432 Class 25 Slides

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Preliminaries

```r
library(skimr)
library(rms)
library(survival)
library(OIsurv)
library(survminer)
library(aplore3) # for a data set
library(ResourceSelection) # for Hosmer-Lemeshow test
library(bestglm) # for a demonstration of all subsets
library(broom)
library(tidyverse)
```

Today's Agenda

- Regression on Time-to-event data
    - Cox Proportional Hazards Model
- Some Loose Ends

Survival Analysis / Cox Regression

A Survival Analysis Example

Source: Chen and Peace (2011) *Clinical Trial Data Analysis Using R*, CRC Press, section 5.1

```
brca <- read.csv("data/breast_cancer.csv") %>% tbl_df
```

The `brca` trial

The `brca` data describes a parallel randomized trial of three treatments, adjuvant to surgery in the treatment of patients with stage-2 carcinoma of the breast. The three treatment groups are:

- `S+CT` = Surgery plus one year of chemotherapy
- `S+IT` = Surgery plus one year of immunotherapy
- `S+CT+IT` = Surgery plus one year of chemotherapy and immunotherapy

The measure of efficacy were “time to death” in weeks. In addition to `treat`, our variables are:

- `trial_weeks`: time in the study, in weeks, to death or censoring
- `last_alive`: 1 if alive at last follow-up (and thus censored), 0 if dead
- `age`: age in years at the start of the trial

brca tibble

```
# A tibble: 31 x 5
   subject treat   trial_weeks last_alive   age
   <fct>   <fct>         <int>      <int> <int>
 1 A01     S+CT            102          0    55
 2 A02     S+IT            192          0    62
 3 A03     S+CT+IT          73          0    72
 4 A04     S+CT             58          1    48
 5 A05     S+CT             48          1    26
 6 A06     S+IT            182          1    52
 7 A07     S+IT            196          1    50
 8 A08     S+CT            177          1    49
 9 A09     S+IT            191          1    62
10 A10     S+CT+IT          36          0    60
# ... with 21 more rows
```

Analytic Objectives

This is a typical right-censored survival data set with interest in the comparative analysis of the three treatments.

1. Does immunotherapy added to surgery plus chemotherapy improve survival? (Comparing S+CT+IT to S+CT)
2. Does chemotherapy add efficacy to surgery plus immunotherapy? (S+CT+IT vs. S+IT)
3. What is the effect of age on survival?

Create survival object

- `trial_weeks`: time in the study, in weeks, to death or censoring
- `last_alive`: 1 if alive at last follow-up (and thus censored), 0 if dead

So `last_alive` = 0 if the event (death) occurs.

What's next?

Create survival object

- trial_weeks: time in the study, in weeks, to death or censoring
- last_alive: 1 if alive at last follow-up (and thus censored), 0 if dead

So last_alive = 0 if the event (death) occurs.

```
brca$S <- with(brca, Surv(trial_weeks, last_alive == 0))

head(brca$S)
```

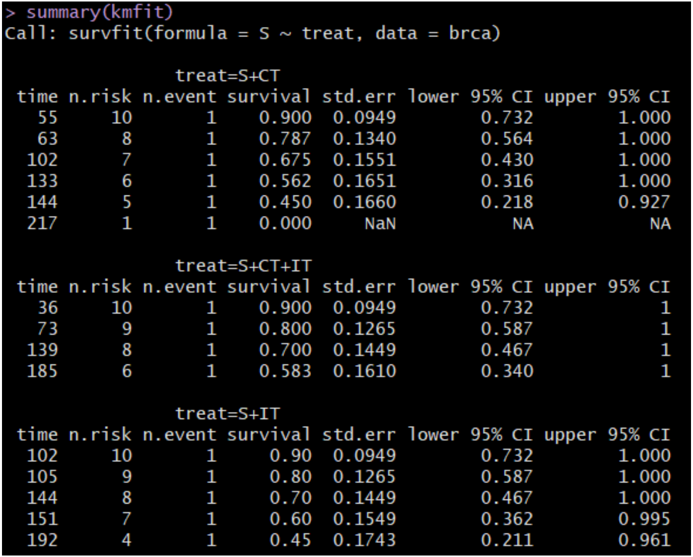
```
[1] 102  192   73   58+  48+ 182+
```

