Biostatistics 209, Lab #3 Discussion

1. Background

The purpose of this lab is to give you practice on checking proportional hazards assumption in Cox regression models.

2. Data

- Download the datasets `lab3-actg019_a.dta` and `lab3-pbc_a.dta` from the website (these are altered datasets from `actg019.dta` and `pbc.dta` that you used before!).

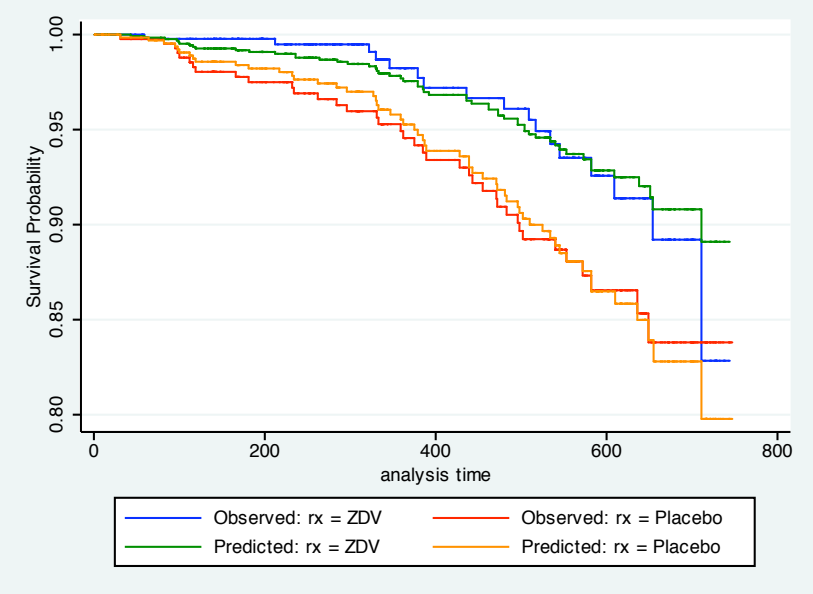
3. Checking the Cox Model for ZDV treatment in `lab3-actg019_a.dta`

Declare the data `lab3-actg019_a.dta` to be survival time data

```
stset days, failure(cens)
```

a. Generate the Cox-KM plot and the log-minus-log KM plot by treatment (`rx`).

```
stcoxkm, by(rx) obs1opts(recast(line) connect(stairstep) lcolor(blue))
obs2opts(recast(line) c(stairstep) lc(red)) pred1opts(recast(line)
c(stairstep) lc(green)) pred2opts(recast(line) c(stairstep) lc(orange))
```



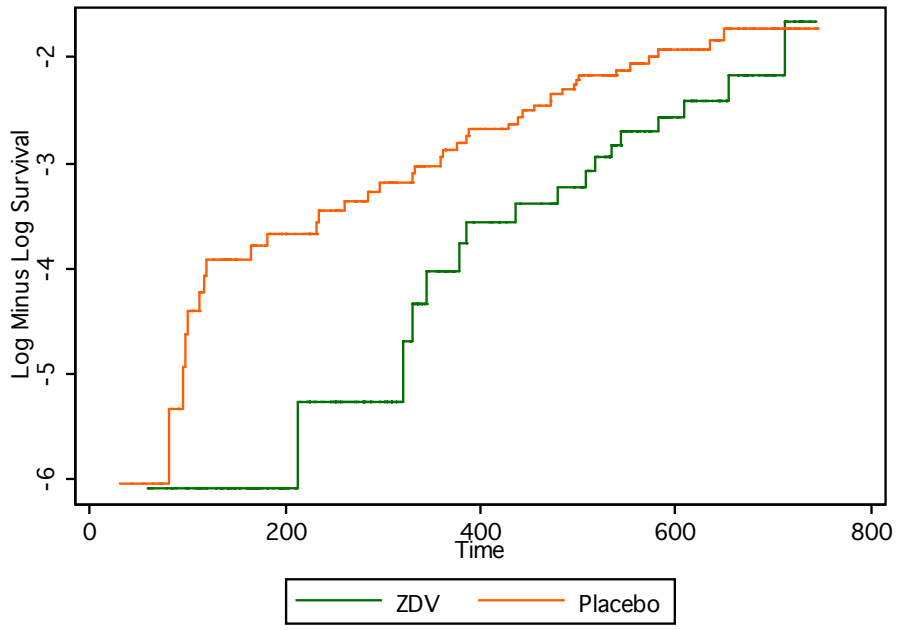
Some options used to customize the graphs:

