mc5296

2023-11-28

```
library(survival)
library(StepReg)
head(rotterdam)
```

```
##      pid year age meno  size grade nodes pgr  er hormon chemo rtime recur dtime
## 1393   1 1992  74    1  <=20     3     0  35 291      0     0  1799     0  1799
## 1416   2 1984  79    1 20-50     3     0  36 611      0     0  2828     0  2828
## 2962   3 1983  44    0  <=20     2     0 138   0      0     0  6012     0  6012
## 1455   4 1985  70    1 20-50     3     0   0  12      0     0  2624     0  2624
## 977    5 1983  75    1  <=20     3     0 260 409      0     0  4915     0  4915
## 617    6 1983  52    0  <=20     3     0 139 303      0     0  5888     0  5888
##      death
## 1393     0
## 1416     0
## 2962     0
## 1455     0
## 977      0
## 617      0
```

```
rfs  <- pmax(rotterdam$recur, rotterdam$death)
rfstime <- with(rotterdam, ifelse(recur==1, rtime, dtime))
rotterdam$tstart = c(rep(0,2982))
surv_object <- with(rotterdam, Surv(tstart, rfstime, rfs)) #with consideration of time-varying covariat
fit1 <- coxph(surv_object ~ pspline(age) + size + grade + nodes + pgr + er + hormon + chemo, data = rot
fit2 <- coxph(Surv(rfstime, rfs)~ pspline(age) + size + grade + nodes + pgr + er + hormon + chemo, data
summary(fit1)
```

```
## Call:
## coxph(formula = surv_object ~ pspline(age) + size + grade + nodes +
##     pgr + er + hormon + chemo, data = rotterdam)
##
##   n= 2982, number of events= 1713
##
##                       coef       se(coef)  se2       Chisq  DF   p
## pspline(age), linear  4.409e-03 2.118e-03 2.118e-03   4.33 1.00 3.7e-02
## pspline(age), nonlin                                  35.87 3.05 8.6e-08
## size20-50             3.337e-01 5.479e-02 5.478e-02  37.09 1.00 1.1e-09
## size>50               5.829e-01 8.278e-02 8.272e-02  49.59 1.00 1.9e-12
## grade                 3.216e-01 6.020e-02 6.018e-02  28.53 1.00 9.2e-08
## nodes                 7.620e-02 4.420e-03 4.417e-03 297.23 1.00 1.3e-66
## pgr                  -1.090e-04 9.704e-05 9.688e-05   1.26 1.00 2.6e-01
## er                   -2.711e-05 9.424e-05 9.400e-05   0.08 1.00 7.7e-01
## hormon               -1.077e-01 7.784e-02 7.775e-02   1.92 1.00 1.7e-01
```

```
## chemo                -9.963e-02 7.012e-02 6.988e-02   2.02 1.00 1.6e-01
##
##           exp(coef) exp(-coef) lower .95 upper .95
## ps(age)3     0.9295     1.0759    0.5901     1.464
## ps(age)4     0.8642     1.1571    0.4200     1.778
## ps(age)5     0.7667     1.3043    0.3412     1.723
## ps(age)6     0.6359     1.5725    0.2851     1.419
## ps(age)7     0.5794     1.7258    0.2636     1.274
## ps(age)8     0.6057     1.6511    0.2758     1.330
## ps(age)9     0.6622     1.5102    0.3008     1.458
## ps(age)10    0.7532     1.3277    0.3415     1.661
## ps(age)11    0.8970     1.1148    0.4055     1.985
## ps(age)12    1.1518     0.8682    0.5089     2.607
## ps(age)13    1.5048     0.6645    0.5966     3.795
## ps(age)14    1.9730     0.5068    0.6055     6.429
## size20-50    1.3961     0.7163    1.2540     1.554
## size>50      1.7913     0.5583    1.5230     2.107
## grade        1.3793     0.7250    1.2258     1.552
## nodes        1.0792     0.9266    1.0699     1.089
## pgr          0.9999     1.0001    0.9997     1.000
## er           1.0000     1.0000    0.9998     1.000
## hormon       0.8979     1.1138    0.7708     1.046
## chemo        0.9052     1.1048    0.7889     1.039
##
## Iterations: 7 outer, 18 Newton-Raphson
##      Theta= 0.9748169
## Degrees of freedom for terms= 4 2 1 1 1 1 1 1
## Concordance= 0.675  (se = 0.007 )
## Likelihood ratio test= 526.2  on 12.03 df,   p=<2e-16
```

```
summary(fit2)
```

