Building and Checking Survival Models

David M. Rocke

May 23, 2017

hodg Lymphoma Data Set from KMsurv

This data set consists of information on 43 bone marrow transplant patients at Ohio State University (Avalos 1993). The patients had either Hodgkin's or non-Hodgkins lymphoma and were treated either with an allogenic (HLA-matched sib) or autogenic bone marrow transplant. In addition to the time to death or relapse (or censored), the data set has the Karnofsky score and the waiting time to transplant in months.

hodg Lymphoma Data Set from KMsurv

gtype	Graft type
	1=allogenic,
	2=autologous
dtype	Disease type
	1=Non Hodgkin lymphoma,
	2=Hodgkins disease
time	Time to death or relapse, days
delta	Death/relapse indicator
	0=alive,
	1=dead
score	Karnofsky score
wtime	Waiting time to transplant in months

Karnofsky Score

Score 80–100: Able to carry on normal activity and to work; no special care needed.
Score 50–70: Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
Score 10-60: Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.

```
> hodg2 <- hodg
> hodg2$gtype <- with(hodg,factor(gtype,labels=c("Allo","Auto")))
> table (hodg2$gtype,hodg$gtype)

       1  2
  Allo 16  0
  Auto  0 27
> hodg2$dtype <- with(hodg,factor(dtype,labels=c("NHL","HOD")))
> table (hodg2$dtype,hodg$dtype)

      1  2
  NHL 23  0
  HOD  0 20

> with(hodg2,(table(gtype,dtype)))
      dtype
gtype  NHL HOD
  Allo  11   5
  Auto  12  15
```

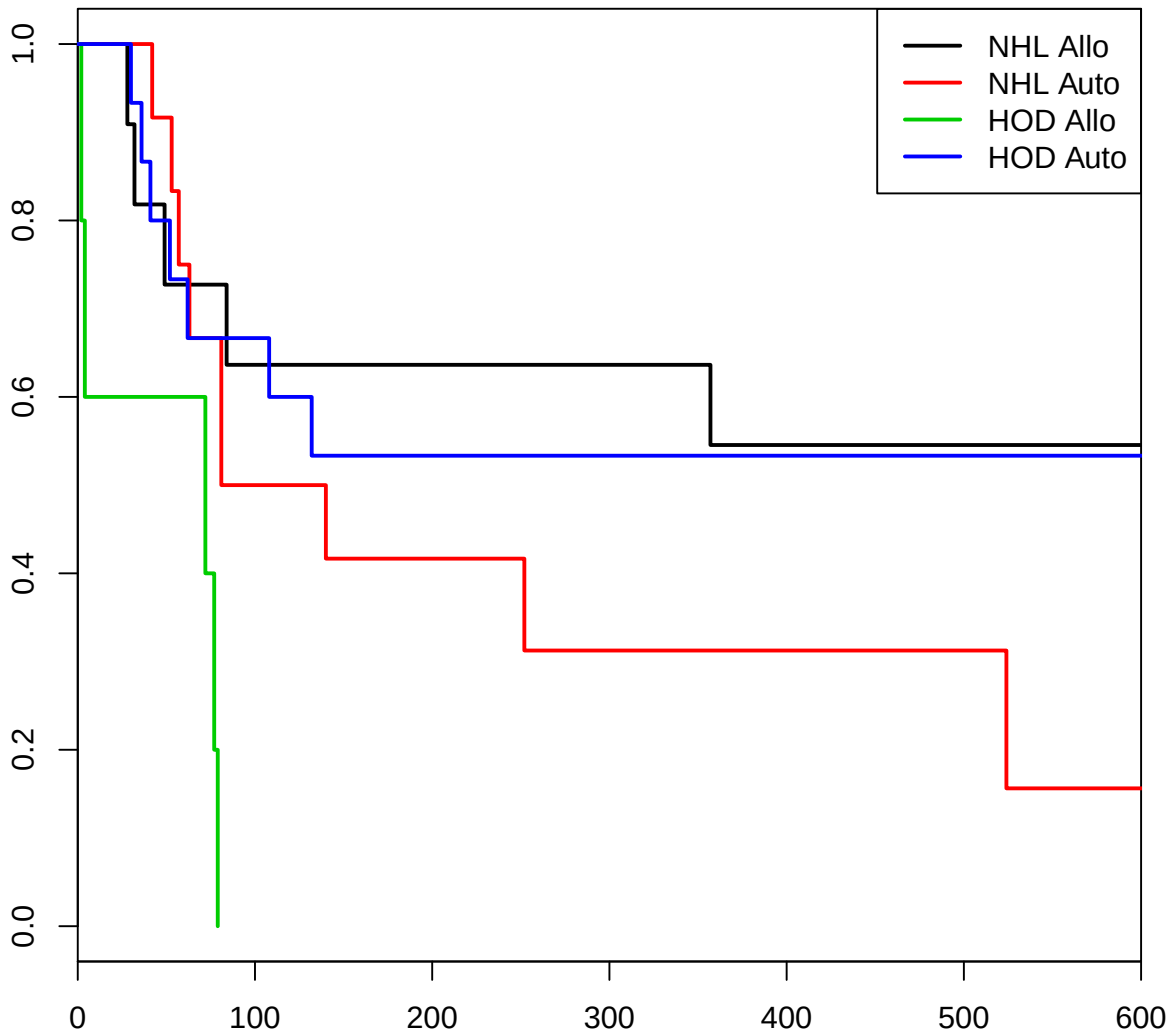
```
> hodg.surv <- with(hodg2,Surv(time,delta))
> hodg.cox1 <- coxph(hodg.surv~gtype*dtype+score+wtime,data=hodg2)
> summary(hodg.cox1)

  n= 43, number of events= 26

                       coef exp(coef) se(coef)      z Pr(>|z|)
gtypeAuto           0.63940   1.89534  0.59372  1.077  0.28151
dtypeHOD            2.76033  15.80504  0.94738  2.914  0.00357 **
score              -0.04948   0.95172  0.01242 -3.984 6.77e-05 ***
wtime              -0.01656   0.98357  0.01021 -1.623  0.10461
gtypeAuto:dtypeHOD -2.37093   0.09339  1.03548 -2.290  0.02204 *
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

                   exp(coef) exp(-coef) lower .95 upper .95
gtypeAuto            1.89534    0.52761   0.59199    6.0682
dtypeHOD            15.80504    0.06327   2.46821  101.2066
score                0.95172    1.05073   0.92884    0.9752
wtime                0.98357    1.01670   0.96409    1.0034
gtypeAuto:dtypeHOD   0.09339   10.70738   0.01227    0.7108
```

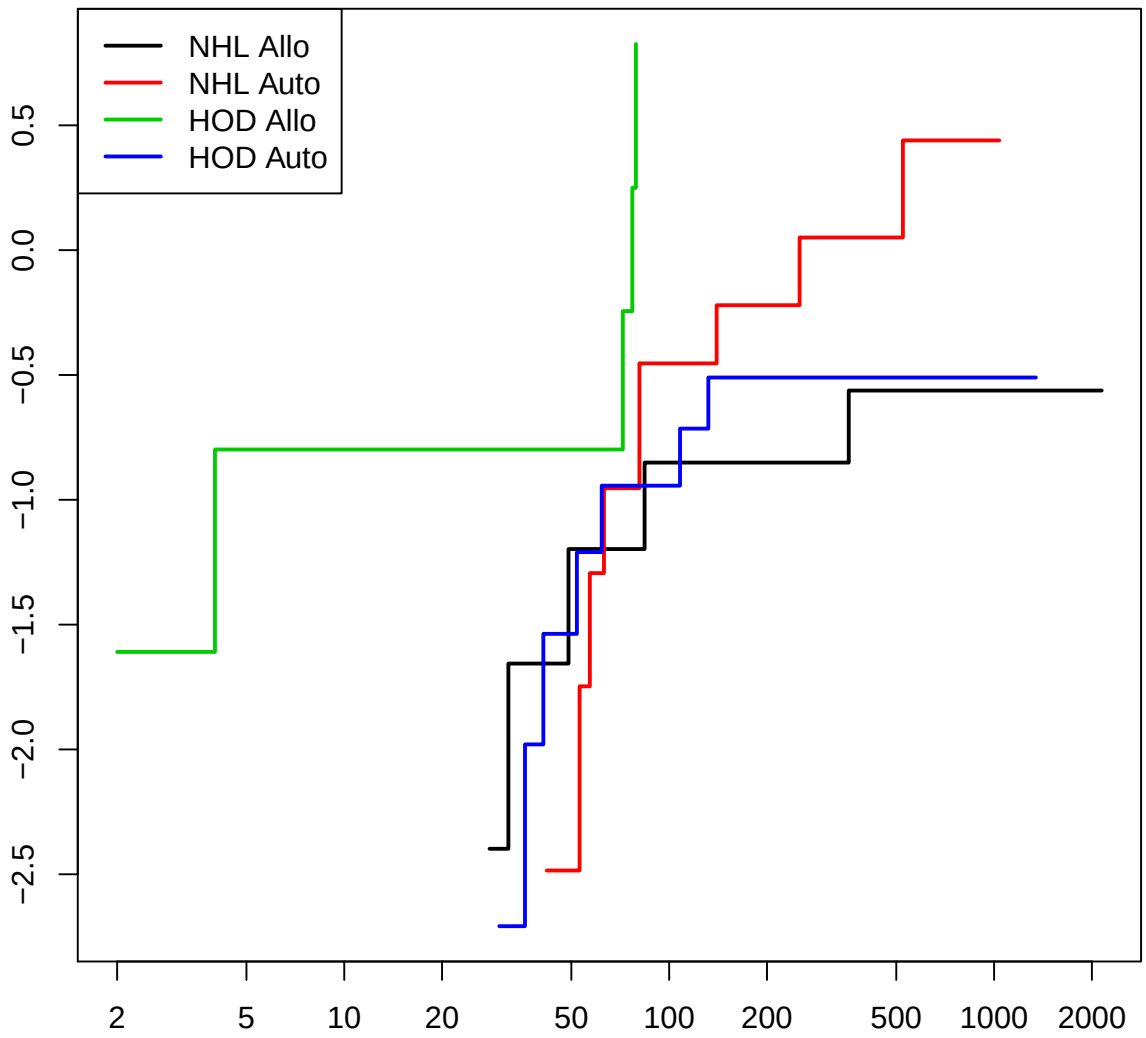
```
> hodg.surv <- with(hodg2,Surv(time,delta))
> hodg.cox1 <- coxph(hodg.surv~gtype*dtype+score+wtime,data=hodg2)
> summary(hodg.cox1)

Concordance= 0.776  (se = 0.061 )
Rsquare= 0.527   (max possible= 0.983 )
Likelihood ratio test= 32.15  on 5 df,   p=5.539e-06
Wald test            = 27.19  on 5 df,   p=5.232e-05
Score (logrank) test = 37.7  on 5 df,   p=4.325e-07
```

