Joint Models for Longitudinal and Survival Data & Dynamic Predictions

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Dynamic predictions for repeated markers and repeated events

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1.1 Introduction

- Over the last 10-15 years increasing interest in joint modeling of longitudinal and time-to-event data (Tsiatis & Davidian, Stat. Sinica, 2004; Yu et al., Stat. Sinica, 2004)

- The majority of the biostatistics literature in this area has focused on:
  - ▷ several extensions of the standard joint model, new estimation approaches, ...

- Recently joint models have been utilized to provide **individualized predictions**
  - ▷ Rizopoulos (Biometrics, 2011); Proust-Lima and Taylor (Biostatistics, 2009); Yu et al. (JASA, 2008)

1.1 Introduction (cont'd)

- **Goals of this talk**:
  - ▷ Introduce joint models
  - ▷ Dynamic individualized predictions of survival probabilities;
  - ▷ Study the importance of the association structure;
  - ▷ Combine predictions from different joint models

1.2 Illustrative Case Study

- Aortic Valve study: Patients who received a human tissue valve in the aortic position
  - ▷ data collected by Erasmus MC (from 1987 to 2008);
    77 received sub-coronary implantation; 209 received root replacement

- Outcomes of interest:
  - ▷ death and re-operation $\longrightarrow$ composite event
  - ▷ aortic gradient

- Research Question:
  - ▷ Can we utilize available aortic gradient measurements to predict survival/re-operation

2.1 Joint Modeling Framework

- To answer our questions of interest we need to postulate a model that relates
  - ▷ the aortic gradient with
  - ▷ the time to death or re-operation

- Problem: Aortic gradient measurement process is an **endogenous** time-dependent covariate (Kalbfleisch and Prentice, 2002, Section 6.3)
  - ▷ Endogenous (aka internal): the future path of the covariate up to any time $t > s$ IS affected by the occurrence of an event at time point s, i.e.,

$$\Pr\{\mathcal{Y}_i(t) \mid \mathcal{Y}_i(s), T_i^* \geq s\} \neq \Pr\{\mathcal{Y}_i(t) \mid \mathcal{Y}_i(s), T_i^* = s\},$$

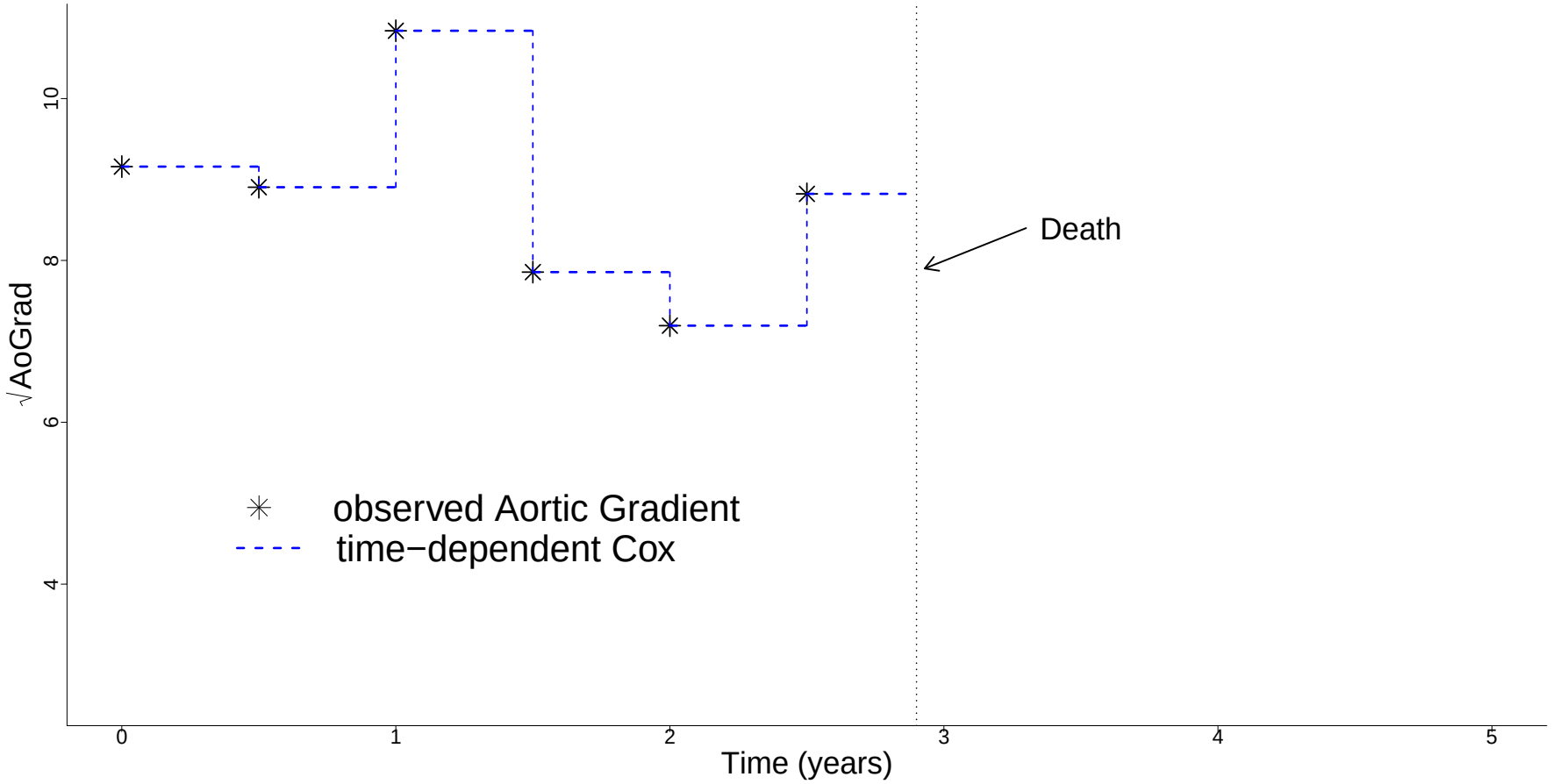
where $0 < s \leq t$ and $\mathcal{Y}_i(t) = \{y_i(s), 0 \leq s < t\}$

2.1 Joint Modeling Framework (cont'd)

- What is special about endogenous time-dependent covariates
  - ▷ measured with error
  - ▷ the complete history is not available
  - ▷ existence directly related to failure status

- What if we use the Cox model?
  - ▷ the association size can be severely underestimated
  - ▷ true potential of the marker will be masked

2.1 Joint Modeling Framework (cont'd)



2.1 Joint Modeling Framework (cont'd)

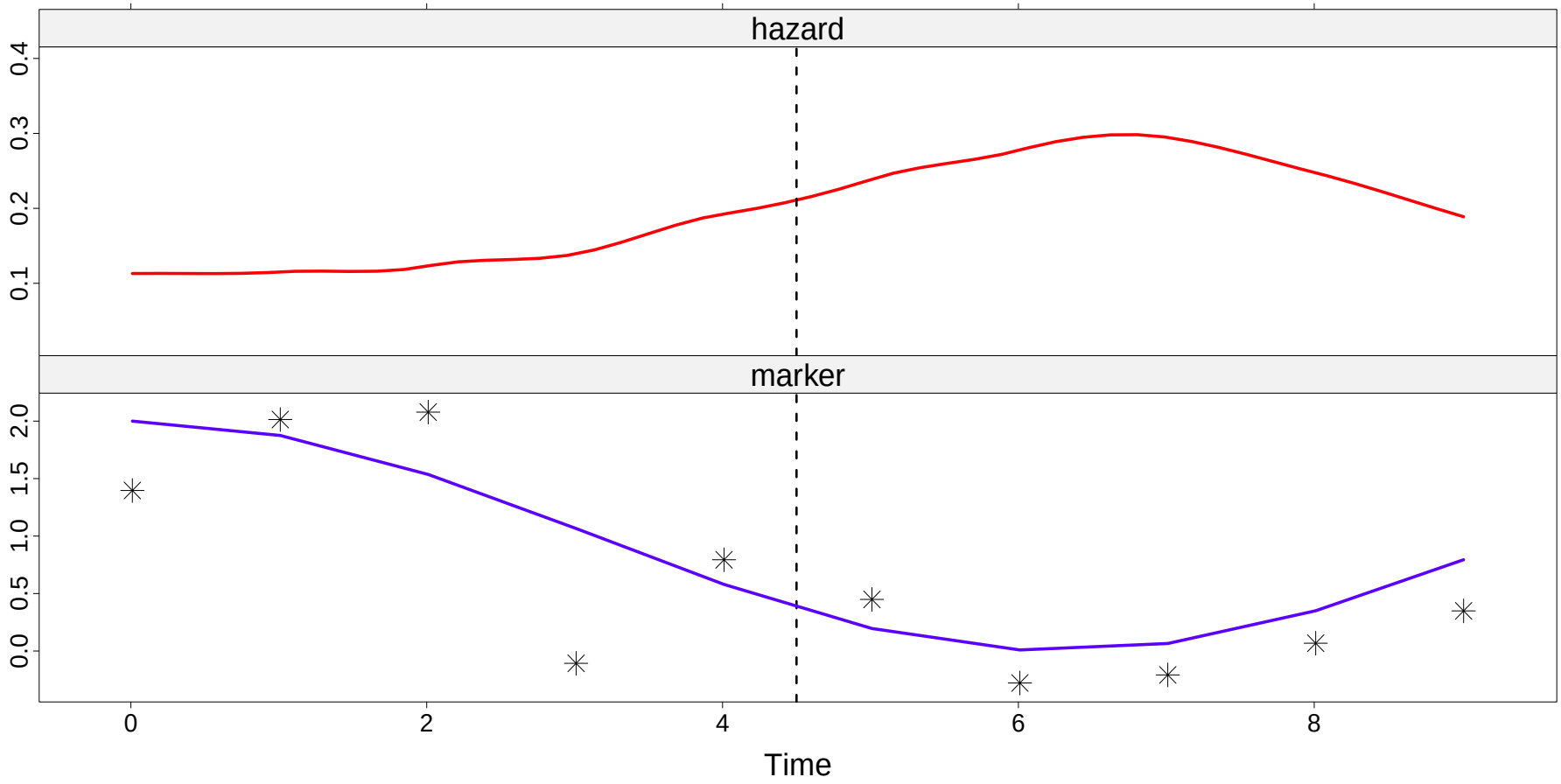
- To account for the special features of these covariates a new class of models has been developed

Joint Models for Longitudinal and Time-to-Event Data

- Intuitive idea behind these models
  1. use an appropriate model to describe the evolution of the marker in time for each patient
  2. the estimated evolutions are then used in a Cox model

- Feature: Marker level is **not** assumed constant between visits

2.1 Joint Modeling Framework (cont'd)



2.1 Joint Modeling Framework (cont'd)

- Some notation
  - ▷ T_i^*: True time-to-death for patient i
  - ▷ T_i: Observed time-to-death for patient i
  - ▷ δ_i: Event indicator, i.e., equals 1 for true events
  - ▷ y_i: Longitudinal aortic gradient measurements

2.1 Joint Modeling Framework (cont'd)

- We define a standard joint model

  ▷ Survival Part: Relative risk model

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp\{\gamma^\top w_i + \alpha m_i(t)\},$$

where

* $m_i(t)$ = the *true* & *unobserved* value of aortic gradient at time t
* $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$
* α quantifies the effect of aortic gradient on the risk for death/re-operation
* w_i baseline covariates

2.1 Joint Modeling Framework (cont'd)

▷ Longitudinal Part: Reconstruct $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$ using $y_i(t)$ and a mixed effects model (we focus on continuous markers)

$$\begin{aligned} y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \qquad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2), \end{aligned}$$

where

* $x_i(t)$ and β: Fixed-effects part
* $z_i(t)$ and b_i: Random-effects part, $b_i \sim \mathcal{N}(0, D)$