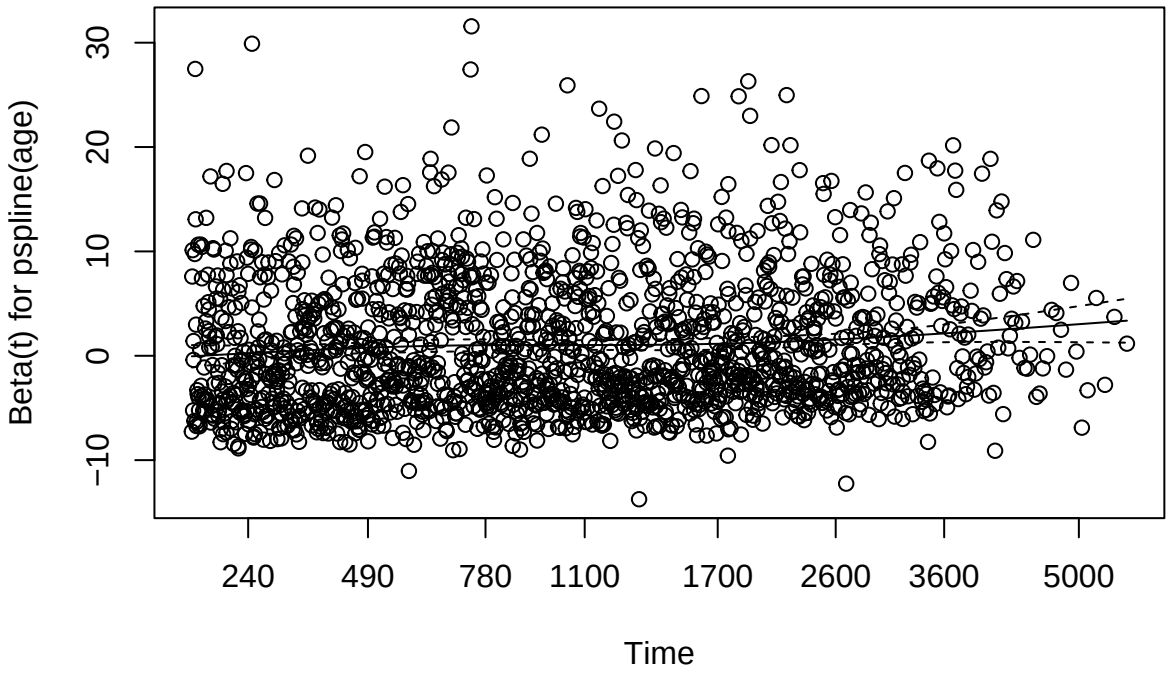
```
## Call:
## coxph(formula = Surv(rfstime, rfs) ~ pspline(age) + size + grade +
##     nodes + pgr + er + hormon + chemo, data = rotterdam)
##
##   n= 2982, number of events= 1713
##
##                       coef       se(coef)  se2       Chisq  DF   p
## pspline(age), linear  4.409e-03 2.118e-03 2.118e-03   4.33 1.00 3.7e-02
## pspline(age), nonlin                                  35.87 3.05 8.6e-08
## size20-50             3.337e-01 5.479e-02 5.478e-02  37.09 1.00 1.1e-09
## size>50               5.829e-01 8.278e-02 8.272e-02  49.59 1.00 1.9e-12
## grade                 3.216e-01 6.020e-02 6.018e-02  28.53 1.00 9.2e-08
## nodes                 7.620e-02 4.420e-03 4.417e-03 297.23 1.00 1.3e-66
## pgr                  -1.090e-04 9.704e-05 9.688e-05   1.26 1.00 2.6e-01
## er                   -2.711e-05 9.424e-05 9.400e-05   0.08 1.00 7.7e-01
## hormon               -1.077e-01 7.784e-02 7.775e-02   1.92 1.00 1.7e-01
## chemo                -9.963e-02 7.012e-02 6.988e-02   2.02 1.00 1.6e-01
##
##           exp(coef) exp(-coef) lower .95 upper .95
## ps(age)3     0.9295     1.0759    0.5901     1.464
## ps(age)4     0.8642     1.1571    0.4200     1.778
## ps(age)5     0.7667     1.3043    0.3412     1.723
```

