Biostatistics 209, Lab #1 Discussion

2. Data

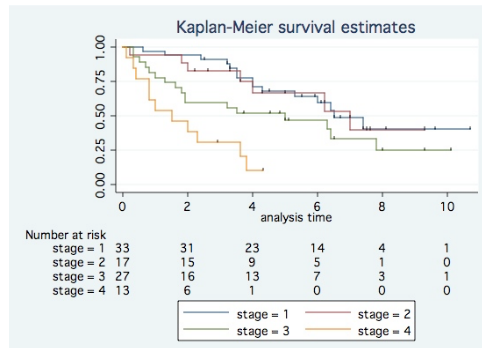
- Without specifying the `failure` option, all times are treated as non-censored events.

3. Exploring Stage Effects Using Kaplan-Meier Curves

Question 3.1.: Based on the Kaplan-Meier curve 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) risktable(1 2 5)

Time	At Risk	Fail	Net Lost	Survivor Function	Std. Error	[95% Conf.	Int.]
stage=1							
1	32	1	0	0.9697	0.0298	0.8037	0.9957
2	31	8	5	0.9394	0.0415	0.7788	0.9845
5	18	5	13	0.6762	0.0847	0.4806	0.8114
stage=2							
1	16	1	0	0.9412	0.0571	0.6502	0.9915
2	15	3	6	0.8235	0.0925	0.5471	0.9394
5	6	2	4	0.6655	0.1255	0.3644	0.8485
stage=3							
1	22	6	0	0.7778	0.0800	0.5709	0.8934
2	16	2	4	0.5926	0.0946	0.3863	0.7499
5	10	4	6	0.4667	0.0995	0.2674	0.6438
stage=4							
1	8	2	0	0.5385	0.1383	0.2477	0.7599
2	6	4	2	0.3846	0.1349	0.1405	0.6280
5	0	0	0	.	.	.	.

Notes: Survival-time summaries shown for specified times in (0, 10.7].
Net Lost equals the number lost minus the number who entered.

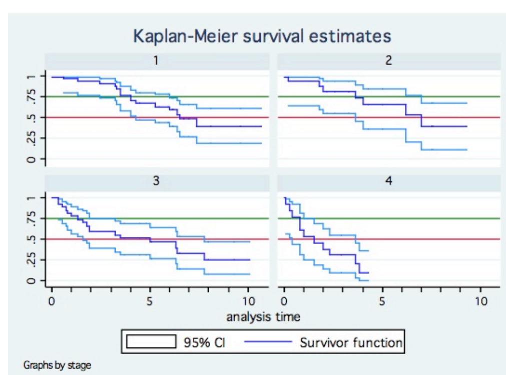
. sts list if stage==2

Time	At Risk	Fail	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

stage	no. of subjects	50%	Std. Err.	[95% Conf.	Interval]
1	33	6.5	.6520345	4.3	.
2	17	7	1.23299	3.6	.
3	27	5	1.983816	1.6	7.8
4	13	1.5	.7189736	.4	3.6
total	90	6	.9049742	3.8	7

. stci, by(stage) p(25)

stage	no. of subjects	25%	Std. Err.	[95% Conf.	Interval]
1	33	4	.4844657	2.4	6
2	17	3.6	.4884008	.2	7
3	27	1.3	.569275	.3	1.9
4	13	.8	.2923527	.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);

4. The Cox Model

Question 4.1.: Is stage a statistically 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]
-------------+----------------------------------------------------------------
       stage |
          2  |   1.067972    .489604     0.14   0.886     .4348436    2.622932
          3  |   1.844227    .655076     1.72   0.085     .9193153     3.69968
          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 4.2.: Obtain the hazard ratio of Stage II vs. Stage I.

```
                                                  LR chi2(3)      =     16.26
Log likelihood  =   -189.08124                    Prob > chi2     =    0.0010
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       stage |
          2  |   1.067972    .489604     0.14   0.886     .4348436    2.622932
          3  |   1.844227    .655076     1.72   0.085     .9193153     3.69968
          4  |   5.600403   2.350266     4.11   0.000      2.46039    12.74778
------------------------------------------------------------------------------
```

The HR comparing Stage II vs. I is 1.07 (95% CI, 0.43 to 2.62).

Question 4.3.: Obtain the hazard ratio of Stage III vs. Stage II.

```
. lincom 3.stage - 2.stage, hr

 ( 1)  - 2.stage + 3.stage = 0
```

```
------------------------------------------------------------------------------
          _t | Haz. ratio   Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
         (1) |   1.726849   .7771455     1.21   0.225     .7147963    4.171827
------------------------------------------------------------------------------
```

The HR comparing Stage III vs. II is 1.73 (95% CI, 0.71 to 4.17).

