Biostatistics 513

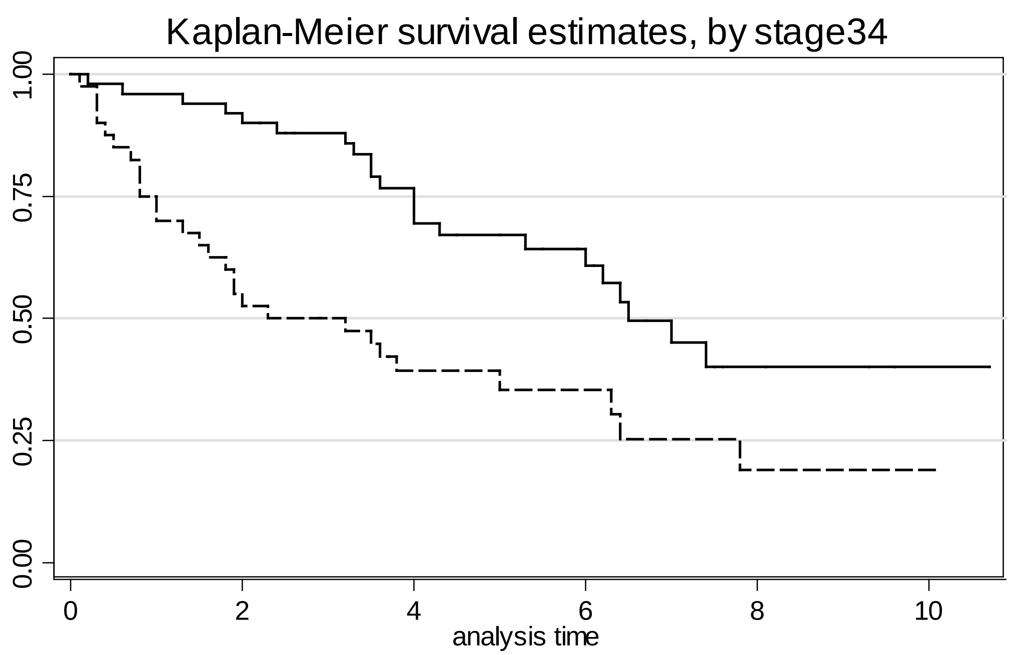
<u>Homework 7 Solutions</u>

1)

a. Using sts list, by(stage34) I find
S_0(3 years) = 0.8795 (95% CI: 0.7513 0.9440)
S_0(6 years) = 0.6077 (95% CI: 0.4411 0.7385)
S_1(3 years) = 0.5000 (95% CI: 0.3383 0.6419)
S_1(6 years) = 0.3537 (95% CI: 0.2040 0.5068)

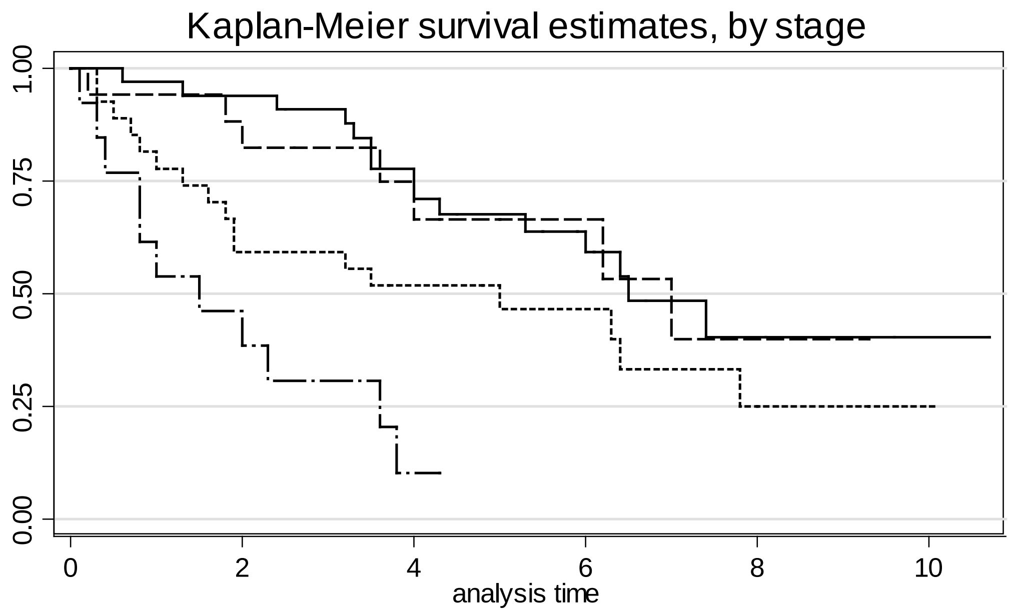
I see no overlap of the confidence intervals at 3 years. While this is not a formal statistical test, there is likely a significant difference in survival by stage at that point. There is some overlap at 6 years so it is harder to tell. You could formally test whether the two survival curves are the same at the specific points in time (i.e., t_0=3 years and t_0=6 years) by obtaining group-level survival estimates and their respective standard errors, at 3 and 6 years for the two groups, and constructing a Wald test.

b. The log-rank test has value 10.13 (p = .0015) and the Wilcoxon test has value 14.06 (p = .0002). Both are 1 df tests. Looking at the KM plots (below) we see that the largest difference are at early and middle times and the difference becomes smaller at later times. Thus, it is not surprising that the log-rank test, which emphasizes later times would have a smaller value compared to the Wilcoxon test which emphasizes earlier times.