`recast(line)`	gives no symbols at the estimate points.
`connect(stairstep)`	asks Stata to connect points using a step function.
`lcolor(red)`	specifies the line color.

```
stphplot, by(rx) nonegative nolntime plot1opts(recast(line)
connect(stairstep)) plot2opts(recast(line) c(stairstep)) ytitle(Log Minus
Log Survival) xtitle(Time) legend(order(1 "ZDV" 2 "Placebo"))
scheme(s1color)
```

Options used:

`nolntime`	prevents Stata from taking the log of the x-axis,
`nonegative`	specifies the log(-log) not -log(-log) plots,



b. Does the `rx` HR appear proportional?

Here we look to see if the log-minus-log curves display a constant distance apart. Instead, we see the two curves coming together. This pattern is typical of a large treatment effect that fades over time. However, it is difficult to discern from this graph how quickly the treatment effect diminishes.

c. Graph the log hazard ratio after fitting the Cox model and save the scaled Schoenfeld residuals. These are needed for subsequent plots and calculations. Note, by default, ZDV is set as the reference group for the variable `rx`.

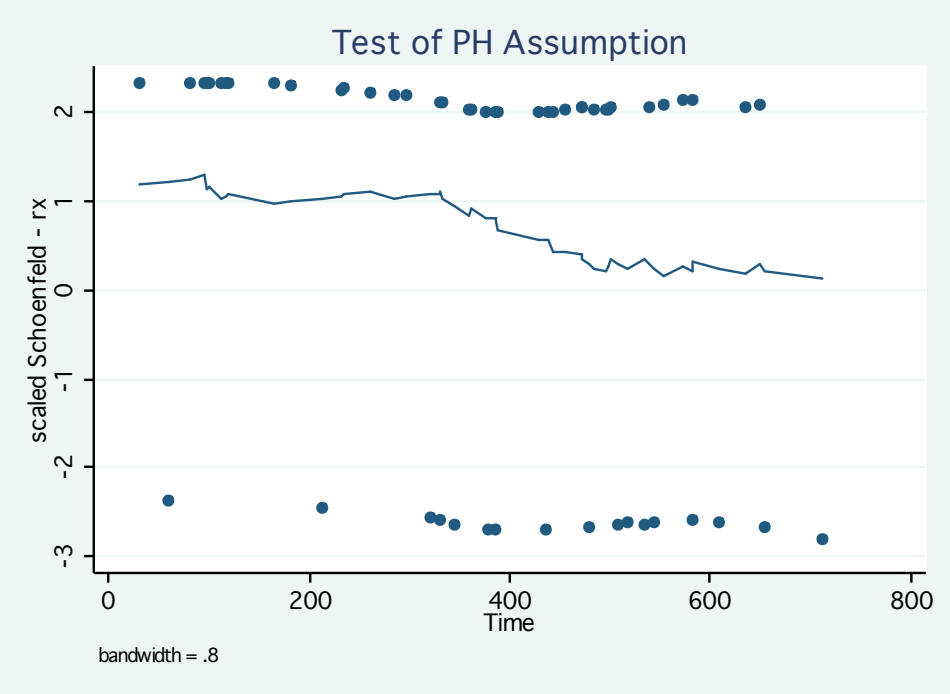
`stcox rx, sca(`*giveAname*`)` *(choose a name to be used later; no "*" b/c only 1 var)*

```
No. of subjects =          880                     Number of obs    =       880
No. of failures =           55
Time at risk    =       354872
                                                    LR chi2(1)       =      5.66
Log likelihood  =   -328.57534                      Prob > chi2      =    0.0174
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
```

```
rx           |   1.957118   .5719375     2.30   0.022     1.103739    3.470304
------------------------------------------------------------------------------
```

Placebo subjects on average have about 2 times hazard of HIV progression compared to subjects on ZDV.