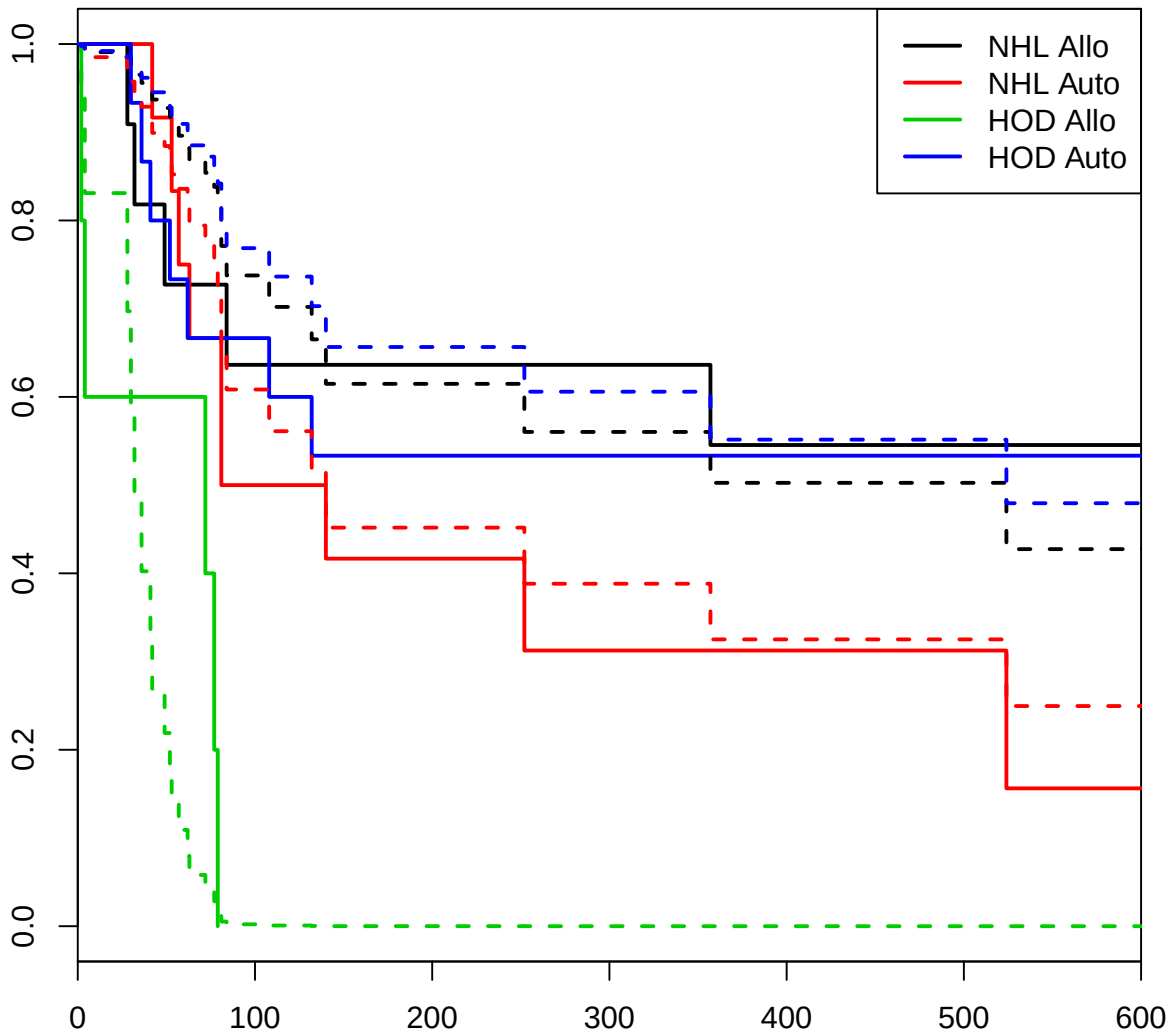
Proportionality

- We first graph the survival function for the four combinations of disease type and graft type.
- We graph the complimentary log-log survival for the four groups.
- Then we graph the observed vs. expected survival functions.
- There appear to be problems with proportionality.

```
plot1 <- function(){
  plot(survfit(hodg.surv~dtype+gtype,data=hodg2),xlim=c(0,600),col=1:4,lwd=2)
  legend("topright",c("NHL Allo","NHL Auto","HOD Allo","HOD Auto"),col=1:4,lwd=2)
  title("Survival Curves for HOD/NHL and Allo/Auto Grafts")
}

plot2 <- function(){
  plot(survfit(hodg.surv~dtype+gtype,data=hodg2,type="fleming"),
     col=1:4,lwd=2,fun="cloglog")
  legend("topleft",c("NHL Allo","NHL Auto","HOD Allo","HOD Auto"),col=1:4,lwd=2)
  title("Complimentary Log-Log Survival Curves")
}

plot3 <- function(){
# score and wtime set to mean values for disease and graft types
    plot(survfit(hodg.surv~dtype+gtype,data=hodg2),xlim=c(0,600),col=1:4,lwd=2)
  lines(survfit(hodg.cox1,data.frame(gtype=c("Allo","Auto","Allo","Auto"),
     dtype=c("NHL","NHL","HOD","HOD"),score=c(75,76,56,85),
     wtime=c(17,23,59,58)),data=hodg2),col=1:4,lwd=2,lty=2)
  legend("topright",c("NHL Allo","NHL Auto","HOD Allo","HOD Auto"),col=1:4,lwd=2)
  title("Observed and Expected Survival Curves")
}
```


Survival Curves for HOD/NHL and Allo/Auto Grafts
NHL Allo
NHL Auto
HOD Allo
HOD Auto
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600


Complimentary Log−Log Survival Curves
NHL Allo
NHL Auto
HOD Allo
HOD Auto
0.5
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
2
5
10
20
50
100
200
500
1000
2000


Observed and Expected Survival Curves
NHL Allo
NHL Auto
HOD Allo
HOD Auto
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600

Types of Residuals

- It is often hard to make a decision from graph appearances, though the process can reveal much.
- Some diagnostic tests are based on residuals as with other regression methods.
- We use Schoenfeld residuals (via `cox.zph`) to test for proportionality.
- We use Cox-Snell residuals to test for goodness of fit.
- We use martingale residuals to look for non-linearity.
- We can also look at dfbeta for influence.

```
residuals.coxph {survival} R Documentation
Calculate Residuals for a coxph Fit

Description

Calculates martingale, deviance, score, or Schoenfeld residuals for a
Cox proportional hazards model.

Usage

residuals(object,
       type=c("martingale", "deviance", "score", "schoenfeld",
      "dfbeta", "dfbetas", "scaledsch","partial"),
       collapse=FALSE, weighted=FALSE, ...)

Arguments

object    an object inheriting from class coxph, representing a fitted Cox
          regression model. Typically this is the output from the coxph function.
```

```
residuals(object,
       type=c("martingale", "deviance", "score", "schoenfeld",
      "dfbeta", "dfbetas", "scaledsch","partial"),
       collapse=FALSE, weighted=FALSE, ...)
```

Arguments

object	an object inheriting from class coxph, representing a fitted Cox regression model. Typically this is the output from the coxph function.
type	character string indicating the type of residual desired. Possible values are "martingale", "deviance", "score", "schoenfeld", "dfbeta"', "dfbetas", and "scaledsch". Only enough of the string to determine a unique match is required.

For martingale and deviance residuals, the returned object is a vector with one element for each subject (without collapse). For score residuals it is a matrix with one row per subject and one column per variable. The row order will match the input data for the original fit. For Schoenfeld residuals, the returned object is a matrix with one row for each event and one column per variable. The rows are ordered by time within strata, and an attribute strata is attached that contains the number of observations in each strata. The scaled Schoenfeld residuals are used in the cox.zph function.

The score residuals are each individual's contribution to the score vector. Two transformations of this are often more useful: dfbeta is the approximate change in the coefficient vector if that observation were dropped, and dfbetas is the approximate change in the coefficients, scaled by the standard error for the coefficients.

Schoenfeld Residuals

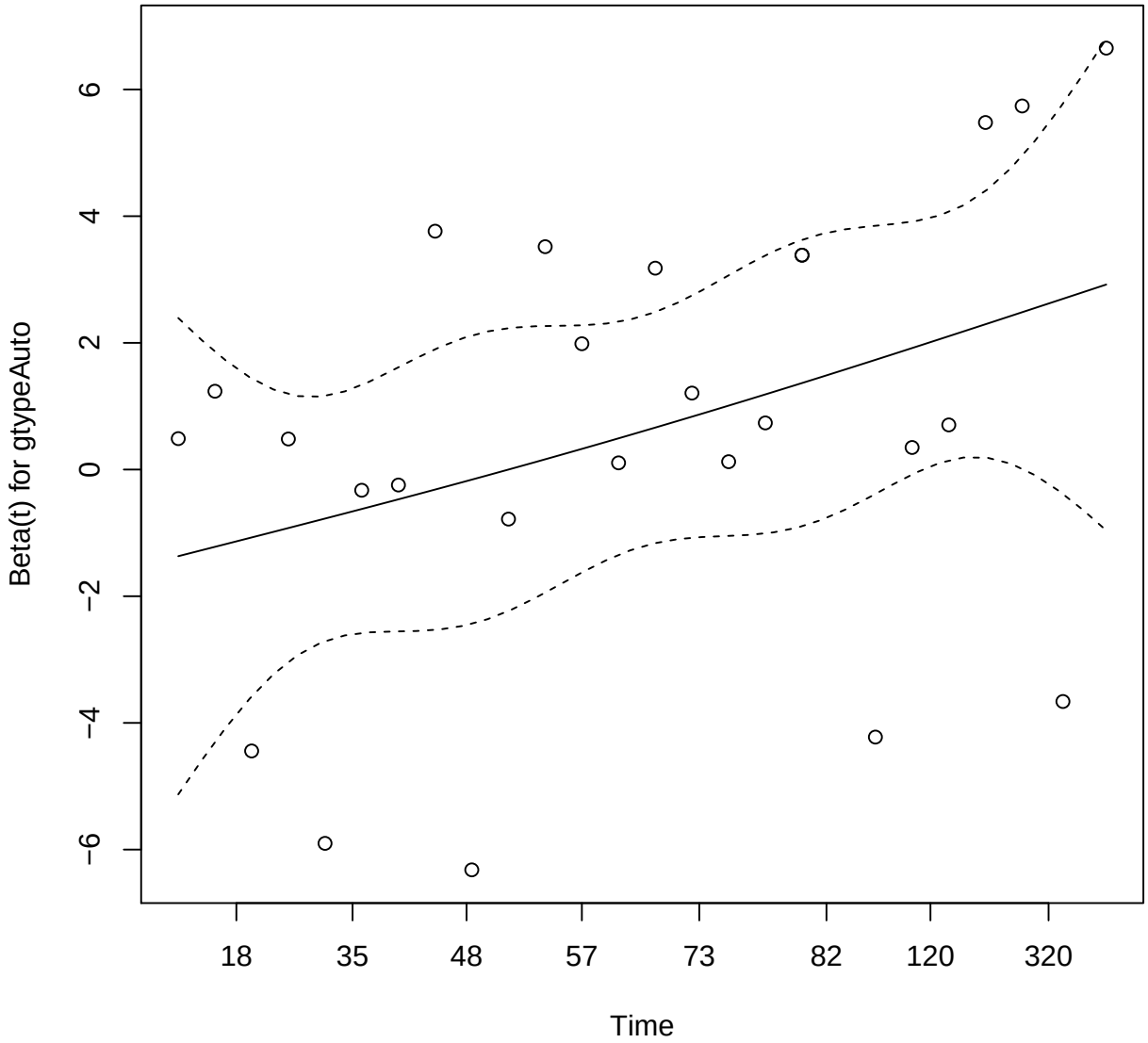
There is a Schoenfeld residual for each subject i with an event (not censored) and for each predictor x_k. At the event time t for that subject, there is a risk set R, and each subject j in the risk set has a risk coefficient θ_j and also a value x_{jk} of the predictor. The Schoenfeld residual is the difference between x_{ik} and the risk-weighted average of all the x_{jk} over the risk set.