Build Kaplan-Meier Estimator

```r
kmfit <- survfit(S ~ treat, dat = brca)

print(kmfit, print.rmean = TRUE)
```

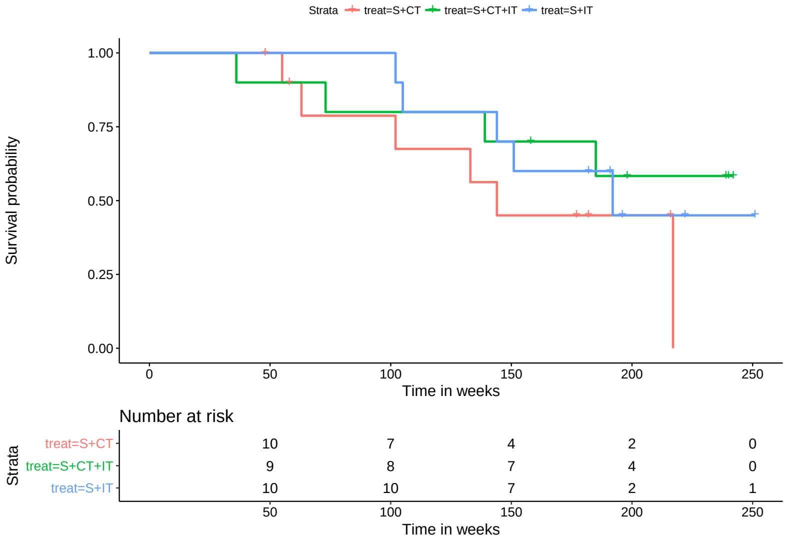
```
Call: survfit(formula = S ~ treat, data = brca)

               n events *rmean *se(rmean) median 0.95LCL
treat=S+CT    11      6    153       21.1    144     102
treat=S+CT+IT 10      4    188       23.7     NA     139
treat=S+IT    10      5    188       17.9    192     144
              0.95UCL
treat=S+CT         NA
treat=S+CT+IT      NA
treat=S+IT         NA
    * restricted mean with upper limit =  242
```

summary(kmfit)



```
> summary(kmfit)
Call: survfit(formula = S ~ treat, data = brca)

                treat=S+CT
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
   55     10       1    0.900  0.0949        0.732        1.000
   63      8       1    0.787  0.1340        0.564        1.000
  102      7       1    0.675  0.1551        0.430        1.000
  133      6       1    0.562  0.1651        0.316        1.000
  144      5       1    0.450  0.1660        0.218        0.927
  217      1       1    0.000     NaN           NA           NA

                treat=S+CT+IT
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
   36     10       1    0.900  0.0949        0.732            1
   73      9       1    0.800  0.1265        0.587            1
  139      8       1    0.700  0.1449        0.467            1
  185      6       1    0.583  0.1610        0.340            1

                treat=S+IT
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
  102     10       1     0.90  0.0949        0.732        1.000
  105      9       1     0.80  0.1265        0.587        1.000
  144      8       1     0.70  0.1449        0.467        1.000
  151      7       1     0.60  0.1549        0.362        0.995
  192      4       1     0.45  0.1743        0.211        0.961
```

K-M Plot via `survminer`



Strata	50	100	150	200	250
treat=S+CT	10	7	4	2	0
treat=S+CT+IT	9	8	7	4	0
treat=S+IT	10	10	7	2	1

K-M Plot via survminer (code)

```
ggsurvplot(kmfit, data = brca,
           risk.table = TRUE,
           risk.table.height = 0.25,
           xlab = "Time in weeks")
```

Testing the difference between curves

```r
survdiff(S ~ treat, dat = brca)
```

```
Call:
survdiff(formula = S ~ treat, data = brca)

               N Observed Expected (O-E)^2/E (O-E)^2/V
treat=S+CT    11        6     3.80    1.2772    1.7647
treat=S+CT+IT 10        4     5.62    0.4676    0.7725
treat=S+IT    10        5     5.58    0.0605    0.0981

 Chisq= 1.9  on 2 degrees of freedom, p= 0.393
```