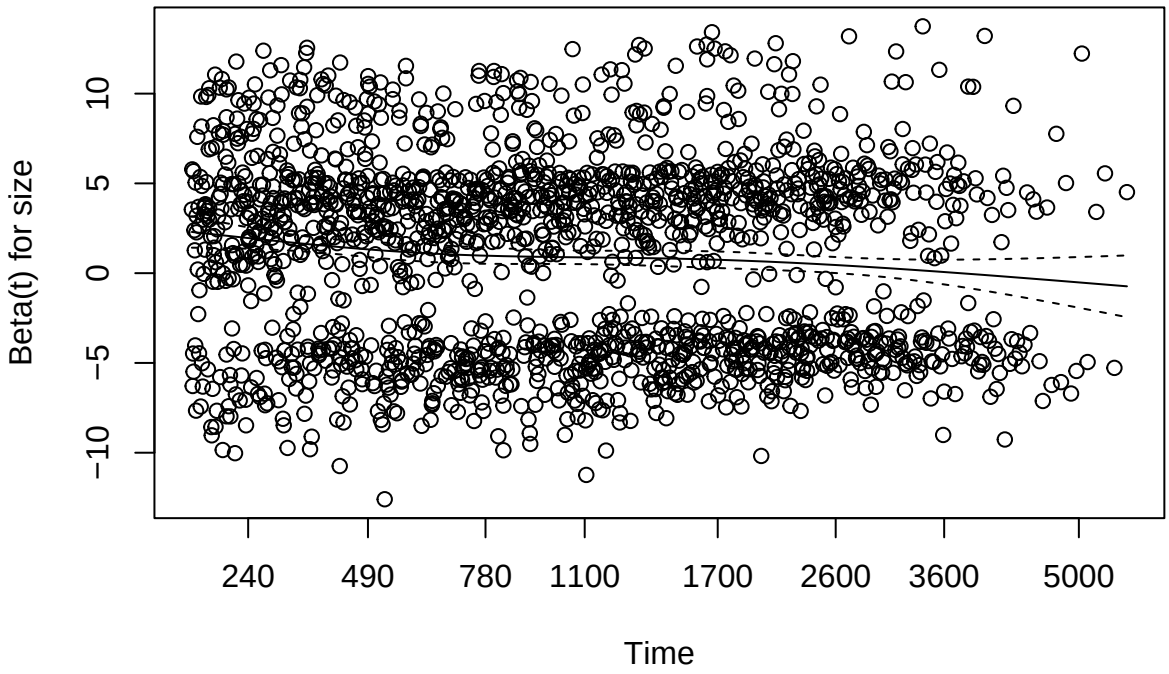
```
## ps(age)6     0.6359     1.5725    0.2851     1.419
## ps(age)7     0.5794     1.7258    0.2636     1.274
## ps(age)8     0.6057     1.6511    0.2758     1.330
## ps(age)9     0.6622     1.5102    0.3008     1.458
## ps(age)10    0.7532     1.3277    0.3415     1.661
## ps(age)11    0.8970     1.1148    0.4055     1.985
## ps(age)12    1.1518     0.8682    0.5089     2.607
## ps(age)13    1.5048     0.6645    0.5966     3.795
## ps(age)14    1.9730     0.5068    0.6055     6.429
## size20-50    1.3961     0.7163    1.2540     1.554
## size>50      1.7913     0.5583    1.5230     2.107
## grade        1.3793     0.7250    1.2258     1.552
## nodes        1.0792     0.9266    1.0699     1.089
## pgr          0.9999     1.0001    0.9997     1.000
## er           1.0000     1.0000    0.9998     1.000
## hormon       0.8979     1.1138    0.7708     1.046
## chemo        0.9052     1.1048    0.7889     1.039
##
## Iterations: 7 outer, 18 Newton-Raphson
##      Theta= 0.9748169
## Degrees of freedom for terms= 4 2 1 1 1 1 1 1
## Concordance= 0.675  (se = 0.007 )
## Likelihood ratio test= 526.2  on 12.03 df,   p=<2e-16
```