2.1 Joint Modeling Framework (cont'd)

- The two processes are associated $\Rightarrow$ define a model for their joint distribution

- Joint Models for such joint distributions are of the following form
  (Tsiatis & Davidian, Stat. Sinica, 2004)

$$p(y_i, T_i, \delta_i) = \int p(y_i \mid b_i) \left\{ h(T_i \mid b_i)^{\delta_i} S(T_i \mid b_i) \right\} p(b_i)\, db_i$$

  where

  ▷ b_i a vector of random effects that explains the interdependencies

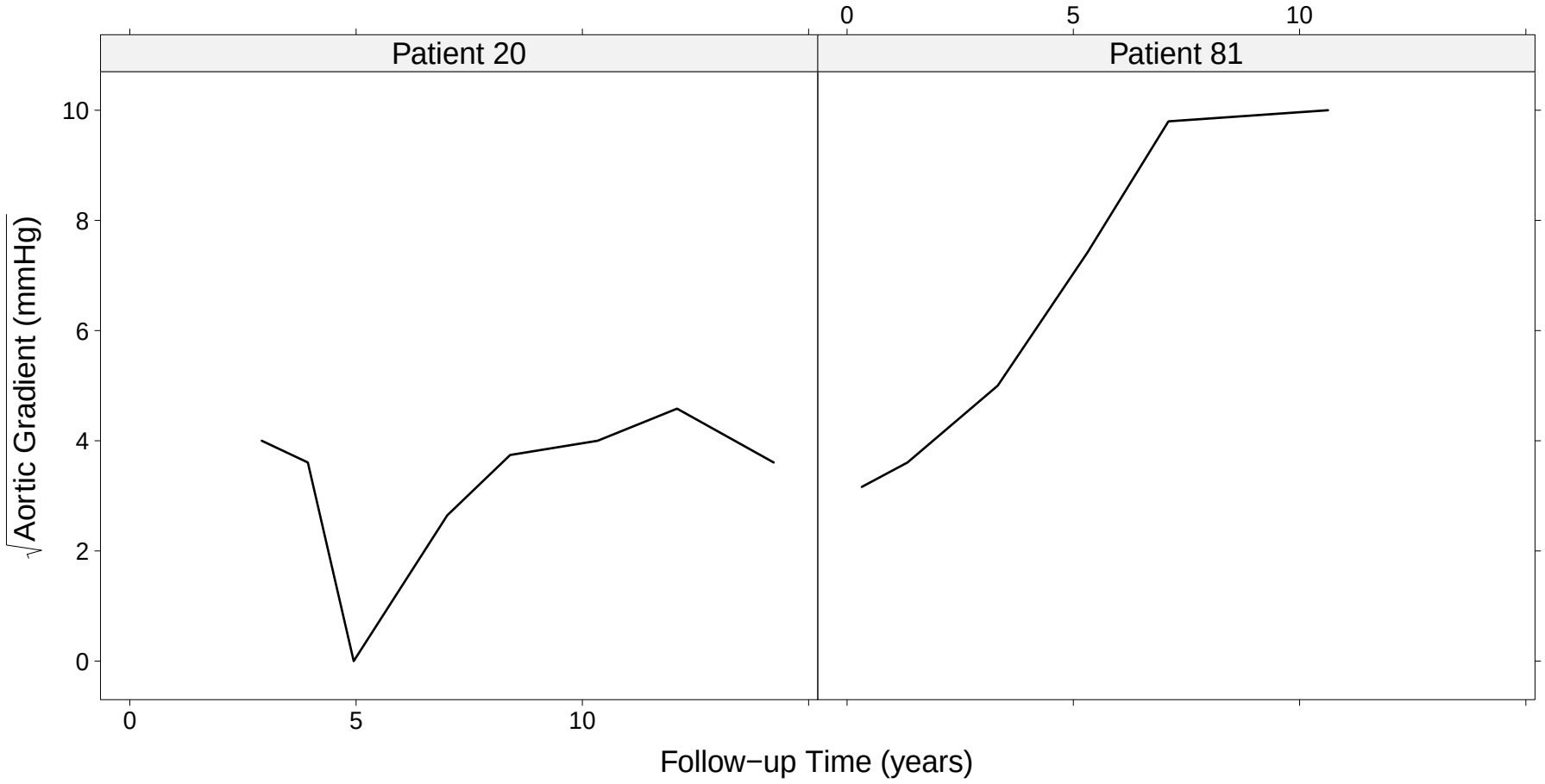
  ▷ $p(\cdot)$ density function; $S(\cdot)$ survival function

3.1 Prediction Survival – Definitions

- We are interested in predicting survival probabilities for a new patient j that has provided a set of aortic gradient measurements up to a specific time point t

- Example: We consider Patients 20 and 81 from the Aortic Valve dataset
  - ▷ **Dynamic Prediction** survival probabilities are dynamically updated as additional longitudinal information is recorded

3.1 Prediction Survival – Definitions (cont'd)



3.1 Prediction Survival – Definitions (cont'd)

- More formally, we have available measurements up to time point t

$$\mathcal{Y}_j(t) = \{y_j(s), 0 \leq s < t\}$$

and we are interested in

$$\pi_j(u \mid t) = \mathsf{Pr}\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n\},$$

where

- ▷ where $u > t$, and
- ▷ $\mathcal{D}_n$ denotes the sample on which the joint model was fitted

3.2 Prediction Survival – Estimation

- Joint model is estimated using MCMC or maximum likelihood

- Based on the fitted model we can estimate the conditional survival probabilities
  - ▷ Empirical Bayes
  - ▷ fully Bayes/Monte Carlo (it allows for easy calculation of s.e.)

- For more details check:
  - ▷ Proust-Lima and Taylor (2009, Biostatistics), Rizopoulos (2011, Biometrics), Taylor et al. (2013, Biometrics)

3.2 Prediction Survival – Estimation (cont'd)

- It is convenient to proceed using a Bayesian formulation of the problem $\Rightarrow$ $\pi_j(u \mid t)$ can be written as

$$\Pr\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n\} = \int \Pr\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t); \theta\}\, p(\theta \mid \mathcal{D}_n)\, d\theta$$

- The first part of the integrand using CI

$$\Pr\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t); \theta\} =$$

$$= \int \frac{S_j\{u \mid \mathcal{M}_j(u, b_j, \theta); \theta\}}{S_i\{t \mid \mathcal{M}_i(t, b_i, \theta); \theta\}}\, p(b_i \mid T_i^* > t, \mathcal{Y}_i(t); \theta)\, db_i$$

3.2 Prediction Survival – Estimation (cont'd)

- A Monte Carlo estimate of $\pi_i(u \mid t)$ can be obtained using the following simulation scheme:

Step 1. draw $\theta^{(\ell)} \sim [\theta \mid \mathcal{D}_n]$ or $\theta^{(\ell)} \sim \mathcal{N}(\hat{\theta}, \widehat{\mathcal{H}})$

Step 2. draw $b_i^{(\ell)} \sim \{b_i \mid T_i^* > t, \mathcal{Y}_i(t), \theta^{(\ell)}\}$

Step 3. compute $\pi_i^{(\ell)}(u \mid t) = S_i\big\{u \mid \mathcal{M}_i(u, b_i^{(\ell)}, \theta^{(\ell)}); \theta^{(\ell)}\big\} \Big/ S_i\big\{t \mid \mathcal{M}_i(t, b_i^{(\ell)}, \theta^{(\ell)}); \theta^{(\ell)}\big\}$

- Repeat Steps 1–3, $\ell = 1, \ldots, L$ times, where L denotes the number of Monte Carlo samples

3.3 Prediction Survival – Illustration

- Example: We fit a joint model to the Aortic Valve data

- Longitudinal submodel
  - ▷ fixed effects: natural cubic splines of time (d.f.$= 3$), operation type, and their interaction
  - ▷ random effects: Intercept, & natural cubic splines of time (d.f.$= 3$)

- Survival submodel
  - ▷ type of operation, age, sex + *underlying* aortic gradient level
  - ▷ log baseline hazard approximated using B-splines

3.3 Prediction Survival – Illustration (cont'd)

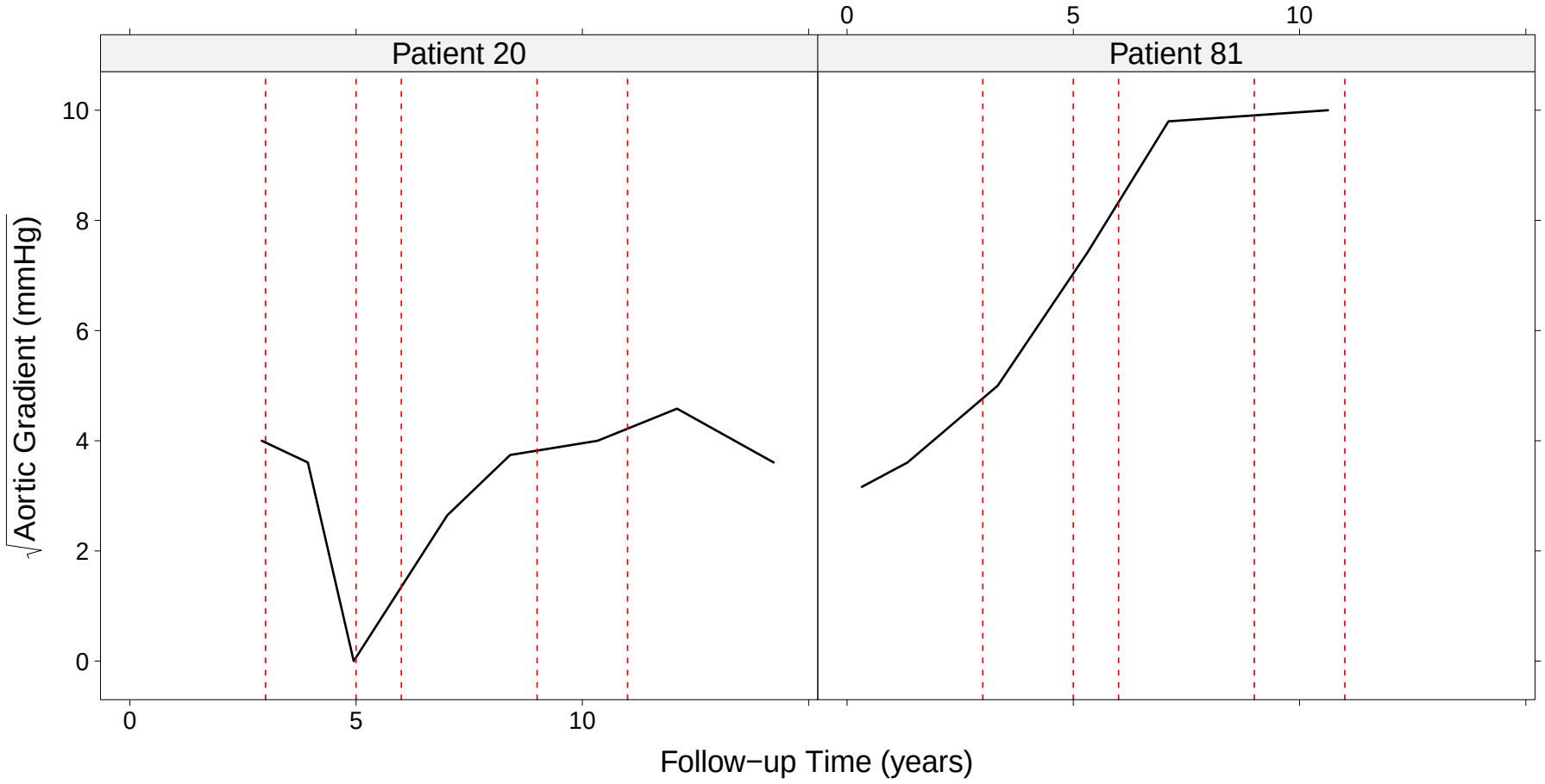
- Based on the fitted joint model we estimate $\pi_j(u \mid t)$ for Patients 20 and 81

