

Survival Analysis

Survival analysis

- So far, have seen:
 - response variable counted or measured (regression)
 - response variable categorized (logistic regression)

and have predicted response from explanatory variables.

- But what if response is time until event (eg. time of survival after surgery)?
- Additional complication: event might not have happened at end of study (eg. patient still alive). But knowing that patient has “not died yet” presumably informative. Such data called *censored*.
- Enter *survival analysis*, in particular the “Cox proportional hazards model”.
- Explanatory variables in this context often called *covariates*.

Example: still dancing?

- 12 women who have just started taking dancing lessons are followed for up to a year, to see whether they are still taking dancing lessons, or have quit. The “event” here is “quit”.
- This might depend on:
 - a treatment (visit to a dance competition)
 - woman's age (at start of study).

Data

| Months | Quit | Treatment | Age |
|--------|------|-----------|-----|
| 1 | 1 | 0 | 16 |
| 2 | 1 | 0 | 24 |
| 2 | 1 | 0 | 18 |
| 3 | 0 | 0 | 27 |
| 4 | 1 | 0 | 25 |
| 7 | 1 | 1 | 26 |
| 8 | 1 | 1 | 36 |
| 10 | 1 | 1 | 38 |
| 10 | 0 | 1 | 45 |
| 12 | 1 | 1 | 47 |

About the data

- `months` and `quit` are kind of combined response:
 - `Months` is number of months a woman was actually observed dancing
 - `quit` is 1 if woman quit, 0 if still dancing at end of study.
- `Treatment` is 1 if woman went to dance competition, 0 otherwise.
- Fit model and see whether `Age` or `Treatment` have effect on survival.
- Want to do predictions for probabilities of still dancing as they depend on whatever is significant, and draw plot.

Packages (for this section)

- Install packages `survival` and `survminer` if not done.
- Load `survival`, `survminer`, `broom` and `tidyverse`, also `marginaleffects` to help with predictions:

```
library(tidyverse)
library(survival)
library(survminer)
library(broom)
library(marginaleffects)
```

Read data

- Column-aligned:

```
url <- "http://ritsokiguess.site/datafiles/dancing.txt"
dance <- read_table(url)
```

```
##
## -- Column specification -----
## cols(
##   Months = col_double(),
##   Quit = col_double(),
##   Treatment = col_double(),
##   Age = col_double()
## )
```

The data

dance

| Months | Quit | Treatment | Age |
|--------|------|-----------|-----|
| 1 | 1 | 0 | 16 |
| 2 | 1 | 0 | 24 |
| 2 | 1 | 0 | 18 |
| 3 | 0 | 0 | 27 |
| 4 | 1 | 0 | 25 |
| 5 | 1 | 0 | 21 |
| 11 | 1 | 0 | 55 |
| 7 | 1 | 1 | 26 |
| 8 | 1 | 1 | 36 |
| 10 | 1 | 1 | 38 |
| 10 | 0 | 1 | 45 |
| 12 | 1 | 1 | 47 |

Examine response and fit model

- Response variable:

```
dance %>% mutate(mth = Surv(Months, Quit)) -> dance  
dance
```

| Months | Quit | Treatment | Age | mth |
|--------|------|-----------|-----|-----|
| 1 | 1 | 0 | 16 | 1 |
| 2 | 1 | 0 | 24 | 2 |
| 2 | 1 | 0 | 18 | 2 |
| 3 | 0 | 0 | 27 | 3+ |
| 4 | 1 | 0 | 25 | 4 |
| 5 | 1 | 0 | 21 | 5 |
| 11 | 1 | 0 | 55 | 11 |
| 7 | 1 | 1 | 26 | 7 |
| 8 | 1 | 1 | 36 | 8 |
| 10 | 1 | 1 | 38 | 10 |
| 10 | 0 | 1 | 45 | 10+ |
| 12 | 1 | 1 | 47 | 12 |