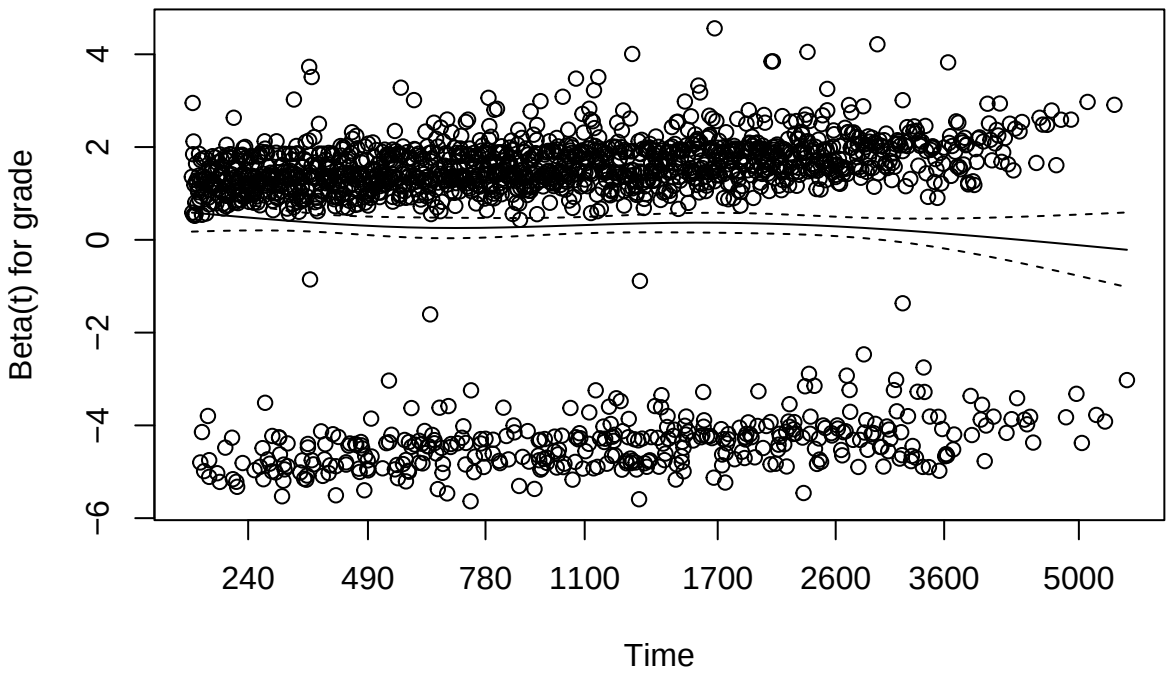
```
# Fit a basic Cox proportional hazards model
cox_model <- stepwiseCox(Surv(rfstime, rfs) ~ age + size + grade + nodes + pgr + er + hormon + chemo, da
summary(cox_model)
```