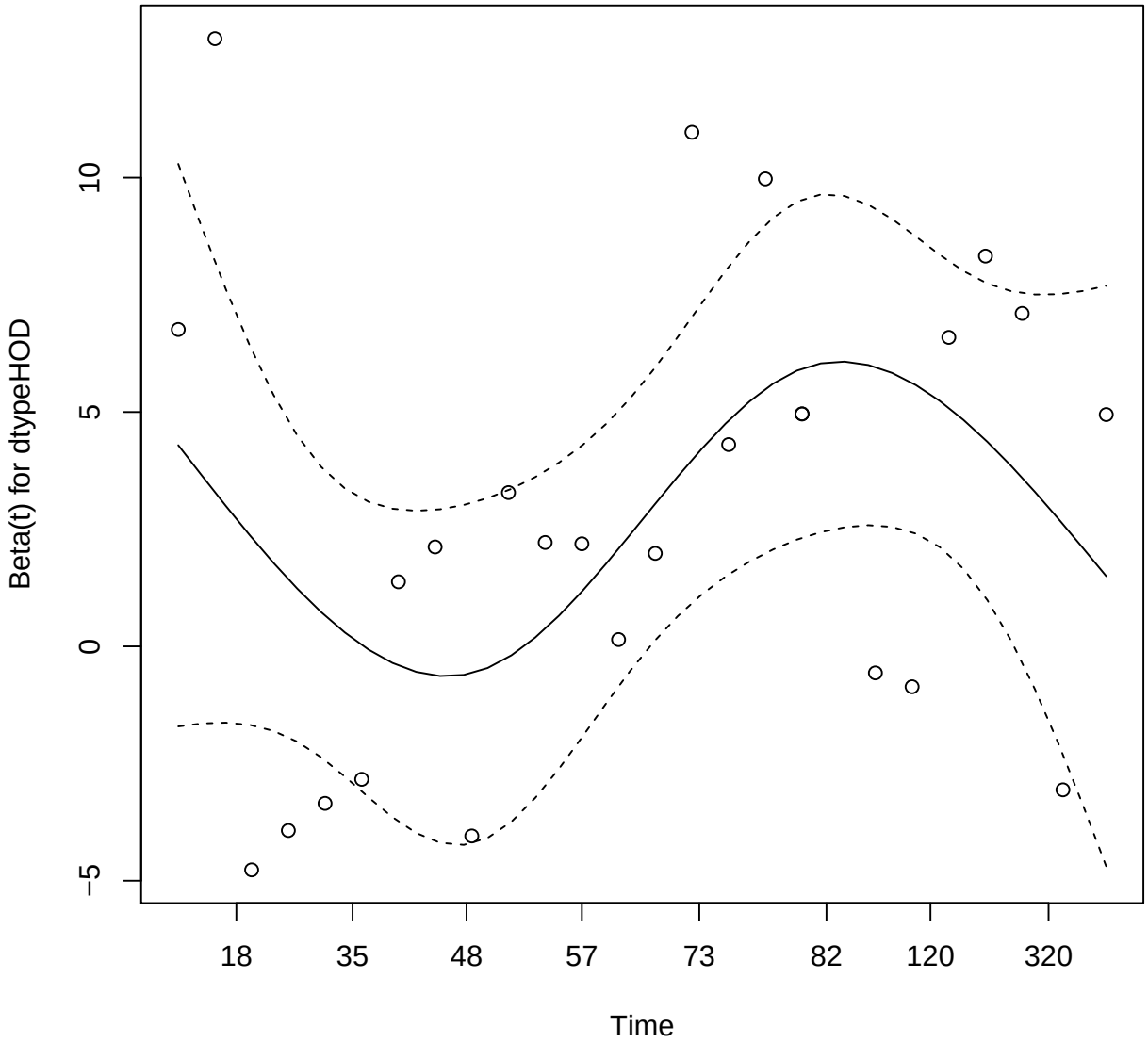
$$r_{ik}^S = x_{ik} - \frac{\sum_{k \in R} x_{jk}\theta_k}{\sum_{k \in R} \theta_k}$$

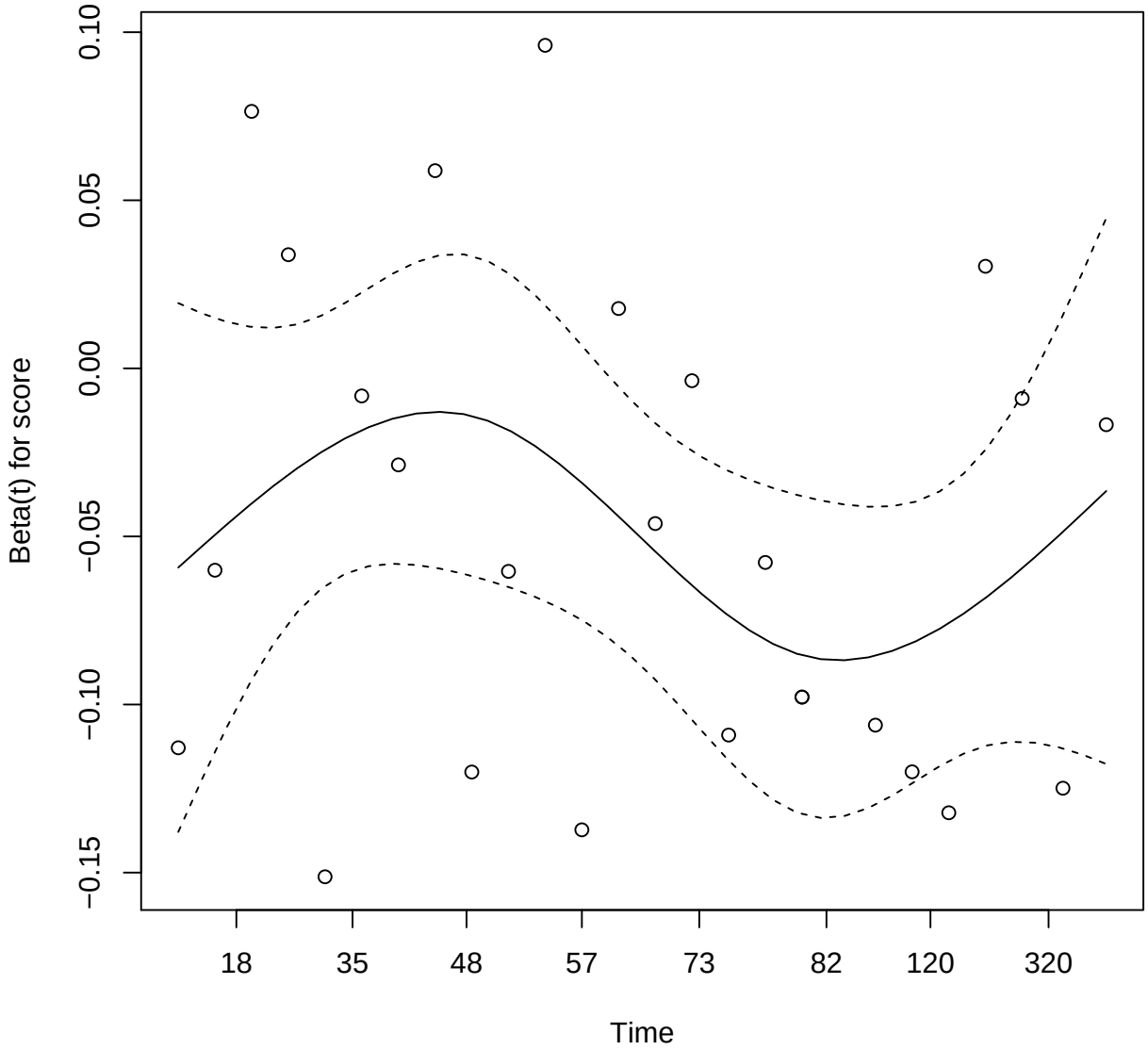
Schoenfeld Residuals

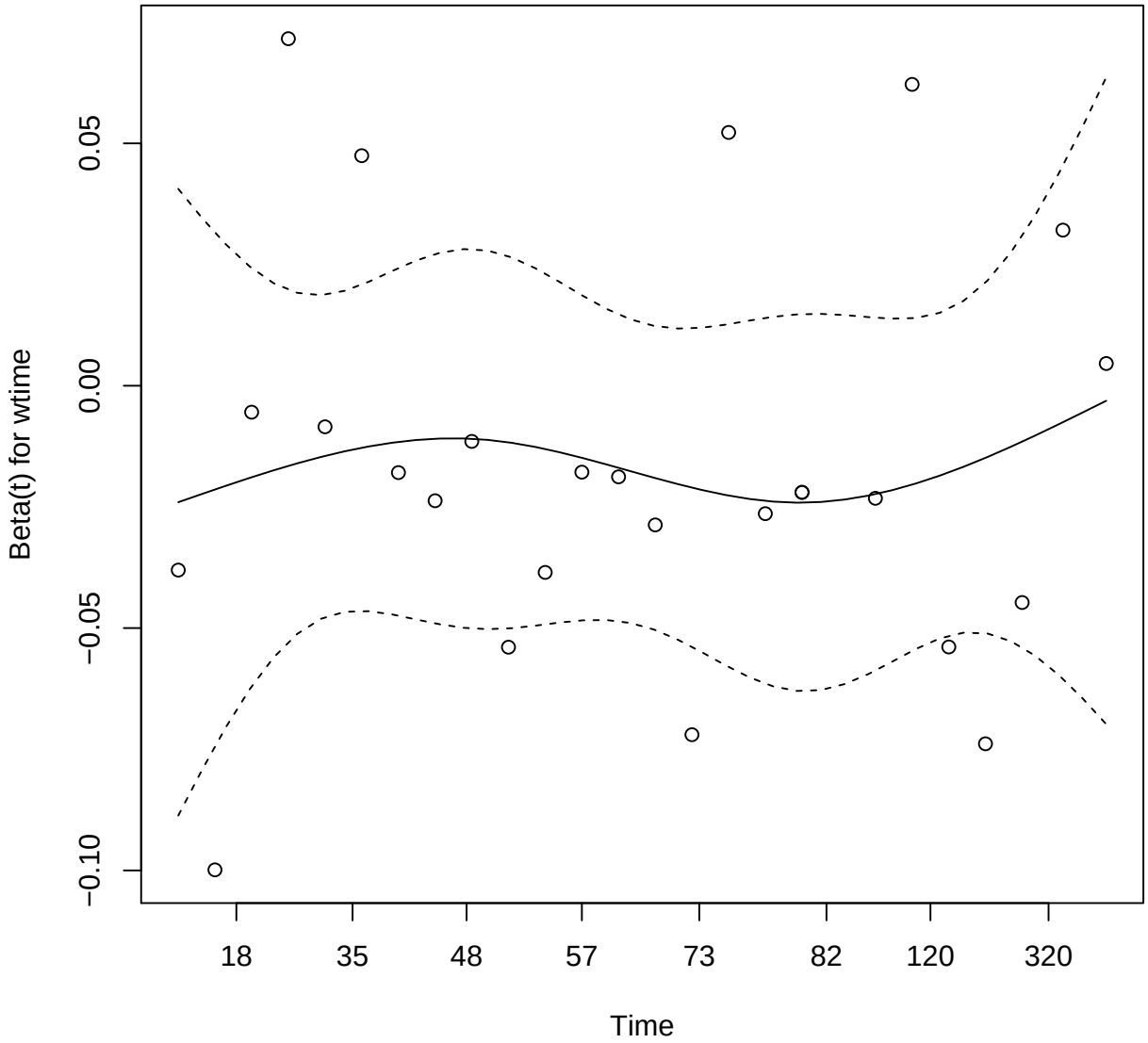
This is a measure of how typical the individual subject is with respect to the covariate at the time of the event. Since subjects should fail more or less uniformly according to risk, the Schoenfeld residuals should be approximately level over time, not increasing or decreasing. We can test this with the correlation with time on some scale, which could be the time itself, the log time, or the rank in the set of failure times. The default is to use the KM curve as a transform, which is similar to the rank but deals better with censoring.

