Joint Modelling For Longitudinal and Survival Data

Why R? Turkey 2021

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Outline

Why Joint Modelling?

To study jointly the following models:

- Longitudinal models of repeated measurements, affected by informative censoring/drop-out
- Incorporation of these longitudinal covariates in to the survival process

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Statistical Background

- To model longitudinal and survival processes together, there exist various methods in the literature. Such as: Extended-Cox Models, Two-stage approach, Joint Modelling Approaches.
- However, existing approaches usually deal with one single longitunal biomarker with survival process.
- We'll focus on two different approaches:
  - Two-stage (TS) approach
  - Joint Modelling (JM) Approach

Main idea behind the naive TS approach

Prentice, 1982; Self and Pawitan, 1992; Tsiatis et al., 1995; Bycott and Taylor, 1998; Dafni and Tsiatis, 1998; Albert and Shih, 2010; Rizopoulos, 2010

- **Stage 1**: Fit a **Linear Mixed Model** model to the longitudinal covariate data.
- **Stage 2**: Fit the **Survival Model** separately, with the random effects predictions or true/unobserved value of the covariate substituted by their estimates/predictions from the first stage.

NOTE: Separate likelihood calculation.

Joint Modelling (JM) Approach

Main idea: To link the longitudinal and survival process in the joint likelihood calculation

- **Y: Longitudinal process affected by informative censoring**
- **S: Survival process with time-varying covariates**
- **W: Latent random effect**

NOTE: Joint likelihood calculation.

Different JM approaches

There are three different ways to calculate the joint likelihood, among others;

- Selection Models

$$[\mathbf{Y},\mathbf{S},\mathbf{W}] = [\mathbf{W}][\mathbf{Y}|\mathbf{W}][\mathbf{S}|\mathbf{Y}]$$

Different JM approaches

There are three different ways to calculate the joint likelihood, among others;

- Selection Models

$$\mathbf{[Y,S,W] = [W][Y|W][S|Y]}$$

- Pattern-Mixture Models

$$\mathbf{[Y,S,W] = [W][S|W][Y|S]}$$

Different JM approaches

There are three different ways to calculate the joint likelihood, among others;

- Selection Models

$$[Y,S,W] = [W][Y|W][S|Y]$$

- Pattern-Mixture Models

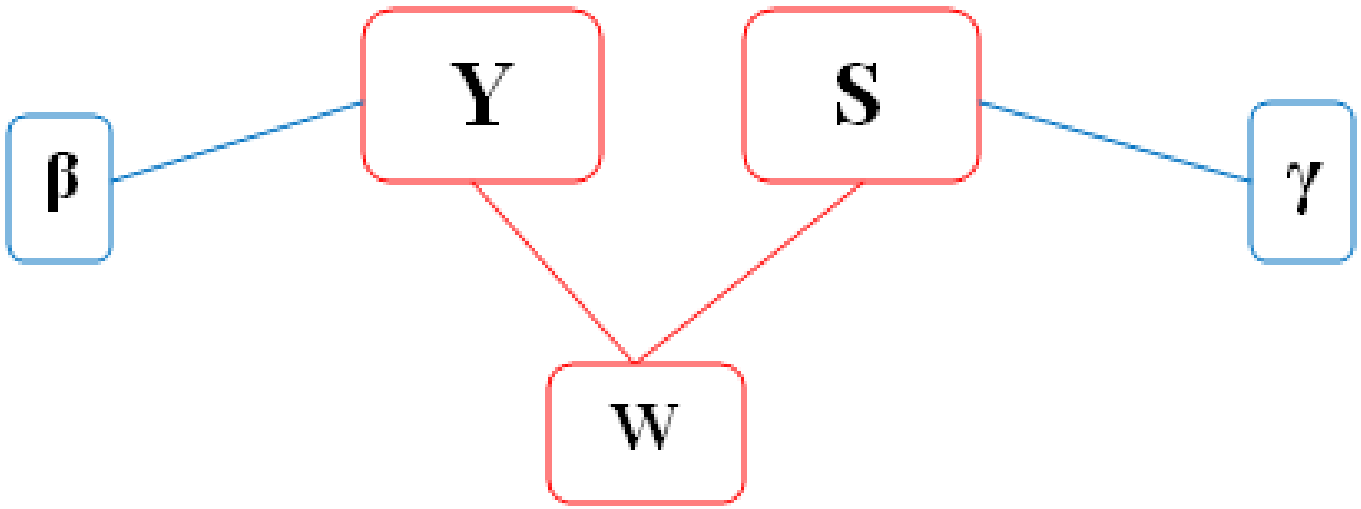
$$[Y,S,W] = [W][S|W][Y|S]$$

- **Shared Random Effect Models**

$$[Y,S,W] = [W][Y|W][S|W]$$

Shared Random Effect Models

Schluchter, 1992; Faucett and Thomas, 1996; Wulfsohn and Tsiatis, 1997; and Henderson et al., 2000



β and γ are the fix parameters of longitudinal and survival processes respectively.

Shared Random Effect Models

Longitudinal sub-model: Linear mixed effects model (Laird and Ware, 1982) *library(nlme)*

$$Y_{ij} = x_{ij}\beta + W_{1i}(t) + \epsilon_i$$

$$W_{1i}(t) = U_{0i} + U_{1i}t_ij$$

where U_{0i} and U_{1i} are individual random intercept and random slope respectively.

Shared Random Effect Models

Survival sub-model: Cox Proportional Hazard Regression, *library(survival)*

$$\lambda(t) = \lambda_0(t) \exp\left(\gamma X_i(t) + \alpha W_1 i(t)\right)$$

- α is termed the association parameter; in this case the association is based on the linear combination of the random intercept and slope predictions.

Different parameterizations

- The random effects predictions at time t (Wulfsohn1997)

$$\lambda_i(t) = \lambda_0(t)\exp(\gamma X_i + \alpha(U_{0i} + U_{1i}t_i))$$

in which α is the association between the longitudinal biomarker and the risk of death at time t with a unit change in the marker corresponding to a $\exp(\alpha)$ fold change in the risk of death.

Different parameterizations

- The true unobserved (current) value at time t (Rizopoulos2012)

$$\lambda_i(t) = \lambda_0(t)\exp(\gamma X_i + \alpha(\beta_0 + \beta_1 t_{ij} + U_{0i} + U_{1i} t_i))$$

in which α represent the association between the longitudinal biomarker and the risk of death at time t taking into account the true value of the longitudinal biomarker both with fixed and random effects predictions.

