Biostatistics 209, Lab #1 Discussion

1. Data

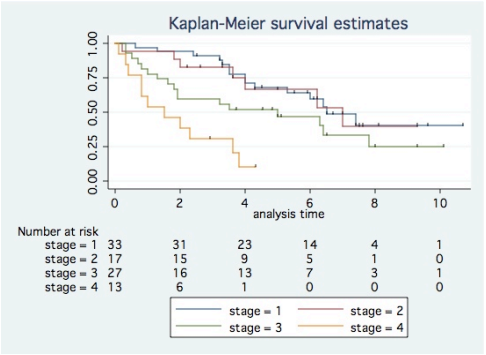
- Without specifying the `failure` option, all times are treated as non-censored events.

2. Exploring Stage Effects Using Kaplan-Meier Curves

Question 2.1.: Based on the Kaplan-Meier's what is your impression of the influence of the stages on death? Does it appear that the effect of 1 unit change in stage is the same across the range of values?

We see a smaller separation between stages I and II in contrast to a wider separation between stages I/II and stage III and stage IV. There appears, overall, to be worsening survival with higher stages of disease, as we'd expect.

This is further confirmed by looking at the Kaplan-Meier curves at years 1 and 2 and by looking at the median survival in the groups.




```
. sts list, by(stage) at(1 2 5)
```

Time	Beg. Total	Fail	Survivor Function	Std. Error	[95% Conf.	Int.]
stage=1						
1	33	1	0.9697	0.0298	0.8037	0.9957
2	32	1	0.9394	0.0415	0.7788	0.9845
5	20	8	0.6762	0.0847	0.4806	0.8114
stage=2						
1	17	1	0.9412	0.0571	0.6502	0.9915
2	15	2	0.8235	0.0925	0.5471	0.9394
5	6	2	0.6655	0.1255	0.3644	0.8485
stage=3						
1	22	6	0.7778	0.0800	0.5709	0.8934
2	18	5	0.5926	0.0946	0.3863	0.7499
5	10	3	0.4667	0.0995	0.2674	0.6438
stage=4						
1	8	6	0.5385	0.1383	0.2477	0.7599
2	6	2	0.3846	0.1349	0.1405	0.6280
5	1	3	.	.	.	.

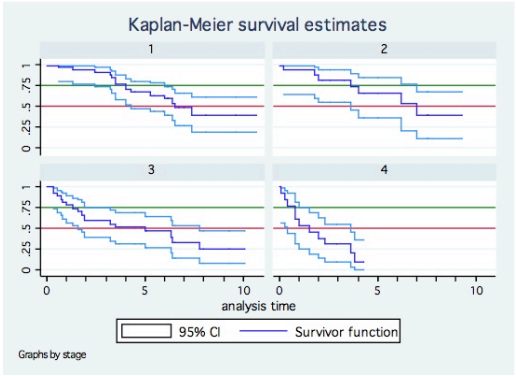
```
. sts list if stage==2
```

Time	Beg. Total	Fail	Net Lost	Survivor Function	Std. Error	[95% Conf.	Int.]
.2	17	1	0	0.9412	0.0571	0.6502	0.9915
1.8	16	1	0	0.8824	0.0781	0.6060	0.9692
2	15	1	0	0.8235	0.0925	0.5471	0.9394
2.2	14	0	1	0.8235	0.0925	0.5471	0.9394
2.6	13	0	1	0.8235	0.0925	0.5471	0.9394
3.3	12	0	1	0.8235	0.0925	0.5471	0.9394
3.6	11	1	1	0.7487	0.1103	0.4562	0.8987
4	9	1	0	0.6655	0.1255	0.3644	0.8485
4.3	8	0	2	0.6655	0.1255	0.3644	0.8485
5	6	0	1	0.6655	0.1255	0.3644	0.8485
6.2	5	1	0	0.5324	0.1557	0.2090	0.7758
7	4	1	0	0.3993	0.1641	0.1100	0.6826
7.5	3	0	1	0.3993	0.1641	0.1100	0.6826
7.6	2	0	1	0.3993	0.1641	0.1100	0.6826
9.3	1	0	1	0.3993	0.1641	0.1100	0.6826

```
Note:  survivor function is calculated over full data and evaluated at
       indicated times; it is not calculated from aggregates shown at left.
```

stage	no. of subjects	50%	Std. Err.	[95% Conf.	Interval]
1	33	6.5	.3919149	4.3	.
2	17	7	.4710023	3.6	.
3	27	5	1.096721	1.6	7.8
4	13	1.5	.2145485	.4	3.6
total	90	6	.9049742	3.8	7

stage	no. of subjects	25%	Std. Err.	[95% Conf.	Interval]
1	33	4	.3194413	2.4	6
2	17	3.6	.231886	.2	7
3	27	1.3	.2720294	.3	1.9
4	13	.8	.0776366	.1	1.5
total	90	2	.660467	1.3	3.5