`estat phtest, plot(rx)` *(this gives a running mean smoother, rather than lowess)*



d. Re-graph the log hazard ratio with a lowess smoother, and save the lowess values in the variable named "`smloghr`" (obviously you can call it something else).

`lowess` *giveAname* `days, generate(smloghr) ytitle(rx Log Hazard Ratio)`


Lowess smoother
rx Log Hazard Ratio
2
1
0
-1
-2
-3
0
200
400
600
800
Days Since Randomization
bandwidth = .8

Note the difference in the smoothers (seen in the two different graphs); the running mean smoother on the left is rather flat, as running mean smoothers tend to be. The lowess shows a more pronounced trajectory. In the lowess graph, we can see that the log HR decreases with time, which indicates violations of proportional hazards. I have included a flat reference line at log(1.96) = 0.67. If hazards were truly proportional the lowess line should be approximately flat.

e. Look at the graph and the variable `smloghr` and fill in the following table.

```
gen smhr=exp(smloghr)
sort days
list days smloghr smhr if cens==1 &(days==95|days==181|days==362|days==540)
```

	log HR	HR
95 days (3 mos)	1.71	5.52
181 days (6 mos)	1.46	4.31
362 days (12 mos)	0.71	2.03
540 days (18 mos)	0.19	1.21

*However, be **aware that choosing a different bandwidth** (default `bwidth=0.8`) would change the values in the table, e.g.*

```
lowess giveAname days, bwidth(.5) generate(smloghr2)
```

leads to:

	log HR	HR
95 days (3 mos)	1.70	5.48
181 days (6 mos)	1.67	5.32
362 days (12 mos)	0.61	1.83
540 days (18 mos)	0.23	1.25

f. Run the Schoenfeld test for the proportional hazards assumption. Is there evidence against that? Does this agree with the plots?

```
estat phtest, detail
```

```
Test of proportional-hazards assumption

  Time:  Time
------------------------------------------------------------------
             |       rho           chi2       df       Prob>chi2
-------------+----------------------------------------------------
rx           |     -0.30819         5.39        1          0.0202
-------------+----------------------------------------------------
global test  |                      5.39        1          0.0202
------------------------------------------------------------------
```

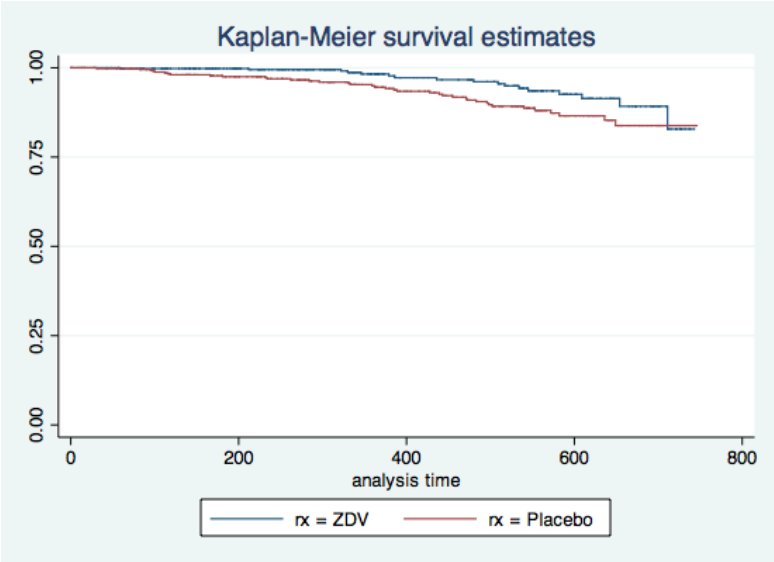
The test agrees closely with the plots in concluding that there is a violation of proportional hazards. The HR's over time appear quite different despite the p-value=0.02 being not overwhelmingly so. This reflects the moderate sample size (55 events).

g. How would you summarize the effect of ZDV on progression of HIV?