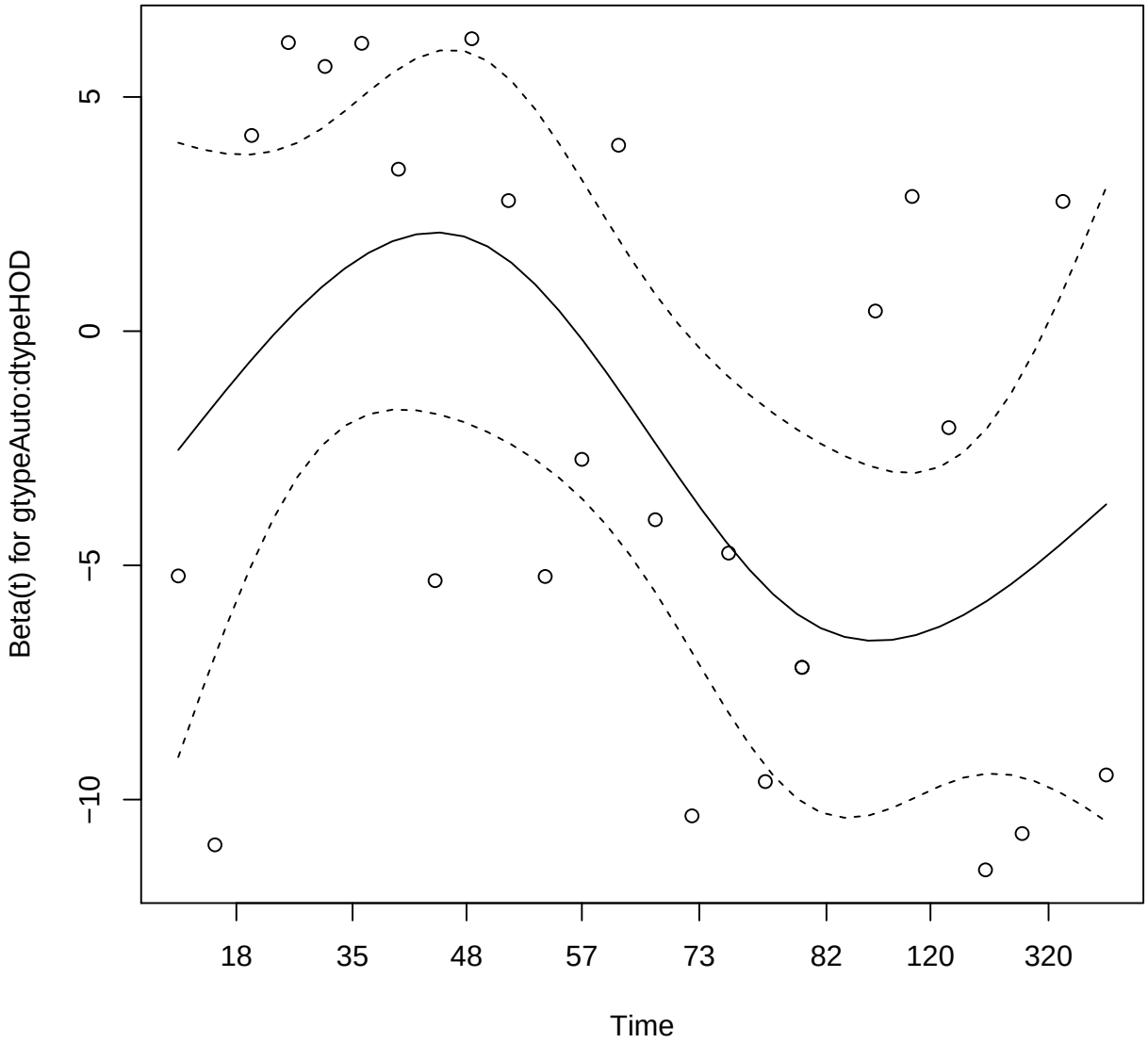
```
> hodg.zph <- cox.zph(hodg.cox1)
> print(hodg.zph)
                        rho    chisq      p
gtypeAuto            0.3796  4.58093 0.0323
dtypeHOD             0.2310  1.38525 0.2392
score               -0.1960  1.24354 0.2648
wtime                0.0202  0.00666 0.9350
gtypeAuto:dtypeHOD -0.3826  5.05625 0.0245
GLOBAL                  NA 10.19554 0.0699

pdf("hodgzph1.pdf")
plot(hodg.zph[1])
dev.off()
pdf("hodgzph2.pdf")
plot(hodg.zph[2])
dev.off()
pdf("hodgzph3.pdf")
plot(hodg.zph[3])
dev.off()
pdf("hodgzph4.pdf")
plot(hodg.zph[4])
dev.off()
pdf("hodgzph5.pdf")
plot(hodg.zph[5])
dev.off()
```


Beta(t) for gtypeAuto
6
4
2
0
−2
−4
−6
18
35
48
57
73
82
120
320
Time


Beta(t) for dtypeHOD
10
5
0
−5
18
35
48
57
73
82
120
320
Time


Beta(t) for score
0.10
0.05
0.00
−0.05
−0.10
−0.15
18
35
48
57
73
82
120
320
Time


Beta(t) for wtime
0.05
0.00
−0.05
−0.10
18
35
48
57
73
82
120
320
Time


Beta(t) for gtypeAuto:dtypeHOD
5
0
−5
−10
18
35
48
57
73
82
120
320
Time

- From the correlation test, the graft type and its interaction with disease type induce modest but statistically significant non-proportionality.
- The sample size here is relatively small (26 events in 43 subjects). If the sample size is large, very small amounts of non-proportionality can induce a significant result.
- As time goes on, autologous grafts are over-represented at their own event times, but those from HOD patients become less represented.
- Both the statistical tests and the plots are useful.

Goodness of Fit using the Cox-Snell Residuals

Suppose that the i^{th} individual has a survival time T_i which has survival function $S_i(t)$, meaning that $\Pr(T_i > t) = S_i(t)$. Then $S_i(T_i)$ has a uniform distribution on $(0, 1)$.

$$\begin{aligned} \Pr(S_i(T_i) \leq u) &= \Pr(T_i > S_i^{-1}(u)) \\ &= S_i(S_i^{-1}(u)) \\ &= u \end{aligned}$$

Goodness of Fit using the Cox-Snell Residuals

Also, if U has a uniform distribution on $(0, 1)$, then what is the distribution of $-\ln(U)$?

$$\begin{aligned} \Pr(-\ln(U) < x) &= \Pr(U > \exp(-x)) \\ &= 1 - e^{-x} \end{aligned}$$

which is the CDF of an exponential distribution with parameter $\lambda = 1$.

Goodness of Fit using the Cox-Snell Residuals

So, $r_i^{CS} = \hat{\Lambda}_i(t_i) = -\ln[\hat{S}_i(t_i)] = -\ln[\hat{S}(t_i|\text{covariates})]$ should have an exponential distribution with constant hazard $\lambda = 1$ if the estimate $\hat{S}_i$ is accurate, which means that these values should look like a censored sample from this exponential distribution. These values are called *generalized residuals* or *Cox-Snell residuals*.

Martingale Residuals

The *martingale residuals* are a slight modification of the Cox-Snell residuals. If the censoring indicator is δ_i, then

$$r_i^M = \delta_i - r_i^{CS}$$

These residuals can be interpreted as an estimate of the excess number of events seen in the data but not predicted by the model. We will use these to examine the functional form of covariates.

Martingale

Originally, a martingale referred to a betting strategy where you bet \$1 on the first play, then you double the bet if you lose and continue until you win. This seems like a sure thing, because at the end of each series when you finally win, you are up \$1. For example, $-1-2-4-8+16=1$. But this assumes that you have infinite resources. Really, you have a large probability of winning \$1, and a small probability of losing everything you have, kind of the opposite of a lottery.

Martingale

In probability, a *martingale* is a sequence of random variables such that the expected value of the next event at any time is the present observed value, and that no better predictor can be derived even with all past values of the series available. At least to a close approximation, the stock market is a martingale. Under the assumptions of the proportional hazards model, the martingale residuals ordered in time form a martingale.

