VA/UW Summer Session: **Exercise Set #2** Day 2: June 21, 2005

Reading: • Kleinbaum *Survival Analysis*, Chapter 3

NOTE: Unless explicitly stated, direct computer output is **not** desired. Typically only part of the computer output is asked for (such as a confidence interval) and then proper interpretation of the statistics is requested.

DATA: The data for these exercises can be found on the class web page:
`http://faculty.washington.edu/heagerty/Courses/VA-summer-epi/` in the *Homeworks* directory (ie. click on Homeworks from the main summer course page).

Survival Analysis: Group comparisons and Cox regression

1. Last week we began to look at the data, `larynx.dat`, which represents the death times of male laryngeal cancer patients that attended a Dutch hospital between 1970 and 1978. Times recorded are the interval (in years) between first treatment and either death, or the end of the study (January 1, 1983). Also recorded are the patient's age at diagnosis and the year of diagnosis.

Define: stage34 = 1 if stage=3 or stage=4, and 0 if stage=2 or stage=1

(a) Use STATA to compute confidence intervals for the following:
S_1(3 years), 3 year survival for stage34=1
S_1(6 years), 6 year survival for stage34=1
S_2(3 years), 3 year survival for stage34=0
S_2(6 years), 6 year survival for stage34=0
Summarize what these confidence intervals imply regarding survival by this classification of stage.

(b) Use STATA to compute both the log-rank and the Wilcoxon (Breslow) tests for groups defined by the two levels of stage34. Interpret the results of these tests. Explain, based on the Kaplan-Meier curves and/or the CI's in (a) why the value of one test statistic is larger than the other.

(c) Now use STATA to compute the log-rank and Wilcoxon (Breslow) test for the 4 groups defined by stage. Interpret the results of these tests. (Do we see much difference between the two test statistics in this case?, Does that surprise you based on the Kaplan-Meier curves?).

(d) Use STATA to perform Cox regression using the 4-level stage variable. First consider dummy variables for the levels of stage (ie. use variables STAGE(2), STAGE(3), and

STAGE(4) that are stage indicator variables). Report the resulting estimated hazard ratios with 95% CI's. Interpret these estimates. Compare these summaries with what is shown in the Kaplan-Meier curves for stage.

(e) Can we use a simple linear model in stage? Perform Cox regression using the stage variable as a linear term in the model. Present and interpret the coefficient (or $\exp(\beta)$) from this regression.

(f) Use a likelihood ratio test to compare the linear model with the dummy variable model. State the null and alternative hypotheses that are being tested and interpret the results of this test.

(g) Graphically assess the fitted Cox regression model. Create a plot (or pair of plots) that compare the Kaplan-Meier fitted survival probabilities to those obtained using Cox regression. Recall that Cox regression assumes a common baseline hazard that is left unspecified, but can be estimated after the regression coefficients are estimated. The 4 stage groups are then assumed to have a survival function that derives from this common baseline estimate and the group's hazard ratio. Kaplan-Meier, on the other hand, simply computes a separate non-parametric estimate for each group (no assumptions about relationships between groups). Specifically create the following plots:

- Kaplan-Meier survival estimates for the 4 groups
- Fitted survival estimates based on the Cox model

(optional) Plot the Cox model $\widehat{S}(t)$ versus the KM $\widehat{S}(t)$

Hand in these plots and comment on the comparison of the KM and Cox model survival functions.

$\star$ See the class web page for details regarding how these plots can be created in STATA.

2. The data for this question contain the survival times of 65 multiple myeloma patients (reference = Krall et al. (1975). A partial list of variables in the data set is given below:

survival time (in months) from time of diagnosis
survival status (0=alive, 1=dead)
platelets at diagnosis (0=abnormal, 1=normal)
age at diagnosis (years)
sex (0=male, 1=female)

Below is output from fitted Cox regression models. The column labeled $p(PH)$ is the p-value from a test for whether the proportional hazards assumption holds for the specific covariate (ie. $H0$: proportional hazards assumption holds for X_j).

Variable	coeff.	s.e.	p-value	Haz Ratio	95% CI		p(PH)
Model 1:							
platelets	0.470	2.854	0.869	1.600	0.006	429.689	0.729
age	0.000	0.037	0.998	1.000	0.930	1.075	0.417
sex	0.183	0.725	0.801	1.200	0.290	4.969	0.405
platelets × age	-0.008	0.041	0.850	0.992	0.915	1.075	0.561
platelets × sex	-0.503	0.804	0.532	0.605	0.125	2.924	0.952
	-2 ln L = 306.080						
Model 2:							
platelets	-0.725	0.401	0.071	0.484	0.221	1.063	0.863
age	-0.005	0.016	0.740	0.995	0.965	1.026	0.405
sex	-0.221	0.311	0.478	0.802	0.436	1.476	0.487
	-2 ln L = 306.505						
Model 3:							
platelets	-0.706	0.401	0.078	0.493	0.225	1.083	0.792
age	-0.003	0.015	0.828	0.997	0.967	1.027	0.450
	-2 ln L = 307.018						
Model 4:							
platelets	-0.705	0.397	0.076	0.494	0.227	1.075	0.860
sex	-0.204	0.307	0.506	0.815	0.447	1.489	0.473
	-2 ln L = 306.616						
Model 5:							
platelets	-0.694	0.397	0.080	0.500	0.230	1.088	0.793
	-2 ln L = 307.065						

(a) For model 1, give an expression that would be used to obtain the estimated hazard ratio comparing the levels of the platelet variable *adjusted* for age and sex (what is the fitted model? does the comparison depend on age or sex?).

(b) Using 2(a), compute the estimated hazard ratio comparing platelet=1 to platelet=0 for a 40 year-old male. Also compute the hazard ratio for a 50 year-old female.

(c) Carry out an appropriate test of the hypothesis to evaluate whether there is any significant interaction in model 1 (this is often called the "chunk" test – that is, testing whether all 2-way interactions of interest are equal to zero). What is your conclusion regarding the interaction terms? (Note: the $\alpha = 0.05$ critical value for a $\chi^2(2)$ is 5.9915. This can be used for the likelihood ratio test).

(d) Considering models 2-5, evaluate whether age and sex appear to be important to control for as confounders if platelet is the predictor of primary interest. Justify your answer.