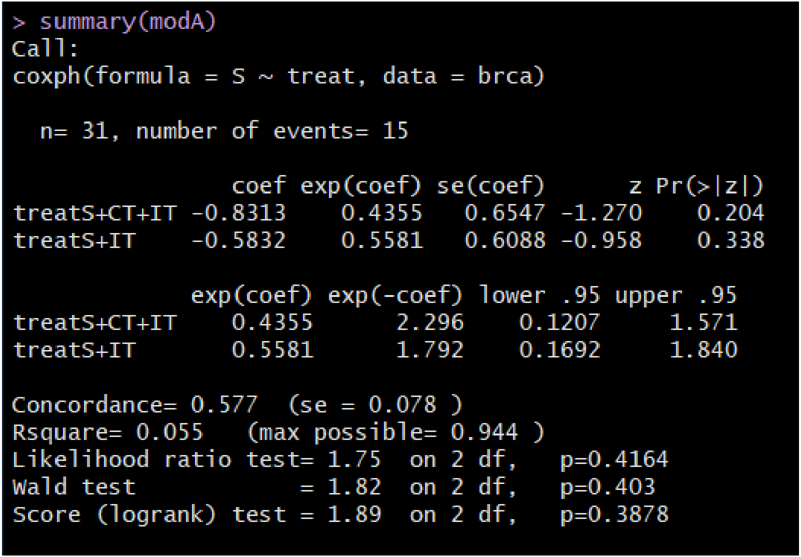
What do we conclude?

Fit Cox Model A: Treatment alone

```
modA <- coxph(S ~ treat, data = brca)
modA
```

```
Call:
coxph(formula = S ~ treat, data = brca)

                coef exp(coef) se(coef)     z    p
treatS+CT+IT -0.831     0.435    0.655 -1.27 0.20
treatS+IT    -0.583     0.558    0.609 -0.96 0.34

Likelihood ratio test=1.75  on 2 df, p=0.416
n= 31, number of events= 15
```

summary(modA)



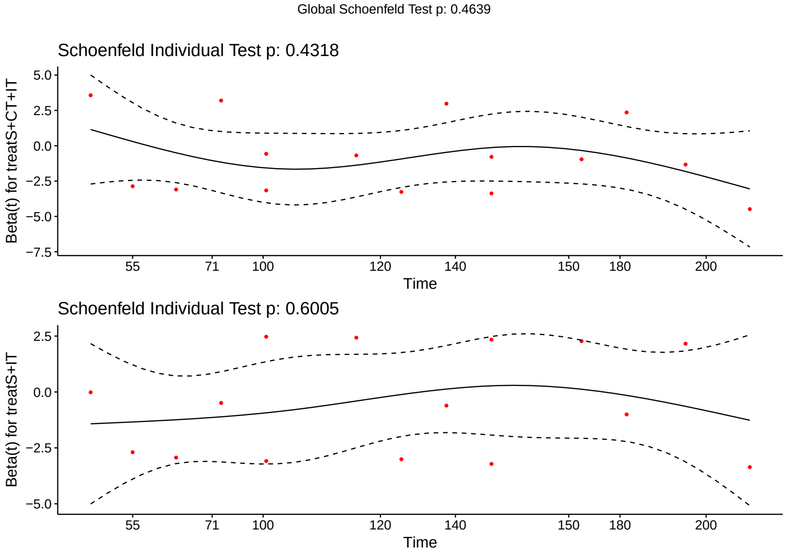
```
> summary(modA)
Call:
coxph(formula = S ~ treat, data = brca)

  n= 31, number of events= 15

                 coef exp(coef) se(coef)      z Pr(>|z|)
treatS+CT+IT -0.8313    0.4355   0.6547 -1.270    0.204
treatS+IT    -0.5832    0.5581   0.6088 -0.958    0.338

             exp(coef) exp(-coef) lower .95 upper .95
treatS+CT+IT    0.4355      2.296    0.1207     1.571
treatS+IT       0.5581      1.792    0.1692     1.840

Concordance= 0.577  (se = 0.078 )
Rsquare= 0.055   (max possible= 0.944 )
Likelihood ratio test= 1.75  on 2 df,   p=0.4164
Wald test            = 1.82  on 2 df,   p=0.403
Score (logrank) test = 1.89  on 2 df,   p=0.3878
```