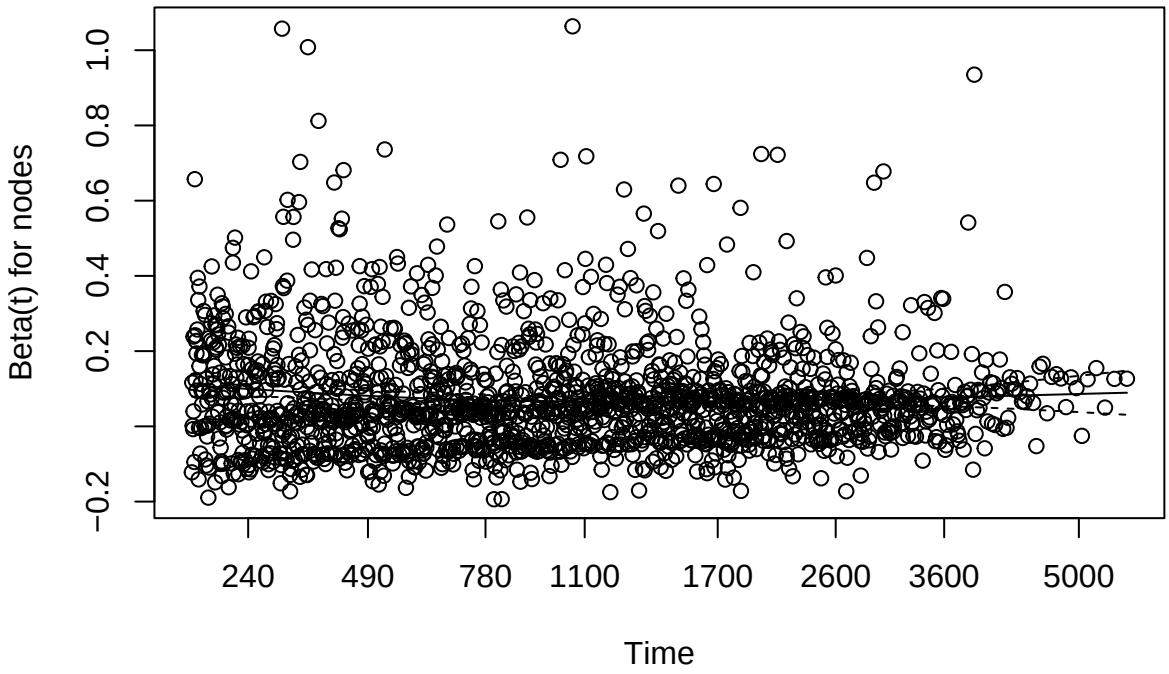
```
##                                      Length Class      Mode
## Summary of Parameters                2      data.frame list
## Variables Type                       2      data.frame list
## Process of Selection                 6      data.frame list
## Selected Varaibles                   6      data.frame list
## Coefficients of the Selected Variables 6    data.frame list
```

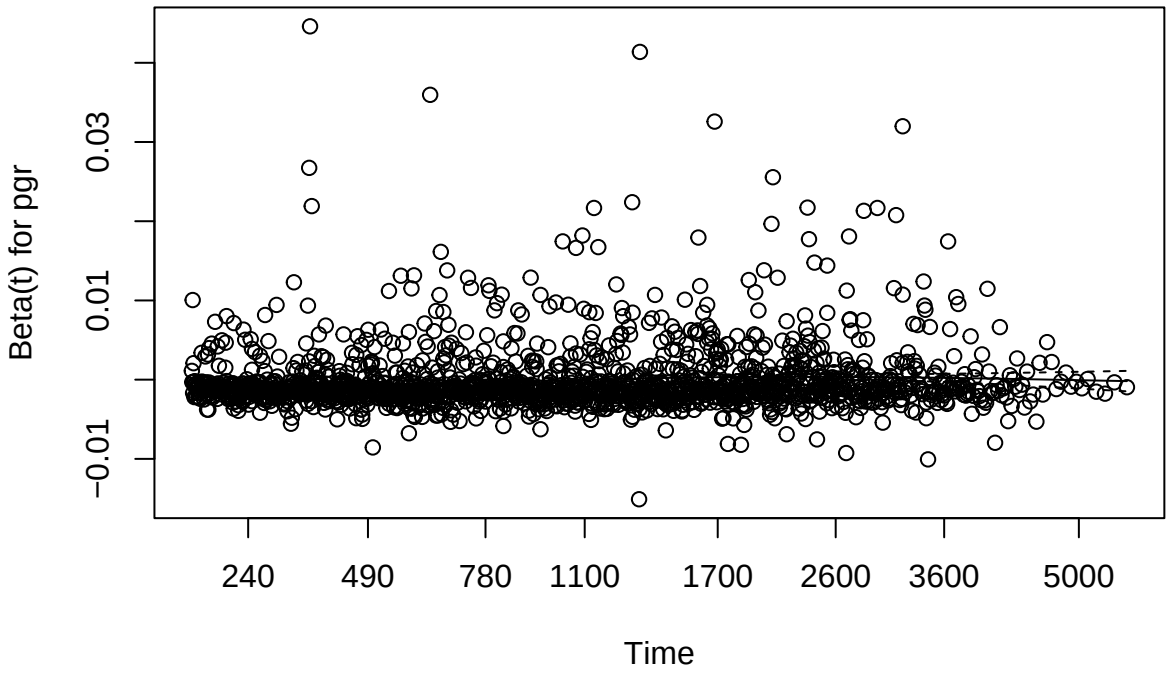
```
# Checking the Proportional Hazards assumption
cox.zph_model <- cox.zph(fit1)
plot(cox.zph_model)
```