Tests and graphical examination showed that the effect of ZDV violated the assumption of proportional hazards (p=0.02); that is, the effect of ZDV appeared to decrease over time.

h. Consider the "stratification" approach to dealing with non-proportional hazards: run the log-rank test to conclude that the effect of ZDV is significant and present the K-M plot to show its effect on being free of HIV progression. Note that this approach does not provide a summary estimate of the ZDV effect (the primary predictor of the study). Also, why do we not use `stcox` here?

```
sts test rx  // the log rank test


         failure _d:  cens
   analysis time _t:  days

Log-rank test for equality of survivor functions

         |    Events         Events
rx       |  observed       expected
---------+-------------------------
ZDV      |        17          25.64
Placebo  |        38          29.36
---------+-------------------------
Total    |        55          55.00

              chi2(1) =       5.48
              Pr>chi2 =     0.0192


sts graph, by(rx)  // K-M plot
```



`stcox` is not used because it provides nothing. We get no estimates for the effect of `rx` because it is defined as the strata and we have no other predictors in the model. We can force a fit of the null model stratified by `rx` an follows:

```
stcox, estimate strata(rx)
```

but the output gives us nothing:

```
failure _d:  cens
analysis time _t:  days


Iteration 0:   log likelihood = -293.76421
Refining estimates:
Iteration 0:   log likelihood = -293.76421

Stratified Cox regr. -- no ties

No. of subjects =          880                     Number of obs    =       880
No. of failures =           55
Time at risk    =       354872
                                                    LR chi2(0)       =      0.00
Log likelihood  =   -293.76421                      Prob > chi2      =         .

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------------------------------------------------------------------
                                                              Stratified by rx
```

`i.` Explore the time-dependent covariate approach.

```
stset days, failure(cens) id(id) // define survival data with multiple
  // observations per subject
stsplit grp, at(365) // split time variable (days) at 1 year to generate new
 // variable: grp. That is, generate multiple rows for each subject; one for each
 // time period up to (and including) the time of censoring or time of death
```

```
recode cens .=0 // recodes all newly generated rows to "censored" status
gen rx01=rx*(grp==0) // This set of commands generates 2 separate
gen rx1p=rx*(grp==365) // rx variables specific to each time interval;
  // that is, rxXX only equals 0 if the patient is on ZDV and the dataset row
  // corresponds to period XX
sort id grp // sort data so prioritized by id and then by grp within id
list id _t0 _t cens rx grp rx01 rx1p in 1/10, sepby(id)
  // take a look at the data -- seems ok
```

	id	_t0	_t	cens	rx	grp	rx01	rx1p
1.	1	0	365	Censored	Placebo	0	1	0
2.	1	365	502	AIDS/Death	Placebo	365	0	1
3.	2	0	365	Censored	ZDV	0	0	0
4.	2	365	496	Censored	ZDV	365	0	0
5.	4	0	365	Censored	Placebo	0	1	0
6.	4	365	565	Censored	Placebo	365	0	1
7.	5	0	308	Censored	Placebo	0	1	0
8.	6	0	365	Censored	Placebo	0	1	0
9.	6	365	383	Censored	Placebo	365	0	1
10.	7	0	365	Censored	Placebo	0	1	0

`stcox rx??, nolog` // fit Cox model – notice HR in 0 to 1 year is 3x that of after

```
failure _d:  cens
  analysis time _t:  days
                id:  id

Cox regression -- Breslow method for ties

No. of subjects =          880                     Number of obs   =      1328
No. of failures =           55
Time at risk    =       354872
                                                    LR chi2(2)      =      8.75
Log likelihood  =   -327.03114                      Prob > chi2     =    0.0126

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        rx01 |   3.695978   1.859151     2.60   0.009      1.37898    9.906056
        rx1p |   1.275121   .4702981     0.66   0.510      .618879    2.627222
------------------------------------------------------------------------------
```

Note that the `stcox rx??, nolog` command is shorthand for

```
stcox rx01 rx1p, nolog
```