Output looks a lot like regression

```
summary(dance.1)
```

```
## Call:
## coxph(formula = mth ~ Treatment + Age, data = dance)
##
##      n= 12, number of events= 10
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## Treatment -4.44915    0.01169  2.60929 -1.705   0.0882 .
## Age       -0.36619    0.69337  0.15381 -2.381   0.0173 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## Treatment    0.01169      85.554 7.026e-05    1.9444
## Age          0.69337      1.442 5.129e-01    0.9373
##
## Concordance= 0.964  (se = 0.039 )
## Likelihood ratio test= 21.68  on 2 df,   p=2e-05
## Wald test              = 5.67  on 2 df,   p=0.06
## Score (logrank) test = 14.75  on 2 df,   p=6e-04
```

Conclusions

- Use $\alpha = 0.10$ here since not much data.
- Three tests at bottom like global F-test. Consensus that something predicts survival time (whether or not dancer quit and how long it took).
- Age (definitely), Treatment (marginally) both predict survival time.

Model checking

- With regression, usually plot residuals against fitted values.
- Not quite same here (nonlinear model), but “martingale residuals” should have no pattern vs. “linear predictor”.
- `ggcoxdiagnostics` from package `survminer` makes plot, to which we add smooth. If smooth trend more or less straight across, model OK.
- Martingale residuals can go very negative, so won't always look normal.

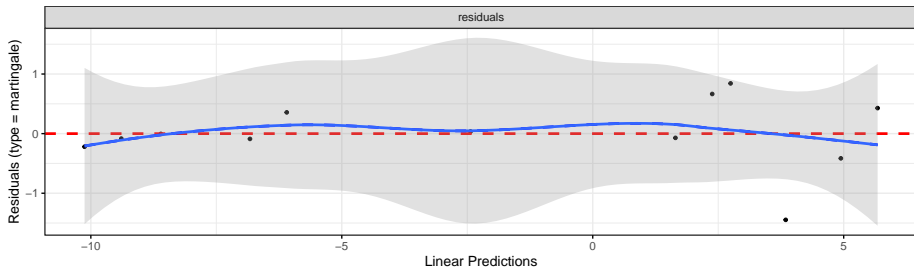
Martingale residual plot for dance data

This looks good (with only 12 points):

```
ggcoxdiagnostics(dance.1) + geom_smooth(se = F)
```

```
## `geom_smooth()` using formula = 'y ~ x'
```

```
## `geom_smooth()` using method = 'loess' and formula = 'y ~ x'
```



Predicted survival probs

- The function we use is called `survfit`, though actually works rather like `predictions`.
- First create a data frame of values to predict from. We'll do all combos of ages 20 and 40, treatment and not, using `datagrid` to get all the combos:

```
treatments <- c(0, 1)
ages <- c(20, 40)
dance.new <- datagrid(Treatment = treatments, Age = ages,
                      model = dance.1)
dance.new
```

| Treatment | Age |
|-----------|-----|
| 0 | 20 |
| 0 | 40 |
| 1 | 20 |
| 1 | 40 |

The predictions

One prediction *for each time* for each combo of age and treatment in `dance.new`:

```
s <- survfit(dance.1, newdata = dance.new, data = dance)
summary(s)
```

```
## Call: survfit(formula = dance.1, newdata = dance.new, data = dance)
```

```
##
```

| ## | time | n.risk | n.event | survival1 | survival2 | survival3 | survival4 |
|----|------|--------|---------|-----------|-----------|-----------|-----------|
| ## | 1 | 12 | 1 | 8.76e-01 | 1.00e+00 | 9.98e-01 | 1.000 |
| ## | 2 | 11 | 2 | 3.99e-01 | 9.99e-01 | 9.89e-01 | 1.000 |
| ## | 4 | 8 | 1 | 1.24e-01 | 9.99e-01 | 9.76e-01 | 1.000 |
| ## | 5 | 7 | 1 | 2.93e-02 | 9.98e-01 | 9.60e-01 | 1.000 |
| ## | 7 | 6 | 1 | 2.96e-323 | 6.13e-01 | 1.70e-04 | 0.994 |
| ## | 8 | 5 | 1 | 0.00e+00 | 2.99e-06 | 1.35e-98 | 0.862 |
| ## | 10 | 4 | 1 | 0.00e+00 | 0.00e+00 | 0.00e+00 | 0.000 |
| ## | 11 | 2 | 1 | 0.00e+00 | 0.00e+00 | 0.00e+00 | 0.000 |
| ## | 12 | 1 | 1 | 0.00e+00 | 0.00e+00 | 0.00e+00 | 0.000 |