Different parameterizations

- Time-dependent slopes including both current value and the slope of the trajectory at time t (Ye2008b)

$$\lambda_i(t) = \lambda_0(t) \exp(\gamma X_i + \alpha_1 \omega_i(t) + \alpha_2 \omega_i'(t))$$

Parameter α_1 has the same interpretation as in true value and α_2 represents for patients having the same level of the true longitudinal biomarker at time t, the log hazard ratio for a unit increase in the current slope of the longitudinal trajectory. This parameterization could capture situations in which, at a specific time point, two patients show similar true marker levels, but they may differ in the rate of change of the marker.

Different parameterizations

- Cumulative effect including the whole area under the trajectory (Rizopoulos2012)

$$\lambda_i(t) = \lambda_0(t)\exp(\gamma X_i + \alpha_1(\int_0^t (\beta_0 + \beta_1 s_i + U_{0i} + U_{1i} s_i)ds))$$

With this parameterization, α_1 is the association between the whole history (area under the trajectory) of the longitudinal biomarker and survival.

Shared Random Effect Models

Joint Likelihood Calculation

$$p(T_i, \delta_i, y_i | W_i; \theta) = p(T_i, \delta_i | W_i; \theta) p(y_i | W_i; \theta)$$

$$p(y_i | W_i; \theta) = \prod_j p y_i(tij) | W_i; \theta$$

Log-likelihood contribution:

$$\log p(T_i, \delta_i, y_i; \theta) = \log \int p(T_i, \delta_i, y_i | W_i; \theta) dW_i$$

$$= log \int p(T_i, \delta_i | W_i; \theta_t, \beta)[\prod p(y_i | W_i; \theta_y)] p(W_i; \theta_W) dW_i$$

where T_i is the time to survival and δ_i is the censoring indicator.

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Extensions on Joint Modelling for longitudinal and survival data

- Multiple longitudinal data
- Dynamic predictions for time-to-event data
- Competing risks on time-to-event data
- Non-linear longitudinal trends
- Non-linear effects in Cox proportional hazard model

Extensions on Joint Modelling for longitudinal and survival data

- Multiple longitudinal data
  Bayesian models and two-stage approaches. *JMbayes* uses IS (Importance Sampling (IS)) two-stage approach to correct the full likelihood. *JMbayes2*
- Dynamic predictions for time-to-event data
  JM, *JMbayes* packages
- Competing risks on time-to-event data
  JMbayes2 package
- Non-linear longitudinal trends
  JM, Two-stage modelling approaches using *mgcv*
- Non-linear effects in Cox proportional hazard model
  Two-stage modelling approaches using *mgcv*

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Motivating Database: Peritoneal Dialysis Program

The Peritoneal Dialysis Programme includes 160 patients at the Unit of the Nephrology Department (Hospital Geral de Santo António, Centro Hospital do Porto) followed up between years: October 1999 and February 2013.

- Baseline characteristics: age, gender
- The event that forced the patient to abandon the treatment program: time to kidney failure with % 66.88 censored times
- The median of follow-up time was 27.4 months (IQR: 12.8-49.0 months)
- Longitudinal biomarkers: Albumin and Calcium measurements among others...

Motivating Database: Peritoneal Dialysis Program

Main Objective: Association between longitudinal Albumin and Calcium measurements and their effects on survival.

- Low albumin level is usually associated with kidney failure
- Calcium levels of the blood may drop when the kidney fails

Motivating Database: Peritoneal Dialysis Program

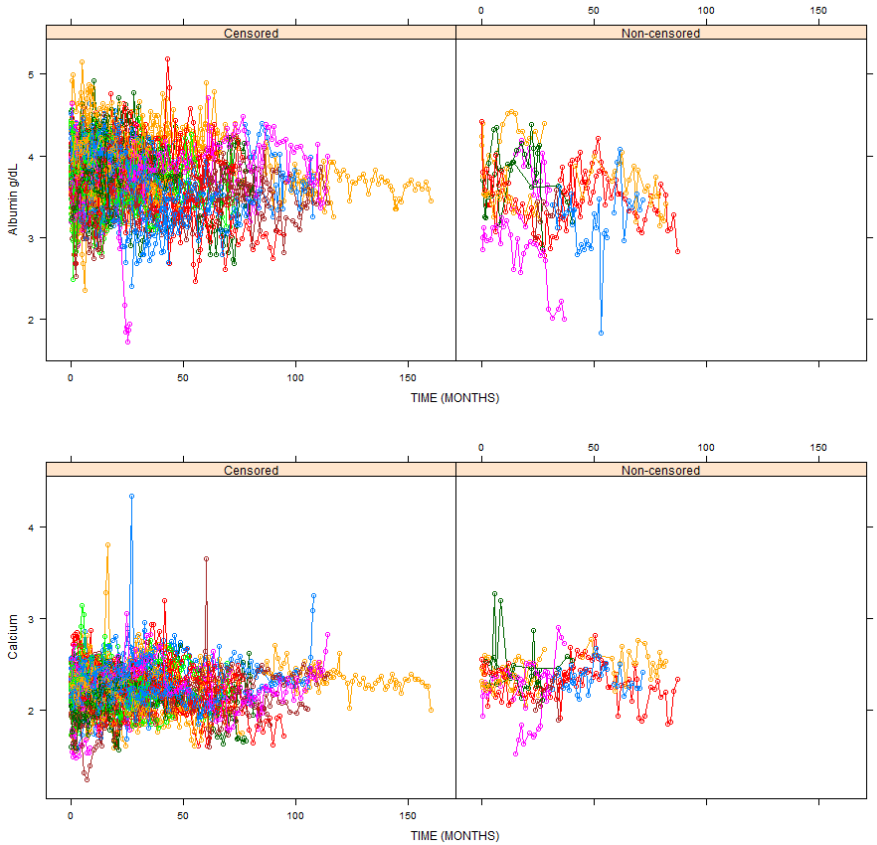

Figure: Subject specific trajectories of Albumin and Calcium levels for censored and non-censored times

Motivating Database : OLT Data

Motivating Database 2: Institutional clinical database, adult patients who underwent OLT in the Hospital Clínico Universitario de Santiago, between July 1994 and July 2011.

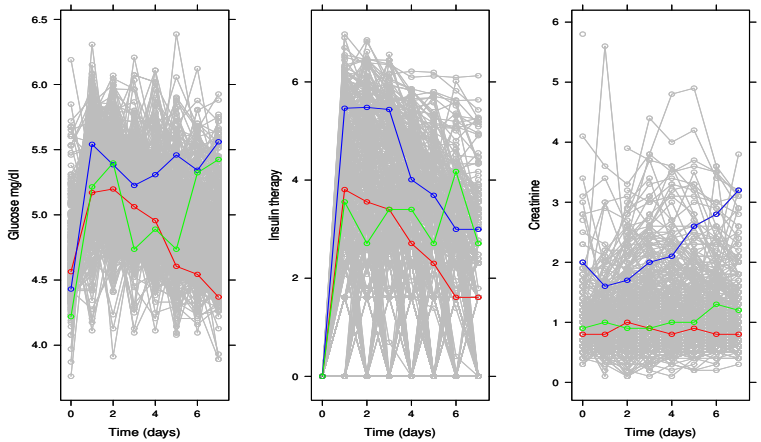

Figure: Glucose, Insulin and Creatinine levels of patients. Subject specific trajectories of 3 patients for each measurements are highlighted in colors.