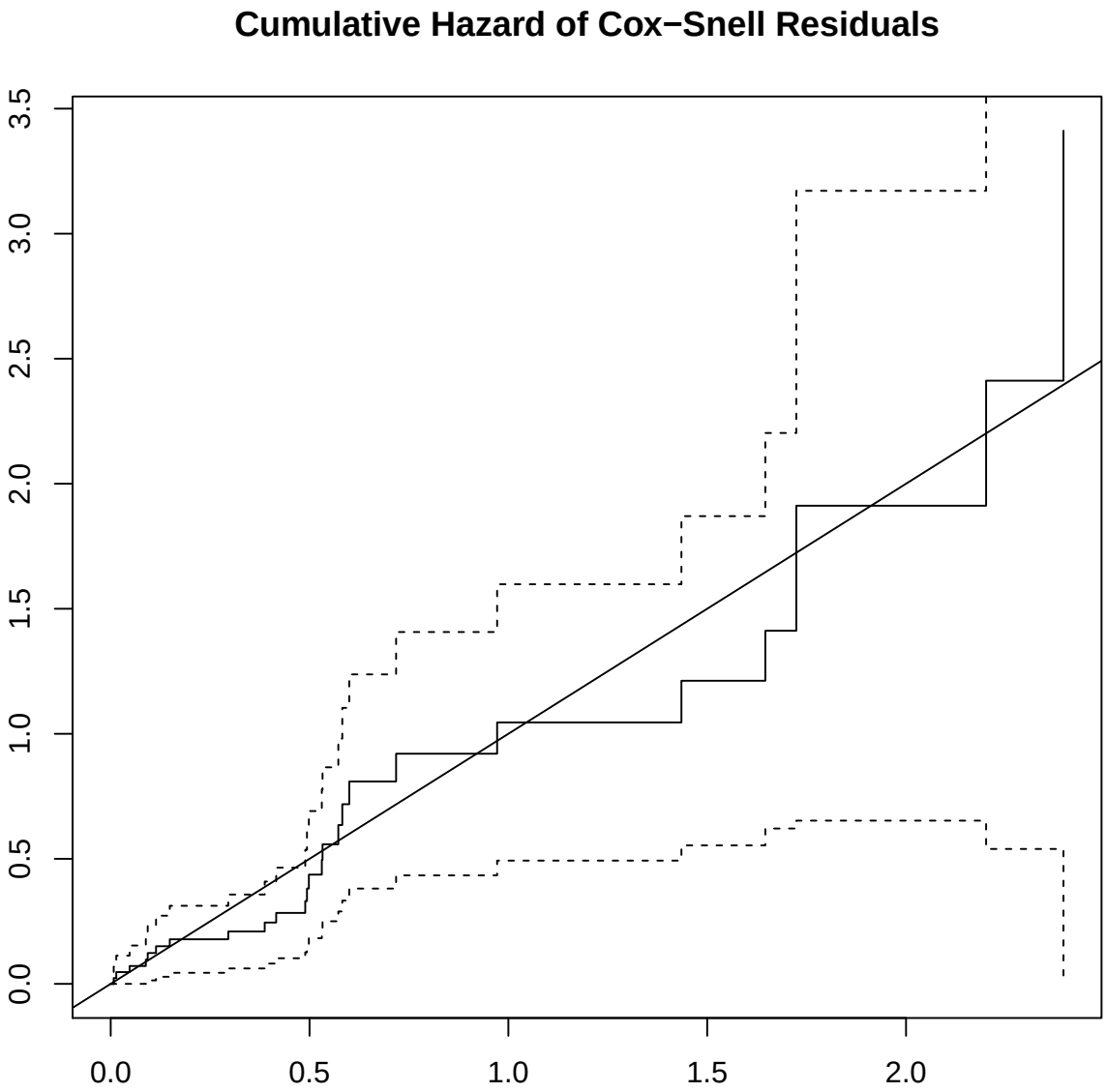
Using Martingale Residuals

Martingale residuals can be used to examine the functional form of a numeric variable. We fit the model without that variable and compute the martingale residuals. We then plot these martingale residuals against the values of the variable. We can see curvature, or a possible suggestion that the variable can be discretized. We will use this to examine the `score` and `wtime` variables in the `hodg` data set.

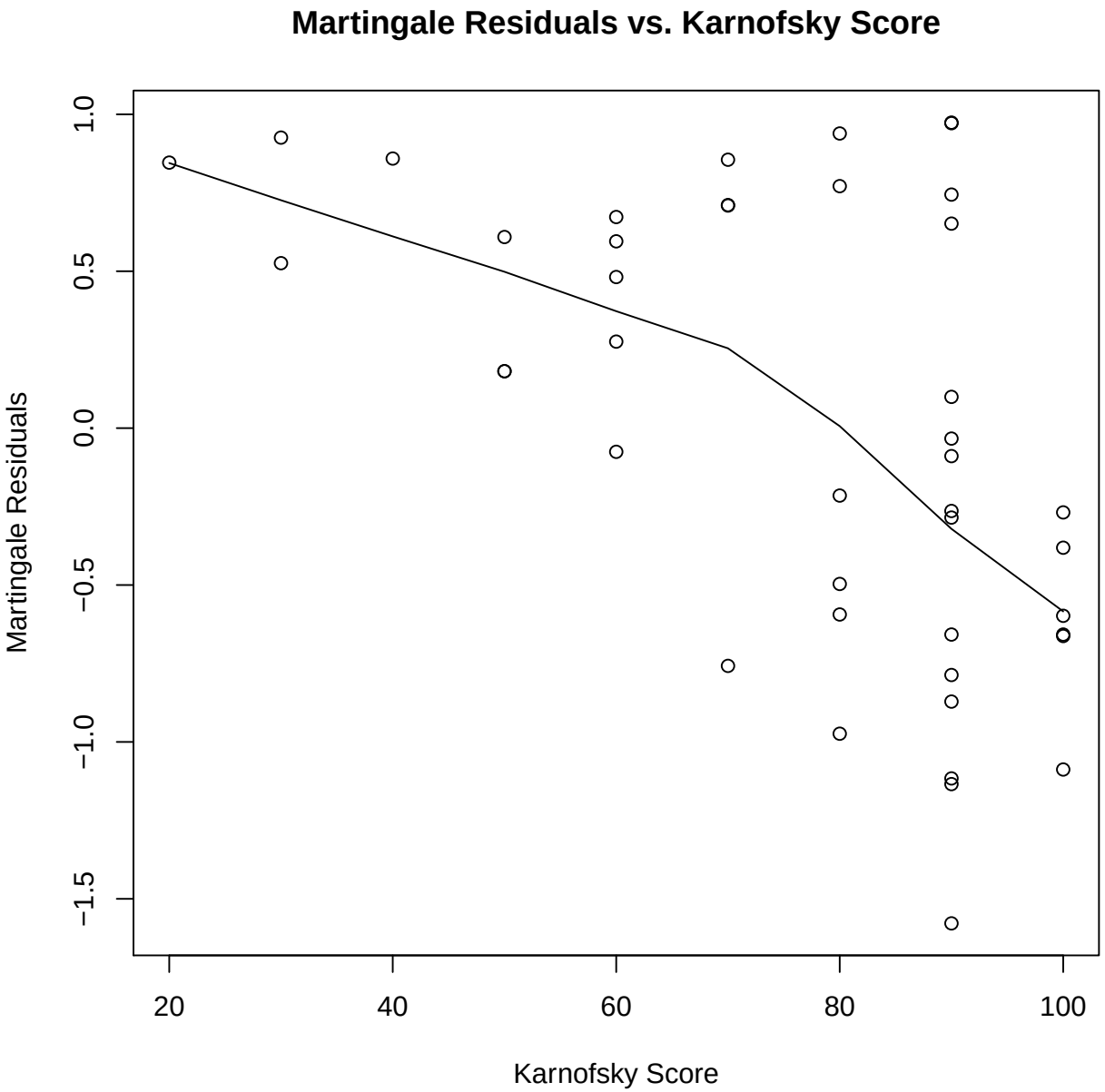
```
hodg.mart <- residuals(hodg.cox1,type="martingale")
hodg.cs <- hodg$delta-hodg.mart

plot1r <- function(){
  surv.csr = survfit(Surv(hodg.cs,hodg2$delta)~1,type="fleming-harrington")
  plot(surv.csr,fun="cumhaz")
  abline(0,1)
  title("Cumulative Hazard of Cox-Snell Residuals")
}

plot2r <- function(){
  mres <- residuals(coxph(hodg.surv~gtype*dtype+wtime,data=hodg2),type="martingale"
  plot(hodg2$score,mres,xlab="Karnofsky Score",ylab="Martingale Residuals")
  lines(lowess(hodg2$score,mres))
  title("Martingale Residuals vs. Karnofsky Score")
}
```

```
hodg.mart <- residuals(hodg.cox1,type="martingale")
hodg.cs <- hodg$delta-hodg.mart

plot3r <- function(){
  mres <- residuals(coxph(hodg.surv~gtype*dtype+score,data=hodg2),type="martingale"
  plot(hodg2$wtime,mres,xlab="Waiting Time",ylab="Martingale Residuals")
  lines(lowess(hodg2$wtime,mres))
  title("Martingale Residuals vs. Waiting Time")
  print(head(cbind(hodg2$wtime,mres)[order(hodg2$wtime,decreasing=T),]))
}
```

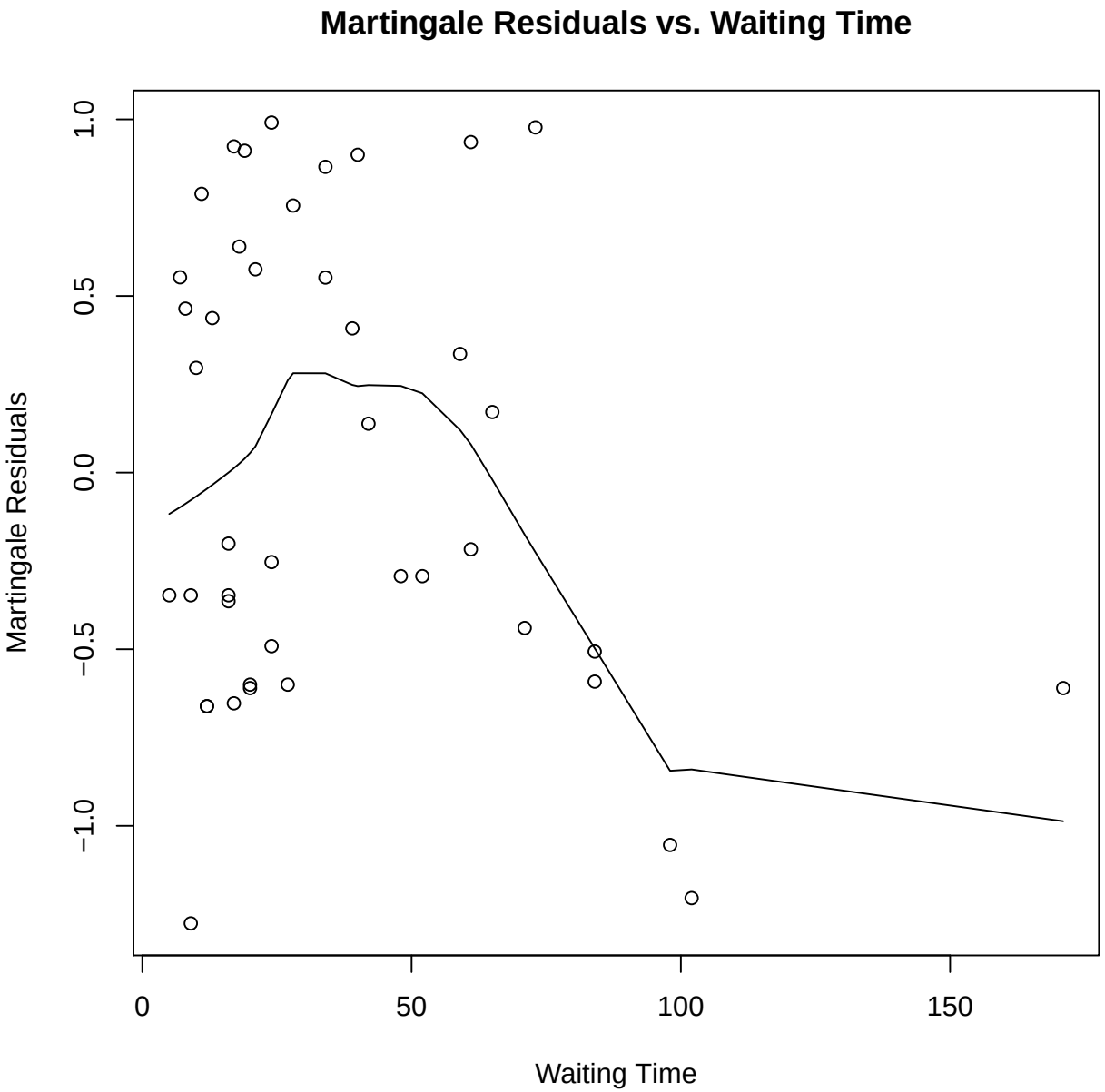
```
             mres
41 171 -0.6099433
15 102 -1.2045188
43  98 -1.0541449
28  84 -0.5916094
40  84 -0.5065709
29  73  0.9774249
```



The line with slope 1 and intercept 0 fits the curve relatively well, so we don't see lack of fit using this procedure.



