

Biost 518: Applied Biostatistics II

Emerson, Winter 2008

Homework #3 Key

February 9, 2008

A file containing the annotated Stata code I used to answer these questions is available on the class web pages.

The following questions pertain to the dataset for the randomized clinical trial of idarubicin versus daunorubicin in the treatment of acute myelogenous leukemia (stored as leukemia.txt on the class web page, with a Stata “do” file containing useful commands for reading in the data also available). For all questions involving statistical inference, provide estimates, confidence intervals, and P values in text suitable for a scientific journal. (We will completely ignore the complicating factor of interim analyses performed on this data.)

1. We are interested in examining how the induction of complete remission varies by treatment group and/or sex.
 - a. Provide suitable descriptive statistics regarding the distribution of complete remission status by treatment group and sex.

Ans: The following table presents the observed probability of inducing a complete remission by treatment and sex. There were slightly more females on the Idarubicin arm and slightly more males on the Daunorubicin arm. The observed remission rate was higher for Idarubicin and higher for females.

	Observed Probability of Complete Remission		
	Idarubicin	Daunorubicin	Both Treatments
Females	30 / 35 (86%)	21 / 30 (70%)	51 / 65 (78%)
Males	21 / 30 (70%)	17 / 35 (49%)	38 / 65 (58%)
Both Sexes	51 / 65 (78%)	38 / 65 (58%)	89 / 130 (68%)

- b. Perform an analysis to determine whether the induction of complete remission differs by treatment group.

Ans: On the Idarubicin arm, 51 of 65 patients (78%) achieved a complete remission, while on the Daunorubicin arm 38 of 65 patients (58%) achieved a complete remission. Based on the chi squared test, the observed absolute difference of 20% in the induction of CR is beyond that that might be expected to occur by chance in the absence of a true treatment effect ($P = 0.0141$; 95% CI for difference in CR rates is an absolute 4.40% to 35.6% higher CR rate in the Idarubicin arm).

- c. Is the analysis in part b confounded by sex? Justify your answer.

Ans: This was a randomized clinical trial, and so at some level there is not confounding: Across repeated such RCTs, there will be no systematic trend toward there being an association between sex and treatment in the sample. However, as we are only going to do one RCT, it might be of interest to consider whether we got unlucky in this particular RCT. In real life, we will have to focus primarily on the analysis that was pre-specified, and exploring questions like this will be judged secondary. That disclaimer aside, as noted in part 1a, there are a higher proportion of women on the Idarubicin arm and a higher proportion of men on

the Daunorubicin arm. To assess whether the 14% difference in the proportion of women on any arm might contribute to substantial confounding, we need to consider whether sex is associated with the incidence of CR independent of treatment effect. One way to do this would be to restrict attention to a single treatment arm—usually we would use the control group. In this case we see that the absolute difference in CR rates between women and men is 21%, a rather substantial effect. Hence, I would indeed worry that some small part of the better survival in the Idarubicin group might be due to the higher prevalence of women in that group. *(Note that the unadjusted estimated OR is very slightly further from the null than is the sex adjusted OR. This does suggest a very slight amount of confounding, because if sex were just a precision variable, the adjusted OR would be expected to be further from the null than the unadjusted OR. But the difference is not anything to write home about. Of course, given the fact that sex does seem to be an independent predictor of CR, the fact that there is so little difference between the adjusted and unadjusted estimates is perchance a sign of confounding.)*

- d. Perform an analysis to determine whether the induction of complete remission differs by treatment group after adjustment for sex using the Mantel-Haenszel statistic.

Ans: Among females, 30 of 35 patients (86%) on the Idarubicin arm and 21 of 30 (70%) on the Daunorubicin arm achieved a complete remission, corresponding to an odds of CR that was 2.57 times higher on the Idarubicin arm than the Daunorubicin arm. Among males 21 of 30 patients (70%) on the Idarubicin arm and 17 of 35 (49%) on the Daunorubicin arm achieved a complete remission, corresponding to an odds of CR that was 2.47 times higher on the Idarubicin arm than the Daunorubicin arm. Based on the Mantel-Haenszel statistic adjusting for sex, the observed odds of CR on the Idarubicin arm is 2.51 times higher than the odds of CR for a patient of the same sex receiving Daunorubicin. This observation is beyond that that might be expected to occur by chance in the absence of a true treatment effect ($P = 0.021$; 95% CI for odds ratio is that the odds of CR for Idarubicin is 1.14 to 5.51 times higher than that on the Daunorubicin arm).

- e. Perform an analysis to determine whether the induction of complete remission differs by treatment group after adjustment for sex using logistic regression.

