Biost 517: Applied Biostatistics I
Emerson, Fall 2005

Homework #7 Key
December 9, 2005

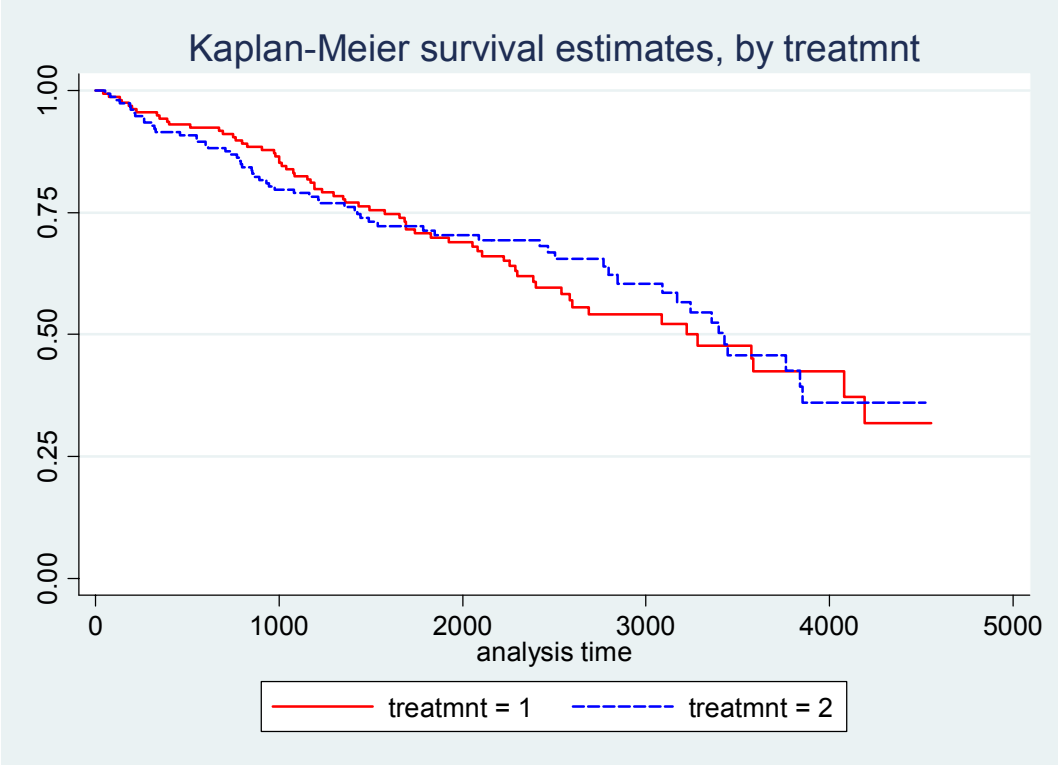
Written problems: To be handed in at the beginning of class on Wednesday, November 30, 2005.

> *On this (as all homeworks) unedited Stata output is **TOTALLY** unacceptable. Instead, prepare a table of statistics gleaned from the Stata output. The table should be appropriate for inclusion in a scientific report, with all statistics rounded to a reasonable number of significant digits. (I am interested in how statistics are used to answer the scientific question.)*

The written problems all refer to the Mayo Clinic PBC data set as stored on the class web pages.
In all problems, provide descriptive plots and as complete statistical inference as possible (i.e., provide point estimates, confidence intervals, and p values where possible, along with a statement of your scientific/statistical conclusions).

1. Perform an analysis to assess whether the probability of surviving for ten years differs between the patients treated with D-penicillamine and the patients receiving placebo.

Ans: The following figure shows Kaplan-Meier estimates of survival probabilities for the two treatment arms: Treatment 1= D-penicillamine; Treatment 2= placebo. There is no clear trend toward better or worse survival from this descriptive graph.