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Software

R packages for Joint Models

- *joineR* by Pete Philipson, Ines Sousa , Peter J. Diggle,Paula Williamson
  Allows one longitudinal and survival data with random effects parameterization only.
- *joineRML* by Graeme L. Hickey, Pete Philipson, Andrea Jorgensen, Ruwanthi Kolamunnage-Dona, Paula Williamson, Dimitris Rizopoulos, Alessandro Gasparini
  Allows joint models for multiple longitudinal and survival data with Monte Carlo Expectation-Maximisation.

Software

R packages for Joint Models

- *JM* by Dimitris Rizopoulos
  Allows one longitudinal and survival data with different parametrizations.
- *JMbayes* by Dimitris Rizopoulos
  Directly implements the MCMC, allows for categorical longitudinal data as well, allows for general transformation functions
- *JMbayes2* by Dimitris Rizopoulos
  Multiple longitudinal outcomes of mixed type (continuous/categorical) and multiple event times (competing risks and multi-state processes) are accommodated.

Example in JMbayes (Rizopoulos example)

```
install.packages("JMbayes")
install.packages("rjags")
library(JMbayes)
library(rjags)

MixedModelFit2 <- mvglmer(list(log(serBilir) ~
year + (year | id),

spiders ~ year + (1 | id)), data = pbc2,
families = list(gaussian, binomial))

JMFit2 <- mvJointModelBayes(MixedModelFit2, CoxFit,
timeVar = "year")
```

Example in JMbayes2, (Rizopoulos example)

```
install.packages("JMbayes2")
# Cox model for the composite event
pbc2.id$status2 <- as.numeric(pbc2.id$status != 'alive')
    CoxFit <- coxph(Surv(years, status2) ~ sex,
     data = pbc2.id)

# a linear mixed model for log serum bilirubin
fm1 <- lme(log(serBilir) ~ year * sex,
data = pbc2, random = ~ year | id)

# a linear mixed model for the prothrombin time
fm2 <- lme(prothrombin ~ year * sex,
data = pbc2, random = ~ year | id)
```

Example in JMbayes2

```
# a mixed effects logistic regression model for ascites
fm3 <- mixed_model(ascites ~ year + sex, data = pbc2,
random = ~ year | id, family = binomial())

# the joint model that links all sub-models
jointFit <- jm(CoxFit, list(fm1, fm2, fm3),
time_var = "year",
n_iter = 12000L, n_burnin = 2000L, n_thin = 5L)
summary(jointFit)
```

Example in JMbayes2

```
library("JMbayes")

MixedModelFit <- mvglmer(list(prothrombin ~
 year * sex + (year | id),
hepatomegaly ~ year * sex + (year | id)),
data = pbc2,
families = list(gaussian, binomial))


pbc2.id$event <- as.numeric(pbc2.id$status != "alive")
CoxFit <- coxph(Surv(years, event) ~ drug + age,
 data = pbc2.id, model = TRUE)
```

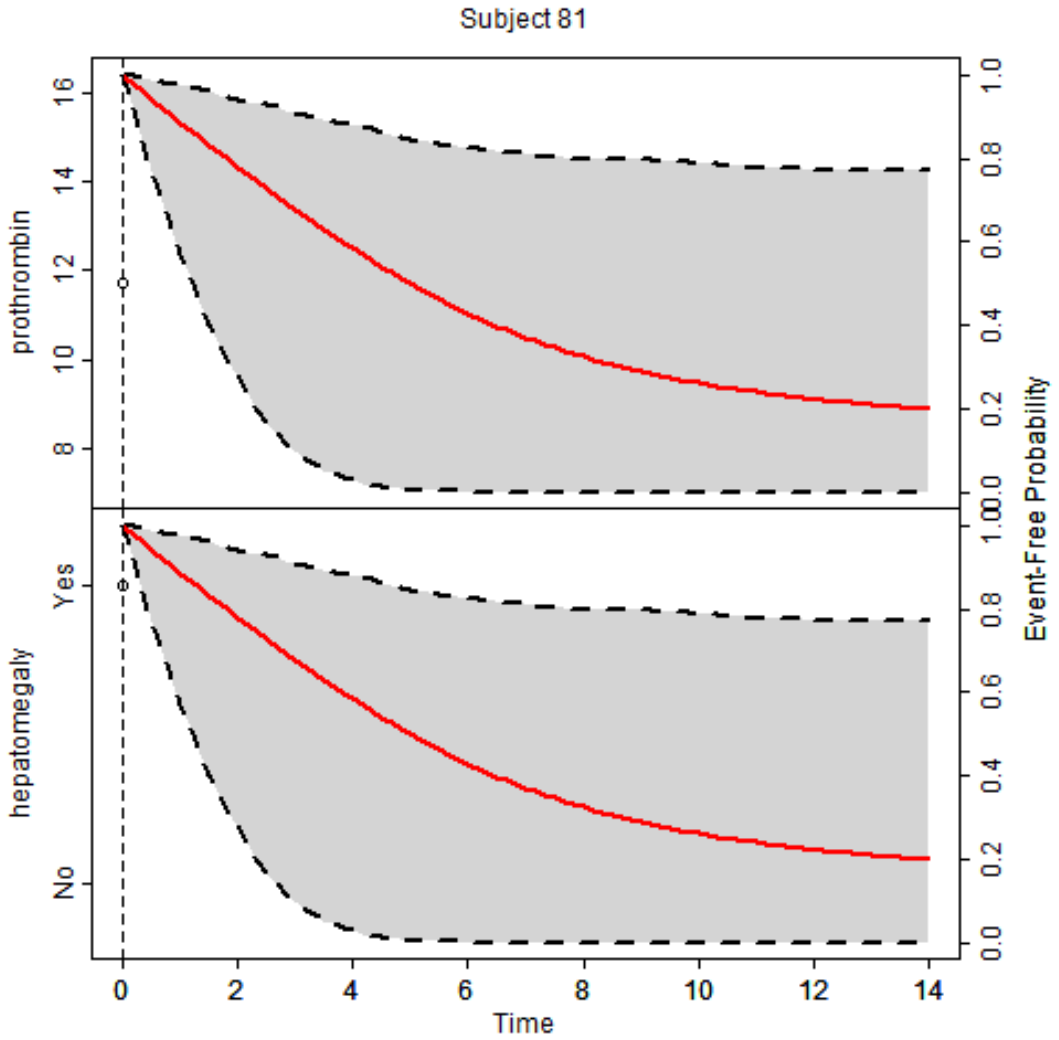
Example in JMbayes2

```
ND <- pbc2[pbc2$id == 81, ]

sprobs <- survfitJM(JMFit, ND)
sprobs

plot(sprobs, split = c(2, 1), surv_in_all = TRUE,
lty_lines_CI = 3, col_lines = "blue",
 col_fill_CI = "pink2",
main = "Patient 81", ylab = c("Prothro", "Hepa"),
col_points = "red", pch_points = 16,
cex_xlab = 0.8, cex_ylab = 0.8, cex_zlab = 0.8,
cex_main = 0.8, cex_axis = 0.7)
```