Ans: Among females, 30 of 35 patients (86%) on the Idarubicin arm and 21 of 30 (70%) on the Daunorubicin arm achieved a complete remission, corresponding to an odds of CR that was 2.57 times higher on the Idarubicin arm than the Daunorubicin arm. Among males 21 of 30 patients (70%) on the Idarubicin arm and 17 of 35 (49%) on the Daunorubicin arm achieved a complete remission, corresponding to an odds of CR that was 2.47 times higher on the Idarubicin arm than the Daunorubicin arm. Based on a logistic regression model adjusting for sex and using robust standard errors, the observed odds of CR on the Idarubicin arm is 2.51 times higher than the odds of CR for a patient of the same sex receiving Daunorubicin. This observation is beyond that that might be expected to occur by chance in the absence of a true treatment effect ($P = 0.022$; 95% CI for odds ratio is that the odds of CR for Idarubicin is 1.14 to 5.53 times higher than that on the Daunorubicin arm).

- f. What similarities and differences do you see in your answers to parts d and e?

Ans: The results to parts d and e are nearly identical. In fact, the Mantel-Haenszel statistic is more closely related to the score statistic from a similar logistic regression model, while we tend to report the Wald statistic (which is based on the parameter estimate divided by its standard error). These two statistics are asymptotically equivalent, but they may differ in small samples. They clearly did not in this case.

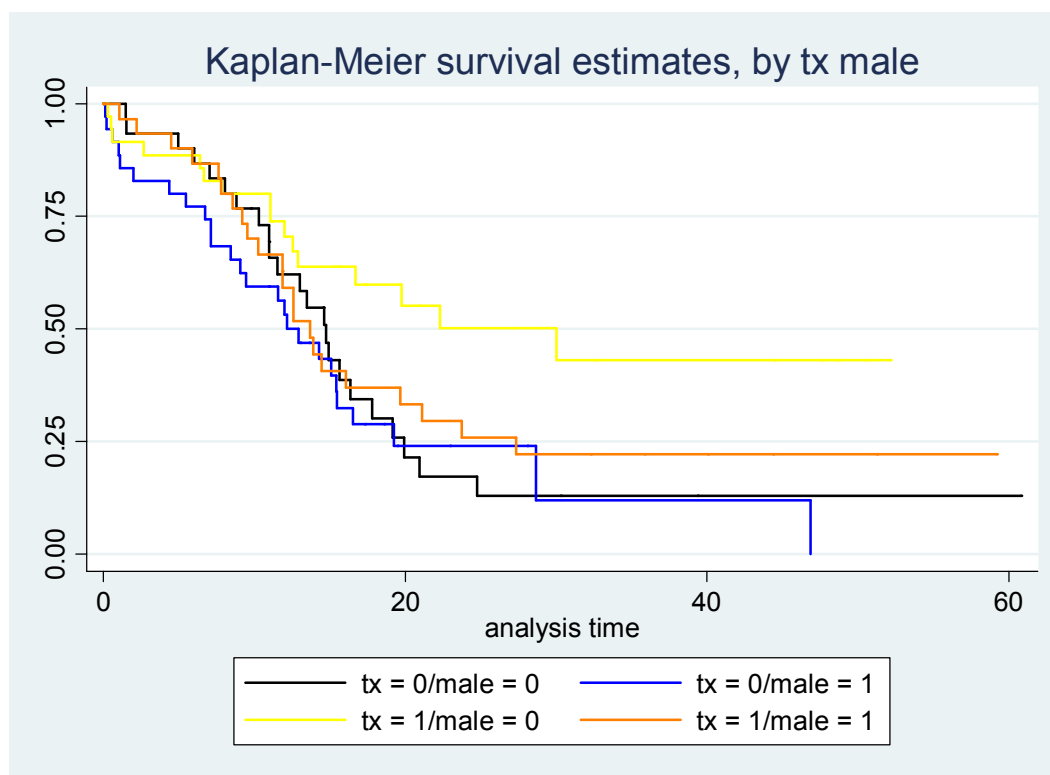
- g. Is there evidence that sex modifies the effect of treatment? Justify your answer.

Ans: Among females, 30 of 35 patients (86%) on the Idarubicin arm and 21 of 30 (70%) on the Daunorubicin arm achieved a complete remission, corresponding to an odds of CR that was 2.57 times higher on the Idarubicin arm than the Daunorubicin arm. Among males 21 of 30 patients (70%) on the Idarubicin arm and 17 of 35 (49%) on the Daunorubicin arm achieved a complete remission, corresponding to an odds of CR that was 2.47 times higher on the Idarubicin arm than the Daunorubicin arm. Based on a logistic regression model adjusting for sex and a sex-treatment interaction, the observed trend toward the OR measuring treatment effect to be 3.92% lower in males than it is in females is not beyond that that might be expected to occur by chance in the absence of a true difference in treatment effect across the sexes ($P = 0.61$). It should be noted that this study did not provide substantial precision with which to detect such effect modification: The 95% CI for the proportionate difference between the odds ratio measuring treatment effect is that the observed results are not incompatible with a treatment effect in males that is 80.6% lower (so only 0.194 as high) or 375% higher (so 4.75 times higher) than the treatment effect in females.