- We used the fully Bayesian approach with 500 Monte Carlo samples, and we took as estimate

$$\hat{\pi}_j(u \mid t) = \frac{1}{L} \sum_{\ell=1}^{L} \pi_j^{(\ell)}(u \mid t)$$

and calculated the corresponding 95% pointwise CIs

3.3 Prediction Survival – Illustration (cont'd)



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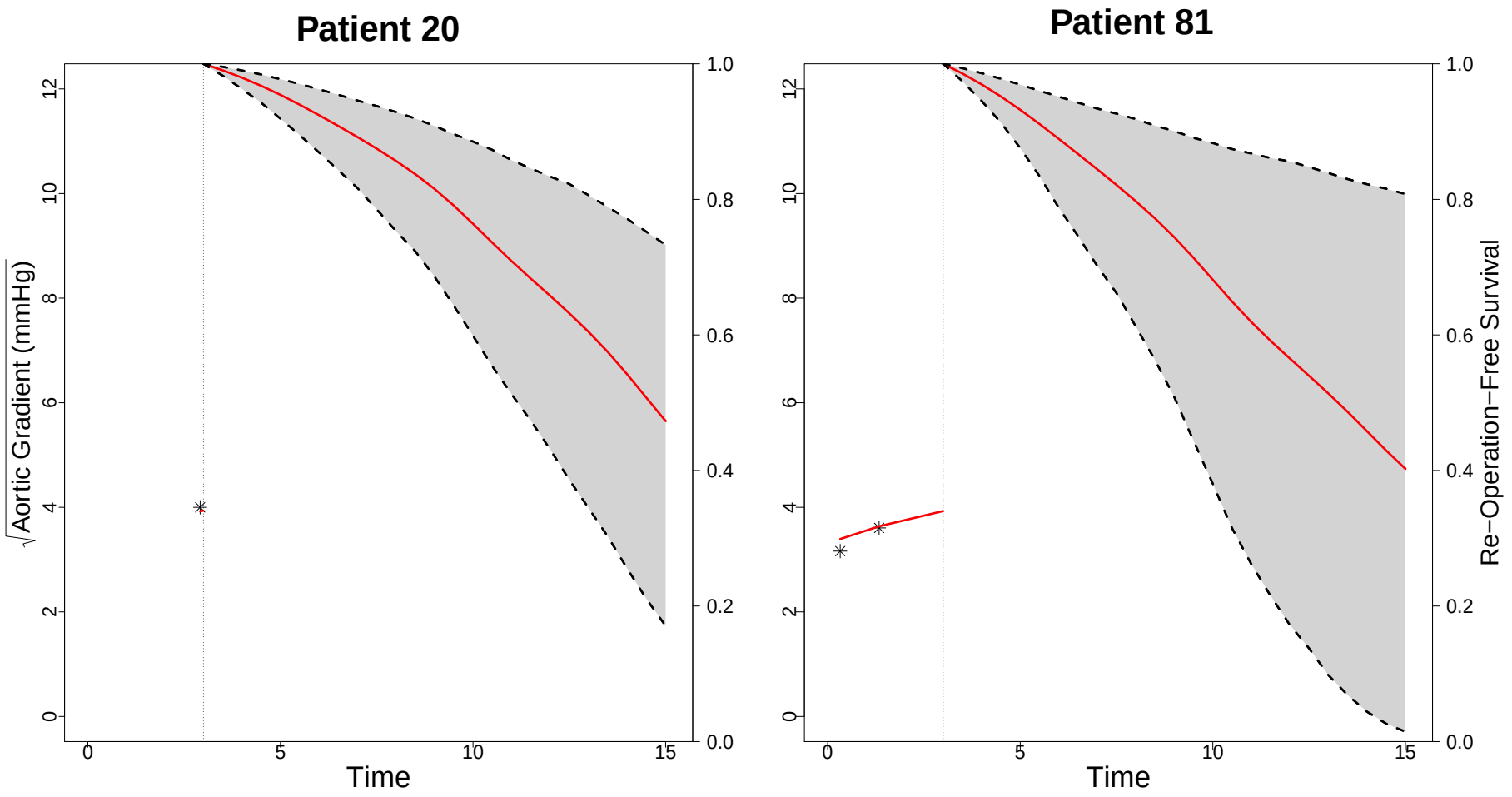
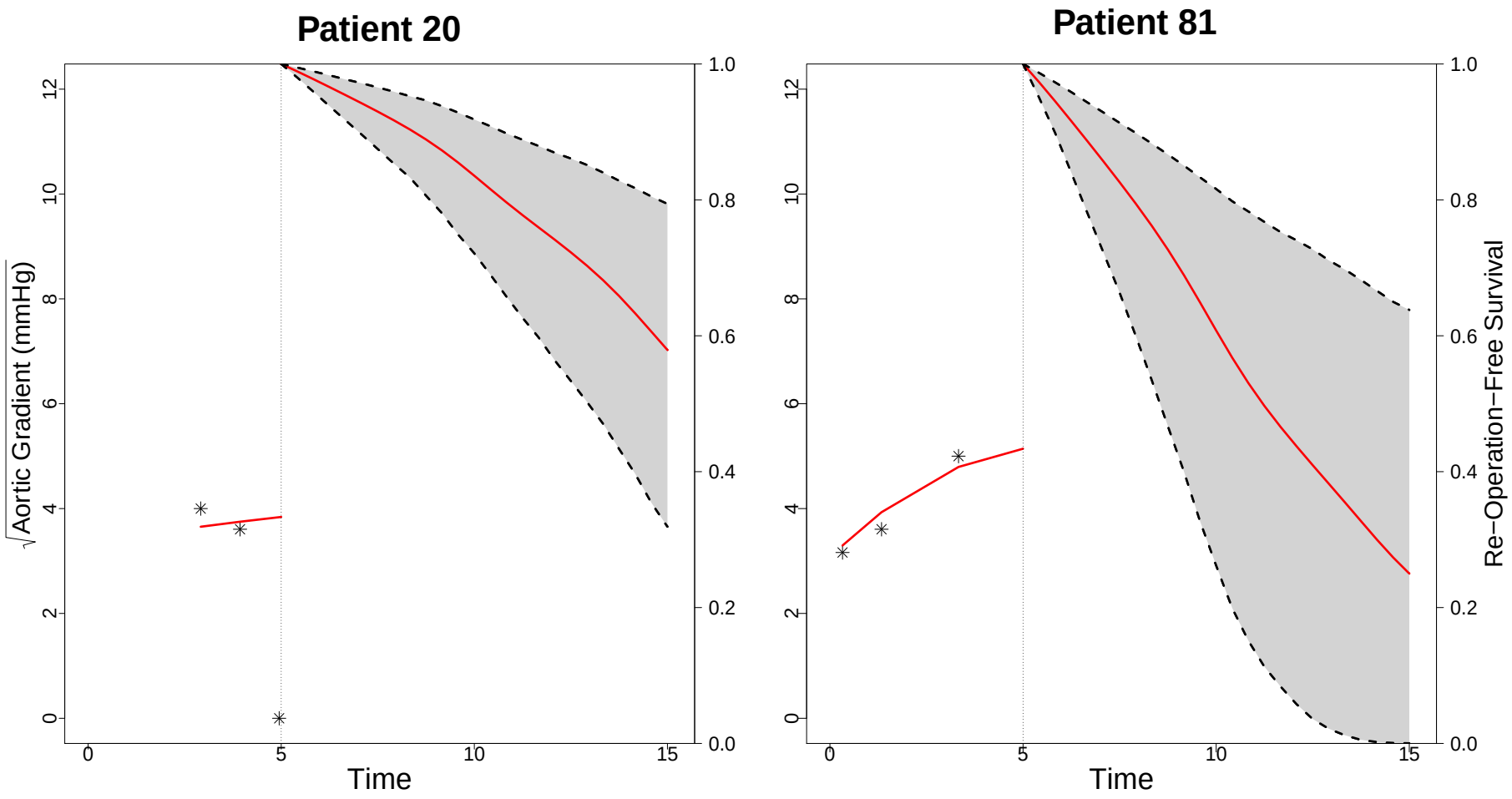


3.3 Prediction Survival – Illustration (cont'd)



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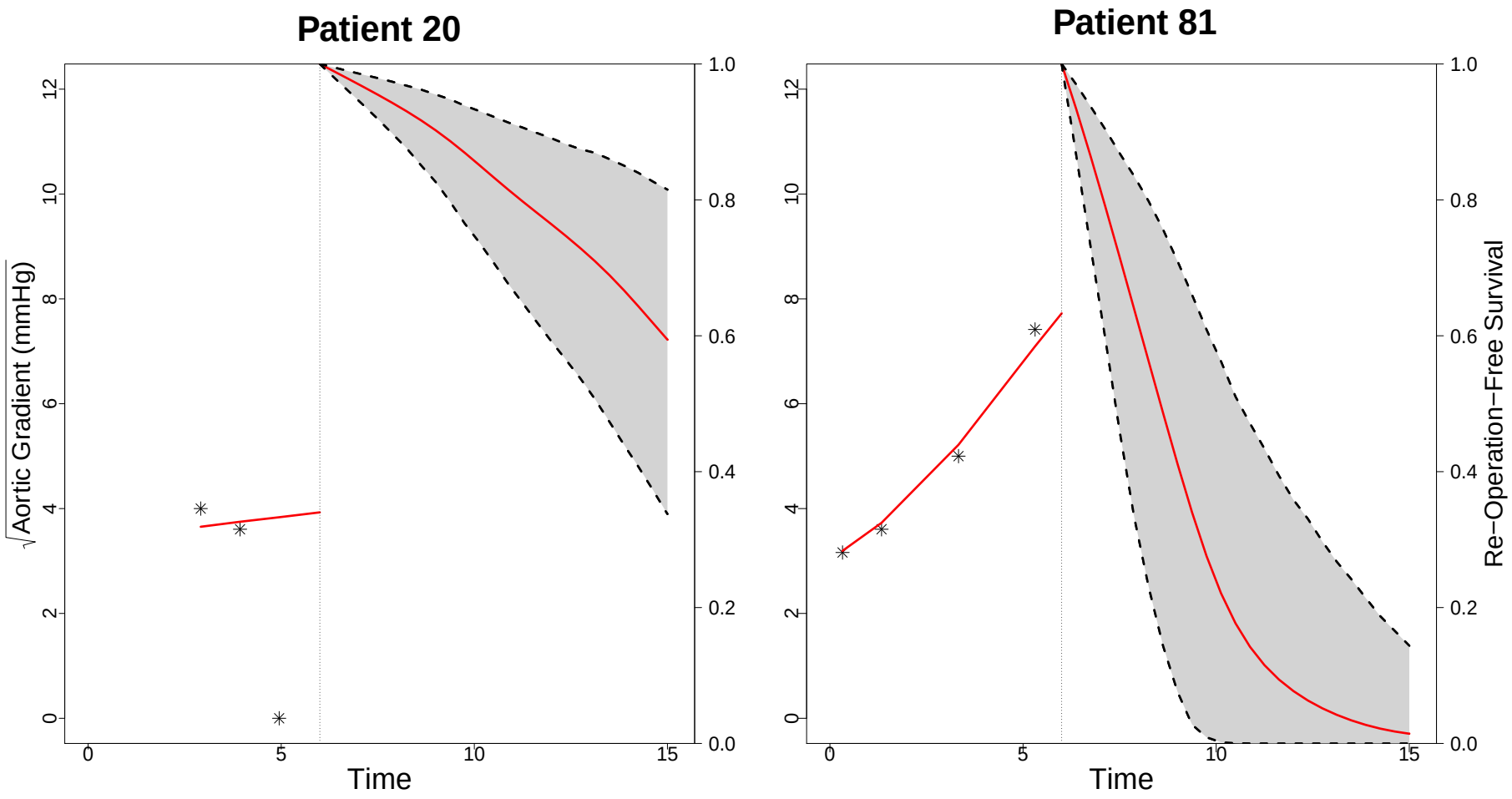

