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 package `survival` if not done. Also use `broom` and `marginaleffects` from earlier.

```
library(tidyverse)
library(survival)
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
```

Fit model

- Response variable has to incorporate both the survival time (`Months`) and whether or not the event, quitting, happened (that is, if `Quit` is 1).
- This is made using `Surv` from `survival` package, with two inputs:
  - the column that has the survival times
  - something that is `TRUE` or 1 if the event happened.
- Easiest for us to create this when we fit the model, predicting response from explanatories:

```
dance.1 <- coxph(Surv(Months, Quit) ~ Treatment + Age, data
```

Output looks a lot like regression

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

```
Call:
coxph(formula = Surv(Months, Quit) ~ 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/or 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.

Predictions with `marginaleffects`

- `marginaleffects` knows about survival models (with sufficient care)
- Predicted survival probabilities depend on:
  - the combination of explanatory variables you are looking at
  - the time at which you are looking at them (when more time has passed, it is more likely that the event has happened, so the "survival probability" should be lower).
- look at effect of age by comparing ages 20 and 40, and later look at the effect of treatment (values 1 and 0).
- Also have to provide some times to predict for, in `Months`.

Effect of age

```
new <- datagrid(model = dance.1, Age = c(20, 40), Months =
new
```

```
  Quit Treatment Age Months rowid
1    1         0  20      3     1
2    1         0  20      5     2
3    1         0  20      7     3
4    1         0  40      3     4
5    1         0  40      5     5
6    1         0  40      7     6
```

These are actually for women who *did not* go to the dance competition.

The predictions

```
cbind(predictions(dance.1, newdata = new, type = "survival'
  select(Age, Treatment, Months, estimate)
```

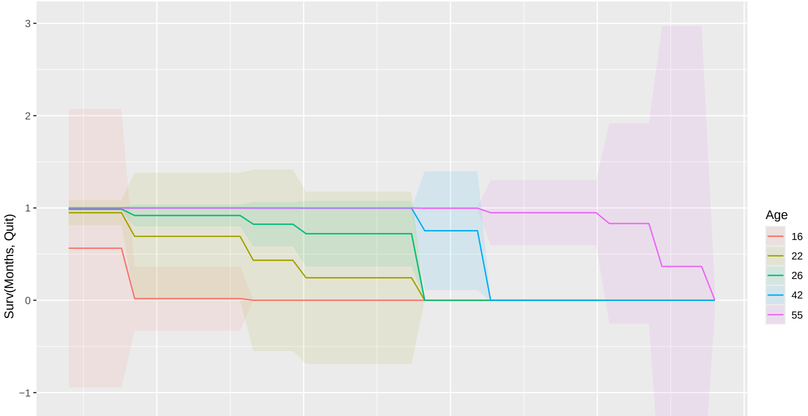
```
  Age Treatment Months      estimate
1  20         0      3  3.987336e-01
2  20         0      5  2.934959e-02
3  20         0      7 2.964394e-323
4  40         0      3  9.993936e-01
5  40         0      5  9.976749e-01
6  40         0      7  6.126327e-01
```

The estimated survival probabilities go down over time. For example a 20-year-old woman here has estimated probability 0.0293 of still dancing after 5 months.

A graph

We can plot the predictions over time for an experimental condition such as age. The key for `plot_predictions` is to put time *first* in the `condition`:

```
plot_predictions(dance.1, condition = c("Months", "Age"),
                 type = "survival")
```



Comments

- The plot picks some representative ages.
- It is (usually) best to be up and to the right (has the highest chance of surviving longest).
- Hence the oldest women have the best chance to still be dancing longest (the youngest women are most likely to quit soonest).

The effect of treatment

The same procedure will get predictions for women who did or did not go to the dance competition, at various times:

```
new <- datagrid(model = dance.1, Treatment = c(0, 1), Month
new
```

```
  Quit  Age Treatment Months rowid
1    1 31.5         0      3     1
2    1 31.5         0      5     2
3    1 31.5         0      7     3
4    1 31.5         1      3     4
5    1 31.5         1      5     5
6    1 31.5         1      7     6
```

The age used for predictions is the mean of all ages.

The predictions