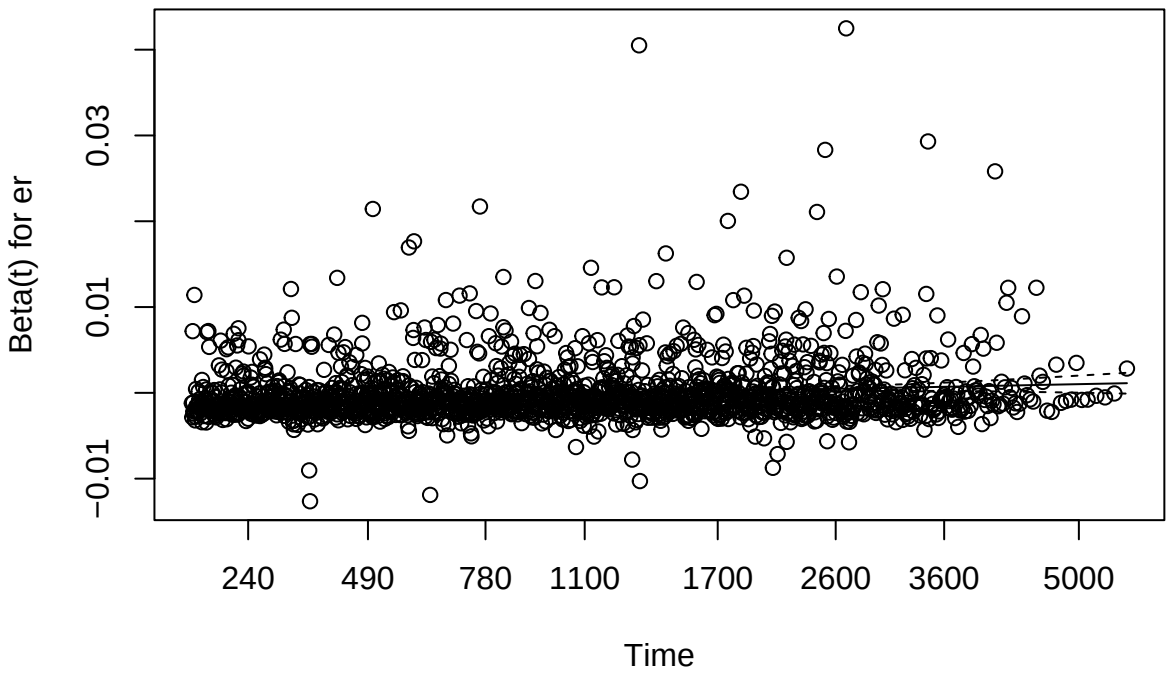

Beta(t) for pspline(age)
30
20
10
0
−10
240
490
780
1100
1700
2600
3600
5000
Time

