

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 <dbl>	Quit <dbl>	Treatment <dbl>	Age <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 <dbl>	Quit <dbl>	Treatment <dbl>	Age <dbl>	mth <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

```
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 $X_1 = \text{age}$, $X_2 = \text{treatment}$, with the β being regression coefficients:
- ▶ Cox model $h(t) = h_0(t) \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots)$, or:
- ▶ $\log(h(t)) = \log(h_0(t)) + \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots$
- ▶ like a generalized linear model with log link.

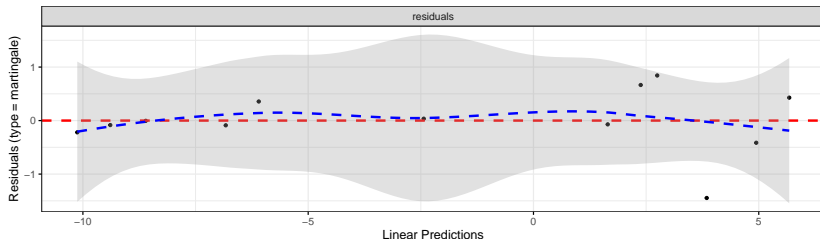
Model checking

- ▶ 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 = treatments,
  age = ages)
dance.new
```

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

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)
```

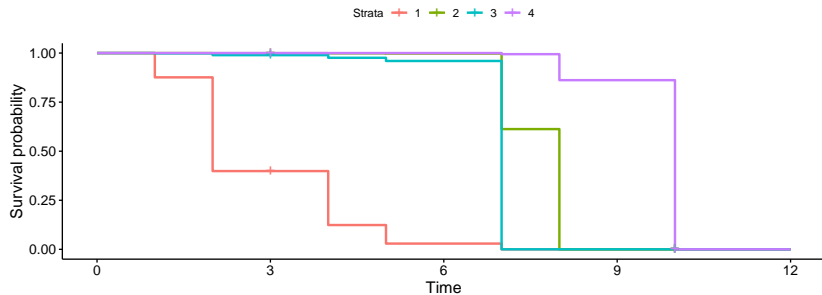
“Strata” (groups)

► uses “strata” thus `(dance.new)`:

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

Plotting survival probabilities

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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
24	15	271	2	59	1	0	90	100	875	12

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.	: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

```
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

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

Making the plot

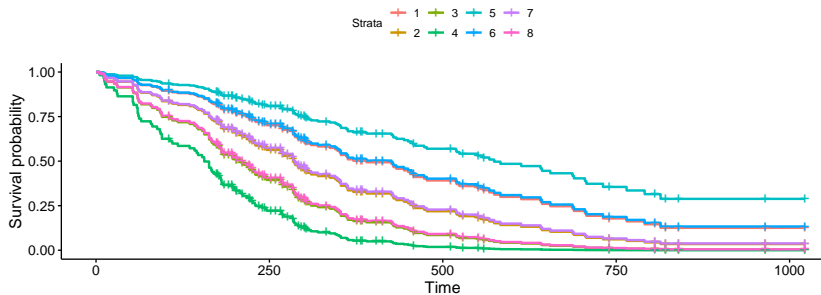
```
s <- survfit(lung.3, newdata = lung.new, data = lung)
summary(s)
```

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

time	n.risk	n.event	survival1	survival2	survival3	survival4
5	167	1	0.996	0.9932	0.98908	0.98237
11	166	1	0.992	0.9865	0.97825	0.96500
12	165	1	0.987	0.9798	0.96743	0.94776
13	164	1	0.983	0.9730	0.95660	0.93063
15	163	1	0.979	0.9662	0.94577	0.91363
26	162	1	0.975	0.9594	0.93502	0.89686
30	161	1	0.970	0.9526	0.92427	0.88022
31	160	1	0.966	0.9457	0.91352	0.86369
53	159	2	0.957	0.9320	0.89222	0.83129
54	157	1	0.953	0.9252	0.88162	0.81535
59	156	1	0.949	0.9183	0.87103	0.79954
60	155	2	0.940	0.9046	0.85000	0.76850
61	153	1	0.936	0.8977	0.83959	0.75223

The plot

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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
```

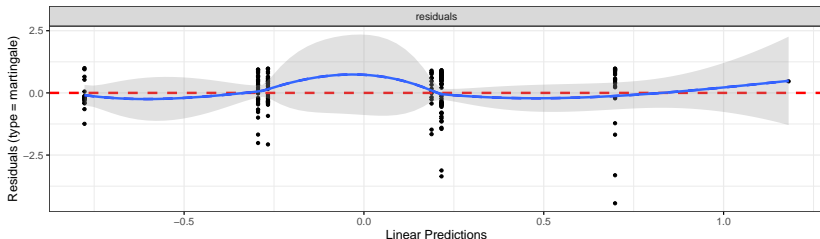
	coef	exp(coef)	se(coef)	z	Pr(> z)	
sex	-0.5101	0.6004	0.1969	-2.591	0.009579	**
ph.ecog	0.4825	1.6201	0.1323	3.647	0.000266	***

```
---
```

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

```
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

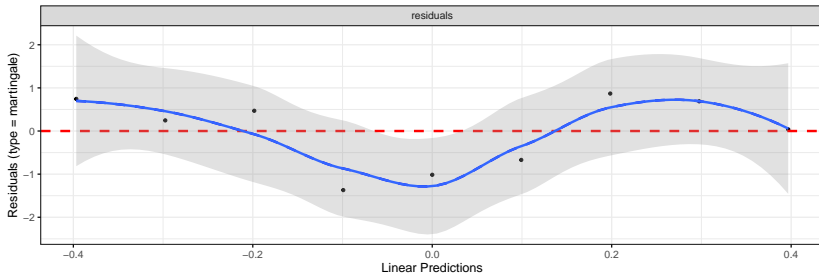
Wald test = 0.33 on 1 df, p=0.6

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)
```