On shaded numbers: at year 5, 3 have failed since year2; stage II has median survival=7 years (where the red horizontal line hits the curves at 1st time survival <0.5); first quartile survival time is 3.6 with 95%CI (.2, .7) for stage II (where the green line hits the curves at 1st time survival <0.75);

3. The Cox Model

Question 3.1.: Is stage a significant predictor? Which stage is at highest risk of death? Which are second and third?

The Cox model output is

```
                                                LR chi2(3)      =     16.26
Log likelihood  =   -189.08124                  Prob > chi2     =    0.0010
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   _Istage_2 |   1.067972    .489604     0.14   0.886     .4348436    2.622932
   _Istage_3 |   1.844227    .655076     1.72   0.085     .9193153     3.69968
   _Istage_4 |   5.600403   2.350266     4.11   0.000      2.46039    12.74778
------------------------------------------------------------------------------
```

Stage is a significant predictor overall. This is evident from the likelihood ratio test in the upper right hand corner. Recall, this examines if all the predictors in the model can be dropped -- this amounts to an overall test of the significance of stage. You might consider comparing this result to the logrank test, which you obtain by typing

```
sts test stage
```

Both of these are significant, confirming that stage associates with risk of death.

Here, stage I is the reference and since all the hazard ratios are above 1, we see that stages II, III and IV all have a higher hazard than stage I. Hence, stage I has the lowest hazard (risk of death). The risk order follows the stage numbering (stage IV highest, stage III next highest, stage II third highest). This is evident by the magnitudes of the hazard ratios as the hazard ratio for the reference is implicitly equal to one.

Question 3.2.: Does it appear that the effect of 1 unit change in stage is the same across the range of values?

Not quite. We see that there is no real difference between stages I and II. This is evident by the HR of 1.07 for stage II relative to stage I.

Question 3.3.: Do your answers above agree with the Kaplan-Meier graphs?

Yes, the magnitudes of the hazard ratios are consistent with the amount of separation between the survival curves.

The HR of stage III compared to stage II is 1.73, which is fairly larger than 1.07 even though not significantly different.

```
. lincom _Istage_3 - _Istage_2, hr

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.726849   .7771455     1.21   0.225     .7147963    4.171827
------------------------------------------------------------------------------
```

Question 3.4.: Obtain the hazard ratio of stage IV compared with Stage III.

The HR between stages IV and III is

```
. lincom _Istage_4 - _Istage_3, hr
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   3.036721   1.233688     2.73   0.006     1.369616     6.73304
------------------------------------------------------------------------------
```

It (3.04) is quite different from the HR of 1.07 between stages II and I. This confirms that the differences between stages are not all equal.

Question 3.5.: Implement a trend test for stage by using the appropriate linear contrast (from Table 4.5, page 82).

```
. test -_Istage_2+_Istage_3+3*_Istage_4 =0

           chi2(  1) =   18.30
         Prob > chi2 =    0.0000
```

This test suggests a significant trend towards shorter survival with higher stage.
Note that

- *If you implement a test for departure from linear trend, it is not quite significant with a p-value of 0.20 (see below)*

```
. xi: stcox i.stage stage

                                                LR chi2(3)      =     16.26
Log likelihood  =   -189.08124                  Prob > chi2     =    0.0010
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   _Istage_2 |   .6013864   .2577513    -1.19   0.235     .2596167    1.393075
   _Istage_3 |   .5847921   .1965367    -1.60   0.110     .3026425    1.129986
       stage |   1.775851   .2484179     4.11   0.000     1.350003    2.336029
------------------------------------------------------------------------------

. testparm _Istage*

 ( 1)  _Istage_2 = 0
 ( 2)  _Istage_3 = 0

           chi2(  2) =    3.19
         Prob > chi2 =    0.2027
```