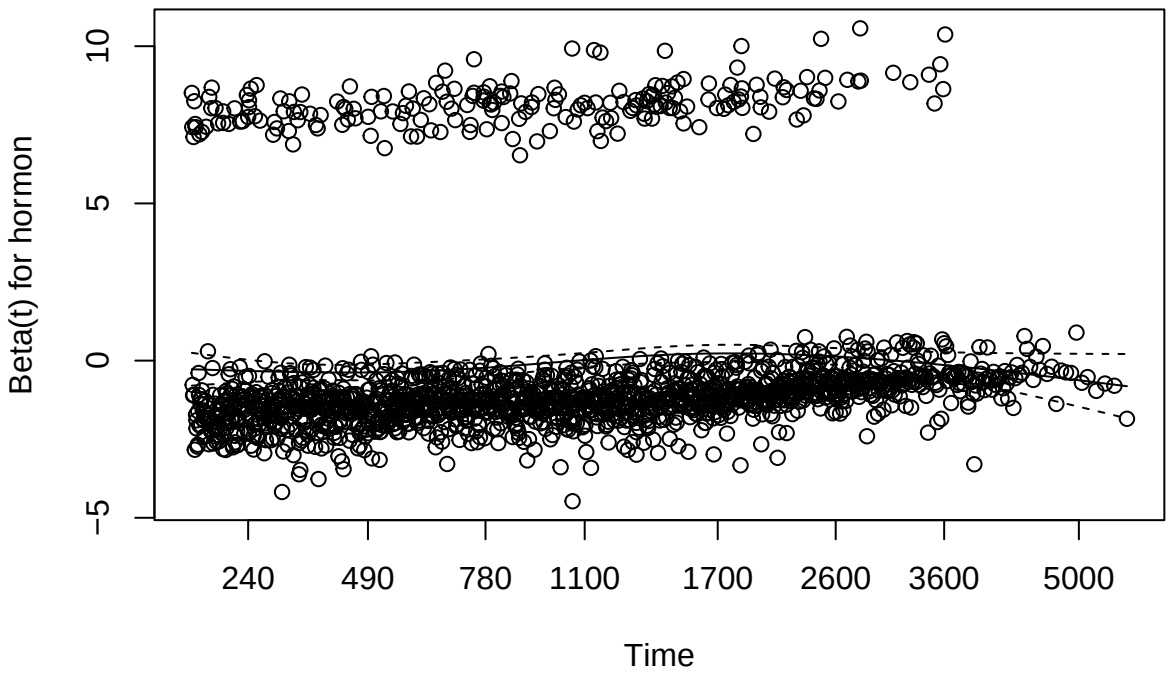

Beta(t) for size
10
5
0
−5
−10
240
490
780
1100
1700
2600
3600
5000
Time

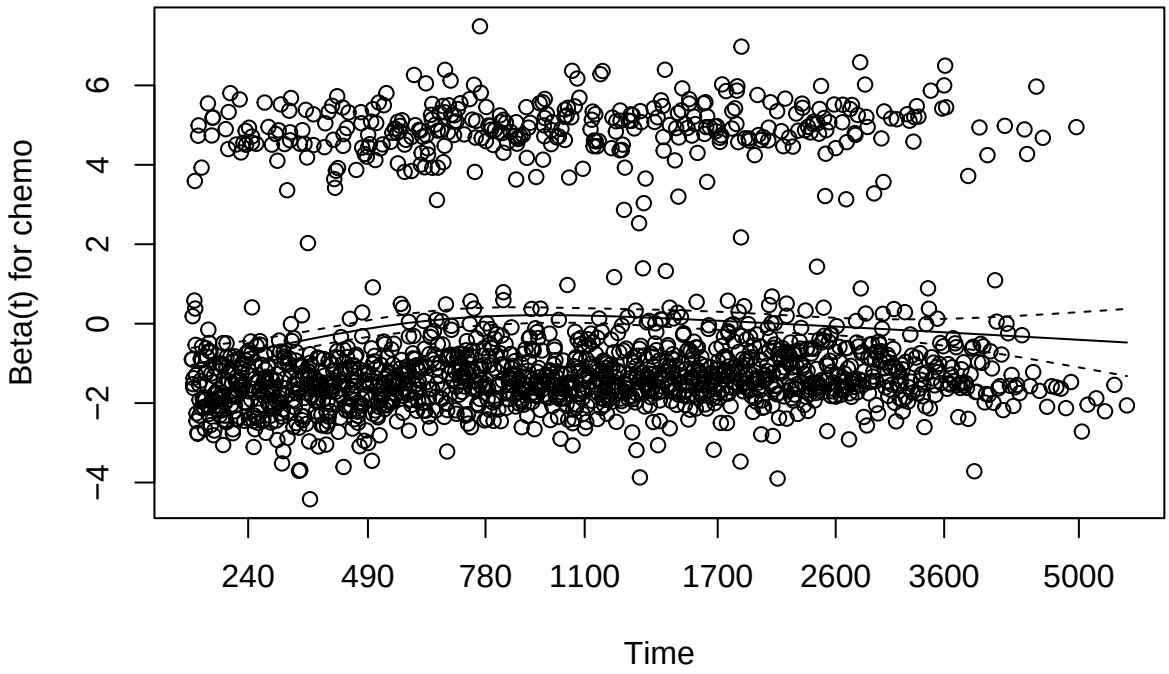

Beta(t) for grade
4
2
0
−2
−4
−6
240
490
780
1100
1700
2600
3600
5000
Time


Beta(t) for nodes
−0.2
0.2
0.4
0.6
0.8
1.0
240
490
780
1100
1700
2600
3600
5000
Time


Beta(t) for pgr
0.03
0.01
−0.01
240
490
780
1100
1700
2600
3600
5000
Time


Beta(t) for er
0.03
0.01
−0.01
240
490
780
1100
1700
2600
3600
5000
Time


Beta(t) for hormon
10
5
0
−5
240
490
780
1100
1700
2600
3600
5000
Time



Age: The residuals for age do not show a clear trend over time, suggesting that age satisfies the proportional hazards assumption.

Size: Similar to age, the plot for size does not indicate any systematic trend, indicating no violation of the proportional hazards assumption.

Grade: The plot for grade shows residuals scattered around the zero line without a distinct pattern, which suggests that the assumption holds.

Nodes: The residuals for nodes are also randomly distributed, which indicates no obvious violation of the assumption.

PGR: The plot for pgr again shows a random scatter, suggesting that the proportional hazards assumption may not be violated.

ER: As with pgr, the plot for er shows a random scatter of residuals, indicating that the assumption is likely met.

Hormon: The residuals for hormon do not display a distinct trend, suggesting the assumption is reasonable.

Chemo: The plot for chemo also shows residuals that are randomly distributed around the zero line, suggesting no violation of the proportional hazards assumption.

Coefficients and Hazard Ratios

Age: For each year increase in age, the hazard increases by a factor of 1.0045 ($p = 0.0447$). This is statistically significant at the 5% level.