Question 4.4.: Obtain the hazard ratio of Stage IV vs. Stage III.

```
. lincom 4.stage - 3.stage, 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
------------------------------------------------------------------------------
```

The HR comparing Stage IV vs. III is 3.03 (95% CI, 1.37 to 6.73).

Question 4.5.: Does it appear that the effect of 1 unit change in stage is the same across the range of values?

Not quite. For example, the hazard ratio for Stage 2 vs. Stage 1 is about 1.07, Stage 3 vs. Stage 2 is roughly 1.73, and Stage 4 vs. Stage 3 jumps to 3.04. This indicates that moving from Stage 3 to Stage 4 has a much larger impact than moving from Stage 2 to Stage 3. Thus, the effect of a one-unit increase in stage varies across its range.

Question 4.6.: 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 3.stage - 2.stage, hr
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.726849   .7771455     1.21   0.225     .7147963    4.171827
------------------------------------------------------------------------------
```

Question 4.7.: Implement a trend test for stage:

```
contrast p.stage
```

Is there evidence of a linear trend?

```
. contrast p.stage
```

```
Contrasts of marginal linear predictions

Margins      : asbalanced

------------------------------------------------
             |         df        chi2     P>chi2
-------------+----------------------------------
       stage |
   (linear)  |          1       18.30     0.0000
(quadratic)  |          1        2.94     0.0862
    (cubic)  |          1        0.00     0.9527
      Joint  |          3       18.95     0.0003
------------------------------------------------

--------------------------------------------------------------
             |   Contrast   Std. Err.     [95% Conf. Interval]
-------------+------------------------------------------------
       stage |
   (linear)  |   .6389356    .149369      .3461777    .9316936
(quadratic)  |   .2612541   .1522514     -.0371532    .5596615
    (cubic)  |   .0093852   .1581767     -.3006354    .3194058
--------------------------------------------------------------
```

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

- *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*

5. Changing the Reference

Questions 5.1.-5.4: Fit a new model for stage using 4 as the baseline group. 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]
-------------+----------------------------------------------------------------
       stage |
          1  |   .1785586   .0749339    -4.11   0.000      .078445    .4064397
          2  |   .1906956   .0949948    -3.33   0.001     .0718316    .5062508
          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-values is somewhat unreliable to assess overall statistical significance for a *predictor. Instead, you should pay close attention to the overall test (which is the same as in the previous fit) and carefully look at any important pairwise comparisons.*

You can see that the pairwise comparisons of stage are exactly the same as those generated in by Questions 4.3 and 4.4. Use

```
lincom 3.stage - 2.stage, hr
lincom         - 3.stage, 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 5.1 present the results in reference to stage IV and that makes the results appear somewhat more statistically significant when they are actually not different.

6. Continuous Predictors

Question 6.1.: What is the effect of age on survival after adjusting for stage?

```
stcox age i.stage
```

```
. stcox age i.stage

Cox regression -- Breslow method for ties

No. of subjects =           90                  Number of obs    =          90
No. of failures =           50
Time at risk    =  377.8000028
                                                LR chi2(4)       =       18.07
Log likelihood  =   -188.17944                  Prob > chi2      =      0.0012

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.019082    .014523     1.33   0.185      .991011    1.047947
             |
       stage |
         2   |   1.148623   .5310148     0.30   0.764     .4641543    2.842449
         3   |   1.893354   .6741862     1.79   0.073     .9421837    3.804766
         4   |    5.43607   2.295152     4.01   0.000     2.376299    12.43567
------------------------------------------------------------------------------

.
```

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, the hazard ratios for `stage` *and associated p-values hardly change.*

Question 6.2.: Obtain the hazard ratio for an increase in age of 10 years. <u>Has the significance level of the age effect become stronger?</u>

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

```
 ( 1)  10*age = 0

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.208063   .1721615     1.33   0.185       .91366     1.59733
------------------------------------------------------------------------------
```

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 as in Question 5.1.

Question 6.3.: Obtain the hazard ratio of a decrease in age of 10 years.

```
. lincom -10*age, hr

 ( 1)  - 10*age = 0

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   .8277713    .117966    -1.33   0.185     .6260447    1.094499
------------------------------------------------------------------------------
```

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 6.4.: Verify that the hazard ratio and limits of its confidence interval in Question 6.3 is the reciprocal (one divided by the value) of the corresponding values in Question 6.2.

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