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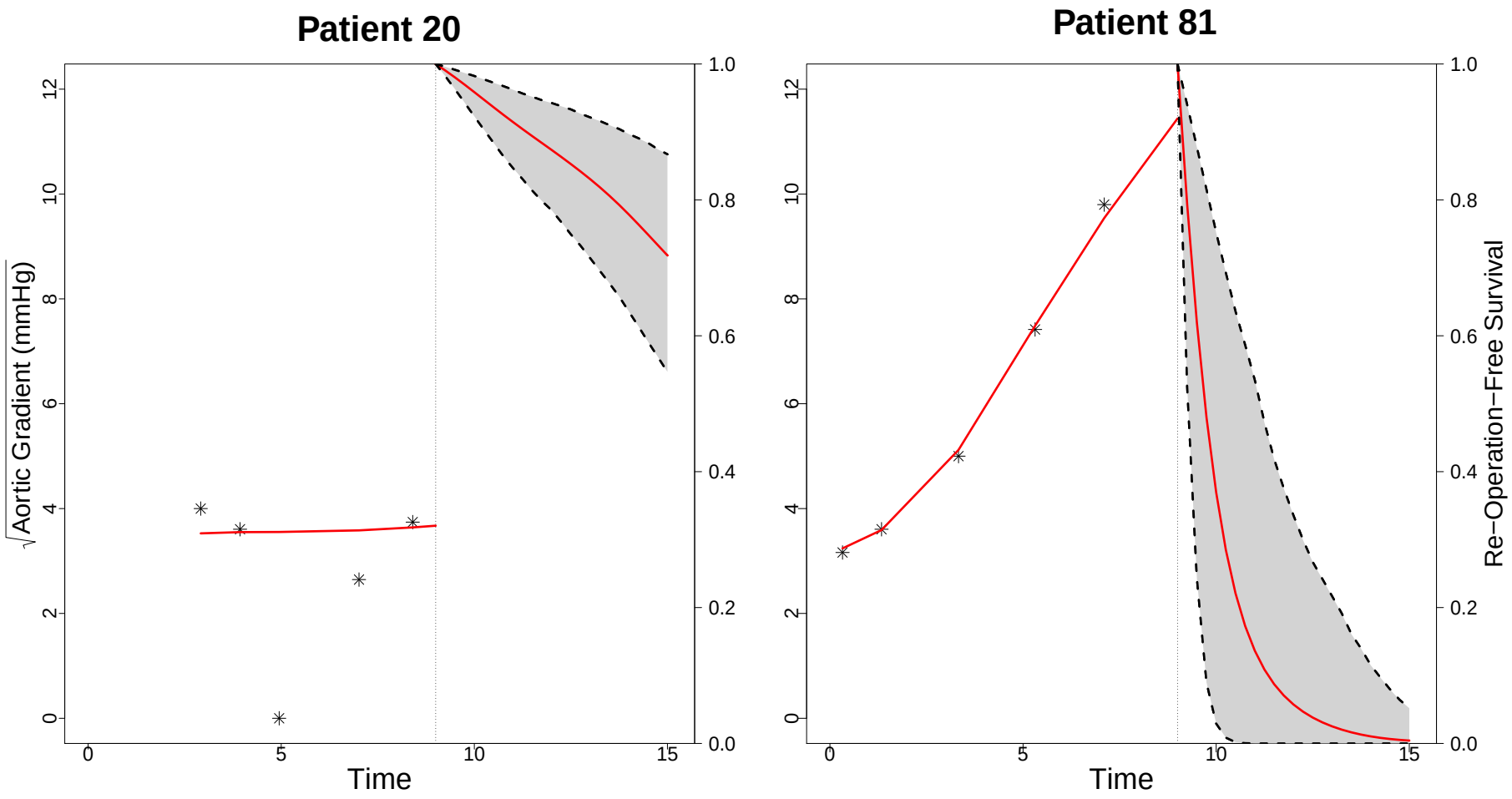

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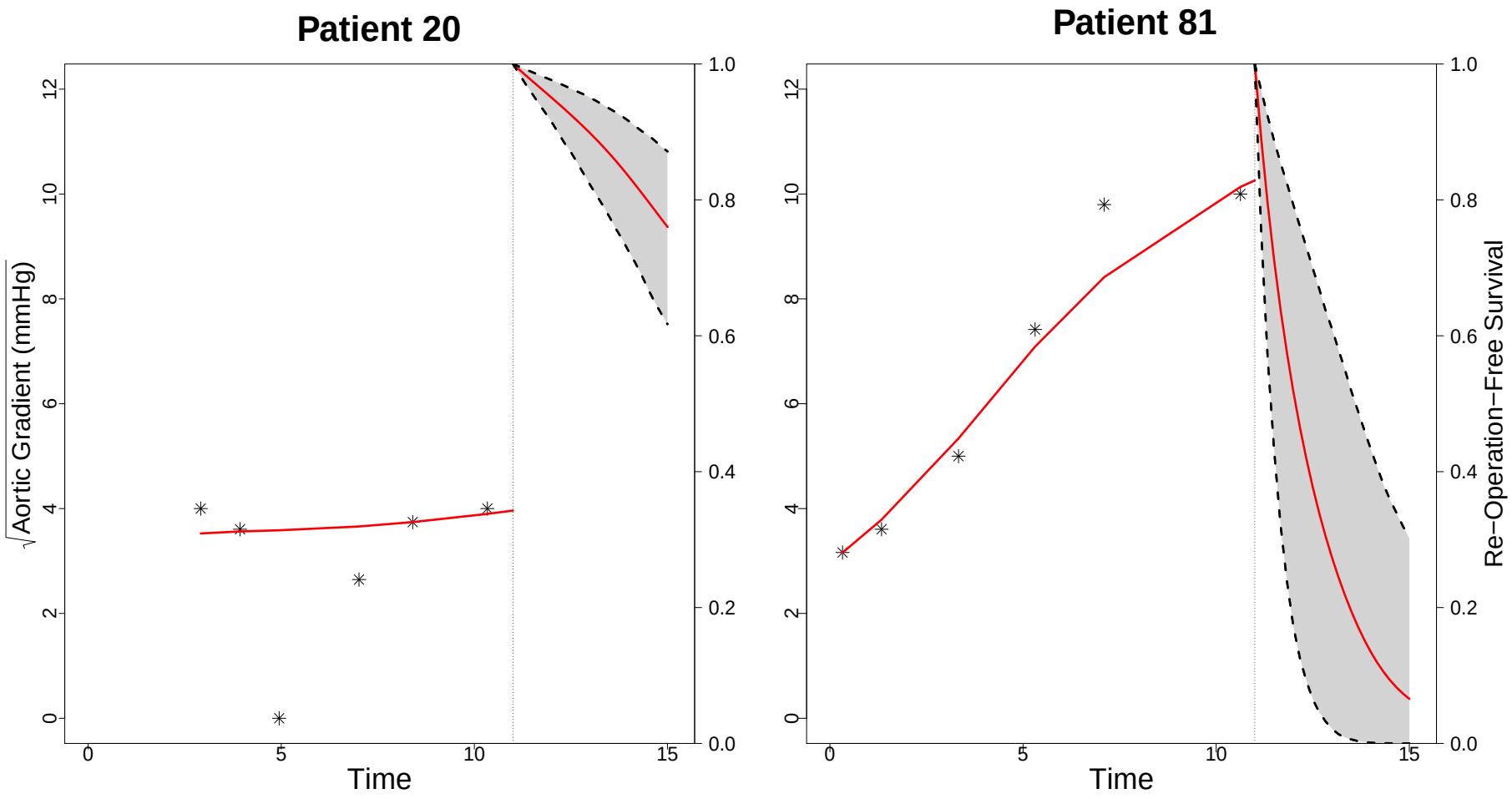


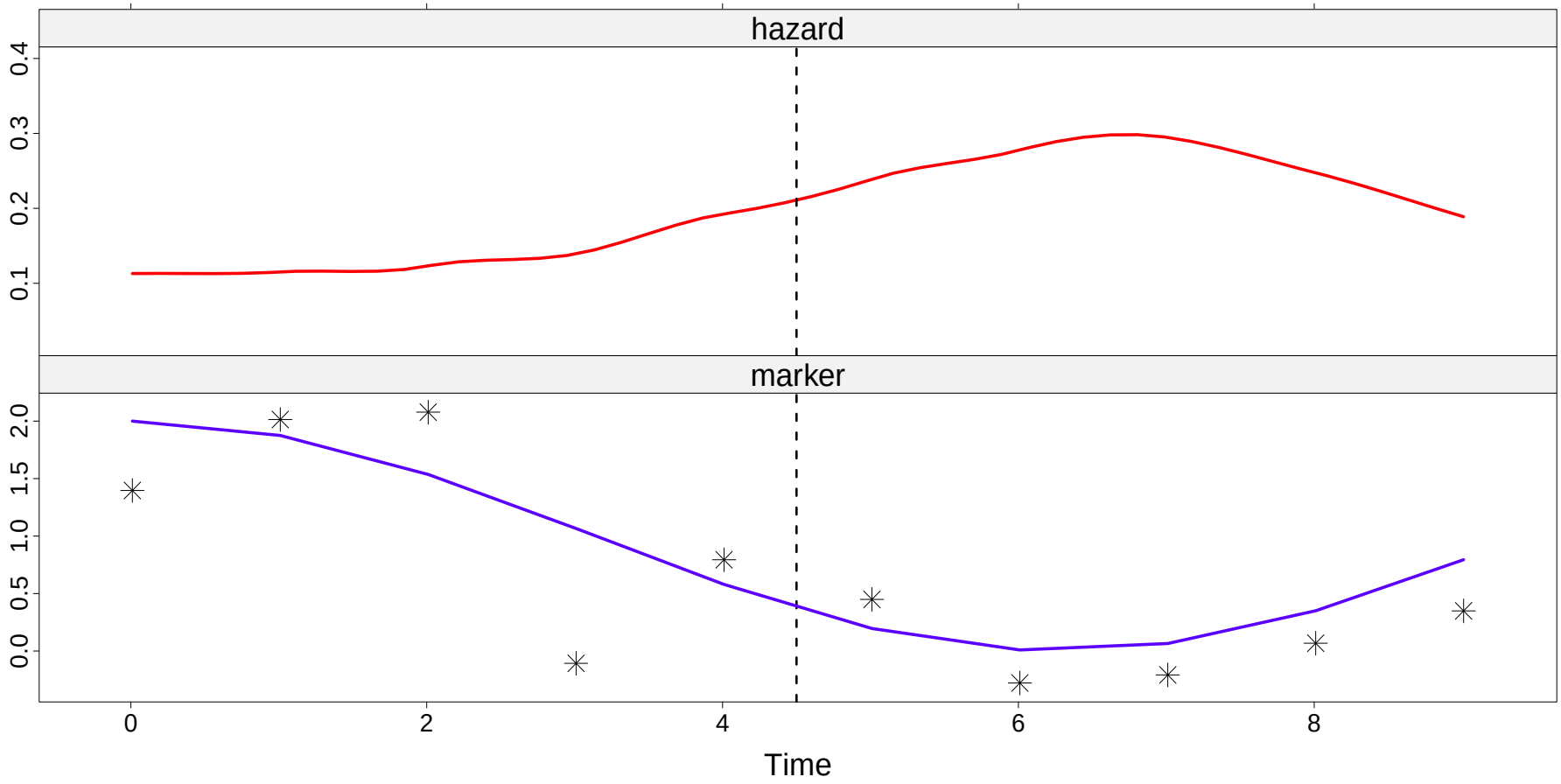
4.1 Association Structures

- The standard joint model

$$\begin{cases} h_i(t \mid \mathcal{M}_i(t)) &= h_0(t)\exp\{\gamma^\top w_i + \alpha m_i(t)\}, \\ \\ y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \end{cases}$$

where $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$

4.1 Association structures (cont'd)



4.1 Association Structures (cont'd)

- The standard joint model

$$\begin{cases} h_i(t \mid \mathcal{M}_i(t)) &= h_0(t)\exp\{\gamma^\top w_i + \alpha m_i(t)\}, \\ \\ y_i(t) &= m_i(t) + \varepsilon_i(t) \\ &= x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \end{cases}$$

where $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$

Is this the only option? Is this the most optimal for prediction?