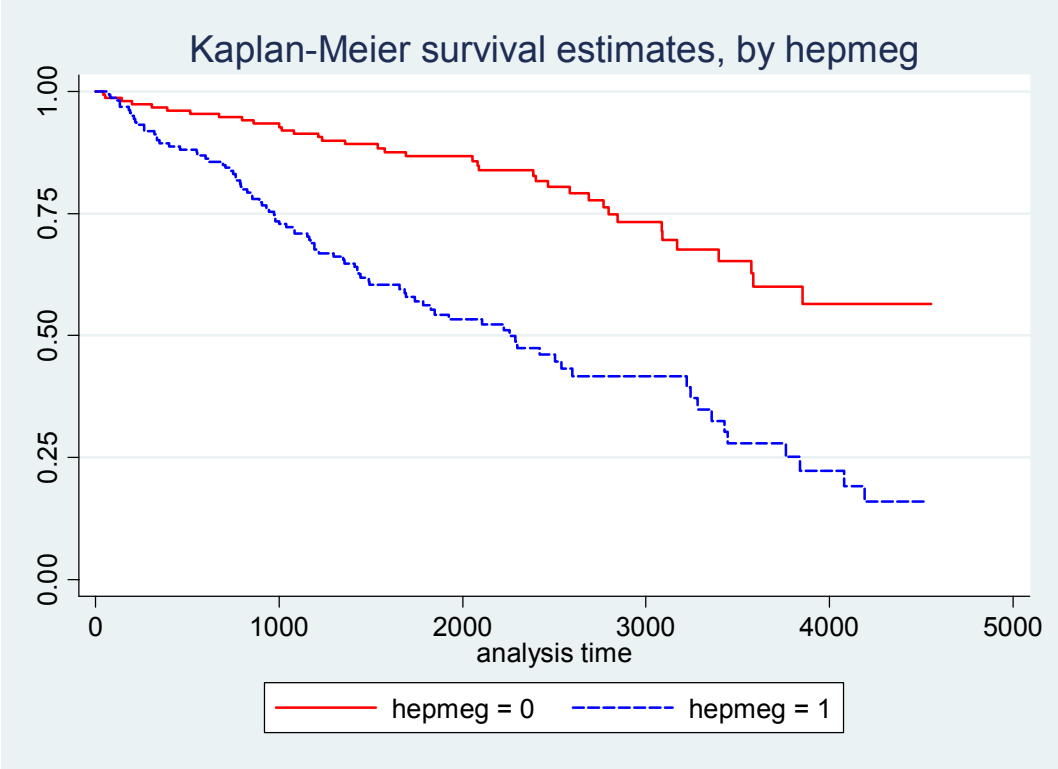
The following table presents 5 and 10 year survival probabilities for each treatment group along with 95% confidence intervals. We estimate that patients treated with D-penicillamine would have

10 year survival probability that was 3.23% lower (absolute difference) than patients treated with placebo. The 95% CI suggests that such results were consistent with a true difference in survival probabilities anywhere from 20.0% lower for D-penicillamine to 13.6% higher for D-penicillamine. Thus these results cannot be interpreted as conclusive evidence that D-penicillamine has any effect on 10 year survival (two-sided P= 0.71).

	5 Year Survival Probability (95% CI)	10 Year Survival Probability (95% CI)
D-penicillamine	70.7% (62.5%, 77.4%)	42.4% (30.5%, 53.8%)
Placebo	71.3% (63.2%, 78.0%)	45.7% (33.4%, 57.1%)
Difference	- 0.6% (-11.1%, 9.9%)	- 3.2% (-20.1%, 13.6%)

2. Perform an analysis to assess whether the risk of death (as measured by the hazard ratio) differs between patients with enlarged livers (hepatomegaly) at the time of randomization and those without.

Ans: The following figure shows Kaplan-Meier estimates of survival probabilities for the two groups defined by presence (hepmeg=1) or absence (hepmeg=0) of hepatomegaly. Clearly evident is a strong trend toward better survival in patients without hepatomegaly at the time of randomization.