[redacted]

c. The log-rank test has value 22.76 and the Wilcoxon test has value 23.18. Both are highly significant and suggest that there are statistically significant difference in survival according to stage. The KM plot (given below) suggests that there isn't much difference between stages 1 and 2, but that survival gets steadily worse through stages 3 and 4.



[redacted]

d. The Cox model output is

```
. xi: stcox i.stage
i.stage           _Istage_1-4         (naturally coded; _Istage_1 omitted)

         failure _d:  status
   analysis time _t:  time

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(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
------------------------------------------------------------------------------
```

From this we see that the HR for stage 2 (compared to stage1) is nearly 1, as one might guess based on the KM plot above. The HR for stage 3 (compared to stage 1) is larger (1.84) and the HR for stage 4 (compared to stage 1) is larger still (5.6). This is in rough agreement with what I see in the KM plot.

e. Using stage as a linear categorical variable I get

```
. stcox 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(1)      =     13.10
Log likelihood  =   -190.66133                     Prob > chi2     =    0.0003

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       stage |   1.657713   .2338867     3.58   0.000     1.257226    2.185774
------------------------------------------------------------------------------
```

The HR of 1.65 means that the hazard of death increases by a factor of 1.65 for each categorical increase in stage.

f. If I write the model as

$$h(t \mid X) = h_0(t)\exp(\beta_1 STAGE + \beta_2 STAGE^2 + \beta_3 STAGE^3)$$

then my hypotheses are $H_o: \beta_2 = \beta_3 = 0$

H_a: at least one $\neq 0$

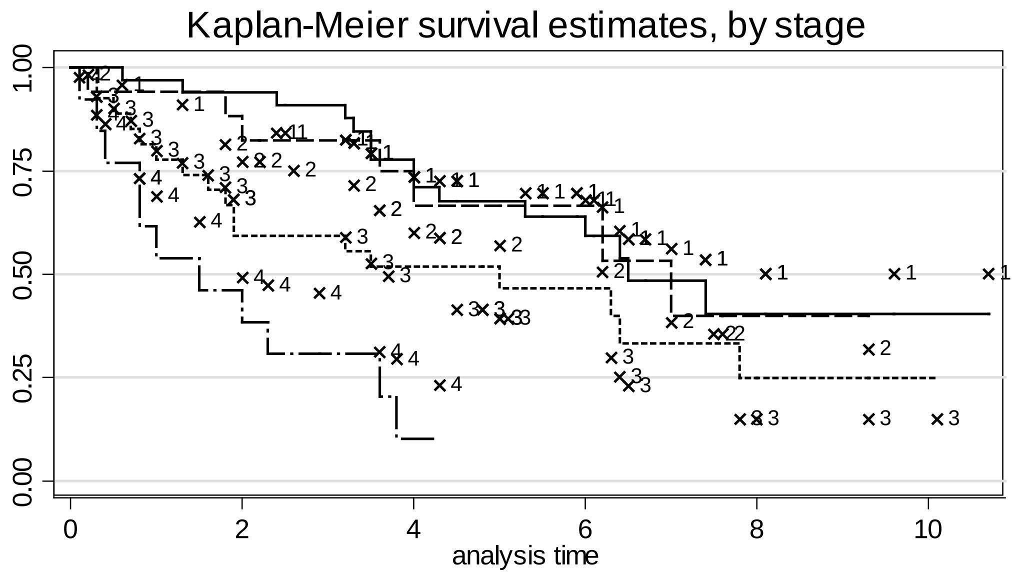
I can do a LR test. The result is

$$LR = 2*(-189.08124 + 190.66133) = 3.16 \text{ with 2 df}$$

I conclude that the linear model is adequate.

g.

```
. stcox stage, nohr basesurv(s0hat)
. generate shat = s0hat^exp(.5054389*stage)
. sts graph, by(stage) plot(scatter shat time, mlabel(stage))
```



[redacted]

The plot is a bit messy but what I see is that the Cox model captures the overall features of the KM curves. However, I see a bigger difference between stages 1 and 2 in the Cox model than I see on the KM curves and the Cox model shows better survival in stage 4 than the KM curve. This is all due to the linearity assumption. If I redid the above exercise using indicator categories in the Cox model, the fit to the KM curves would be better.

2)

a. $HR_{platlets}$(age,sex) = exp(.470 - .008*AGE - .503*SEX). This is the HR comparing individuals with normal platelets to those with abnormal platelets controlling for (i.e. holding fixed) AGE and SEX.

b. $HR_{platlets}$(40,male) = exp(.470 - .008*40 - .503*0) = 1.16
$HR_{platlets}$(50,female) = exp(.470 - .008*50 - .503*1) = 0.65

c. I will compare model 1 to model 2 using a LR test.
LR = 306.5 - 306.1 = 0.4
Comparing this LR to $\chi^2(2)$ I conclude that there is no evidence of interaction (effect modification). I should drop the interaction terms.

d. Comparing the coefficient of platelets in model 5 (unadjusted) to the coefficients in models 3, 4 and 2 (adjusted for age, sex and both, respectively) I see very little change between the adjusted and unadjusted models, so I conclude that age and sex are not confounding the effect of platelets.