4.3 Time-dependent Slopes

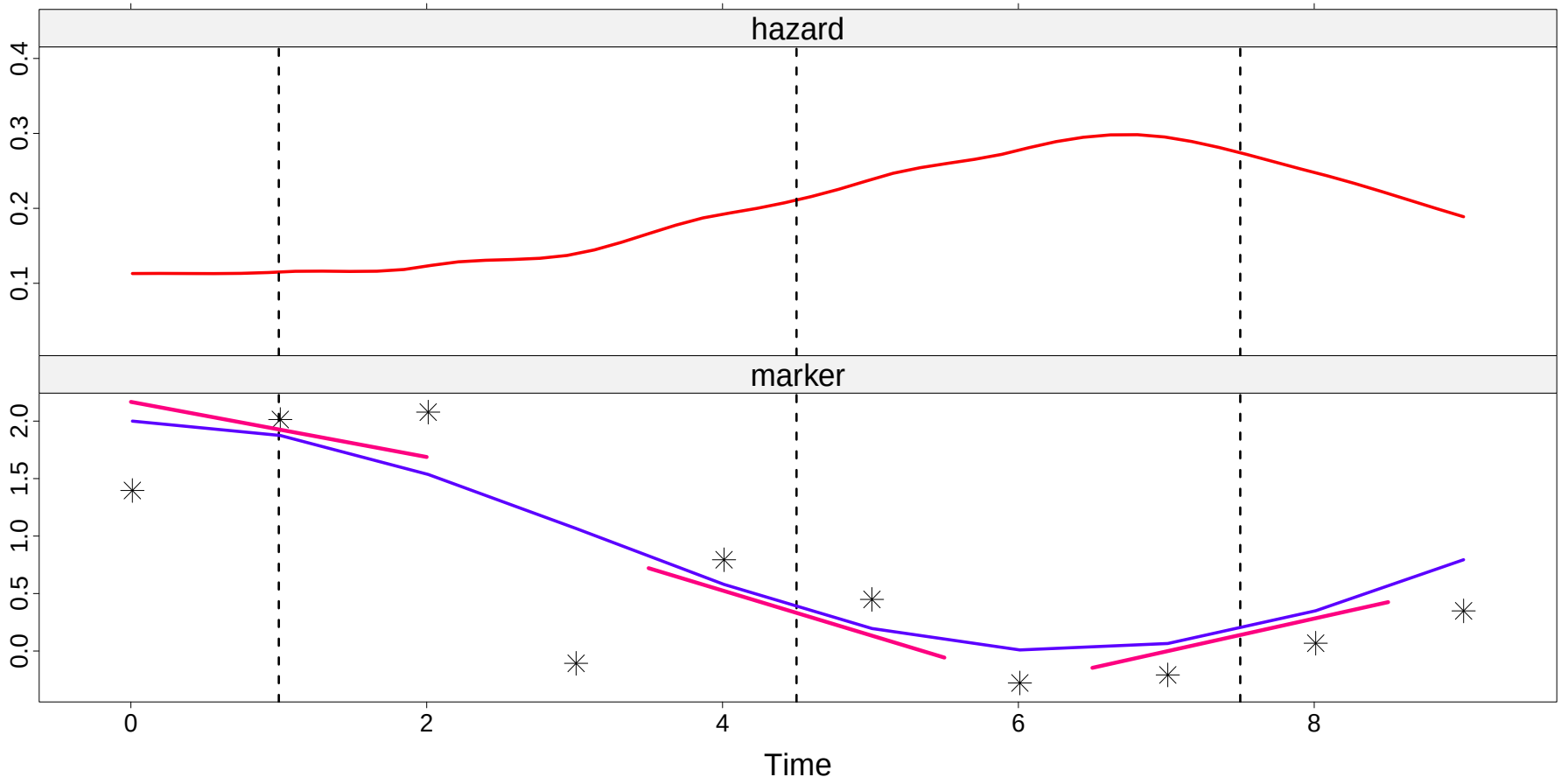
- The hazard for an event at t is associated with both the current value and the slope of the trajectory at t (Ye et al., 2008, Biometrics):

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp\{\gamma^\top w_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\},$$

where

$$m_i'(t) = \frac{d}{dt}\{x_i^\top(t)\beta + z_i^\top(t) b_i\}$$

4.3 Time-dependent Slopes (cont'd)



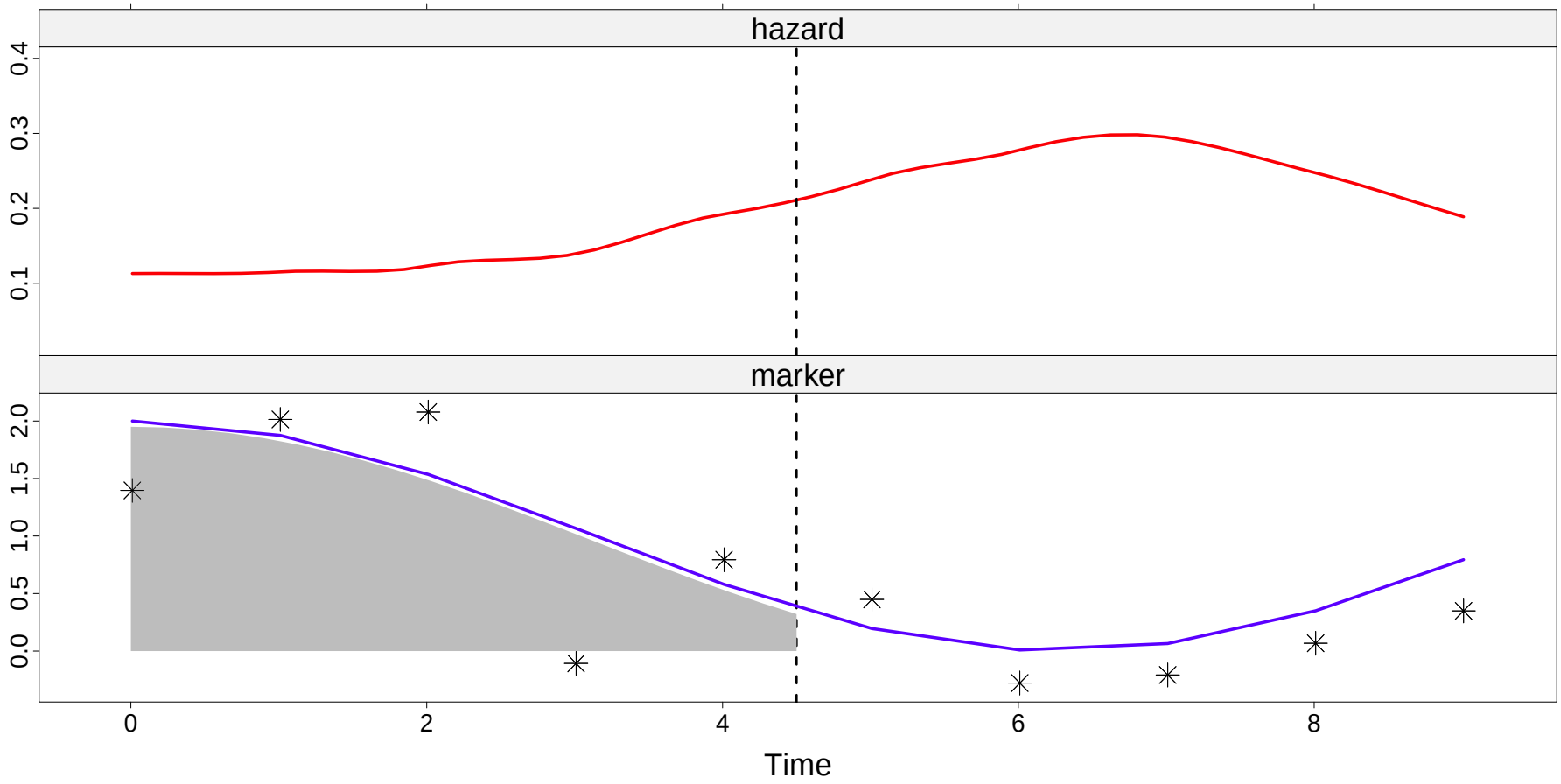
4.4 Cumulative Effects

- The hazard for an event at t is associated with area under the trajectory up to t:

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp\left\{\gamma^\top w_i + \alpha \int_0^t m_i(s)\, ds\right\}$$

- Area under the longitudinal trajectory taken as a summary of $\mathcal{M}_i(t)$

4.4 Cumulative Effects (cont'd)



4.5 Weighted Cumulative Effects

- The hazard for an event at t is associated with the area under the weighted trajectory up to t:

$$h_i(t \mid \mathcal{M}_i(t)) \;=\; h_0(t)\exp\Big\{\gamma^\top w_i + \alpha \int_0^t \varpi(t-s) m_i(s)\; ds\Big\},$$

where $\varpi(\cdot)$ appropriately chosen weight function, e.g.,

- ▷ Gaussian density
- ▷ Student's-t density
- ▷ ...

4.6 Shared Random Effects

- The hazard for an event at t is associated with the random effects of the longitudinal submodel:

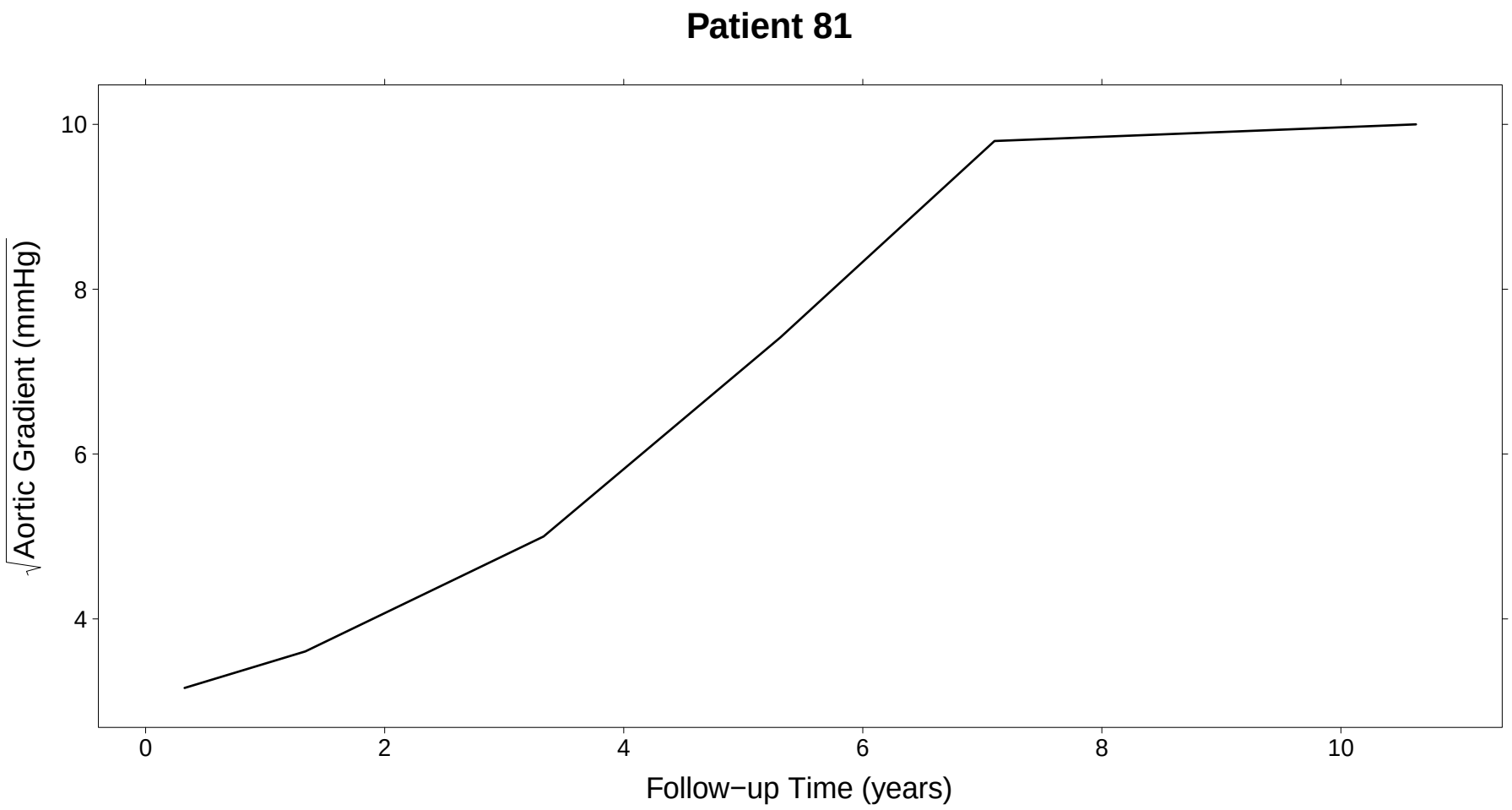
$$h_i(t \mid \mathcal{M}_i(t)) \;=\; h_0(t)\exp(\gamma^\top w_i + \alpha^\top b_i)$$

Features

▷ time-independent (no need to approximate the survival function)

▷ interpretation more difficult when we use something more than random-intercepts & random-slopes

4.7 Parameterizations & Predictions



4.7 Parameterizations & Predictions (cont'd)

- Five joint models for the Aortic Valve dataset
  - ▷ the same longitudinal submodel, and
  - ▷ relative risk submodels

$$h_i(t) = h_0(t)\exp\{\gamma_1 \texttt{TypeOP}_i + \gamma_2 \texttt{Sex}_i + \gamma_3 \texttt{Age}_i + \alpha_1 m_i(t)\},$$

$$h_i(t) = h_0(t)\exp\{\gamma_1 \texttt{TypeOP}_i + \gamma_2 \texttt{Sex}_i + \gamma_3 \texttt{Age}_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\},$$

$$h_i(t) = h_0(t)\exp\left\{\gamma_1 \texttt{TypeOP}_i + \gamma_2 \texttt{Sex}_i + \gamma_3 \texttt{Age}_i + \alpha_1 \int_0^t m_i(s)ds\right\}$$

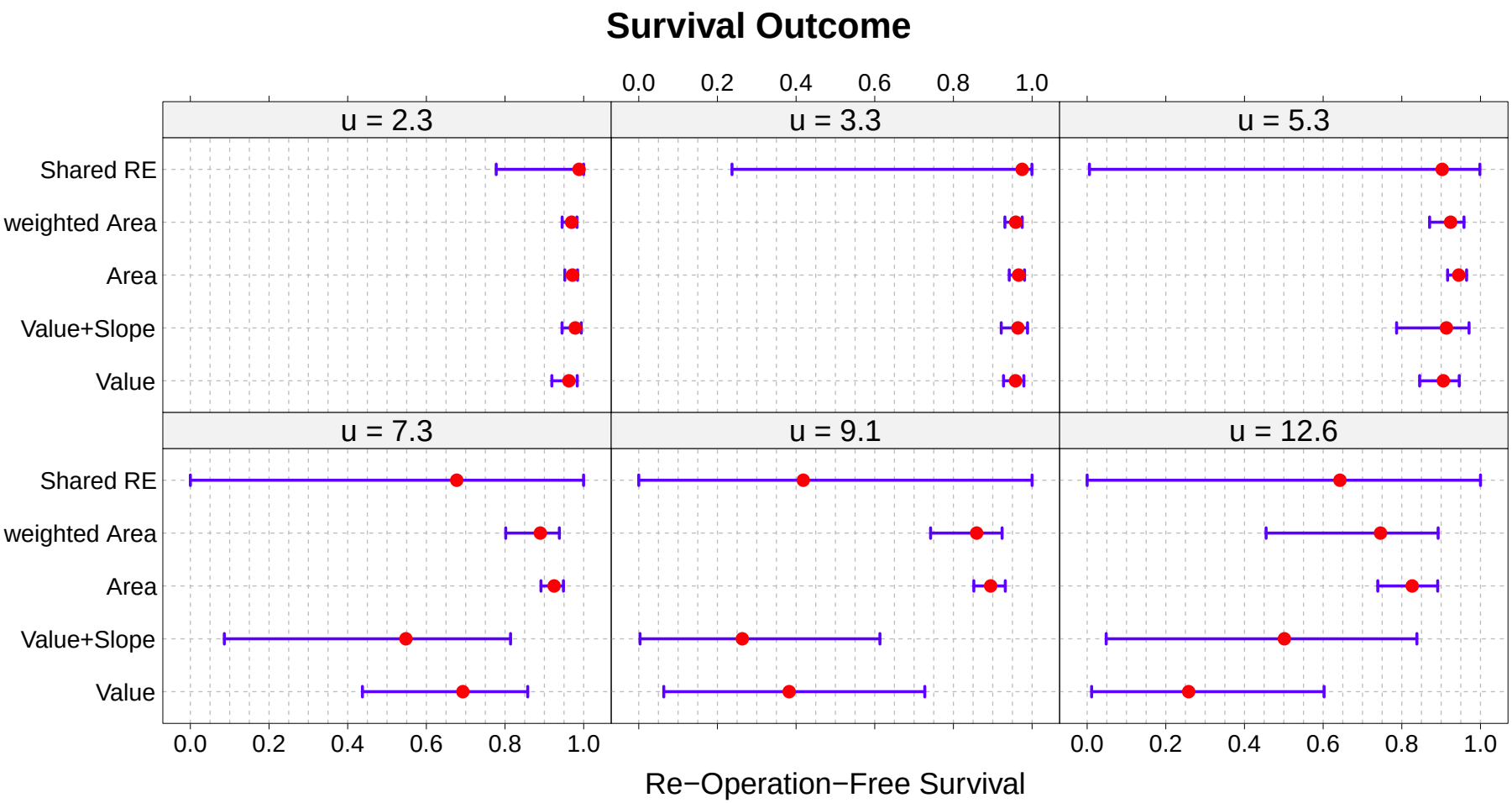
4.7 Parameterizations & Predictions (cont'd)

$$h_i(t) = h_0(t)\exp\Big\{\gamma_1 \texttt{TypeOP}_i + \gamma_2 \texttt{Sex}_i + \gamma_3 \texttt{Age}_i + \alpha_1 \int_0^t \varpi(t-s) m_i(s) ds\Big\},$$

where $\varpi(t-s) = \phi(t-s)/\{\Phi(t) - 0.5\}$, with $\phi(\cdot)$ and $\Phi(\cdot)$ the normal pdf and cdf, respectively

$$h_i(t) = h_0(t)\exp(\gamma_1 \texttt{TypeOP}_i + \gamma_2 \texttt{Sex}_i + \gamma_3 \texttt{Age}_i + \alpha_1 b_{i0} + \alpha_2 b_{i1} + \alpha_3 b_{i2} + \alpha_4 b_{i4})$$

4.7 Parameterizations & Predictions (cont'd)



4.7 Parameterizations & Predictions (cont'd)

- The chosen parameterization can influence the derived predictions
  - ▷ especially for the survival outcome

How to choose between the competing association structures?

4.7 Parameterizations & Predictions (cont'd)

- The easy answer is to employ information criteria, e.g., AIC, BIC, DIC, ...

- However, a problem is that the longitudinal information dominates the joint likelihood
  $\Rightarrow$ will not be sensitive enough wrt predicting survival probabilities

- In addition, thinking a bit more deeply, is the same single model the most appropriate
  - ▷ for all future patients?
  - ▷ for the same patient during the whole follow-up?

The most probable answer is No

4.8 Combining Joint Models

- To address this issue we will use Bayesian Model Averaging (BMA) ideas

- In particular, we assume $M_1, \ldots, M_K$
  - ▷ different association structures
  - ▷ different baseline covariates in the survival submodel
  - ▷ different formulation of the mixed model
  - ▷ ...

- Typically, this list of models will not be exhaustive

4.8 Combining Joint Models (cont'd)

- The aim is the same as before, using the available information for a future patient j up to time t, i.e.,
  - $\triangleright\ T_j^* > t$
  - $\triangleright\ \mathcal{Y}_j(t) = \{y_j(s), 0 \leq s \leq t\}$

- We want to estimate

$$\pi_j(u \mid t) = \mathsf{Pr}\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n\},$$

  by averaging over the posited joint models

4.8 Combining Joint Models (cont'd)

- More formally we have

$$\Pr\{T_j^* \geq u \mid \mathcal{D}_j(t), \mathcal{D}_n\} = \sum_{k=1}^{K} \Pr(T_j^* > u \mid M_k, \mathcal{D}_j(t), \mathcal{D}_n)\, p(M_k \mid \mathcal{D}_j(t), \mathcal{D}_n)$$

  where

  - $\mathcal{D}_j(t) = \{T_j^* > t, y_j(s), 0 \leq s \leq t\}$
  - $\mathcal{D}_n = \{T_i, \delta_i, y_i, i = 1, \ldots, n\}$

- The first part, $\Pr(T_j^* > u \mid M_k, \mathcal{D}_j(t), \mathcal{D}_n)$, the same as before
  - i.e., model-specific conditional survival probabilities

4.8 Combining Joint Models (cont'd)

- Working out the marginal distribution of each competing model we found some very attractive features of BMA,

$$p(M_k \mid \mathcal{D}_j(t), \mathcal{D}_n) = \frac{p(\mathcal{D}_j(t) \mid M_k)\, p(\mathcal{D}_n \mid M_k)\, p(M_k)}{\sum_{\ell=1}^{K} p(\mathcal{D}_j(t) \mid M_\ell)\, p(\mathcal{D}_n \mid M_\ell)\, p(M_\ell)}$$

  - ▷ $p(\mathcal{D}_n \mid M_k)$ marginal likelihood based on the available data
  - ▷ $p(\mathcal{D}_j(t) \mid M_k)$ marginal likelihood based on the new data of patient j