```
cbind(predictions(dance.1, newdata = new, type = "survival'
  select(Age, Treatment, Months, estimate)
```

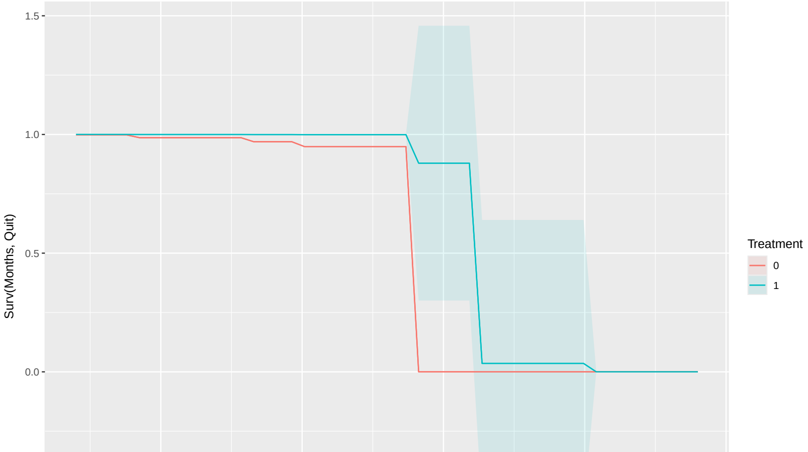
```
   Age Treatment Months     estimate
1 31.5         0      3 9.864573e-01
2 31.5         0      5 9.490195e-01
3 31.5         0      7 1.646297e-05
4 31.5         1      3 9.998406e-01
5 31.5         1      5 9.993886e-01
6 31.5         1      7 8.792014e-01
```

Women of this age have a high (0.879) chance of still dancing after 7 months if they went to the dance competition, but much lower (0.165) if they did not.

A graph

In `condition`, put the time variable first, and then the effect of interest:

```
plot_predictions(dance.1, condition = c("Months", "Treatmen
                 type = "survival")
```



Comments

- The survival curve for Treatment 1 is higher all the way along
- Hence at any time, the women who went to the dance competition have a higher chance of still dancing than those who did not.

The model summary again

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

```
Call:
coxph(formula = Surv(Months, Quit) ~ Treatment + Age, data

  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 '

          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 )
```

Comments

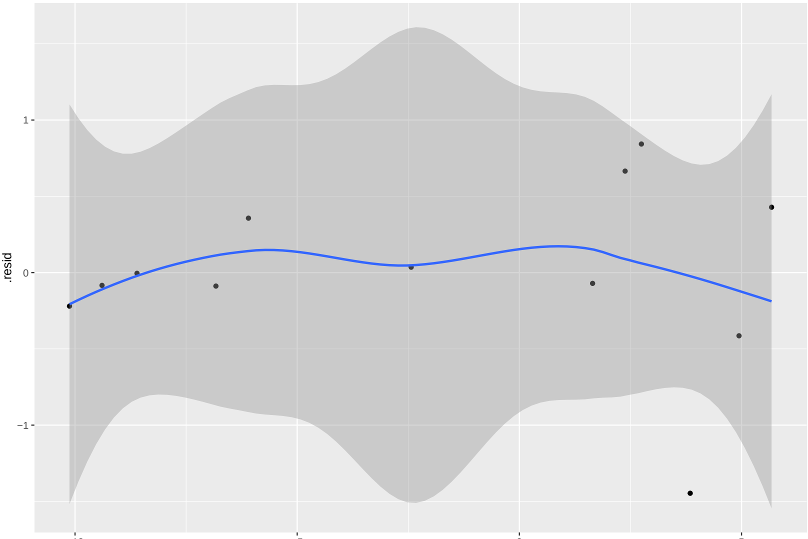
- The numbers in the `coef` column describe effect of that variable on log-hazard of quitting.
- Both numbers are negative, so a higher value on both variables goes with a lower hazard of quitting:
  - an older woman is less likely to quit soon (more likely to be still dancing)
  - a woman who went to the dance competition (`Treatment = 1`) is less likely to quit soon vs. a woman who didn't (more likely to be still dancing).

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".
- Use `broom` ideas to get them, in `.resid` and `.fitted` as below.
- Martingale residuals can go very negative, so won't always look normal.

Martingale residuals

```
dance.1 %>% augment(dance) %>%
  ggplot(aes(x = .fitted, y = .resid)) + geom_point() + geo
```



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

```r
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

```
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.   :3
 1st Qu.: 3.00   1st Qu.: 174.5   1st Qu.:1.000   1st Qu.:5
 Median :11.00   Median : 268.0   Median :2.000   Median :6
 Mean   :10.71   Mean   : 309.9   Mean   :1.719   Mean   :6
 3rd Qu.:15.00   3rd Qu.: 419.5   3rd Qu.:2.000   3rd Qu.:7
 Max.   :32.00   Max.   :1022.0   Max.   :2.000   Max.   :8
      sex           ph.ecog          ph.karno        pat.ka
 Min.   :1.000   Min.   :0.0000   Min.   : 50.00   Min.   
 1st Qu.:1.000   1st Qu.:0.0000   1st Qu.: 70.00   1st Qu.
 Median :1.000   Median :1.0000   Median : 80.00   Median 
 Mean   :1.383   Mean   :0.9581   Mean   : 82.04   Mean   
 3rd Qu.:2.000   3rd Qu.:1.0000   3rd Qu.: 90.00   3rd Qu.
 Max.   :2.000   Max.   :3.0000   Max.   :100.00   Max.   
    meal.cal         wt.loss
 Min.   :  96.0   Min.   :-24.000
```