The line is almost straight. It could be some modest transformation of the Karnofsky score would help, but it might not make much difference.



The line could suggest a step function. To see where the drop is, we can look at the largest waiting times and the associated martingale residual.

```
hodg.mart <- residuals(hodg.cox1,type="martingale")
hodg.cs <- hodg$delta-hodg.mart

plot3r <- function(){
  mres <- residuals(coxph(hodg.surv~gtype*dtype+score,data=hodg),type="martingale")
  plot(hodg$wtime,mres,xlab="Waiting Time",ylab="Martingale Residuals")
  lines(lowess(hodg$wtime,mres))
  title("Martingale Residuals vs. Waiting Time")
  print(head(cbind(hodg$wtime,mres)[order(hodg$wtime,decreasing=T),]))
}
```

```
             mres
41 171 -0.6099433
15 102 -1.2045188
43  98 -1.0541449
28  84 -0.5916094
40  84 -0.5065709
29  73  0.9774249
```

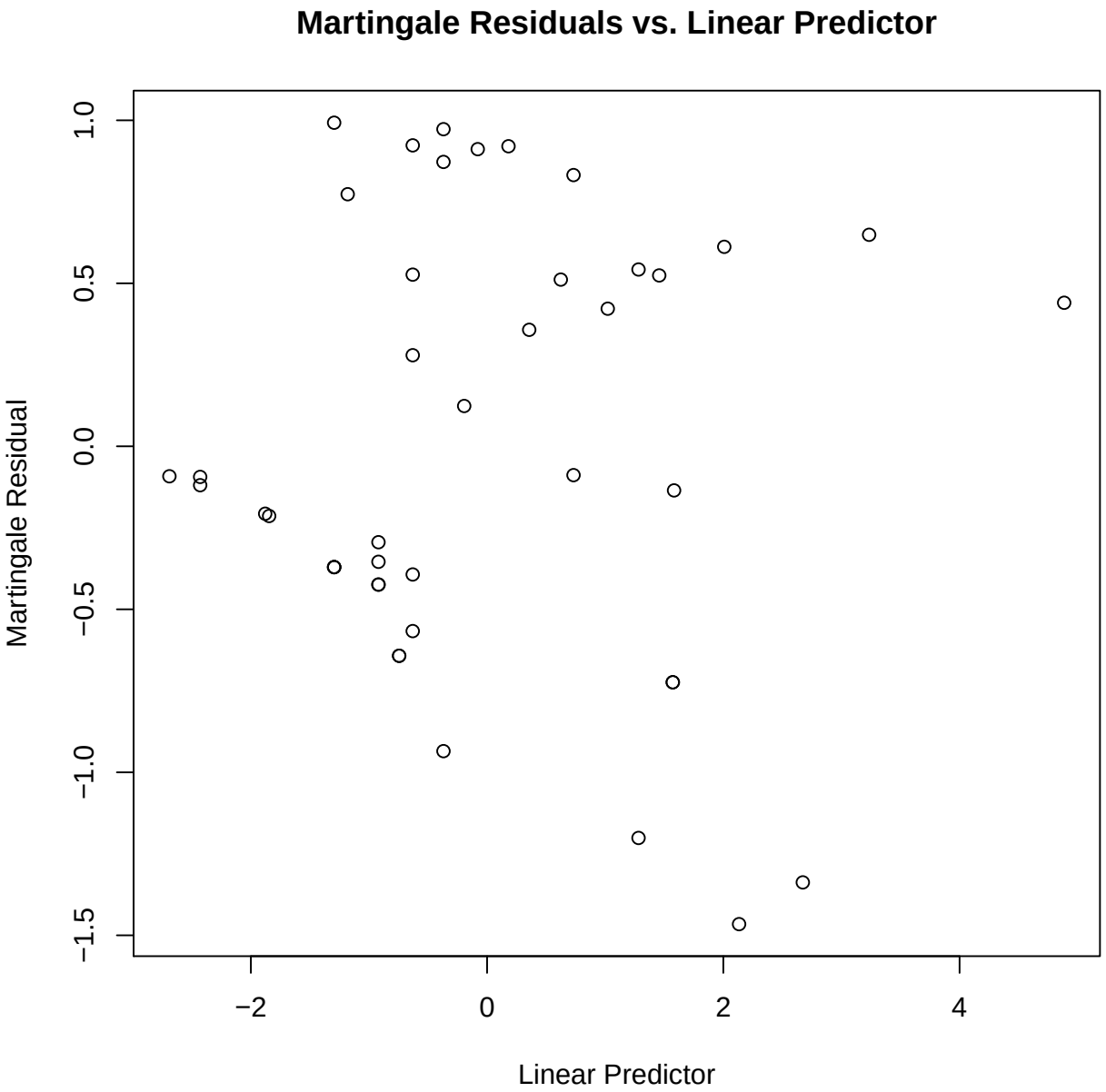
The martingale residuals are all negative for wtime >83 and positive for the next smallest value.
A reasonable cut-point is 80 days.
We reformulate the model with dichotomized wtime.

```
wt2 <- cut(hodg2$wtime,c(0,80,200),labels=c("short","long"))
hodg.cox2 <- coxph(hodg.surv~gtype*dtype+score+wt2,data=hodg2)
print(drop1(hodg.cox1,test="Chisq"))

Model:
hodg.surv ~ gtype * dtype + score + wtime
            Df    AIC     LRT Pr(>Chi)
<none>         152.36
score        1 167.60 17.2365  3.3e-05 ***
wtime        1 153.64  3.2792  0.07016 .
gtype:dtype  1 155.80  5.4357  0.01973 *
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

print(drop1(hodg.cox2,test="Chisq"))      #New model has better AIC
                                          #and smaller p-values.
Model:
hodg.surv ~ gtype * dtype + score + wt2
            Df    AIC     LRT  Pr(>Chi)
<none>         149.03
score        1 168.64 21.6042 3.351e-06 ***
wt2          1 153.64  6.6081   0.01015 *
gtype:dtype  1 152.00  4.9697   0.02580 *
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
```

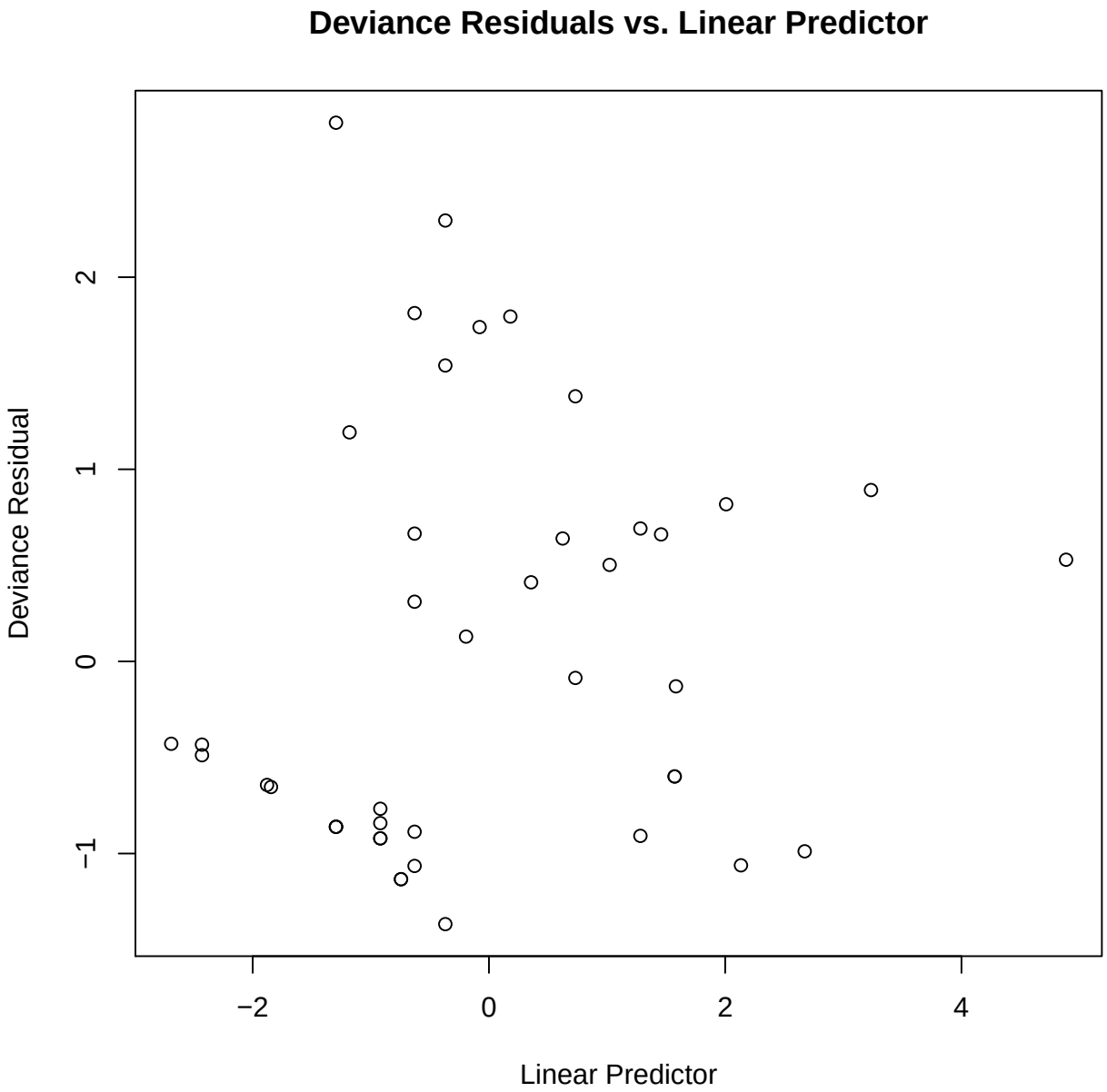
Checking for Outliers and Influential Observations

We will check for outliers using the deviance residuals. The martingale residuals show excess events or the opposite, but highly skewed, with the maximum possible value being 1, but the smallest value can be very large negative. Martingale residuals can detect unexpectedly long-lived patients, but patients who die unexpectedly early show up only in the deviance residual. Influence will be examined using dfbeta in a similar way to linear regression, logistic regression, or Poisson regression.