Conclusions from predicted probs

- Older women more likely to be still dancing than younger women (compare “profiles” for same treatment group).
- Effect of treatment seems to be to increase prob of still dancing (compare “profiles” for same age for treatment group vs. not)
- Would be nice to see this on a graph. This is `ggsurvplot` from package `survminer`:

```
g <- ggsurvplot(s, conf.int = FALSE)
```

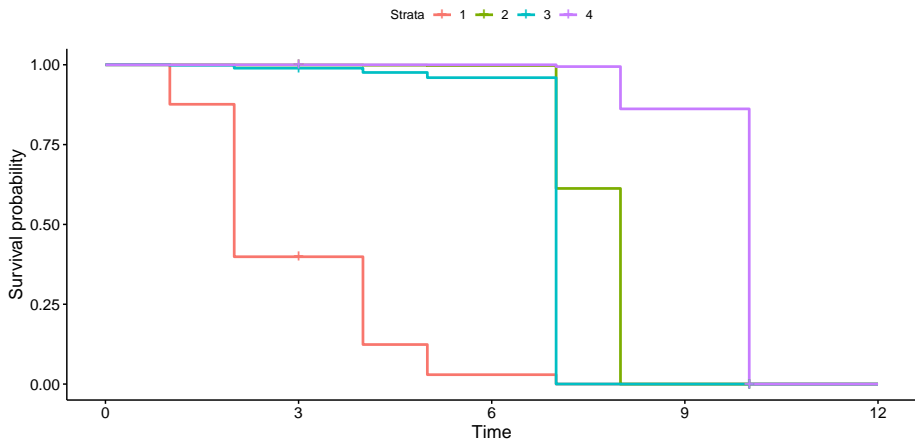

“Strata” (groups)

- uses “strata” thus (`dance.new`):

| Treatment | Age |
|-----------|-----|
| 0 | 20 |
| 0 | 40 |
| 1 | 20 |
| 1 | 40 |

Plotting survival probabilities

09



Discussion

- Survivor curve farther to the right is better (better chance of surviving longer).
- Best is age 40 with treatment, worst age 20 without.
- Appears to be:
 - age effect (40 better than 20)
 - treatment effect (treatment better than not)
 - In analysis, treatment effect only marginally significant.

A more realistic example: lung cancer

- When you load in an R package, get data sets to illustrate functions in the package.
- One such is `lung`. Data set measuring survival in patients with advanced lung cancer.
- Along with survival time, number of “performance scores” included, measuring how well patients can perform daily activities.
- Sometimes high good, but sometimes bad!
- Variables below, from the data set help file (`?lung`).

The variables

Format

| | |
|------------|---|
| inst: | Institution code |
| time: | Survival time in days |
| status: | censoring status 1=censored, 2=dead |
| age: | Age in years |
| sex: | Male=1 Female=2 |
| ph.ecog: | ECOG performance score (0=good 5=dead) |
| ph.karno: | Karnofsky performance score (bad=0-good=100) rated by physician |
| pat.karno: | Karnofsky performance score as rated by patient |
| meal.cal: | Calories consumed at meals |
| wt.loss: | Weight loss in last six months |

