Survival Analysis

Survival analysis

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

Packages

- Install packages `survival` and `survminer` if not done.

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

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.

Read data

- Column-aligned:

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

The data

```
dance
```

```
# A tibble: 12 x 4
   Months  Quit Treatment   Age
    <dbl> <dbl>     <dbl> <dbl>
 1      1     1         0    16
 2      2     1         0    24
 3      2     1         0    18
 4      3     0         0    27
 5      4     1         0    25
 6      5     1         0    21
 7     11     1         0    55
 8      7     1         1    26
 9      8     1         1    36
10     10     1         1    38
11     10     0         1    45
12     12     1         1    47
```

Examine response and fit model

- Response variable:

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

```
# A tibble: 12 x 5
   Months  Quit Treatment   Age    mth
    <dbl> <dbl>     <dbl> <dbl> <Surv>
 1      1     1         0    16     1
 2      2     1         0    24     2
 3      2     1         0    18     2
 4      3     0         0    27     3+
 5      4     1         0    25     4
 6      5     1         0    21     5
 7     11     1         0    55    11
 8      7     1         1    26     7
 9      8     1         1    36     8
10     10     1         1    38    10
11     10     0         1    45    10+
12     12     1         1    47    12
```

- Then fit model, predicting `mth` from explanatories:

Output looks a lot like regression

```r
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.

Behind the scenes

- All depends on *hazard rate*, which is based on probability that event happens in the next short time period, given that event has not happened yet:
- X denotes time to event, δ is small time interval:
- $h(t) = P(X \leq t + \delta | X \geq t)/\delta$
- if $h(t)$ large, event likely to happen soon (lifetime short)
- if $h(t)$ small, event unlikely to happen soon (lifetime long).

Modelling lifetime

- want to model hazard rate
- but hazard rate always positive, so actually model *log* of hazard rate
- modelling how (log-)hazard rate depends on other things eg $X_1 =$ age, $X_2 =$ treatment, with the β being regression coefficients:
- Cox model $h(t) = h_0(t) \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots)$, or:
- $\log(h(t)) = \log(h_0(t)) + \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots$
- like a generalized linear model with log link.

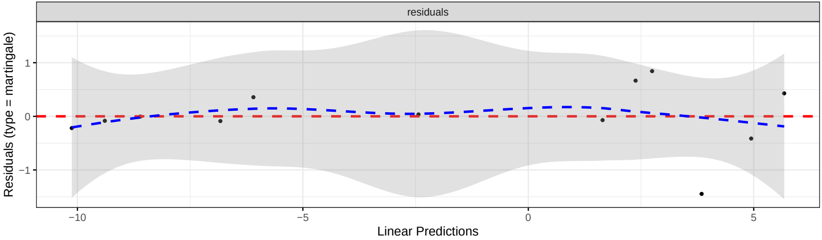
Model checking

- 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)
```



Predicted survival probs

- The function we use is called `survfit`, though actually works rather like `predict`.
- 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(model = dance.1, Treatment = treatmen
dance.new
```

```
  Treatment Age
1         0  20
2         0  40
3         1  20
4         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 = F)
```

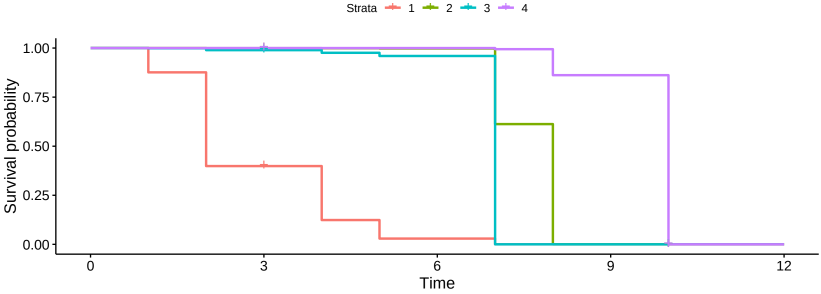
“Strata” (groups)

- uses “strata” thus (`dance.new`):

```
  Treatment Age
1         0  20
2         0  40
3         1  20
4         1  40
```

Plotting survival probabilities