Model 1: use everything except `inst`

```r
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:

```r
lung.1 <- coxph(Surv(time, status == 2) ~ . - inst - time -
  data = lung.complete
)
```

"Dot" means "all the other variables".

summary of model 1

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

```
Call:
coxph(formula = Surv(time, status == 2) ~ . - 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:

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

```
Analysis of Deviance Table
 Cox model: response is  Surv(time, status == 2)
 Model 1: ~ sex + ph.ecog + ph.karno + wt.loss
 Model 2: ~ (inst + age + sex + ph.ecog + ph.karno + pat.ka
   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 = Surv(time, status == 2) ~ sex + ph.ecog, da

  n= 167, number of events= 120
```

Check whether that was OK

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

```
Analysis of Deviance Table
 Cox model: response is  Surv(time, status == 2)
 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

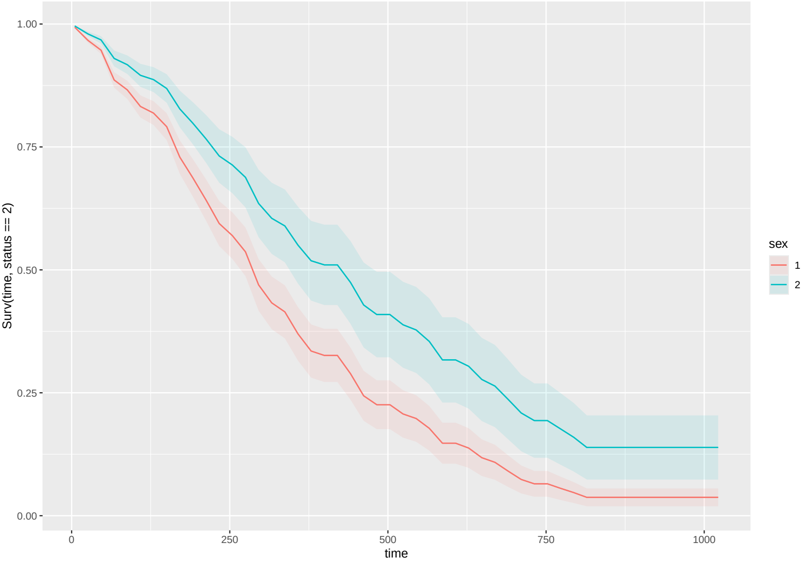
- OK (just) to take out those two covariates.
- Both remaining variables strongly significant.
- Nature of effect on survival time? Consider later.
- Picture?

Plotting survival probabilities

- Assess (separately) the effect of `sex` and `ph.ecog` score using `plot_predictions`
- Don't forget to add time (here actually called `time`) to the `condition`.

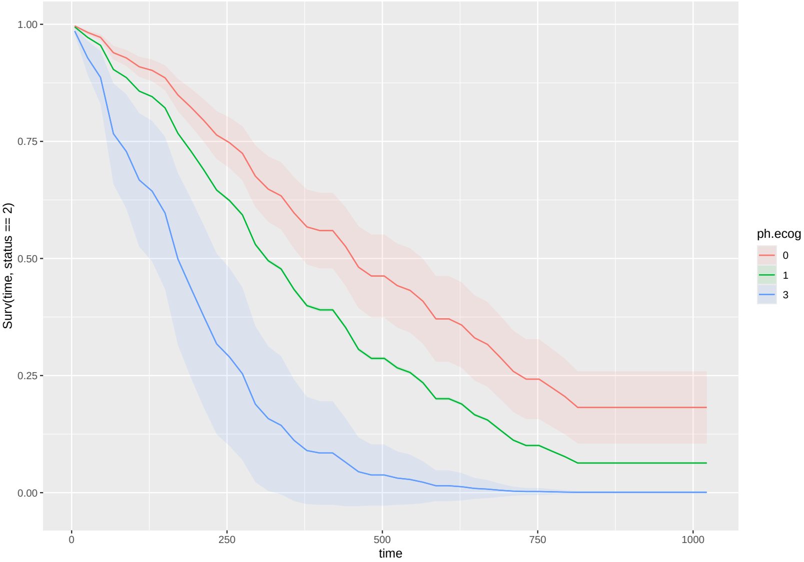
Effect of sex:

```
plot_predictions(lung.3, condition = c("time", "sex"), type
```



Effect of `ph.ecog` score:

```
plot_predictions(lung.3, condition = c("time", "ph.ecog"),
```

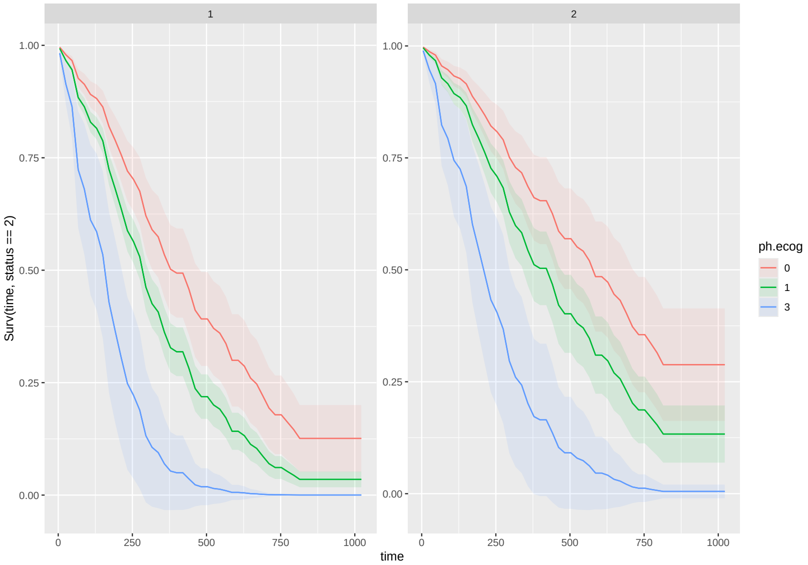


Comments

- A lower `ph.ecog` score is better.
- For example, a patient with a score of 0 has almost a 50-50 chance of living 500 days, but a patient with a score of 3 has almost no chance to survive that long.
- Is this for males or females? See over. (The comparison of scores is the same for both.)

Sex and `ph.ecog` score

```
plot_predictions(lung.3, condition = c("time", "ph.ecog", '
```



Comments

- I think the previous graph was males.
- This pair of graphs shows the effect of `ph.ecog` score (above and below on each facet), and the effect of males (left) vs. females (right).
- The difference between males and females is about the same as 1 point on the `ph.ecog` scale (compare the red curve on the left facet with the green curve on the right facet).

The summary again

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

```
Call:
coxph(formula = Surv(time, status == 2) ~ sex + ph.ecog, da

  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 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '

        exp(coef) exp(-coef) lower .95 upper .95
sex        0.6004     1.6655    0.4082    0.8832
ph.ecog    1.6201     0.6172    1.2501    2.0998

Concordance= 0.641  (se = 0.031 )
```

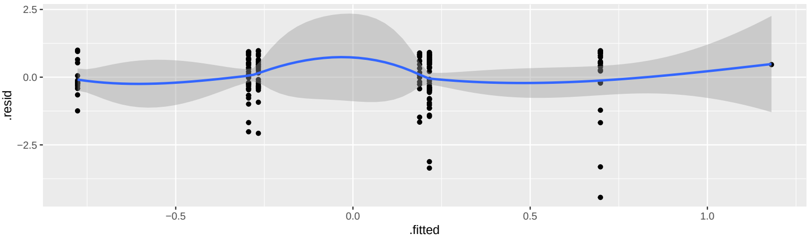
Comments

- A higher-numbered sex (female) has a lower hazard of death (negative coef). That is, females are more likely to survive longer than males.
- A higher `ph.ecog` score goes with a *higher* hazard of death (positive coef). So patients with a *lower* score are more likely to survive longer.
- These are consistent with the graphs we drew.

Martingale residuals for this model

No problems here:

```
lung.3 %>% augment(lung.complete) %>%
  ggplot(aes(x = .fitted, y = .resid)) + geom_point() + geo
```



When the Cox model fails (optional)

- 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

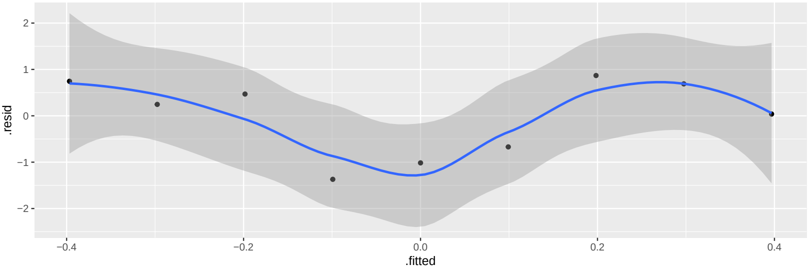
```r
y.1 <- coxph(y ~ age, data = d)
summary(y.1)
```

```
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:

```
y.1 %>% augment(d) %>%
  ggplot(aes(x = .fitted, y = .resid)) + geom_point() + geo
```



Attempt 2

Add squared term in age:

```r
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:

```
y.2 %>% augment(d) %>%
  ggplot(aes(x = .fitted, y = .resid)) + geom_point() + geo
```