Check Proportional Hazards Assumption

```r
cox.zph(modA)
```

```
                 rho chisq     p
treatS+CT+IT -0.198 0.618 0.432
treatS+IT     0.138 0.274 0.601
GLOBAL           NA 1.536 0.464
```

Graphical PH Test `ggcoxzph(cox.zph(modA))`

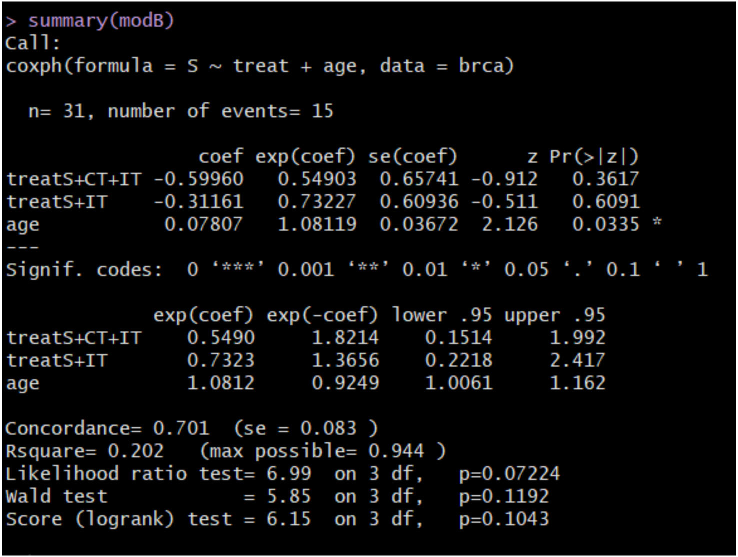


Fit Cox Model B: Treatment + Age

```
modB <- coxph(S ~ treat + age, data = brca)
modB
```

```
Call:
coxph(formula = S ~ treat + age, data = brca)

                coef exp(coef) se(coef)     z     p
treatS+CT+IT -0.5996    0.5490   0.6574 -0.91 0.362
treatS+IT    -0.3116    0.7323   0.6094 -0.51 0.609
age           0.0781    1.0812   0.0367  2.13 0.034

Likelihood ratio test=6.99  on 3 df, p=0.0722
n= 31, number of events= 15
```

summary(modB)



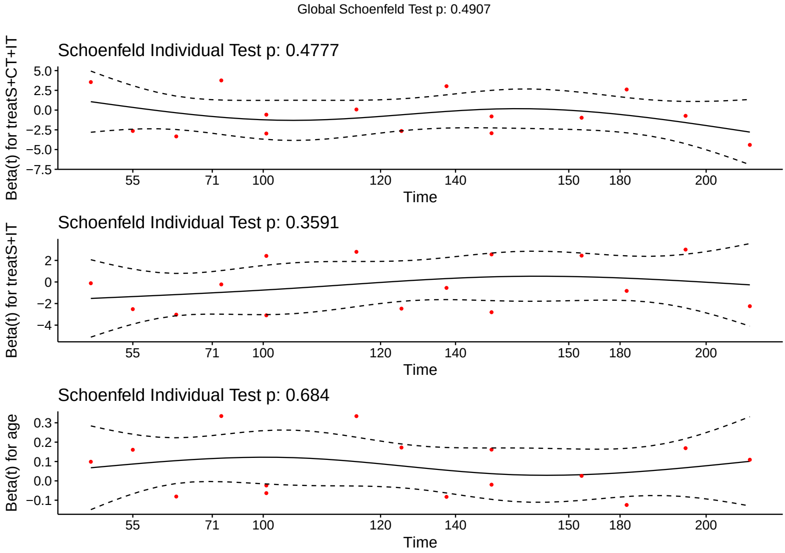
```
> summary(modB)
Call:
coxph(formula = S ~ treat + age, data = brca)

  n= 31, number of events= 15

                 coef exp(coef) se(coef)      z Pr(>|z|)
treatS+CT+IT -0.59960   0.54903  0.65741 -0.912   0.3617
treatS+IT    -0.31161   0.73227  0.60936 -0.511   0.6091
age           0.07807   1.08119  0.03672  2.126   0.0335 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

             exp(coef) exp(-coef) lower .95 upper .95
treatS+CT+IT    0.5490     1.8214    0.1514     1.992
treatS+IT       0.7323     1.3656    0.2218     2.417
age             1.0812     0.9249    1.0061     1.162

Concordance= 0.701  (se = 0.083 )
Rsquare= 0.202   (max possible= 0.944 )
Likelihood ratio test= 6.99  on 3 df,   p=0.07224
Wald test            = 5.85  on 3 df,   p=0.1192
Score (logrank) test = 6.15  on 3 df,   p=0.1043
```

