A Handbook of Statistical Analyses Using R — 3rd Edition

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Survival Analysis: Glioma Treatment and Breast Cancer Survival

11.1 Introduction

11.2 Survival Analysis

11.3 Analysis Using R

11.3.1 Glioma Radioimmunotherapy

Figure 11.1 leads to the impression that patients treated with the novel radioimmunotherapy survive longer, regardless of the tumor type. In order to assess if this informal finding is reliable, we may perform a log-rank test via

```
R> survdiff(Surv(time, event) ~ group, data = g3)
```

```
Call:
survdiff(formula = Surv(time, event) ~ group, data = g3)

              N Observed Expected (O-E)^2/E (O-E)^2/V
group=Control  6        4     1.49      4.23      6.06
group=RIT     11        2     4.51      1.40      6.06

 Chisq= 6.1  on 1 degrees of freedom, p= 0.01
```

which indicates that the survival times are indeed different in both groups. However, the number of patients is rather limited and so it might be dangerous to rely on asymptotic tests. As shown in Chapter 4, conditioning on the data and computing the distribution of the test statistics without additional assumptions are one alternative. The function `surv_test` from package **coin** (Hothorn et al., 2006, 2013) can be used to compute an exact conditional test answering the question whether the survival times differ for grade III patients. For all possible permutations of the groups on the censored response variable, the test statistic is computed and the fraction of whose being greater than the observed statistic defines the exact p-value:

```
R> library("coin")
R> logrank_test(Surv(time, event) ~ group, data = g3,
+               distribution = "exact")
```
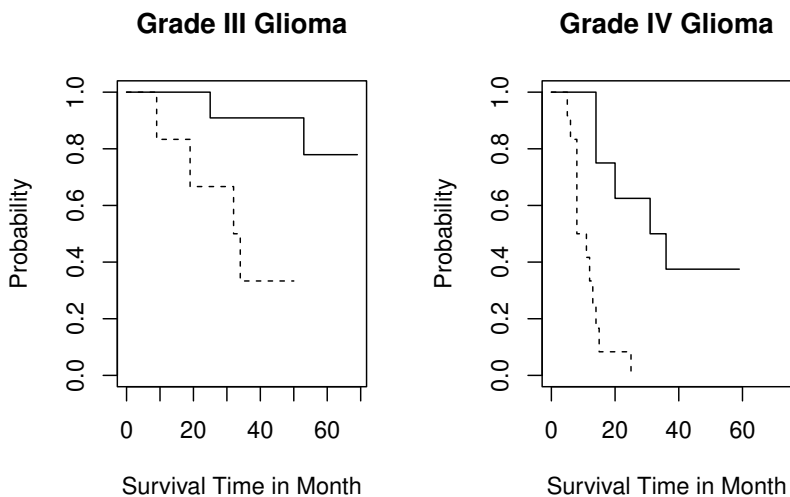
```
        Exact Two-Sample Logrank Test

data:  Surv(time, event) by group (Control, RIT)
Z = -2, p-value = 0.03
alternative hypothesis: true theta is not equal to 1
```

```
R> data("glioma", package = "coin")
R> library("survival")
R> layout(matrix(1:2, ncol = 2))
R> g3 <- subset(glioma, histology == "Grade3")
R> plot(survfit(Surv(time, event) ~ group, data = g3),
+        main = "Grade III Glioma", lty = c(2, 1),
+        ylab = "Probability", xlab = "Survival Time in Month",
+        legend.text = c("Control", "Treated"),
+        legend.bty = "n")
R> g4 <- subset(glioma, histology == "GBM")
R> plot(survfit(Surv(time, event) ~ group, data = g4),
+        main = "Grade IV Glioma", ylab = "Probability",
+        lty = c(2, 1), xlab = "Survival Time in Month",
+        xlim = c(0, max(glioma$time) * 1.05))
```


Figure 11.1   Survival times comparing treated and control patients.

which, in this case, confirms the above results. The same exercise can be performed for patients with grade IV glioma

```
R> logrank_test(Surv(time, event) ~ group, data = g4,
+                distribution = "exact")
```

```
        Exact Two-Sample Logrank Test

data:  Surv(time, event) by group (Control, RIT)
Z = -3, p-value = 2e-04
alternative hypothesis: true theta is not equal to 1
```

which shows a difference as well. However, it might be more appropriate to

answer the question whether the novel therapy is superior for both groups of tumors simultaneously. This can be implemented by *stratifying*, or *blocking*, with respect to tumor grading:

```
R> logrank_test(Surv(time, event) ~ group | histology,
+                   data = glioma, distribution = approximate(B = 10000))

        Approximative Two-Sample Logrank Test

data:  Surv(time, event) by
        group (Control, RIT)
        stratified by histology
Z = -4, p-value = 1e-04
alternative hypothesis: true theta is not equal to 1
```

Here, we need to approximate the exact conditional distribution since the exact distribution is hard to compute. The result supports the initial impression implied by Figure 11.1.