Uh oh, missing values

```
lung %>% slice(1:16)
```

| inst | time | status | age | sex | ph.ecog | ph.karno | pat.karno | meal.cal | wt.loss |
|------|------|--------|-----|-----|---------|----------|-----------|----------|---------|
| 3 | 306 | 2 | 74 | 1 | 1 | 90 | 100 | 1175 | NA |
| 3 | 455 | 2 | 68 | 1 | 0 | 90 | 90 | 1225 | 15 |
| 3 | 1010 | 1 | 56 | 1 | 0 | 90 | 90 | NA | 15 |
| 5 | 210 | 2 | 57 | 1 | 1 | 90 | 60 | 1150 | 11 |
| 1 | 883 | 2 | 60 | 1 | 0 | 100 | 90 | NA | 0 |
| 12 | 1022 | 1 | 74 | 1 | 1 | 50 | 80 | 513 | 0 |
| 7 | 310 | 2 | 68 | 2 | 2 | 70 | 60 | 384 | 10 |
| 11 | 361 | 2 | 71 | 2 | 2 | 60 | 80 | 538 | 1 |
| 1 | 218 | 2 | 53 | 1 | 1 | 70 | 80 | 825 | 16 |
| 7 | 166 | 2 | 61 | 1 | 2 | 70 | 70 | 271 | 34 |
| 6 | 170 | 2 | 57 | 1 | 1 | 80 | 80 | 1025 | 27 |
| 16 | 654 | 2 | 68 | 2 | 2 | 70 | 70 | NA | 23 |
| 11 | 728 | 2 | 68 | 2 | 1 | 90 | 90 | NA | 5 |
| 21 | 71 | 2 | 60 | 1 | NA | 60 | 70 | 1225 | 32 |
| 12 | 567 | 2 | 57 | 1 | 1 | 80 | 70 | 2600 | 60 |
| 1 | 144 | 2 | 67 | 1 | 1 | 80 | 90 | NA | 15 |

A closer look

```
summary(lung)
```

```
##      inst      time      status      age      sex
## Min.   : 1.00   Min.    : 5.0   Min.    :1.000   Min.    :39.00   Min.    :1.000
## 1st Qu.: 3.00   1st Qu.: 166.8   1st Qu.:1.000   1st Qu.:56.00   1st Qu.:1.000
## Median :11.00   Median : 255.5   Median :2.000   Median :63.00   Median :1.000
## Mean   :11.09   Mean    : 305.2   Mean    :1.724   Mean    :62.45   Mean    :1.395
## 3rd Qu.:16.00   3rd Qu.: 396.5   3rd Qu.:2.000   3rd Qu.:69.00   3rd Qu.:2.000
## Max.   :33.00   Max.    :1022.0   Max.    :2.000   Max.    :82.00   Max.    :2.000
## NA's   :1
##      ph.ecog      ph.karno      pat.karno      meal.cal      wt.loss
## Min.   :0.0000   Min.    : 50.00   Min.    : 30.00   Min.    : 96.0   Min.    :~24.000
## 1st Qu.:0.0000   1st Qu.: 75.00   1st Qu.: 70.00   1st Qu.: 635.0   1st Qu.: 0.000
## Median :1.0000   Median : 80.00   Median : 80.00   Median : 975.0   Median : 7.000
## Mean   :0.9515   Mean    : 81.94   Mean    : 79.96   Mean    : 928.8   Mean    : 9.832
## 3rd Qu.:1.0000   3rd Qu.: 90.00   3rd Qu.: 90.00   3rd Qu.:1150.0   3rd Qu.: 15.750
## Max.   :3.0000   Max.    :100.00   Max.    :100.00   Max.    :2600.0   Max.    : 68.000
## NA's   :1       NA's    :1       NA's    :3       NA's    :47       NA's    :14
```

Remove obs with *any* missing values

```
lung %>% drop_na() -> lung.complete  
lung.complete %>%  
  select(meal.cal:wt.loss) %>%  
  slice(1:8)
```

| | meal.cal | wt.loss |
|----|----------|---------|
| 2 | 1225 | 15 |
| 4 | 1150 | 11 |
| 6 | 513 | 0 |
| 7 | 384 | 10 |
| 8 | 538 | 1 |
| 9 | 825 | 16 |
| 10 | 271 | 34 |
| 11 | 1025 | 27 |

Missing values seem to be gone.