```
g
```



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
```

	inst	time	status	age	sex	ph.ecog	ph.karno	pat.karno	meal.cal	wt.loss
1	3	306	2	74	1	1	90	100	1175	NA
2	3	455	2	68	1	0	90	90	1225	15
3	3	1010	1	56	1	0	90	90	NA	15
4	5	210	2	57	1	1	90	60	1150	11
5	1	883	2	60	1	0	100	90	NA	0
6	12	1022	1	74	1	1	50	80	513	0
7	7	310	2	68	2	2	70	60	384	10
8	11	361	2	71	2	2	60	80	538	1
9	1	218	2	53	1	1	70	80	825	16
10	7	166	2	61	1	2	70	70	271	34
11	6	170	2	57	1	1	80	80	1025	27
12	16	654	2	68	2	2	70	70	NA	23
13	11	728	2	68	2	1	90	90	NA	5
14	21	71	2	60	1	NA	60	70	1225	32
15	12	567	2	57	1	1	80	70	2600	60
16	1	144	2	67	1	1	80	90	NA	15
17	22	613	2	70	1	1	90	100	1150	-5
18	16	707	2	63	1	2	50	70	1025	22
19	1	61	2	56	2	2	60	60	238	10
20	21	88	2	57	1	1	90	80	1175	NA
21	11	301	2	67	1	1	80	80	1025	17
22	6	81	2	49	2	0	100	70	1175	-8
23	11	624	2	50	1	1	70	80	NA	16

A closer look

```r
summary(lung)
```

```
      inst            time            status            age       
 Min.   : 1.00   Min.   :   5.0   Min.   :1.000   Min.   :39.00  
 1st Qu.: 3.00   1st Qu.: 166.8   1st Qu.:1.000   1st Qu.:56.00  
 Median :11.00   Median : 255.5   Median :2.000   Median :63.00  
 Mean   :11.09   Mean   : 305.2   Mean   :1.724   Mean   :62.45  
 3rd Qu.:16.00   3rd Qu.: 396.5   3rd Qu.:2.000   3rd Qu.:69.00  
 Max.   :33.00   Max.   :1022.0   Max.   :2.000   Max.   :82.00  
 NA's   :1                                                        
      sex           ph.ecog          ph.karno        pat.karno     
 Min.   :1.000   Min.   :0.0000   Min.   : 50.00   Min.   : 30.00  
 1st Qu.:1.000   1st Qu.:0.0000   1st Qu.: 75.00   1st Qu.: 70.00  
 Median :1.000   Median :1.0000   Median : 80.00   Median : 80.00  
 Mean   :1.395   Mean   :0.9515   Mean   : 81.94   Mean   : 79.96  
 3rd Qu.:2.000   3rd Qu.:1.0000   3rd Qu.: 90.00   3rd Qu.: 90.00  
 Max.   :2.000   Max.   :3.0000   Max.   :100.00   Max.   :100.00  
                 NA's   :1        NA's   :1        NA's   :3       
    meal.cal         wt.loss       
 Min.   :  96.0   Min.   :-24.000  
 1st Qu.: 635.0   1st Qu.:  0.000  
 Median : 975.0   Median :  7.000  
 Mean   : 928.8   Mean   :  9.832  
 3rd Qu.:1150.0   3rd Qu.: 15.750  
 Max.   :2600.0   Max.   : 68.000  
 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(1:10)
```

```
   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
15     2600      60
17     1150      -5
```

Missing values seem to be gone.

Check!

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

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

```r
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"))
```

```
# A tibble: 1 x 4
  p.value.log p.value.sc p.value.wald p.value.robust
        <dbl>      <dbl>        <dbl>          <dbl>
1    0.000205   0.000193     0.000271             NA
```

All strongly significant. *Something* predicts survival.

Coefficients for model 1

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

```
# A tibble: 7 x 2
  term       p.value
  <chr>        <dbl>
1 ph.ecog    0.00101
2 sex        0.00603
3 ph.karno   0.0457
4 wt.loss    0.0675
5 pat.karno  0.137
6 age        0.352
7 meal.cal   0.913
```

- `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)
```

```
# A tibble: 4 x 2
  term      p.value
  <chr>       <dbl>
1 sex      0.00409
2 ph.ecog  0.000112
3 ph.karno 0.101
4 wt.loss  0.108
```

Compare with first model:

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

```
Analysis of Deviance Table
 Cox model: response is  resp
 Model 1: ~ sex + ph.ecog + ph.karno + wt.loss
 Model 2: ~ (inst + time + status + age + sex + ph.ecog + p
   loglik Chisq Df Pr(>|Chi|)
1 -495.67
2 -494.03 3.269  3      0.352
```

- 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)
```

```
# A tibble: 2 x 3
  term    estimate  p.value
  <chr>      <dbl>    <dbl>
1 sex       -0.510 0.00958
2 ph.ecog    0.483 0.000266
```

```
summary(lung.3)
```

```
Call:
coxph(formula = resp ~ sex + ph.ecog, data = lung.complete)

  n= 167, number of events= 120

           coef exp(coef) se(coef)      z Pr(>|z|)
```

Check whether that was OK

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

```
Analysis of Deviance Table
 Cox model: response is  resp
 Model 1: ~ sex + ph.ecog
 Model 2: ~ sex + ph.ecog + ph.karno + wt.loss
   loglik  Chisq Df Pr(>|Chi|)
1 -498.38
2 -495.67 5.4135  2    0.06675 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '
```