Example in JMbayes2

```
N <- nrow(ND)
dyn_sprobs <- vector("list", N)

for (i in seq_len(N)) {
dyn_sprobs[[i]] <- survfitJM(JMFit, ND[1:i, ],
survTimes = seq(0, 14, length.out = 85))
plot(dyn_sprobs[[i]], split = c(2, 1),
surv_in_all = TRUE)
}
```

Dynamic Predictions of Survival Data



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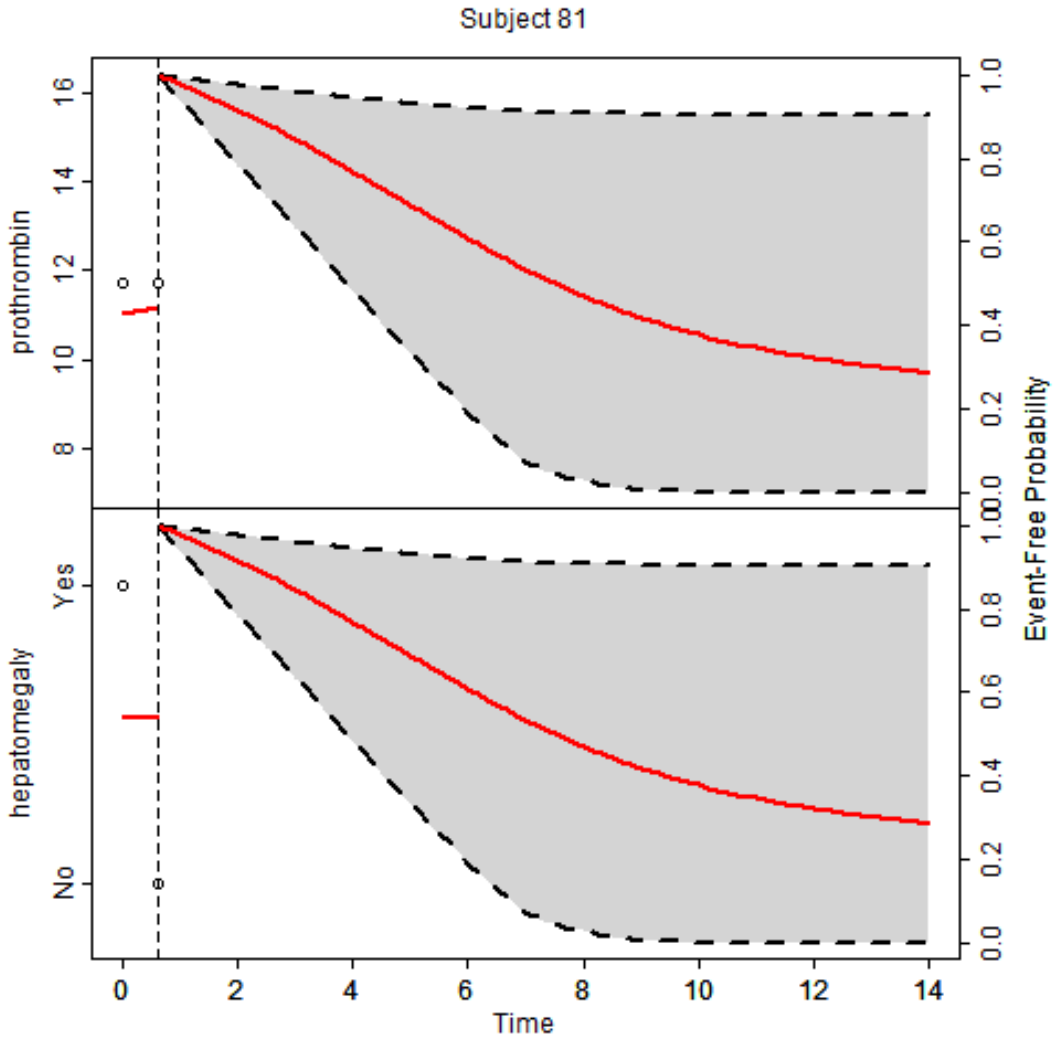