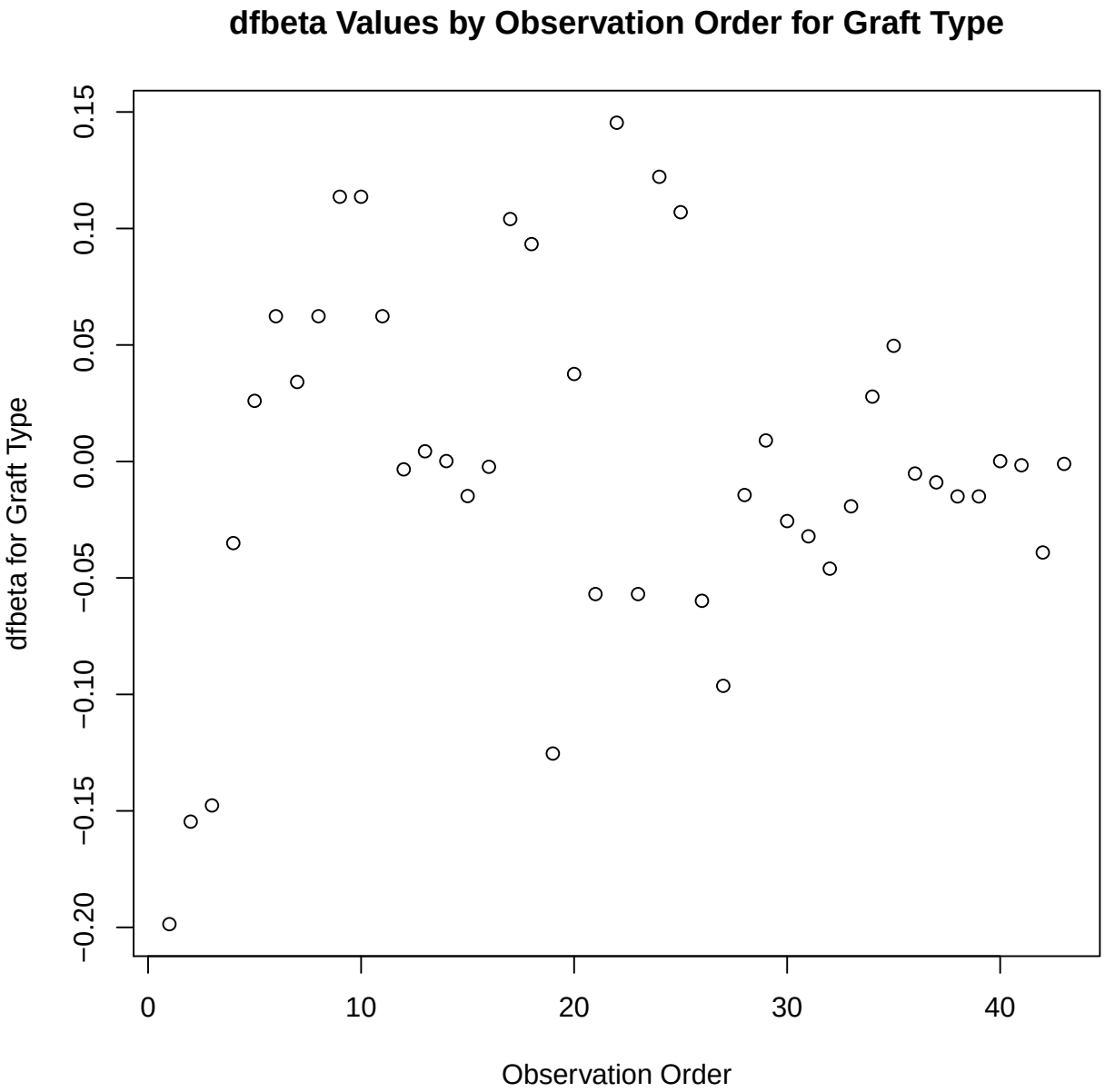
```
hodg.mart <- residuals(hodg.cox2,type="martingale")
hodg.dev <- residuals(hodg.cox2,type="deviance")
hodg.dfb <- residuals(hodg.cox2,type="dfbeta")
hodg.preds <- predict(hodg.cox2)                    #linear predictor

plotr21 <- function(){
  plot(hodg.preds,hodg.mart,xlab="Linear Predictor",ylab="Martingale Residual")
  title("Martingale Residuals vs. Linear Predictor")
}

plotr22 <- function(){
  plot(hodg.preds,hodg.dev,xlab="Linear Predictor",ylab="Deviance Residual")
  title("Deviance Residuals vs. Linear Predictor")
}

plotr23 <- function(){
  plot(hodg.dfb[,1],xlab="Observation Order",ylab="dfbeta for Graft Type")
  title("dfbeta Values by Observation Order for Graft Type")
}
.........
```



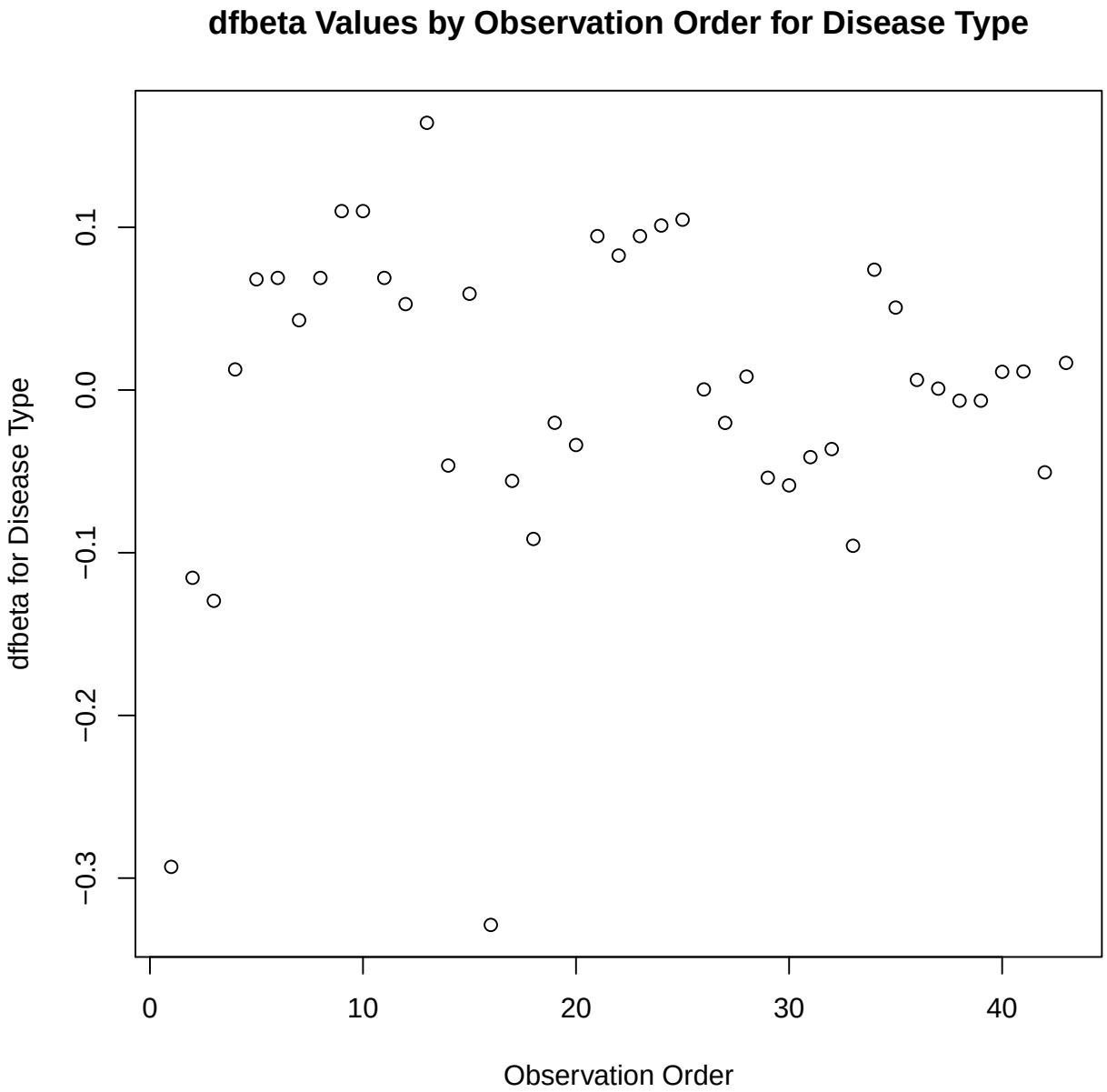
The smallest three martingale residuals in order are observations 1, 29, and 18.



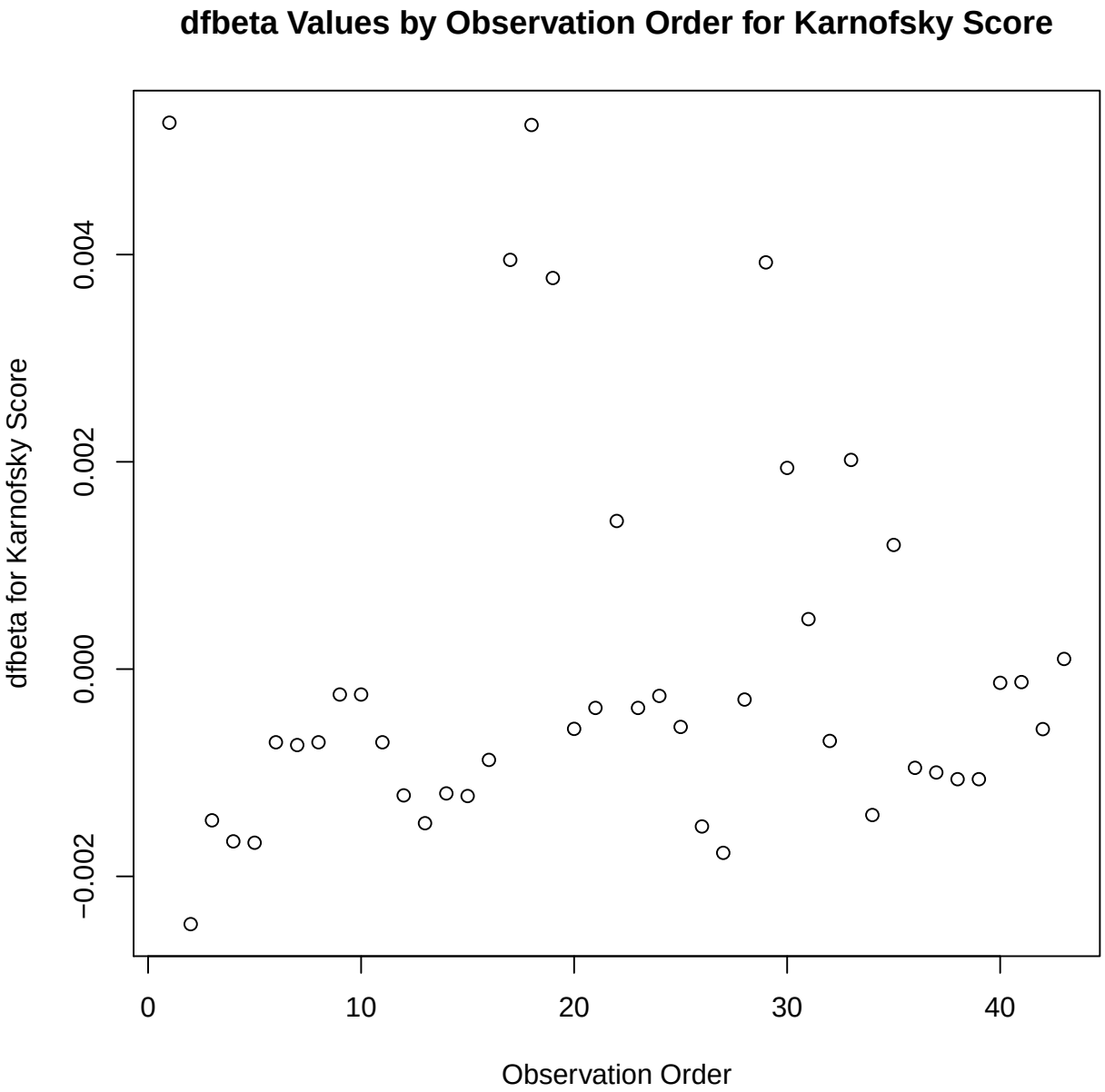
The two largest deviance residuals are observations 1 and 29. Worth examining.