- *(optional) Examine the following* `lincom` *results and compare them to the hazard ratios results in Questions 3.1-3.4 above?*

```
. lincom stage + _Istage_2, hr                    (stage II relative to stage I)
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.067972    .489604     0.14   0.886     .4348436    2.622932
```

```
. lincom 2*stage + _Istage_3, hr                  (stage III relative to stage I)
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.844227    .655076     1.72   0.085     .9193153     3.69968
```

```
. lincom 3*stage, hr                                          (stage IV relative to stage I)
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------------
         (1) |   5.600403   2.350266     4.11   0.000      2.46039    12.74778

. lincom stage + _Istage_3- _Istage_2, hr                     (stage III relative to stage II)
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------------
         (1) |   1.726849   .7771455     1.21   0.225     .7147963    4.171827

. lincom stage - _Istage_3, hr                                (stage IV relative to stage III)
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------------
         (1) |   3.036721   1.233688     2.73   0.006     1.369616     6.73304
```

- *To see another example of a trend test being used for survival data, see the age results for the WHI paper on HRT by age and years since menopause JAMA. 2007; 297:1465-1477.*

4. Changing the Reference

Questions 4.1.-4.4: Fit a new model for stage. How does it compare to the previous model? Is stage a stronger predictor?

```
No. of subjects =           90                     Number of obs   =        90
No. of failures =           50
Time at risk    =  377.8000028
                                                   LR chi2(3)      =     16.26
Log likelihood  =   -189.08124                     Prob > chi2     =    0.0010

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   _Istage_1 |   .1785586   .0749339    -4.11   0.000      .078445    .4064397
   _Istage_2 |   .1906956   .0949948    -3.33   0.001     .0718316    .5062508
   _Istage_3 |   .3293025   .1337813    -2.73   0.006     .1485213    .7301318
------------------------------------------------------------------------------
```

Only superficially. It appears to be stronger because we see that all the coefficients have p-values that are significant, where the model before showed only 1 p-value to be significant. This is why looking at those p-value is somewhat unreliable. Instead, you should pay close attention to the overall test (which is the same as the previous fit) and carefully look at any important pairwise comparisons.

You see in Questions 4.2 and 4.3 that the pairwise comparisons of stage are exactly the same. Use

```
lincom _Istage_3-_Istage_2, hr
lincom          -_Istage_3, hr
```

Hence, the short answer is that the model and results are actually exactly the same. All that has changed is how `Stata` displays them. The results given in Question 4.1 present the results in reference to stage IV that makes the results appear somewhat more statistically significant when they are actually not different.

5. Continuous Predictors

Question 5.1.: What is the effect of age on survival after adjusting for stage?

```
xi: stcox age i.stage
```

The effect of age is an approximate 2% increase in the hazard of death for each year increase in age, the 95% confidence interval is a 1% decrease to a 5% increase. Since the CI for the HR spans 1, the effect of age is not statistically significant. However, stage remains significant. The hazard ratios for `stage` *hardly change and likelihood ratio chi-square is 15.5 (in contrast to 16.3 above) with 3 degrees of freedom, giving a p-value of 0.002.*

Question 5.2.: Obtain the hazard ratio of a 10 years increase in age. Has the significance level of the age effect become stronger?

```
lincom 10*age, hr
```

The effect of age (in decades) is a 21% increase in the hazard of death. 95% CI, 9% decrease to 60% increase, adjusting for stage. No, the test statistic (1.33) and thus the p-value are the same.

Question 5.3.: Obtain the hazard ratio of a 10 years decrease in age.

```
lincom -10*age, hr
```

The effect of a 10-year decrease in age is a 17% decrease in the hazard of death. 95% CI, 9% increase to a 37% decrease, adjusting for stage.

Question 5.4.: Verify that the hazard ratio and limits of its confidence interval in Question 5.3 is the reciprocal (one divided by the value) of the corresponding values in Question 5.2.

We see the correspondence below. The key thing is that the upper and lower limits of confidence intervals change places. The HR of 0.91 is the lower limit for a 10-year increase but it's reciprocal 1.09 is the upper limit of the CI for a 10-year decrease.

	10 increase	**10 decrease**
HR	1.20	1/1.20 = 0.83
limit of 95% CI	0.91	1/0.91 = 1.09
limit of 95% CI	1.60	1/1.60 = 0.63