Model weights are both patient- and time-dependent

4.8 Combining Joint Models (cont'd)

- For different subjects, and even for the same subject but at different times points, different models may have higher posterior probabilities

$$\Downarrow$$

Predictions better tailored to each subject than in standard prognostic models

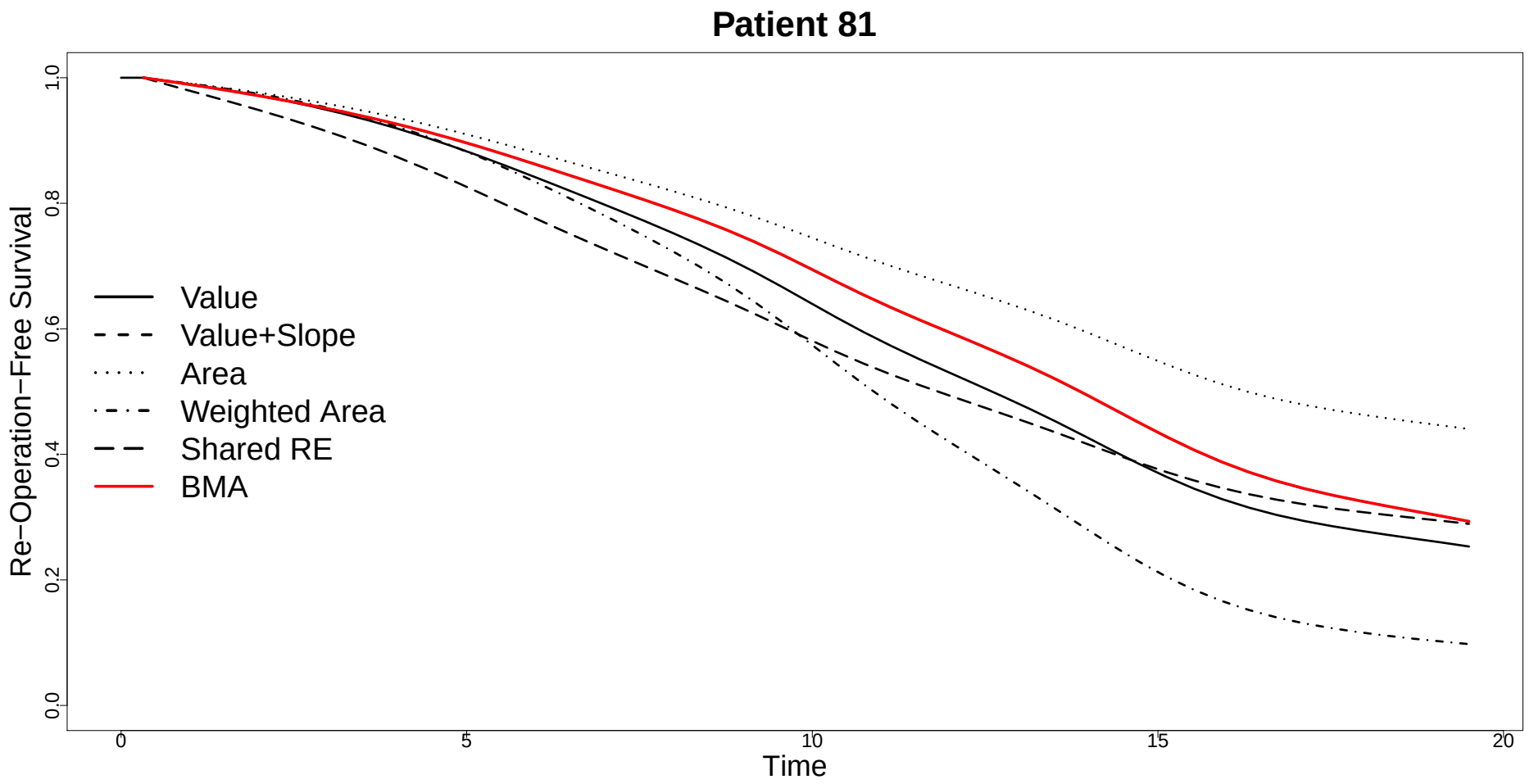
- In addition, the longitudinal model likelihood, which is
  - ▷ hidden in $p(\mathcal{D}_n \mid M_k)$, and
  - ▷ is not affected by the chosen association structure

  will cancel out because it is both in the numerator and denominator

4.8 Combining Joint Models (cont'd)

- Example: Based on the five fitted joint models
  - ▷ we compute BMA predictions for Patient 81, and
  - ▷ compare with the predictions from each individual model

4.8 Combining Joint Models (cont'd)



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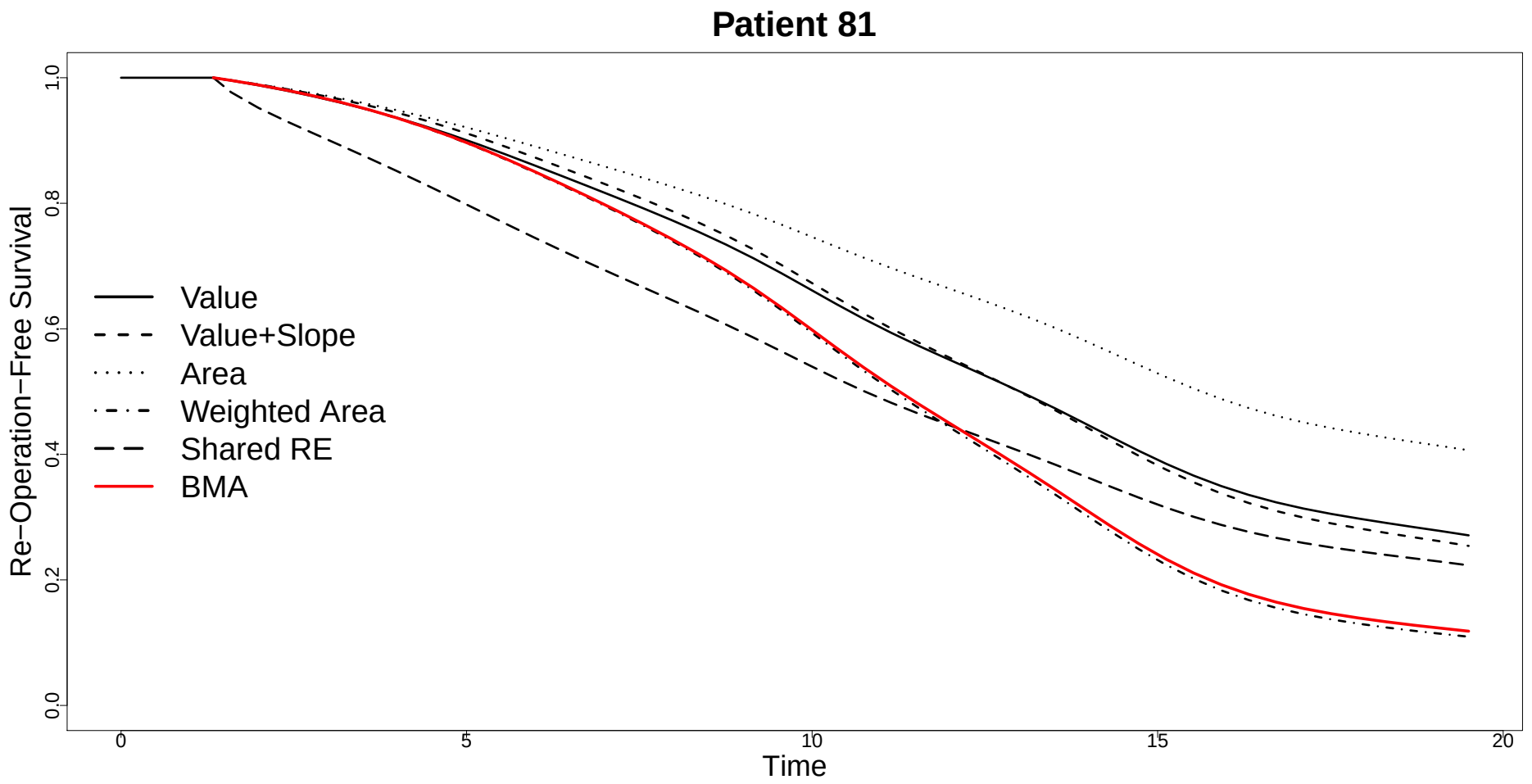

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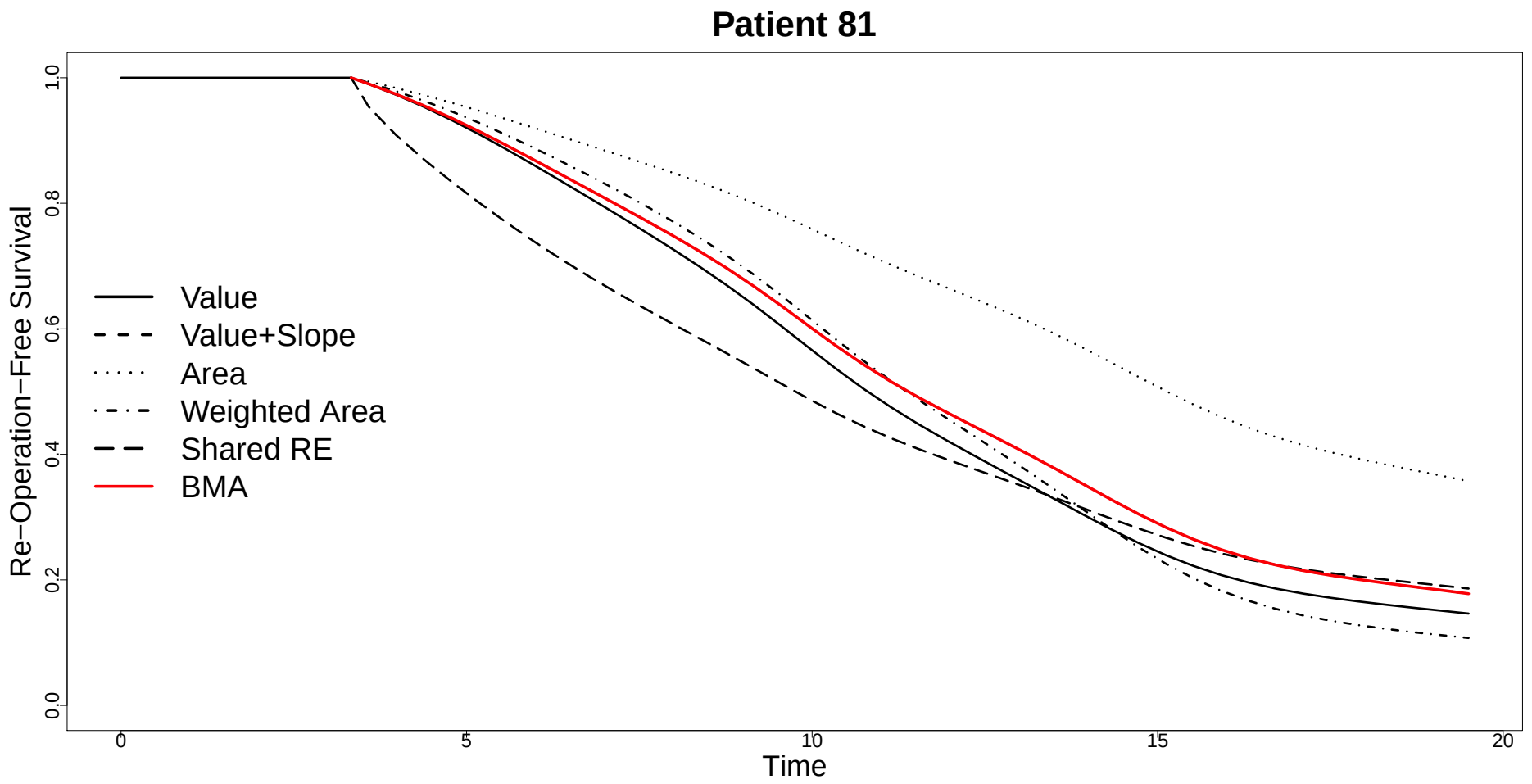