11.3.2 Breast Cancer Survival

Before fitting a Cox model to the GBSG2 data, we again derive a Kaplan-Meier estimate of the survival function of the data, here stratified with respect to whether a patient received hormonal therapy or not (see Figure 11.2).

Fitting a Cox model follows roughly the same rules as shown for linear models in Chapter 6 with the exception that the response variable is again coded as a *Surv* object. For the GBSG2 data, the model is fitted via

```
R> GBSG2_coxph <- coxph(Surv(time, cens) ~ ., data = GBSG2)
```

and the results as given by the summary method are given in Figure 11.3. Since we are especially interested in the relative risk for patients who underwent hormonal therapy, we can compute an estimate of the relative risk and a corresponding confidence interval via

```
R> ci <- confint(GBSG2_coxph)
R> exp(cbind(coef(GBSG2_coxph), ci))["horThyes",]
        2.5 % 97.5 %
 0.707  0.549  0.911
```

This result implies that patients treated with hormonal therapy had a lower risk and thus survived longer compared to women who were not treated this way.

Model checking and model selection for proportional hazards models are complicated by the fact that easy-to-use residuals, such as those discussed in Chapter 6 for linear regression models, are not available, but several possibilities do exist. A check of the proportional hazards assumption can be done by looking at the parameter estimates $\beta_1, \ldots, \beta_q$ over time. We can safely assume proportional hazards when the estimates don't vary much over time. The null hypothesis of constant regression coefficients can be tested, both globally as well as for each covariate, by using the cox.zph function

```
R> GBSG2_zph <- cox.zph(GBSG2_coxph)
R> GBSG2_zph
```

```
R> data("GBSG2", package = "TH.data")
R> plot(survfit(Surv(time, cens) ~ horTh, data = GBSG2),
+        lty = 1:2, mark.time = FALSE,  ylab = "Probability",
+        xlab = "Survival Time in Days")
R> legend(250, 0.2, legend = c("yes", "no"), lty = c(2, 1),
+          title = "Hormonal Therapy", bty = "n")
```
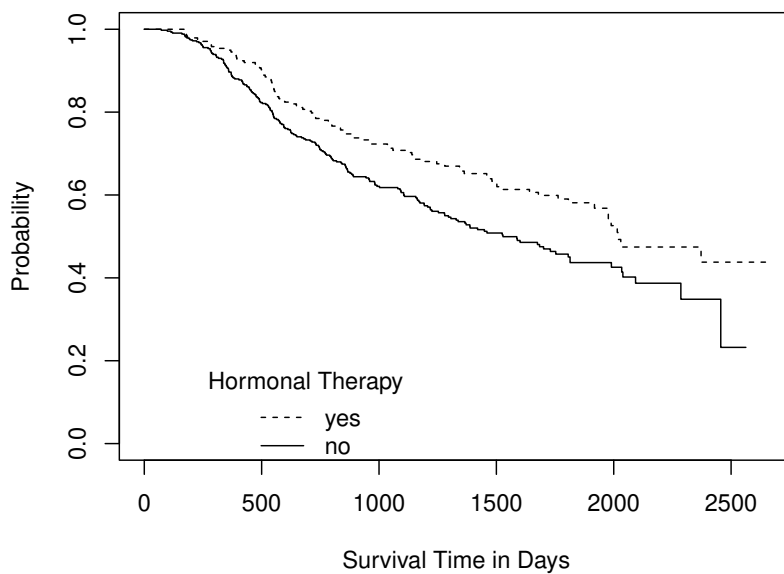

Figure 11.2   Kaplan-Meier estimates for breast cancer patients who either received hormonal therapy or not.

	chisq	df	p
horTh	0.239	1	0.6253
age	10.438	1	0.0012
menostat	5.406	1	0.0201
tsize	0.191	1	0.6620
tgrade	10.712	2	0.0047
pnodes	0.808	1	0.3688
progrec	4.386	1	0.0362
estrec	5.893	1	0.0152
GLOBAL	24.421	9	0.0037