Proportional Hazards Assumption: Model B Check

```r
cox.zph(modB)
```

```
                 rho chisq     p
treatS+CT+IT -0.179 0.504 0.478
treatS+IT     0.244 0.841 0.359
age          -0.106 0.166 0.684
GLOBAL           NA 2.416 0.491
```

Graphical PH Test `ggcoxzph(cox.zph(modB))`



What to do if the PH assumption is violated

- If the PH assumption fails on a categorical predictor, fit a Cox model stratified by that predictor (use `strata(var)` rather than `var` in the specification of the `coxph` model.)
- If the PH assumption is violated, this means the hazard isn't constant over time, so we could fit separate Cox models for a series of time intervals.
- Use an extension of the Cox model that permits covariates to vary over time.

Visit https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf for details on building the relevant data sets and models, with examples.

Using Restricted Cubic Splines

Explaining a Model with a Restricted Cubic Spline

Restricted cubic splines are an easy way to include an explanatory variable in a smooth and non-linear fashion in your model.

- The number of knots, k, are specified in advance, and this is the key issue to determining what the spline will do. We could use AIC to select k, or follow the general idea that for small n, k should be 3, for large n, k should be 5, and so often k = 4.
- The location of those knots is not important in most situations, so R places knots by default where the data exist, at fixed quantiles of the predictor's distribution.
- The "restricted" piece means that the tails of the spline (outside the outermost knots) behave in a linear fashion.

The "Formula" from a Model with a Restricted Cubic Spline

- The best way to demonstrate what a spline does is to draw a picture of it. When in doubt, do that: show us how the spline affects the predictions made by the model.
- But you can get a model equation for the spline out of R (heaven only knows what you would do with it.) Use the `latex` function in the `rms` package, for instance.

An Example

```
d <- datadist(iris)
options(datadist = "d")
m1 <- ols(Sepal.Length ~ rcs(Petal.Length, 4) + Petal.Width,
          data = iris, x = TRUE, y = TRUE)
m1
```

```
Linear Regression Model

 ols(formula = Sepal.Length ~ rcs(Petal.Length, 4) + Petal.Wi
     data = iris, x = TRUE, y = TRUE)

                Model Likelihood     Discrimination
                   Ratio Test           Indexes
 Obs       150    LR chi2     253.23    R2       0.815
 sigma0.3609    d.f.             4    R2 adj   0.810
 d.f.      145    Pr(> chi2) 0.0000    g        0.844
```

Function(m1)

```
Function(m1)
```

```
function (Petal.Length = 4.35, Petal.Width = 1.3)
{
    4.7226352 + 0.24335435 * Petal.Length + 0.021780541 * pmax
        1.3, 0)^3 - 0.037888523 * pmax(Petal.Length - 3.33, 0)
        0.00031123969 * pmax(Petal.Length - 4.8, 0)^3 + 0.0157
        pmax(Petal.Length - 6.1, 0)^3 - 0.33400958 * Petal.Wi
}
<environment: 0x0000000024bed340>
```

What's in `Function(m1)`?

```
4.72 + 0.243  * Petal.Length
     + 0.022  * pmax( Petal.Length-1.3,  0)^3
     - 0.038  * pmax( Petal.Length-3.33, 0)^3
     + 0.0003 * pmax( Petal.Length-4.8,  0)^3
     + 0.016  * pmax( Petal.Length-6.1,  0)^3
     - 0.334  * Petal.Width
```

where `pmax` is the maximum of the arguments inside its parentheses.