Check!

```
summary(lung.complete)
```

```
##      inst      time      status      age      sex
## Min.   : 1.00   Min.    : 5.0   Min.    :1.000   Min.    :39.00   Min.    :1.000
## 1st Qu.: 3.00   1st Qu.: 174.5   1st Qu.:1.000   1st Qu.:57.00   1st Qu.:1.000
## Median :11.00   Median : 268.0   Median :2.000   Median :64.00   Median :1.000
## Mean   :10.71   Mean    : 309.9   Mean    :1.719   Mean    :62.57   Mean    :1.383
## 3rd Qu.:15.00   3rd Qu.: 419.5   3rd Qu.:2.000   3rd Qu.:70.00   3rd Qu.:2.000
## Max.   :32.00   Max.    :1022.0   Max.    :2.000   Max.    :82.00   Max.    :2.000
##   ph.ecog   ph.karno   pat.karno   meal.cal   wt.loss
## Min.    :0.0000   Min.    : 50.00   Min.    : 30.00   Min.    : 96.0   Min.    : -24.000
## 1st Qu.:0.0000   1st Qu.: 70.00   1st Qu.: 70.00   1st Qu.: 619.0   1st Qu.:  0.000
## Median :1.0000   Median : 80.00   Median : 80.00   Median : 975.0   Median :  7.000
## Mean    :0.9581   Mean     : 82.04   Mean     : 79.58   Mean     : 929.1   Mean     :  9.719
## 3rd Qu.:1.0000   3rd Qu.: 90.00   3rd Qu.: 90.00   3rd Qu.:1162.5   3rd Qu.: 15.000
## Max.    :3.0000   Max.     :100.00   Max.     :100.00   Max.     :2600.0   Max.     : 68.000
```

No missing values left.

Model 1: use everything except inst

```
names(lung.complete)
```

```
## [1] "inst"      "time"      "status"    "age"       "sex"       "ph.eco"
## [8] "pat.karno" "meal.cal"  "wt.loss"
```

- Event was death, goes with status of 2:

```
lung.complete %>%
  mutate(resp = Surv(time, status == 2)) ->
  lung.complete
lung.1 <- coxph(resp ~ . - inst - time - status,
  data = lung.complete
)
```

“Dot” means “all the other variables”.

summary of model 1: too tiny to see!

```
summary(lung.1)
```

```
## Call:
## coxph(formula = resp ~ . - inst - time - status, data = lung.complete)
##
## n= 167, number of events= 120
##
##              coef exp(coef)    se(coef)      z Pr(>|z|)
## age           1.080e-02  1.011e+00  1.160e-02  0.931  0.35168
## sex           -5.536e-01  5.749e-01  2.016e-01 -2.746  0.00603 **
## ph.ecog        7.395e-01  2.095e+00  2.250e-01  3.287  0.00101 **
## ph.karno       2.244e-02  1.023e+00  1.123e-02  1.998  0.04575 *
## pat.karno     -1.207e-02  9.880e-01  8.116e-03 -1.488  0.13685
## meal.cal       2.835e-05  1.000e+00  2.594e-04  0.109  0.91298
## wt.loss       -1.420e-02  9.859e-01  7.766e-03 -1.828  0.06748 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## age           1.0109      0.9893    0.9881    1.0341
## sex           0.5749      1.7395    0.3872    0.8534
## ph.ecog        2.0950      0.4773    1.3479    3.2560
## ph.karno       1.0227      0.9778    1.0004    1.0455
## pat.karno      0.9880      1.0121    0.9724    1.0038
## meal.cal       1.0000      1.0000    0.9995    1.0005
## wt.loss        0.9859      1.0143    0.9710    1.0010
##
## Concordance= 0.653 (se = 0.029 )
## Likelihood ratio test= 28.16 on 7 df,  p=2e-04
## Wald test               = 27.5 on 7 df,  p=3e-04
## Score (logrank) test = 28.31 on 7 df,  p=2e-04
```

Overall significance

The three tests of overall significance:

```
glance(lung.1) %>% select(starts_with("p.value"))
```

| p.value.log | p.value.sc | p.value.wald | p.value.robust |
|-------------|------------|--------------|----------------|
| 0.0002053 | 0.0001929 | 0.0002711 | NA |

All strongly significant. *Something* predicts survival.

Coefficients for model 1

```
tidy(lung.1) %>% select(term, p.value) %>% arrange(p.value)
```

| term | p.value |
|-----------|-----------|
| ph.ecog | 0.0010126 |
| sex | 0.0060268 |
| ph.karno | 0.0457479 |
| wt.loss | 0.0674829 |
| pat.karno | 0.1368514 |
| age | 0.3516810 |
| meal.cal | 0.9129766 |

- sex and ph.ecog definitely significant here
- age, pat.karno and meal.cal definitely not
- Take out definitely non-sig variables, and try again.