4. Checking the Cox Model for Cholesterol in `lab3-pbc_a.dta`

Declare the data `lab3-pbc_a.dta` to be survival time data

```
stset years, failure(status)
```

a. **(Question 4.1)** Fit the Cox model for the effect of cholesterol and run the Schoenfeld test for the proportional hazards assumption. Is there evidence suggesting a violation of this assumption?

```
stcox chol, sca(giveAname)          (Did you give the same name as before?)
```

```
No. of subjects =          284                     Number of obs    =       284
No. of failures =          114
Time at risk    =  1908.583167
                                                   LR chi2(1)       =      6.37
Log likelihood  =   -565.65984                     Prob > chi2      =    0.0116

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     cholest |   1.000758   .0002714     2.79   0.005     1.000226     1.00129
------------------------------------------------------------------------------
```

```
estat phtest
```

```
Test of proportional-hazards assumption
      Time:  Time
      ----------------------------------------------------------------
                  |       rho            chi2       df       Prob>chi2
      ------------+---------------------------------------------------
      cholest     |      0.29729         7.77        1          0.0053
      ------------+---------------------------------------------------
```

The test indicates a violation of proportional hazards with a p-value of 0.005. However, we need to look at the graph to understand the nature of the violation.

b. Graph the log hazard ratio. What does the graph suggest? Do you have any concerns about the test?

```
lowess giveAname years, ytitle(cholesterol Log Hazard Ratio)
```

The graph shows two large outliers, which appears to be greatly affecting the correlations with time. These two values may have a large effect on the test of proportional hazards. You would want to redo the test without these points.

c. **(Question 4.2)** Try deleting some potential influential points and then re-run the plot and test for the proportional hazards assumption. What do you conclude?

First, to re-run you either have to use a different name in the `sca( )` *option or drop the variable you named it before.*

```
drop giveAname
stcox chol if years <= 12, sca(giveAname)
```

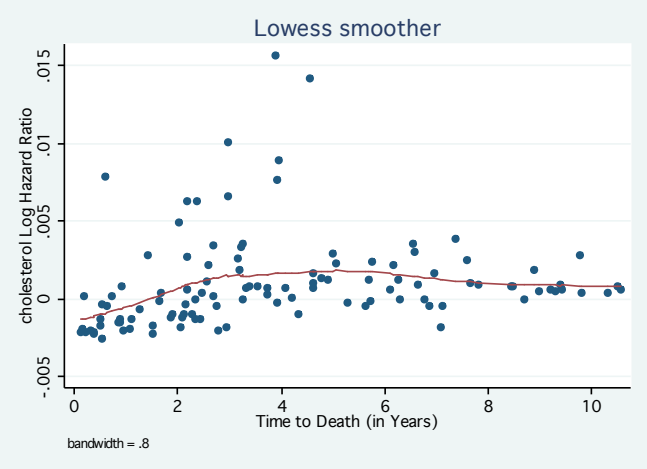
```
No. of subjects =          266                     Number of obs    =       266
No. of failures =          112
Time at risk    =  1338.001372
                                                   LR chi2(1)       =      8.15
Log likelihood  =   -537.48194                     Prob > chi2      =    0.0043

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     cholest |   1.001022   .0003138     3.26   0.001     1.000407    1.001637
------------------------------------------------------------------------------
```

```
estat phtest, detail
```

```
Test of proportional-hazards assumption

   Time:  Time
   ----------------------------------------------------------------
                |       rho             chi2       df       Prob>chi2
   -------------+--------------------------------------------------
   cholest      |       0.15694          2.31        1          0.1282
```

```
------------+------------------------------------------------------------
global test |                        2.31        1         0.1282
------------------------------------------------------------------------
```

Here, we see that deleting the two points made the violation of proportional hazards no longer significant (p>0.05). This is further reinforced by the graph, *although it shows some possible evidence against proportional hazards.*



For example, if you try

```
estat phtest, rank
estat phtest, log
```

or

i.e., so that you are considering a transformation of the time axis, then you get a statistically significant test (i.e., a statistically significant correlation with the residuals).

The bottom line is that the test of proportional hazards can be greatly affected by outlying values. It is important to always accompany the test by a graph so that you judge the directions, the magnitude of the violation and whether there appear to be points exerting a large influence on the test.