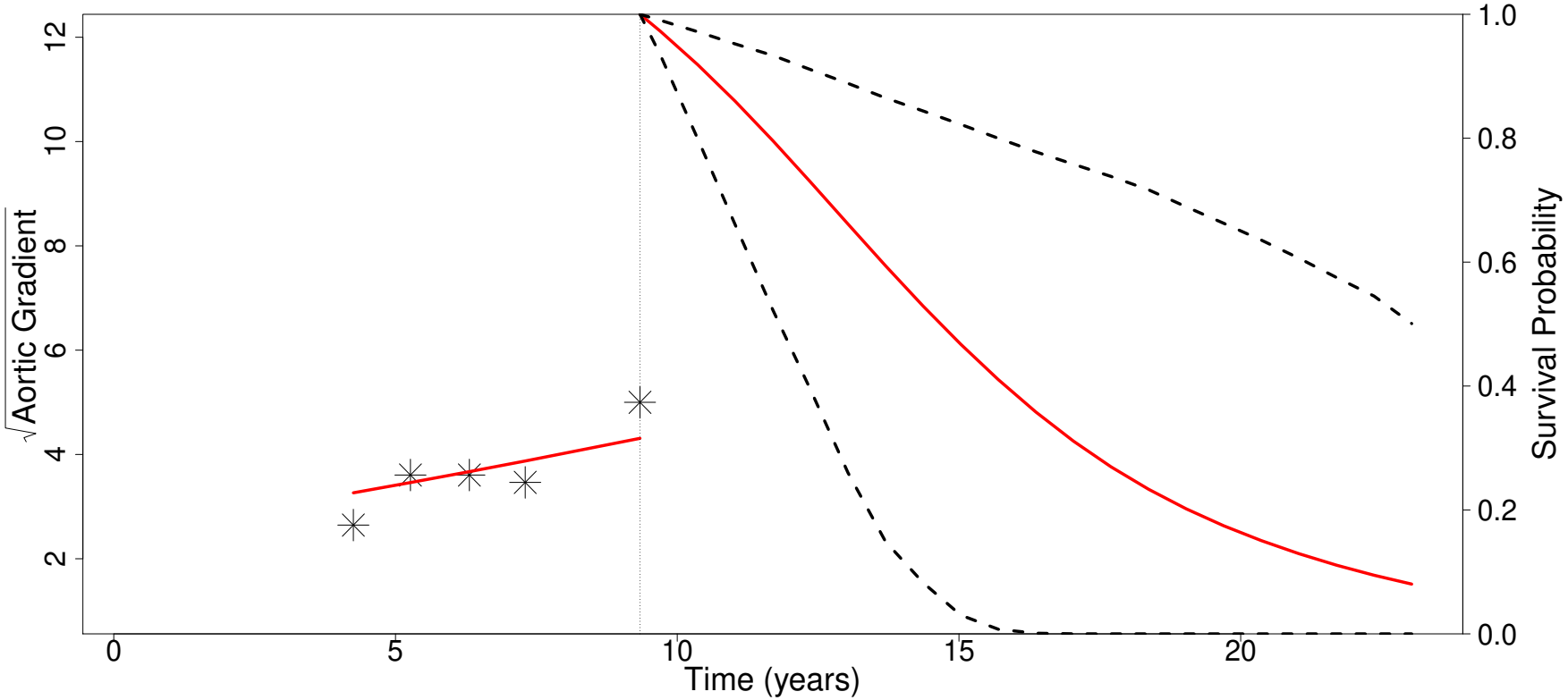
Time-Varying Effects (cont'd)

Dynamic predictions - Patient 2:



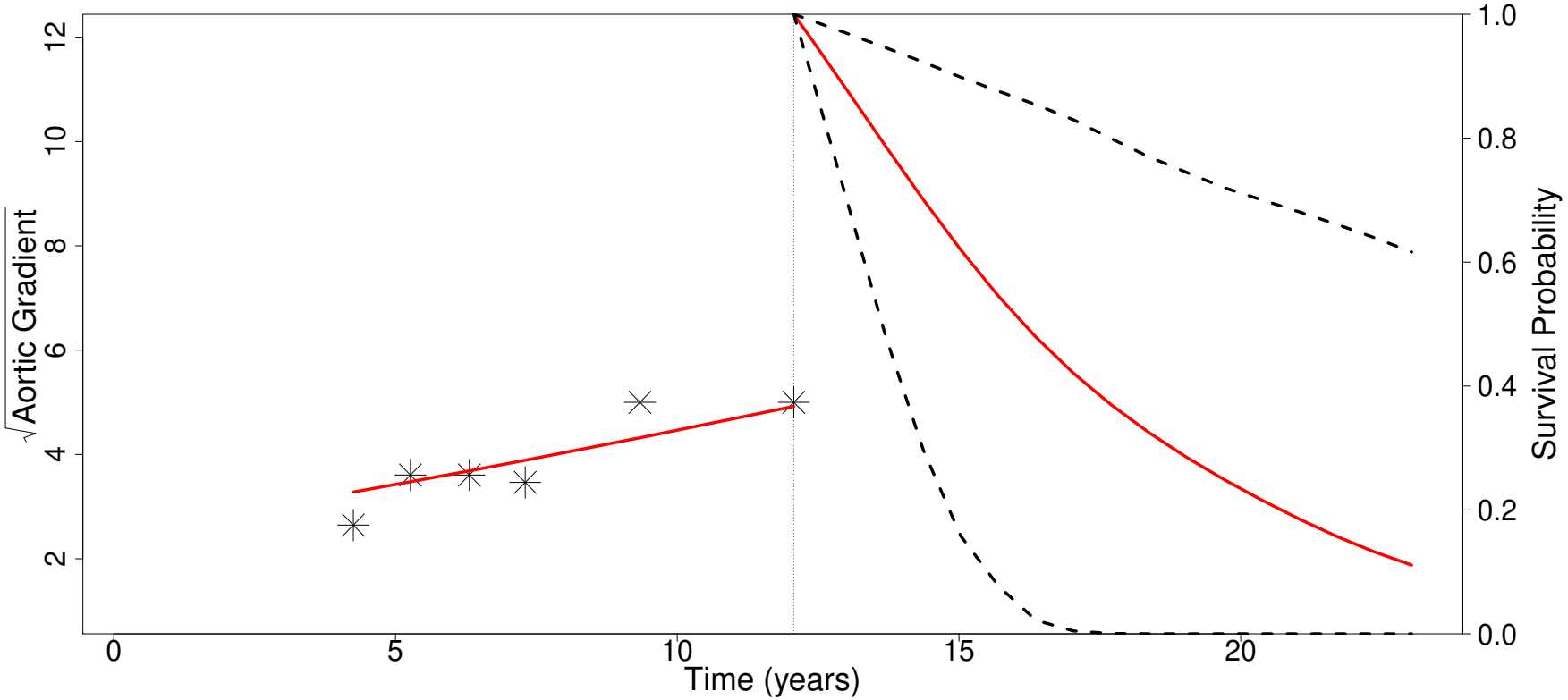
Time-Varying Effects (cont'd)

Dynamic predictions - Patient 2:



Time-Varying Effects (cont'd)

Dynamic predictions - **Patient 2**:



Discussion

- Joint models - popular framework
- Software
  - ▷ `JM, JMbayes`: **R**
  - ▷ `joineR, joineRML`: **R**
  - ▷ `stjm`: **Stata**
  - ▷ `JMFit`: **SAS**

Thank you!

Any questions?