Model 2

```
lung.2 <- update(lung.1, . ~ . - age - pat.karno - meal.cal)
tidy(lung.2) %>% select(term, p.value)
```

| term | p.value |
|----------|-----------|
| sex | 0.0040915 |
| ph.ecog | 0.0001119 |
| ph.karno | 0.1005838 |
| wt.loss | 0.1079748 |

Compare with first model:

```
anova(lung.2, lung.1)
```

| loglik | Chisq | Df | Pr(> Chi) |
|-----------|----------|----|------------|
| -495.6689 | NA | NA | NA |
| -494.0344 | 3.268999 | 3 | 0.3519808 |

- No harm in taking out those variables.

Model 3

Take out ph.karno and wt.loss as well.

```
lung.3 <- update(lung.2, . ~ . - ph.karno - wt.loss)
```

```
tidy(lung.3) %>% select(term, estimate, p.value)
```

| term | estimate | p.value |
|---------|------------|-----------|
| sex | -0.5100991 | 0.0095794 |
| ph.ecog | 0.4825185 | 0.0002656 |

Check whether that was OK

```
anova(lung.3, lung.2)
```

| loglik | Chisq | Df | Pr(> Chi) |
|-----------|----------|----|------------|
| -498.3757 | NA | NA | NA |
| -495.6689 | 5.413508 | 2 | 0.0667531 |

Just OK.

Commentary

- OK (just) to take out those two covariates.
- Both remaining variables strongly significant.
- Nature of effect on survival time? Consider later.
- Picture?

Plotting survival probabilities

- Create new data frame of values to predict for, then predict:

```
sexes <- c(1, 2)
ph.ecogs <- 0:3
lung.new <- datagrid(sex = sexes, ph.ecog = ph.ecogs, model = lung.3)
lung.new
```

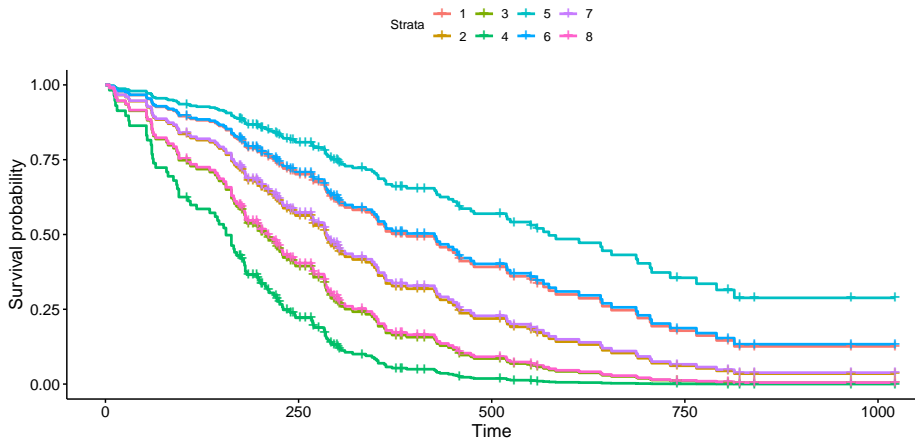
| sex | ph.ecog |
|-----|---------|
| 1 | 0 |
| 1 | 1 |
| 1 | 2 |
| 1 | 3 |
| 2 | 0 |
| 2 | 1 |
| 2 | 2 |
| 2 | 3 |

Making the plot

```
s <- survfit(lung.3, newdata = lung.new, data = lung)
g <- ggsurvplot(s, conf.int = FALSE)
```

The plot

gg



Discussion of survival curves

- Best survival is teal-blue curve, stratum 5, females with ph.ecog score 0.
- Next best: blue, stratum 6, females with score 1, and red, stratum 1, males score 0.
- Worst: green, stratum 4, males score 3.
- For any given ph.ecog score, females have better predicted survival than males.
- For both genders, a lower score associated with better survival.