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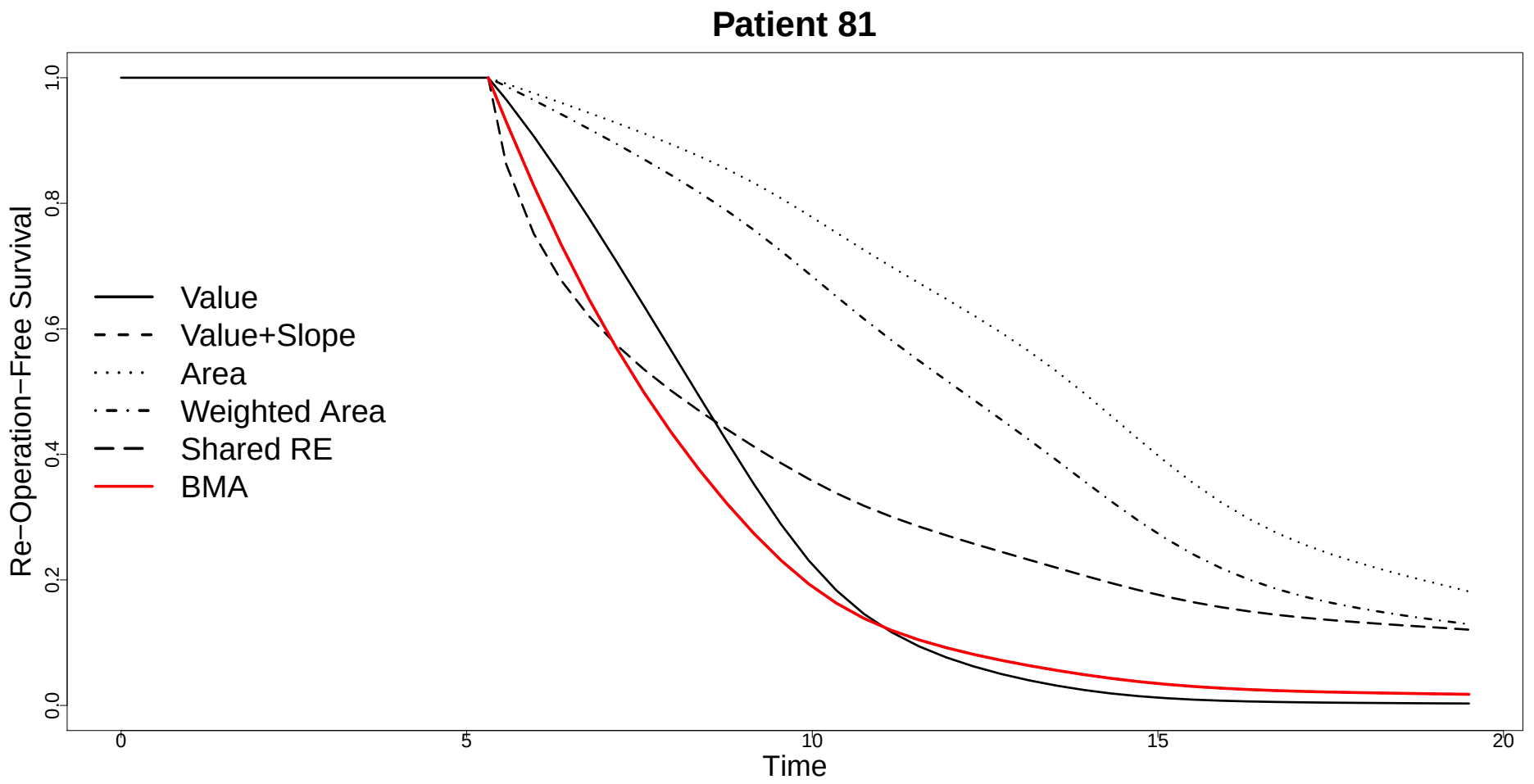

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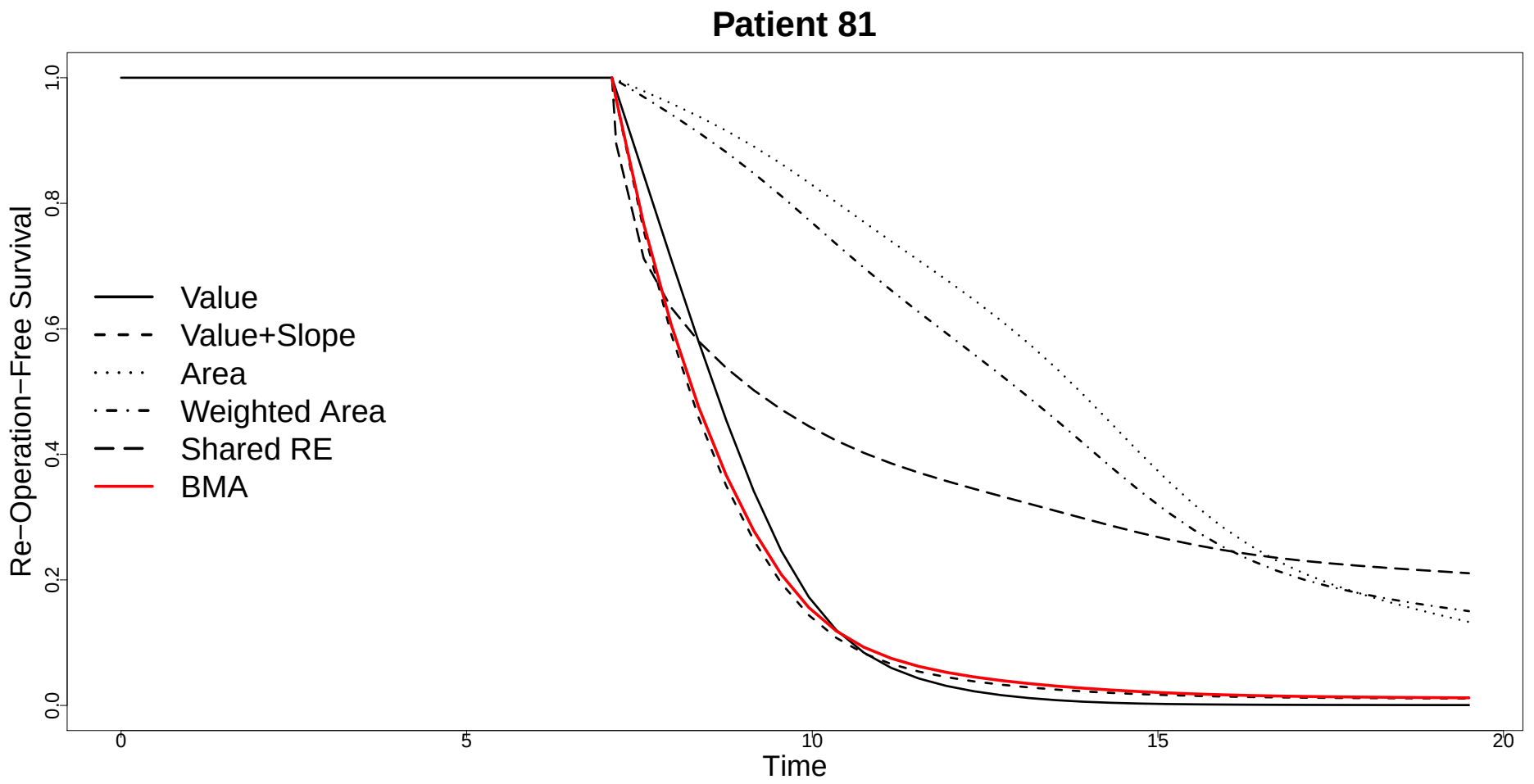
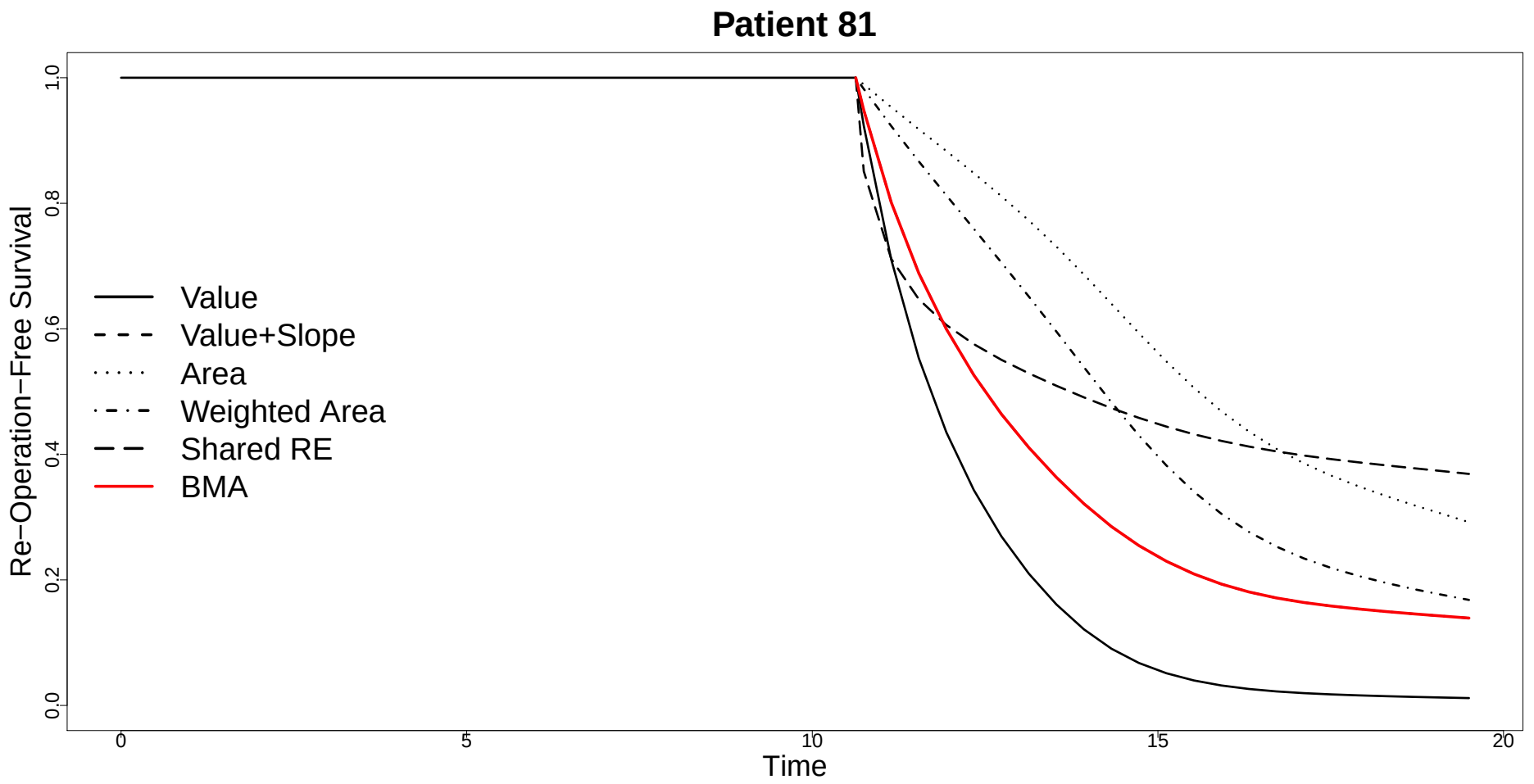


4.8 Combining Joint Models (cont'd)



5. Software – I

- Software: R package **JM** freely available via `http://cran.r-project.org/package=JM`
  - ▷ it can fit a variety of joint models + many other features
  - ▷ relevant to this talk: Functions `survfitJM()` and `predict()`

- More info available at:

Rizopoulos, D. (2012). *Joint Models for Longitudinal and Time-to-Event Data, with Applications in R*. Boca Raton: Chapman & Hall/CRC.

Web site: `http://jmr.r-forge.r-project.org/`

5. Software – II

- Software: R package **JMbayes** freely available via `http://cran.r-project.org/package=JMbayes`
  - ▷ it can fit a variety of joint models + many other features
  - ▷ relevant to this talk: Functions `survfitJM()`, `predict()` and `bma.combine()`

Thank you for your attention!