Size (20-50 vs <=20): The hazard is 1.4287 times higher for size 20-50 compared to <=20 ($p < 2e\text{-}16$), which is statistically significant.

Size (>50 vs <=20): The hazard is 1.9040 times higher for size >50 compared to <=20 ($p < 2e\text{-}16$), also statistically significant.

Grade: Each unit increase in grade is associated with a 1.3845 times increase in the hazard ($p < 2e\text{-}16$), which is statistically significant.

Nodes: Each additional node is associated with a 1.0773 times increase in the hazard ($p < 2e\text{-}16$), which is statistically significant.

Pgr and ER: The hazard ratios are very close to 1, and the p-values indicate that these are not statistically significant predictors in the model.

Hormon: Being on hormone treatment is associated with a hazard ratio of 0.8798 compared to not being on hormone treatment, but this is not statistically significant at the 5% level ($p = 0.0978$).

Chemo: Being on chemotherapy is associated with a hazard ratio of 0.9109 compared to not being on chemotherapy, but this is not statistically significant at the 5% level ($p = 0.1746$).

Model Fit

Concordance: 0.668. This statistic is a measure of the model's predictive ability (1 is perfect, 0.5 is no better than chance). Likelihood Ratio Test: 490.1 on 9 degrees of freedom with $p < 2e\text{-}16$, indicating that the model as a whole is statistically significant.

Wald Test: 614.3 on 9 degrees of freedom with $p < 2e\text{-}16$, also indicating the overall significance of the model.

Score (Logrank) Test: 678.1 on 9 degrees of freedom with $p < 2e\text{-}16$, further confirming the model's significance.