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   1       0
2   1       1
3   1       2
4   1       3
5   2       0
6   2       1
7   2       2
8   2       3
```

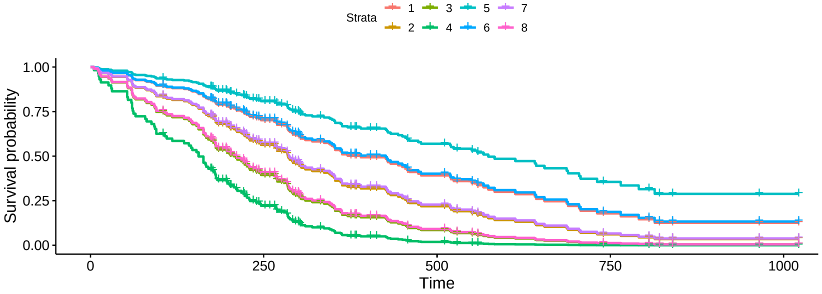
Making the plot

```r
s <- survfit(lung.3, newdata = lung.new, data = lung)
summary(s)
```

```
Call: survfit(formula = lung.3, newdata = lung.new, data =

 time n.risk n.event survival1 survival2 survival3 surviva
    5    167       1     0.996    0.9932   0.98908  0.9823
   11    166       1     0.992    0.9865   0.97825  0.9650
   12    165       1     0.987    0.9798   0.96743  0.9477
   13    164       1     0.983    0.9730   0.95660  0.9306
   15    163       1     0.979    0.9662   0.94577  0.9136
   26    162       1     0.975    0.9594   0.93502  0.8968
   30    161       1     0.970    0.9526   0.92427  0.8802
   31    160       1     0.966    0.9457   0.91352  0.8636
   53    159       2     0.957    0.9320   0.89222  0.8312
   54    157       1     0.953    0.9252   0.88162  0.8153
   59    156       1     0.949    0.9183   0.87103  0.7995
   60    155       2     0.940    0.9046   0.85000  0.7685
```

The plot

```
g
```



Strata
1
2
3
4
5
6
7
8
Survival probability
1.00
0.75
0.50
0.25
0.00
0
250
500
750
1000
Time

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)
```

```
# A tibble: 2 x 3
  term     estimate  p.value
  <chr>       <dbl>    <dbl>
1 sex        -0.510 0.00958
2 ph.ecog     0.483 0.000266
```

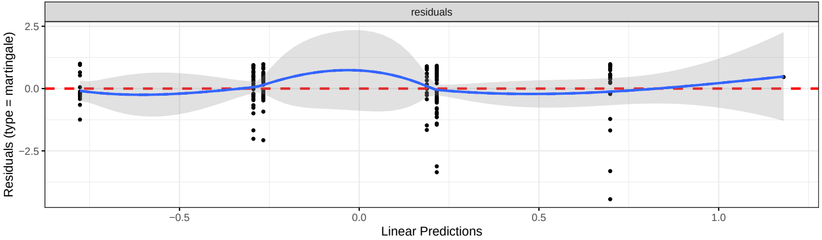
```
summary(lung.3)
```

```
Call:
coxph(formula = resp ~ sex + ph.ecog, data = lung.complete)

  n= 167, number of events= 120

           coef exp(coef) se(coef)      z Pr(>|z|)
sex     -0.5101    0.6004   0.1969 -2.591 0.009579 **
ph.ecog  0.4825    1.6201   0.1323  3.647 0.000266 ***
---
```

Martingale residuals for this model

No problems here:

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



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

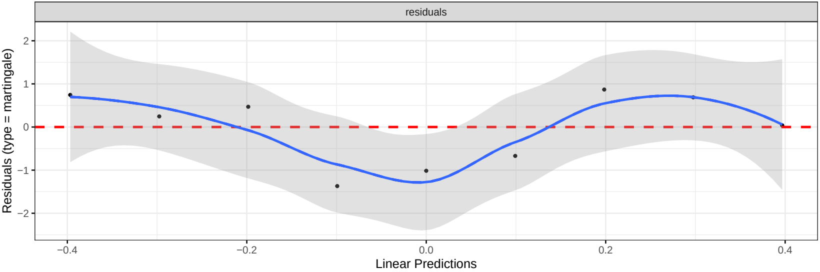
```r
y.1 <- coxph(y ~ age, data = d)
summary(y.1)
```

```
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)
```

```
# A tibble: 2 x 3
  term      estimate p.value
  <chr>        <dbl>   <dbl>
1 age       -0.380    0.116
2 I(age^2)  0.00483   0.0977
```

- (Marginally) helpful.

Martingale residuals this time

Not great, but less problematic than before:

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