Asssessing the Quality of a Logistic Regression Model

A Quick Example

SOURCE: Hosmer and Lemeshow (2000) Applied Logistic Regression: Second Edition. These data are copyrighted by John Wiley & Sons Inc. and must be acknowledged and used accordingly. Data were collected at Baystate Medical Center, Springfield, Massachusetts during 1986.

```
# uses aplore3 package for data set
lbw <- aplore3::lowbwt
head(lbw,3)
```

```
  id      low age lwt  race smoke  ptl  ht  ui       ftv
1  4 < 2500 g  28 120 Other   Yes  One  No Yes       None
2 10 < 2500 g  29 130 White    No None  No Yes Two, etc.
3 11 < 2500 g  34 187 Black   Yes None Yes  No       None
   bwt
1  709
2 1021
3 1135
```

Fit a logistic regression model

```r
model_10 <- glm(low ~ lwt + ptl + ht,
                data = lbw, family = binomial)
model_10
```

```

Call:  glm(formula = low ~ lwt + ptl + ht, family = binomial,

Coefficients:
 (Intercept)          lwt        ptlOne  ptlTwo, etc.
     1.17016     -0.01851       1.74219       0.15105
       htYes
     1.91234

Degrees of Freedom: 188 Total (i.e. Null);  184 Residual
Null Deviance:      234.7
Residual Deviance: 207.4    AIC: 217.4
```

What is this model predicting, exactly?

```
levels(lbw$low)
```

```
[1] ">= 2500 g" "< 2500 g"
```

```
lbw %>% count(low)
```

```
# A tibble: 2 x 2
  low            n
  <fct>      <int>
1 >= 2500 g    130
2 < 2500 g      59
```

The model predicts the probability of a LOW birth weight, because $<$ 2500 g is listed second here.

- Our `model_10` is a model fit to y $=$ 1 when low $<$ 2500 g
- If y $=$ 1 indicated that low $>=$ 2500 g, this would be the opposite of our `model_10`.

Proving the direction of `model_10`

```r
lbw <- lbw %>% mutate(y1 = ifelse(low == "< 2500 g", 1, 0),
                      y2 = ifelse(low == ">= 2500 g", 1, 0))
mod_1 <- glm(y1 ~ lwt + ptl + ht,
                  data = lbw, family = binomial)
mod_2 <- glm(y2 ~ lwt + ptl + ht,
                  data = lbw, family = binomial)
```

- `mod_1` predicts Pr(birth weight $<$ 2500 g)
- `mod_2` predicts Pr(birth weight $>=$ 2500 g)

So, what does `model_10` predict?

- `mod_1` predicts Pr(birth weight $<$ 2500 g)
- `mod_2` predicts Pr(birth weight $>=$ 2500 g)

```
head(fitted(mod_1),3)
```

```
        1         2         3 
0.6661398 0.2250375 0.4062585 
```

```
head(fitted(mod_2),3)
```

```
        1         2         3 
0.3338602 0.7749625 0.5937415 
```

```
head(fitted(model_10),3)
```

```
        1         2         3 
0.6661398 0.2250375 0.4062585 
```

Classification Table for this Model

```
table(fitted(model_10) >= 0.5, lbw$low)
```

```
      >= 2500 g < 2500 g
FALSE       123       39
TRUE          7       20
```

Next Time

- Retrospective Power and why most smart folks avoid it
    - Type S and Type M error: Saying something more useful
- Replicable Research and the Crisis in Science
    - ASA Statement on P values
    - Is changing the *p* value cutoff the right strategy?
    - Second-generation *p* values: A next step?