The coefficients in model 3

```
tidy(lung.3) %>% select(term, estimate, p.value)
```

| term | estimate | p.value |
|---------|------------|-----------|
| sex | -0.5100991 | 0.0095794 |
| ph.ecog | 0.4825185 | 0.0002656 |

- sex coeff negative, so being higher sex value (female) goes with *less* hazard of dying.
- ph.ecog coeff positive, so higher ph.ecog score goes with *more* hazard of dying
- Two coeffs about same size, so being male rather than female corresponds to 1-point increase in ph.ecog score. Note how survival curves come in 3 pairs plus 2 odd.

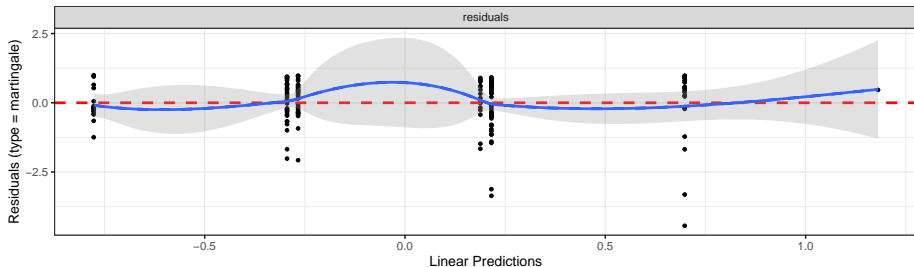
Martingale residuals for this model

No problems here:

```
ggcoxdiagnostics(lung.3) + geom_smooth(se = F)
```

```
## `geom_smooth()` using formula = 'y ~ x'
```

```
## `geom_smooth()` using method = 'loess' and formula = 'y ~ x'
```



When the Cox model fails

- Invent some data where survival is best at middling age, and worse at high *and* low age:

```
age <- seq(20, 60, 5)
survtime <- c(10, 12, 11, 21, 15, 20, 8, 9, 11)
stat <- c(1, 1, 1, 1, 0, 1, 1, 1, 1)
d <- tibble(age, survtime, stat)
d %>% mutate(y = Surv(survtime, stat)) -> d
```

- Small survival time 15 in middle was actually censored, so would have been longer if observed.

Fit Cox model

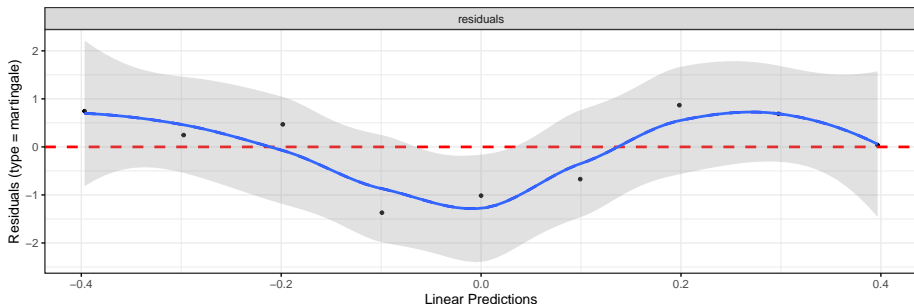
```
y.1 <- coxph(y ~ age, data = d)
summary(y.1)
```

```
## Call:
## coxph(formula = y ~ age, data = d)
##
##      n= 9, number of events= 8
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## age 0.01984      1.02003  0.03446  0.576    0.565
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age          1.02      0.9804    0.9534    1.091
##
## Concordance= 0.545  (se = 0.105 )
## Likelihood ratio test= 0.33  on 1 df,   p=0.6
## Wald test               = 0.33  on 1 df,   p=0.6
## Score (logrank) test = 0.33  on 1 df,   p=0.6
```

Martingale residuals

Down-and-up indicates incorrect relationship between age and survival:

```
ggcoxdiagnostics(y.1) + geom_smooth(se = F)
```



Attempt 2

Add squared term in age:

```
y.2 <- coxph(y ~ age + I(age^2), data = d)
tidy(y.2) %>% select(term, estimate, p.value)
```

| term | estimate | p.value |
|----------|------------|-----------|
| age | -0.3801838 | 0.1156031 |
| I(age^2) | 0.0048324 | 0.0976903 |

- (Marginally) helpful.

Martingale residuals this time

Not great, but less problematic than before:

```
ggcoxdiagnostics(y.2) + geom_smooth(se = F)
```