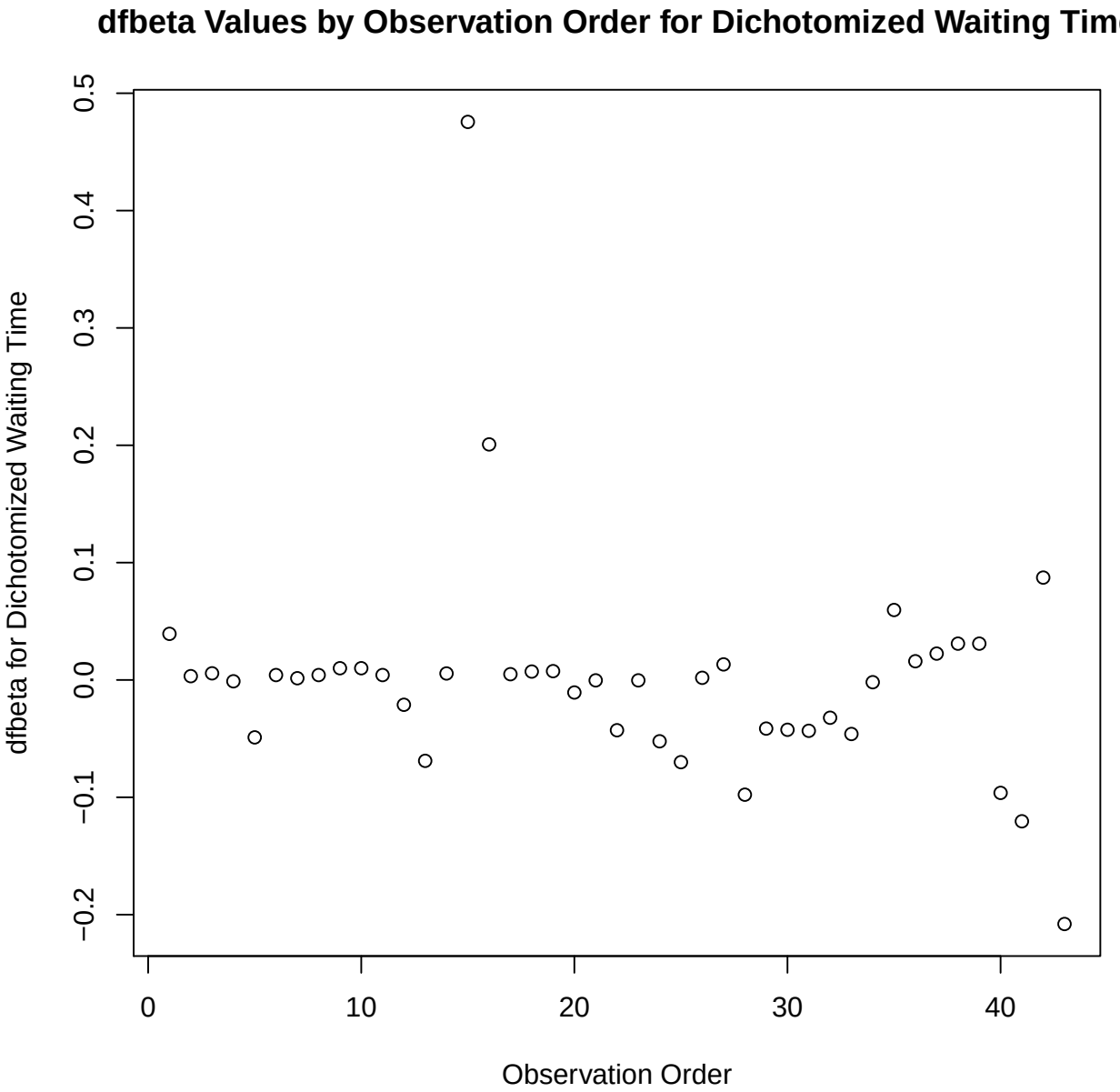
The smallest dfbeta for graft type is observation 1.



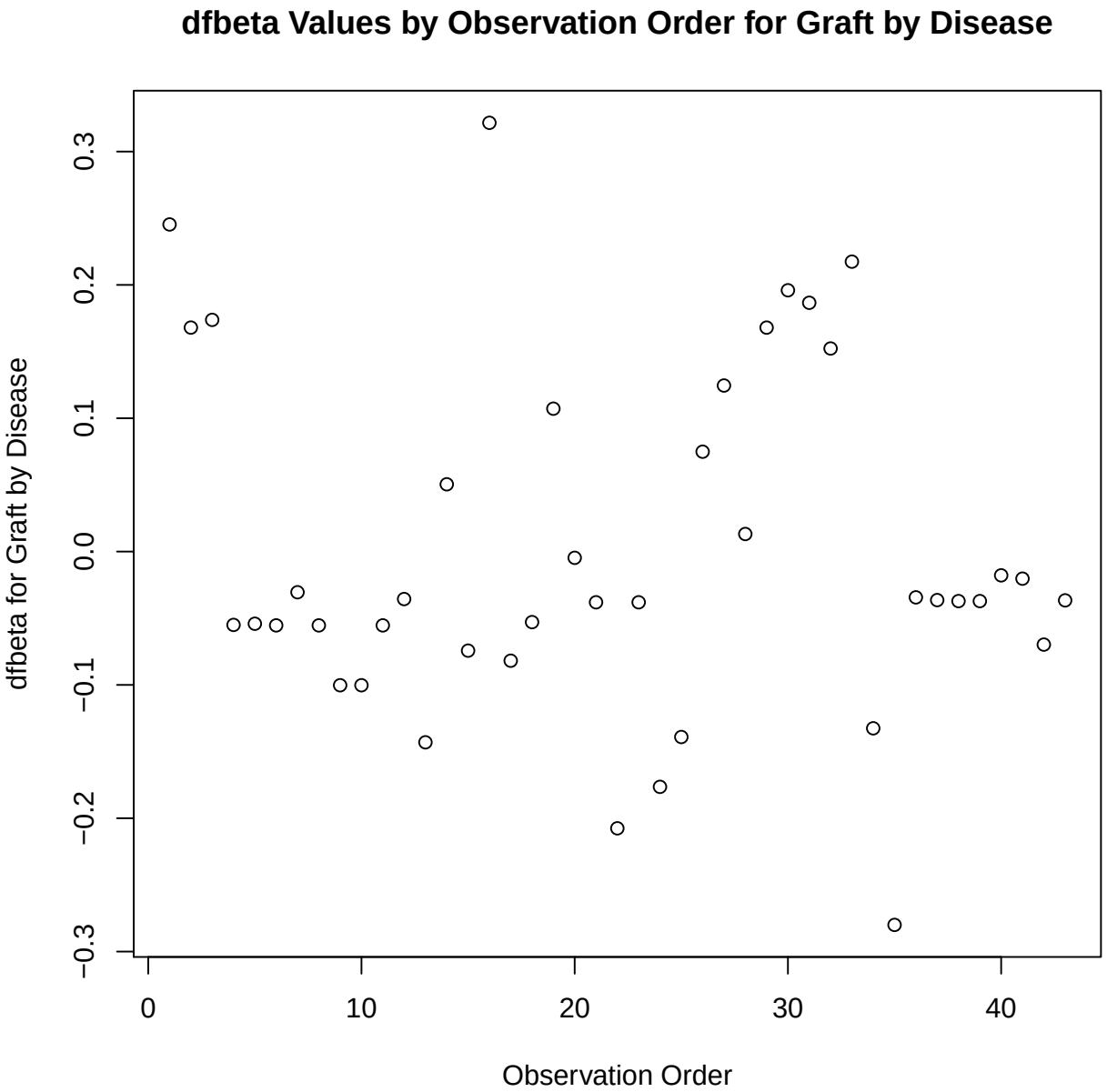
The smallest two dfbeta values for disease type are observations 1 and 16.



The two highest dfbeta values for score are observations 1 and 18. The next three are observations 17, 29, and 19. The smallest value is observation 2.



The two large values of dfbeta for dichotomized waiting time are observations 15 and 16. This may have to do with the discretization of waiting time.



The two largest values are observations 1 and 16. The smallest value is observation 35.

Table: Observations to Examine by Residuals and Influence

Martingale Residuals	1, 29, 18
Deviance Residuals	1, 29
Graft Type Influence	1
Disease Type Influence	1, 16
Karnofsky Score Influence	1, 18 (17, 29, 19)
Waiting Time Influence	15, 16
Graft by Disease Influence	1, 16, 35

The most important observations to examine seem to be 1, 15, 16, 18, and 29.

```
> with(hodg,summary(time[delta==1]))
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
   2.00   41.25   62.50   97.62   83.25  524.00
> with(hodg,summary(wtime))
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
    5.0    16.0    24.0    37.7    55.5   171.0
> with(hodg,summary(score))
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  20.00   60.00   80.00   76.28   90.00  100.00

> hodg.cox2
                      coef exp(coef) se(coef)     z        p
gtypeAuto           0.6651    1.9447   0.5943  1.12   0.2631
dtypeHOD            2.3273   10.2505   0.7332  3.17   0.0015
score              -0.0550    0.9464   0.0123 -4.46 8.2e-06
wt2long            -2.0598    0.1275   1.0507 -1.96   0.0499
gtypeAuto:dtypeHOD -2.0668    0.1266   0.9258 -2.23   0.0256

> hodg[c(1,15,16,18,29),]
   gtype dtype time delta score wtime
1      1     1   28     1    90    24    #early death, good score, low risk grp
15     1     2   77     1    60   102    #high risk grp, long wait, poor score
16     1     2   79     1    70    71    #high risk grp, short wait, poor score
18     2     1   53     1    90    17    #early death, good score, med risk grp
29     2     2   30     1    90    73    #early death, good score, med risk grp
```

Action Items

- Unusual points may need checking, particularly if the data are not completely cleaned. In this case, observations 15 and 16 may show some trouble with the dichotomization of waiting time, but it still may be useful.
- The two largest residuals seem to be due to unexpectedly early deaths, but unfortunately this can occur.

- If hazards don't look proportional, then we may need to use strata, between which the base hazards are permitted to be different. For this problem, the natural strata are the two diseases, because they could need to be managed differently anyway.
- A main point that we want to be sure of is the relative risk difference by disease type and graft type.

Table: Linear Risk Predictors for Lymphoma

Disease	Graft Type	Linear Predictor
Non-Hodgkin's	Allogenic	0
Non-Hodgkin's	Autologous	0.6651
Hodgkin's	Allogenic	2.3273
Hodgkin's	Autologous	0.9256

For Non-Hodgkin's, the allogenic graft is better. For Hodgkin's, the autologous graft is much better.