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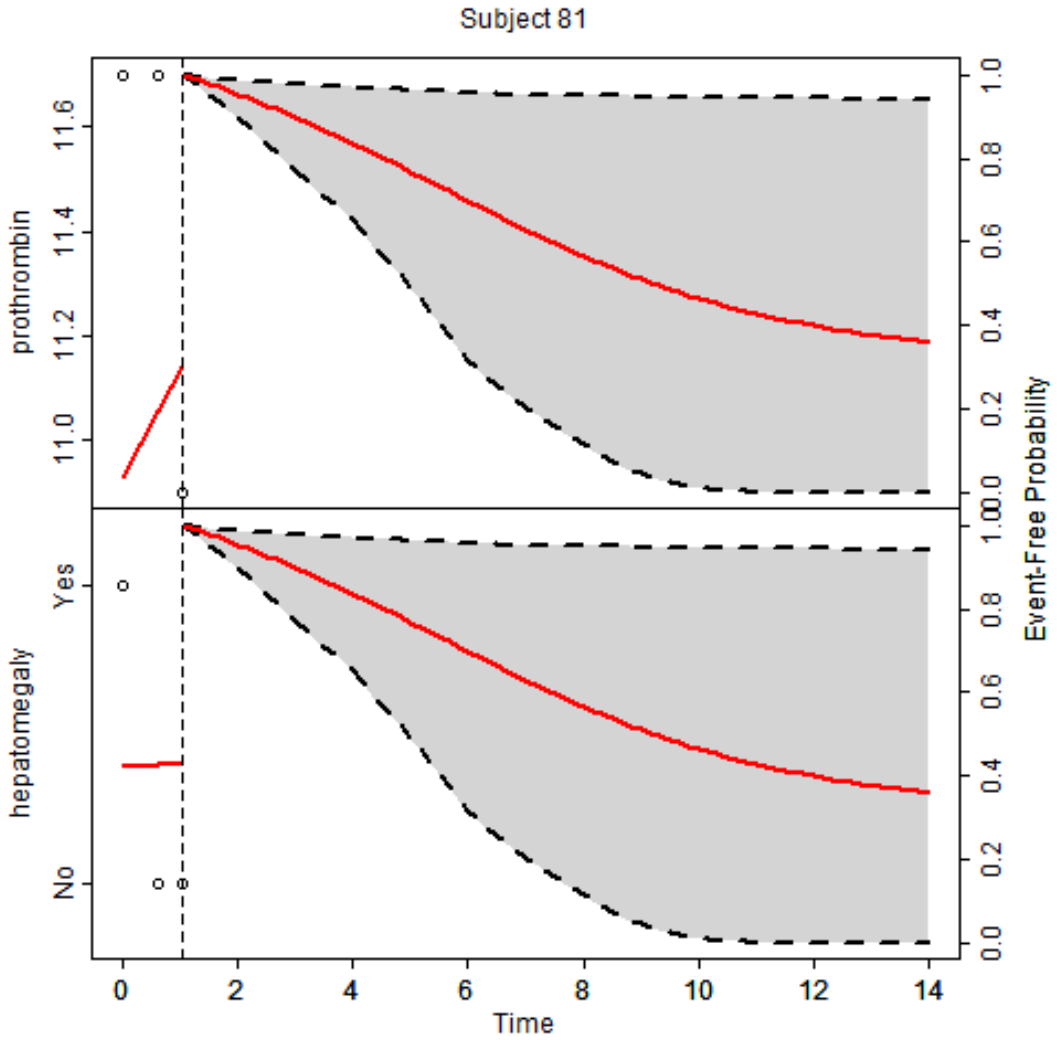
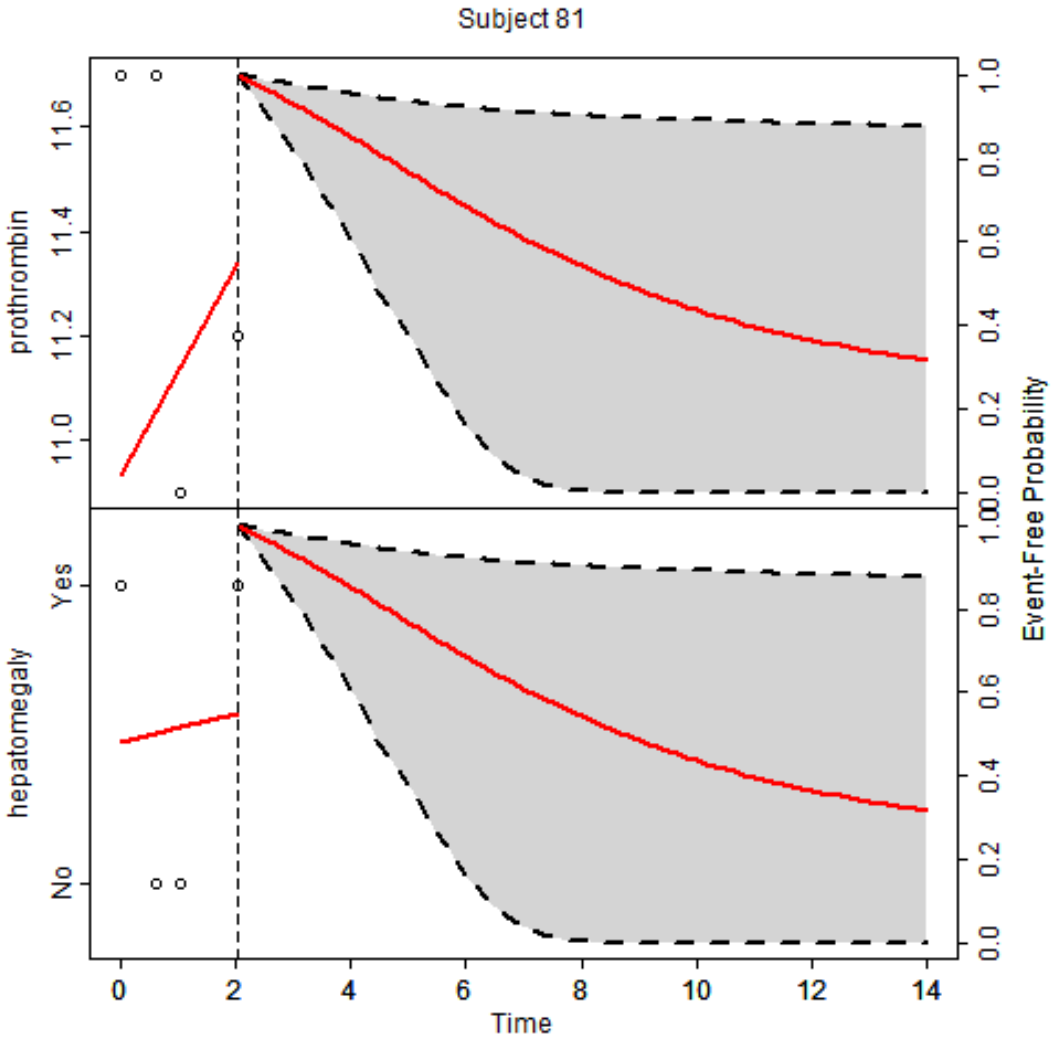