There seems to be some evidence of time-varying effects, especially for age and tumor grading. A graphical representation of the estimated regression coeffi-

```
R> summary(GBSG2_coxph)

Call:
coxph(formula = Surv(time, cens) ~ ., data = GBSG2)

  n= 686, number of events= 299

                  coef exp(coef)  se(coef)      z Pr(>|z|)
horThyes     -0.346278  0.707316  0.129075  -2.68  0.00730
age          -0.009459  0.990585  0.009301  -1.02  0.30913
menostatPost  0.258445  1.294915  0.183476   1.41  0.15895
tsize         0.007796  1.007827  0.003939   1.98  0.04779
tgrade.L      0.551299  1.735506  0.189844   2.90  0.00368
tgrade.Q     -0.201091  0.817838  0.121965  -1.65  0.09920
pnodes        0.048789  1.049998  0.007447   6.55  5.7e-11
progrec      -0.002217  0.997785  0.000574  -3.87  0.00011
estrec        0.000197  1.000197  0.000450   0.44  0.66131

             exp(coef) exp(-coef) lower .95 upper .95
horThyes         0.707      1.414     0.549     0.911
age              0.991      1.010     0.973     1.009
menostatPost     1.295      0.772     0.904     1.855
tsize            1.008      0.992     1.000     1.016
tgrade.L         1.736      0.576     1.196     2.518
tgrade.Q         0.818      1.223     0.644     1.039
pnodes           1.050      0.952     1.035     1.065
progrec          0.998      1.002     0.997     0.999
estrec           1.000      1.000     0.999     1.001

Concordance= 0.692  (se = 0.015 )
Likelihood ratio test= 105  on 9 df,   p=<2e-16
Wald test            = 115  on 9 df,   p=<2e-16
Score (logrank) test = 121  on 9 df,   p=<2e-16
```

**Figure 11.3**   R output of the `summary` method for `GBSG2_coxph`.

cient over time is shown in Figure 11.4. We refer to Therneau and Grambsch (2000) for a detailed theoretical description of these topics.

The tree-structured regression models applied to continuous and binary responses in Chapter 9 are applicable to censored responses in survival analysis as well. Such a simple prognostic model with only a few terminal nodes might be helpful for relating the risk to certain subgroups of patients. Both `rpart` and the `ctree` function from package **partykit** can be applied to the GBSG2 data, where the conditional trees of the latter select cutpoints based on log-rank statistics

```
R> GBSG2_ctree <- ctree(Surv(time, cens) ~ ., data = GBSG2)
```

and the `plot` method applied to this tree produces the graphical representation in Figure 11.6. The number of positive lymph nodes (`pnodes`) is the most important variable in the tree, corresponding to the *p*-value associated with this variable in Cox's regression; see Figure 11.3. Women with not more than three positive lymph nodes who have undergone hormonal therapy seem to have the best prognosis whereas a large number of positive lymph nodes and a small value of the progesterone receptor indicates a bad prognosis.

```
R> plot(GBSG2_zph, var = "age")
```
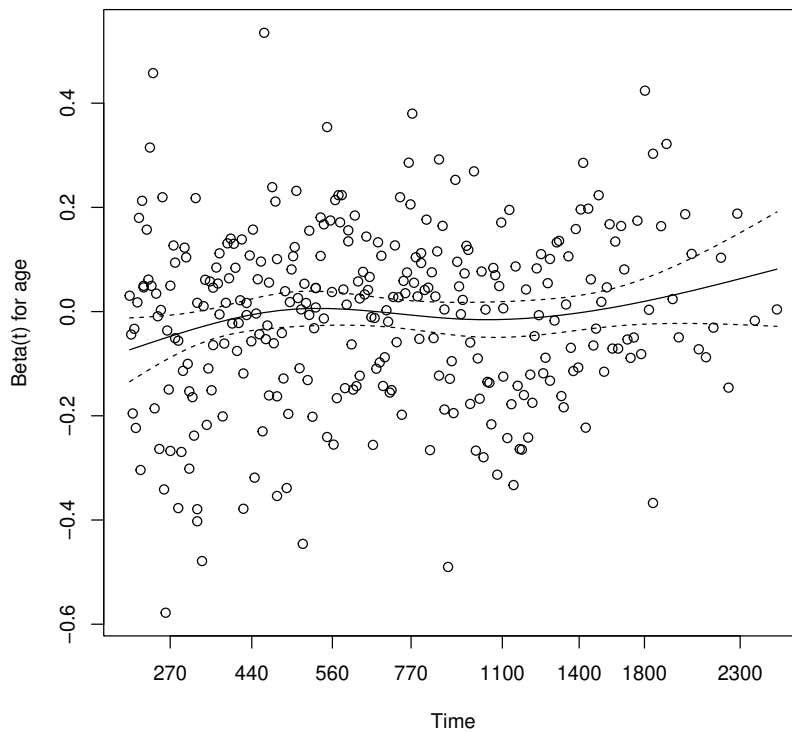