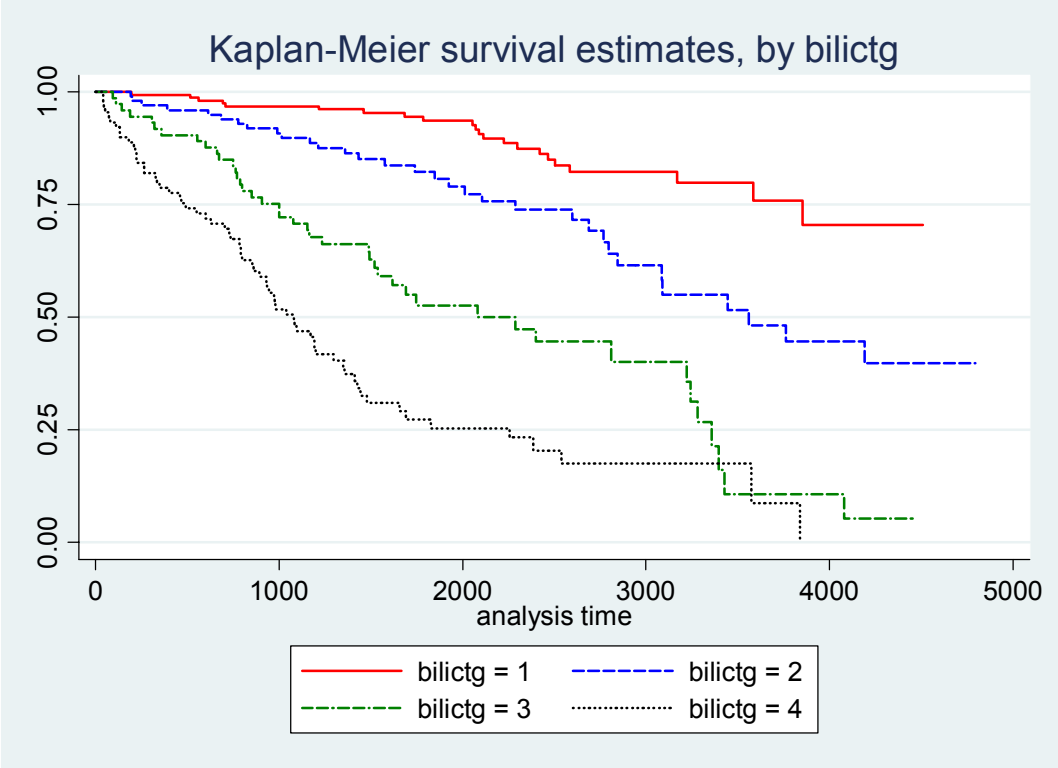
The following table presents 5 and 10 year survival probabilities for each group defined by hepatomegaly status at randomization along with 95% confidence intervals.

	5 Year Survival Probability (95% CI)	10 Year Survival Probability (95% CI)
No Hepatomegaly	86.7% (79.9%, 91.3%)	60.0% (46.8%, 71.0%)
Hepatomegaly	56.2% (47.7%, 63.8%)	27.9% (17.5%, 39.2%)
Difference	30.6% (20.7%, 40.4%)	32.1% (15.7%, 48.6%)

A proportional hazards regression analysis of the association between hepatomegaly and time to death estimates that patients with hepatomegaly at the time of randomization have a risk of death that is 3.27 times that of patients without hepatomegaly at baseline (95% CI for relative risk 2.24 to 4.79). These results were highly statistically significant (two-sided P< 0.0001). We can therefore with high confidence state that the presence of hepatomegaly is strongly associated with worse survival.

3. Perform an analysis to assess whether the risk of death (as measured by the hazard ratio) differs among patients according to the value of serum bilirubin at the time of randomization.

Ans: The following figure shows Kaplan-Meier estimates of survival probabilities for four strata defined by level of bilirubin at time of randomization (bilictg=1: bilirubin ≤ 1; bilictg=2: 1 < bilirubin ≤ 2; bilictg=3: 2 < bilirubin ≤ 4; bilictg=4: 4 < bilirubin). Clearly evident is a strong consistent trend toward worse survival in patients with higher levels of bilirubin at the time of randomization.



The following table presents 5 and 10 year survival probabilities for each group defined by bilirubin levels at randomization along with 95% confidence intervals.

	5 Year Survival Probability (95% CI)	10 Year Survival Probability (95% CI)
Bilirubin ≤ 1 mg/dl	93.6% (88.1%, 96.7%)	75.9% (62.4%, 85.1%)
1 mg/dl < Bilirubin ≤ 2 mg/dl	82.2% (72.4%, 88.8%)	48.1% (32.2%, 62.4%)
2 mg/dl < Bilirubin ≤ 4 mg/dl	52.7% (39.3%, 64.3%)	10.7% (2.1%, 27.5%)
4 mg/dl < Bilirubin	27.3% (17.6%, 38.0%)	8.7% (1.1%, 26.9%)

A proportional hazards regression analysis of the association between bilirubin level at randomization and time to death estimates that for each 1 mg/dl difference in bilirubin level the risk of death is 15.2% higher in patients with higher bilirubin levels (95% CI for relative risk 1.12 to 1.18 per 1 mg/dl difference in bilirubin levels). These results were highly statistically significant (two-sided P< 0.0001). We can therefore with high confidence state that higher bilirubin levels at randomization is strongly associated with worse survival.

An alternative analysis based on log transformed bilirubin:

> ***A proportional hazards regression analysis of the association between bilirubin level at randomization and time to death estimates that for each doubling of bilirubin level the risk of death in patients with higher bilirubin levels is 1.98 times higher than that in patients with only half as high a bilirubin level (95% CI for relative risk 1.78 to 2.21 per doubling of bilirubin levels). These results were highly statistically significant (two-sided P< 0.0001). We can therefore with high confidence state that higher bilirubin levels at randomization is strongly associated with worse survival.***