Dynamic Predictions of Survival Data



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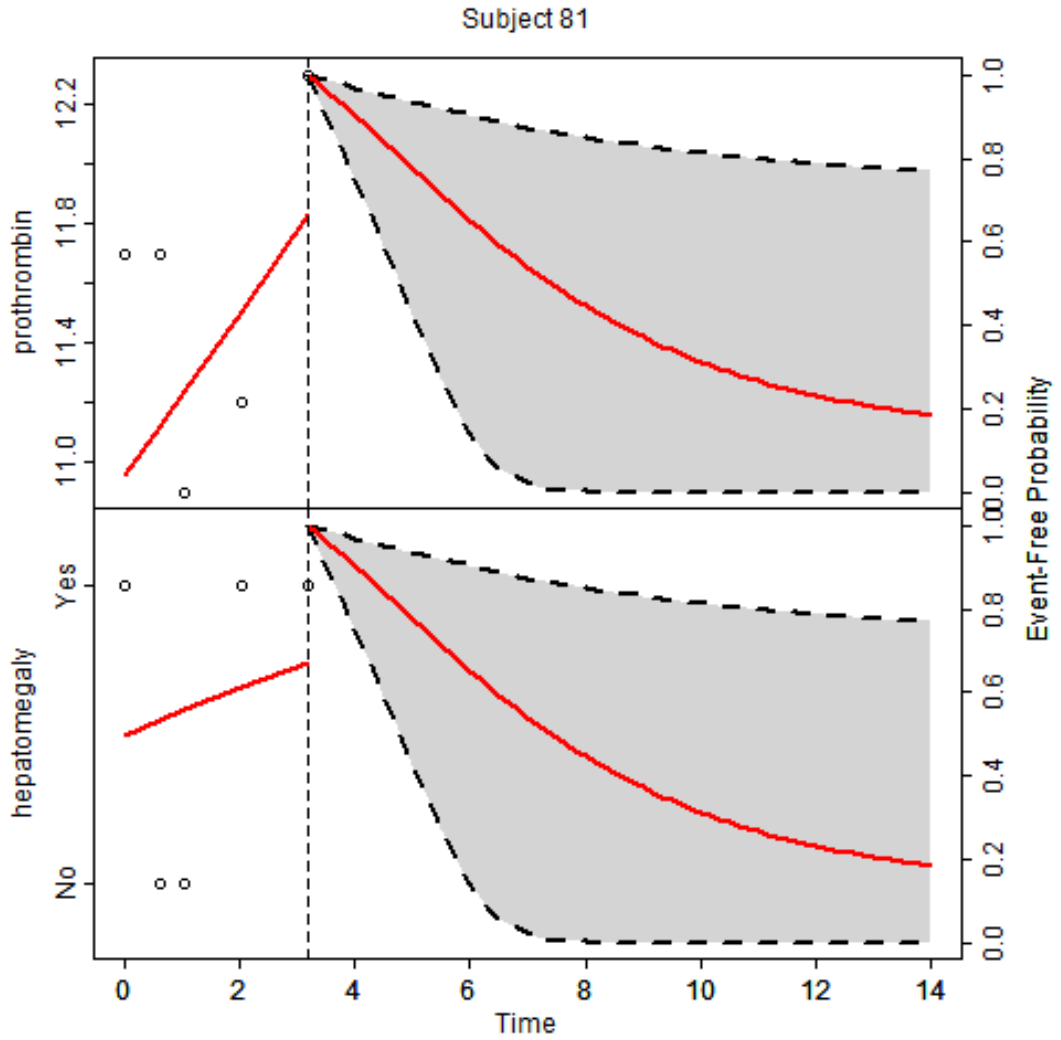

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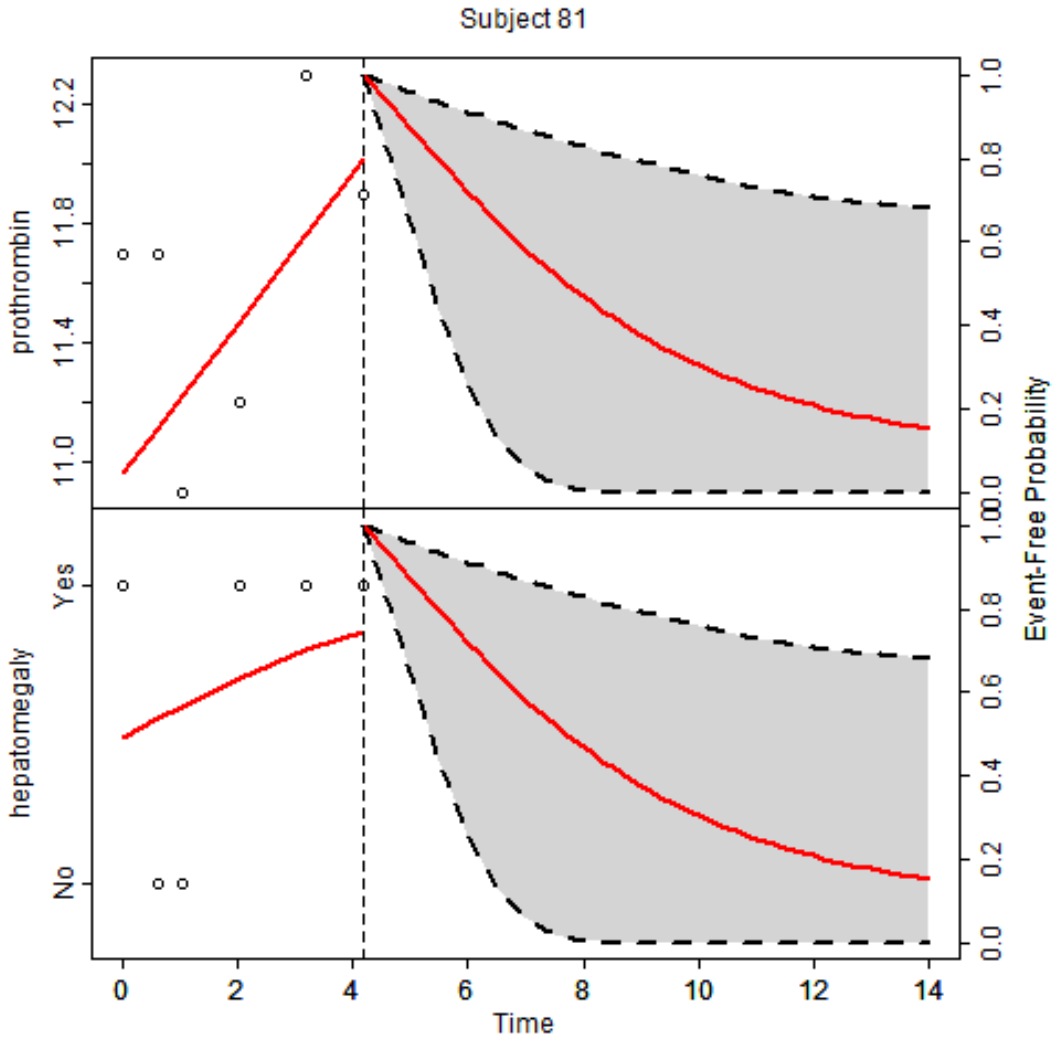