Figure 11.4   Estimated regression coefficient for `age` depending on time for the GBSG2 data.
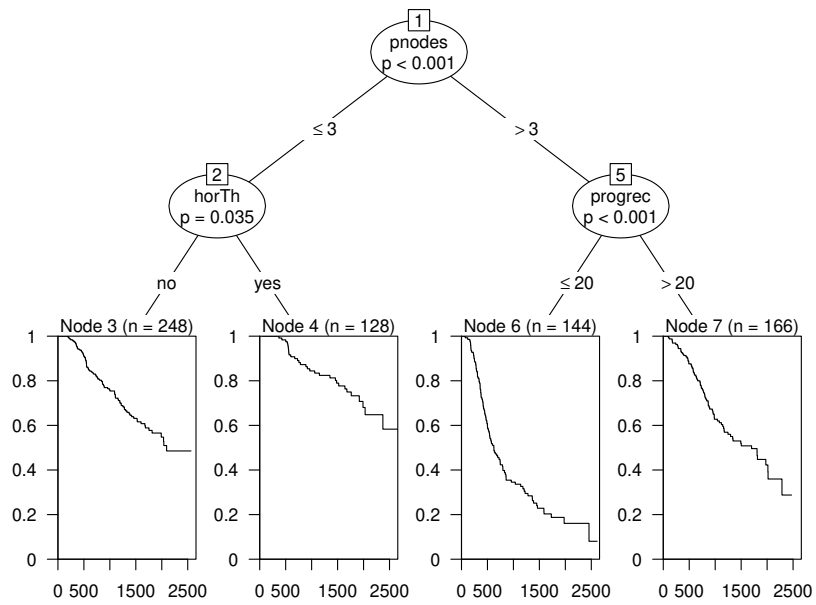
```
R> layout(matrix(1:3, ncol = 3))
R> res <- residuals(GBSG2_coxph)
R> plot(res ~ age, data = GBSG2, ylim = c(-2.5, 1.5),
+        pch = ".", ylab = "Martingale Residuals")
R> abline(h = 0, lty = 3)
R> plot(res ~ pnodes, data = GBSG2, ylim = c(-2.5, 1.5),
+        pch = ".", ylab = "")
R> abline(h = 0, lty = 3)
R> plot(res ~ log(progrec), data = GBSG2, ylim = c(-2.5, 1.5),
+        pch = ".", ylab = "")
R> abline(h = 0, lty = 3)
```
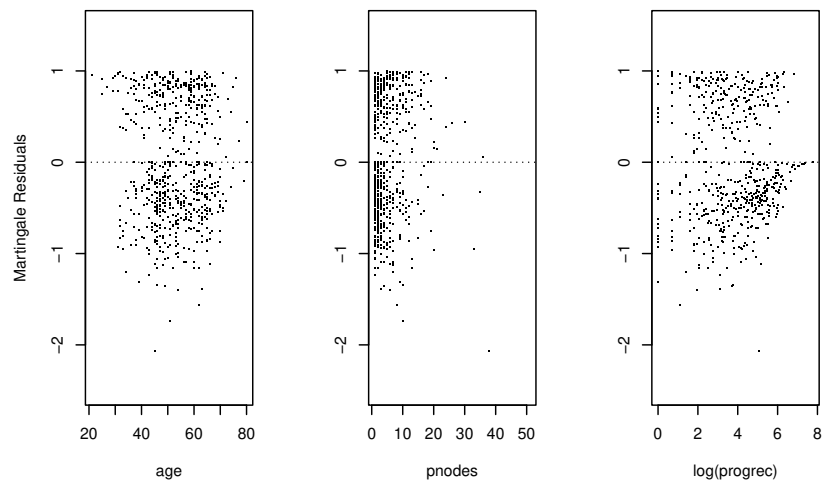

Figure 11.5   Martingale residuals for the GBSG2 data.

```
R> plot(GBSG2_ctree)
```


Figure 11.6 Conditional inference tree for the GBSG2 data with the survival func-
tion, estimated by Kaplan-Meier, shown for every subgroup of patients
identified by the tree.

Bibliography

Hothorn, T., Hornik, K., van de Wiel, M., and Zeileis, A. (2013), *coin: Conditional Inference Procedures in a Permutation Test Framework*, URL `http://CRAN.R-project.org/package=coin`, R package version 1.0-23.

Hothorn, T., Hornik, K., van de Wiel, M. A., and Zeileis, A. (2006), "A Lego system for conditional inference," *The American Statistician*, 60, 257–263.

Therneau, T. M. and Grambsch, P. M. (2000), *Modeling Survival Data: Extending the Cox Model*, New York, USA: Springer-Verlag.