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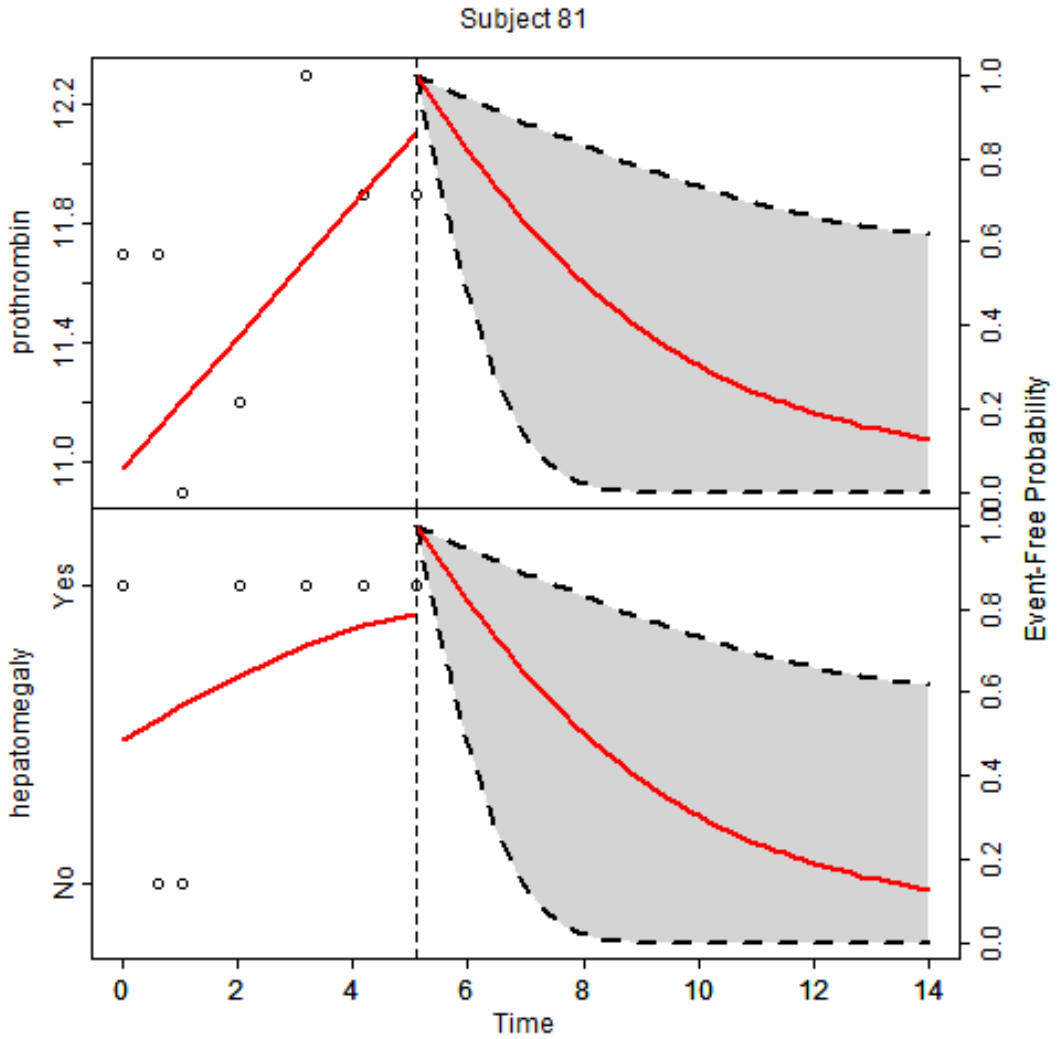

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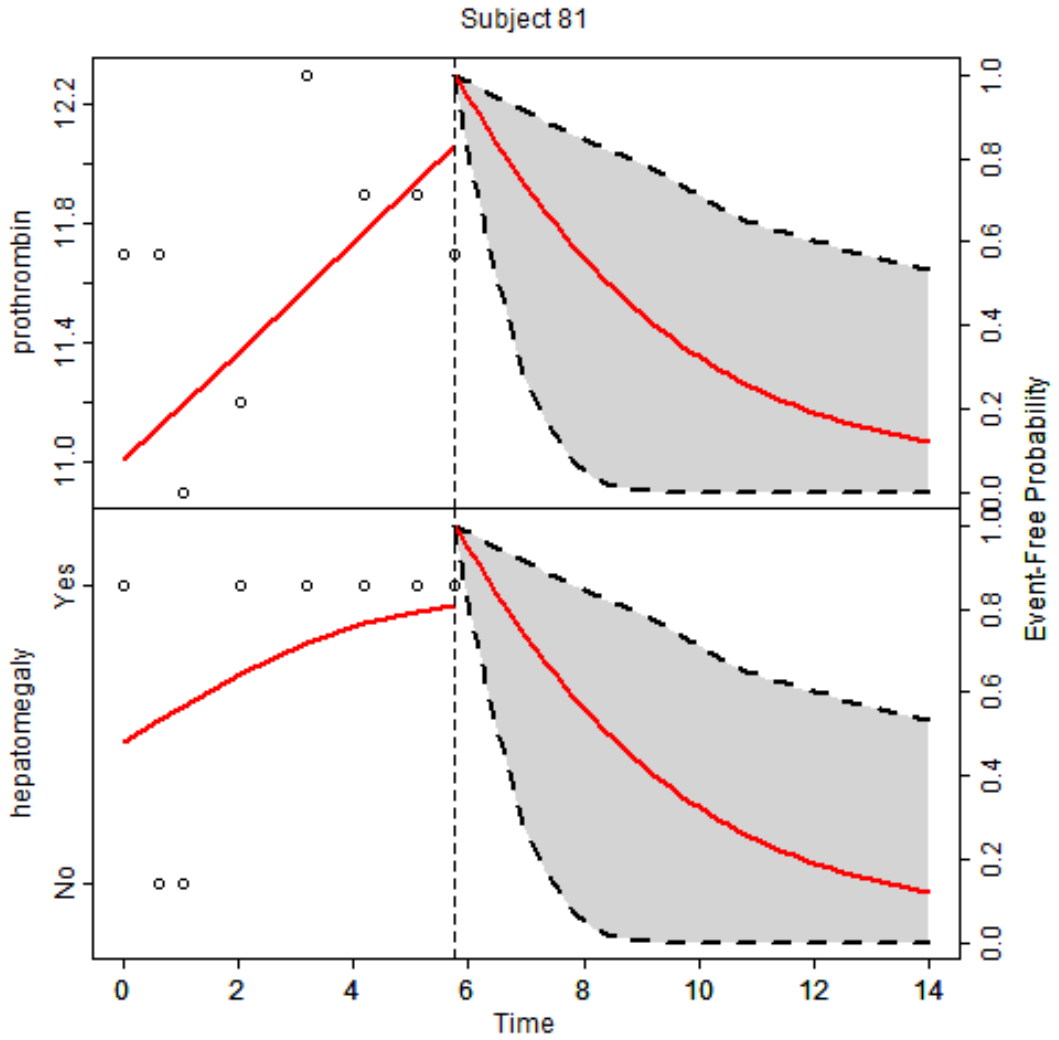

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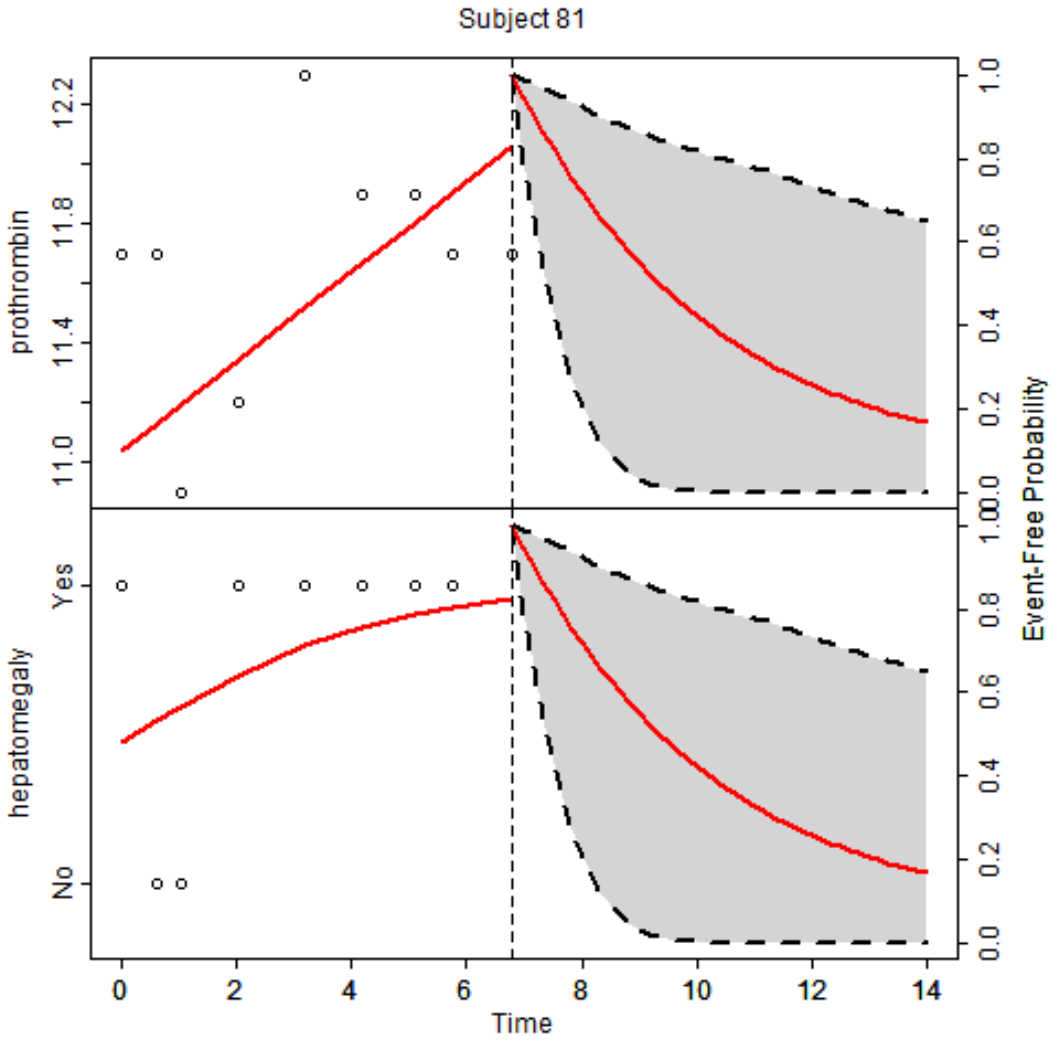

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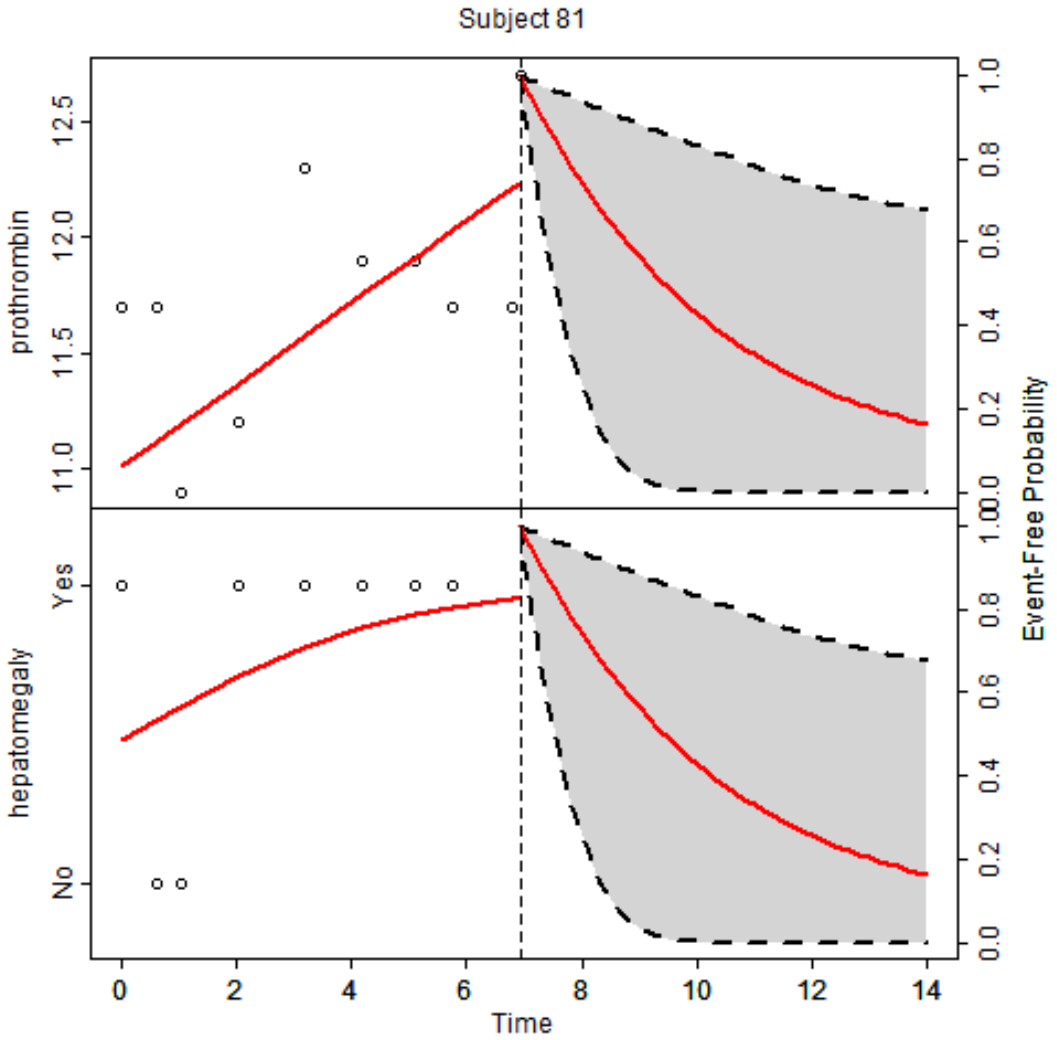

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