2. We are interested in examining how the time to death varies by treatment group and/or sex.
 - a. Provide suitable descriptive statistics regarding the distribution of time to death by treatment group and sex.

Ans: The following table and figure present the observed probability of survival by treatment and sex. There were slightly more females on the Idarubicin arm and slightly more males on the Daunorubicin arm. The observed survival probabilities tended to be higher for Idarubicin and higher for females.

	Kaplan-Meier Estimates of Survival Probabilities					
	Males			Females		
	n	1 year	2 year	n	1 year	2 year
Idarubicin	30	0.59	0.26	35	0.74	0.50
Daunorubicin	35	0.53	0.24	30	0.62	0.17



- b. Perform an analysis to determine whether the time to death differs by treatment group.

Ans: The instantaneous risk of death on the Idarubicin arm is estimated to be only 60.7% of the risk of death for patients on the Daunorubicin arm. Based on the proportional hazards regression analysis using robust standard errors, this observed reduced risk of death on the Idarubicin arm is beyond that that might be expected to occur by chance in the absence of a true treatment effect ($P = 0.021$; 95% CI for hazard ratio is 0.397 to 0.929, with the lower risk of death in the Idarubicin arm).

- c. Is the analysis in part b confounded by sex? Justify your answer.

Ans: This was a randomized clinical trial, and so at some level there is not confounding: Across repeated such RCTs, there will be no systematic trend toward there being an association between sex and treatment in the sample. However, as we are only going to do one RCT, it might be of interest to consider whether we got unlucky in this particular RCT. In real life, we will have to focus primarily on the analysis that was pre-specified, and exploring questions like this will be judged secondary. That disclaimer aside, as noted in part 1a, there are a higher proportion of women on the Idarubicin arm and a higher proportion of men on the Daunorubicin arm. To assess whether the 14% difference in the proportion of women on any arm might contribute to substantial confounding, we need to consider whether sex is associated with the risk of death independent of treatment effect. One way to do this would be to restrict attention to a single treatment arm—usually we would use the control group. In this case we see from a proportional hazards regression that the relative risk of death between women and men is that men have a 17% higher hazard. This is not such a particularly strong association, hence I would not expect that much, if any, confounding exists. (Note that the unadjusted estimated HR is very slightly further from the null than is the sex adjusted HR. This does suggest a very slight amount of confounding, because if sex were just a precision variable, the

adjusted HR would be expected to be further from the null than the unadjusted HR. But the difference is not anything to write home about.)

- d. Perform an analysis to determine whether the time to death differs by treatment group after adjustment for sex.

Ans: A proportional hazards regression analysis of the instantaneous risk of death across treatment groups after adjustment for sex finds that the instantaneous risk of death for a patient on the Idarubicin arm is estimated to be only 61.8% of the risk of death for a patient of the same sex on the Daunorubicin arm. Based on this proportional hazards regression analysis using robust standard errors, this observed reduced risk of death on the Idarubicin arm is beyond that that might be expected to occur by chance in the absence of a true treatment effect ($P = 0.026$; 95% CI for the sex adjusted hazard ratio is 0.405 to 0.944, with the lower risk of death in the Idarubicin arm).

- e. Is there evidence that sex modifies the effect of treatment? Justify your answer. (This can be effected by modeling treatment, sex, and a new variable that is equal to the product of sex times treatment.

Ans: From a proportional hazards regression analysis modeling treatment, sex, and a sex-treatment interaction, the instantaneous risk of death for a female on the Idarubicin arm is estimated to be only 49.0% of the risk of death for a female on the Daunorubicin arm, while the instantaneous risk of death for a male on the Idarubicin arm is estimated to be 74.7% of the risk of death for a male on the Daunorubicin arm. Based on the proportional hazards regression analysis using robust standard errors, the observed trend toward the hazard ratio measuring treatment effect to be 52.6% higher in males than it is in females ($0.747 / 0.490 = 1.526$) is not beyond that that might be expected to occur by chance in the absence of a true difference in treatment effect across the sexes ($P = 0.33$). It should be noted that this study did not provide substantial precision with which to detect such effect modification: The 95% CI for the proportionate difference between the hazard ratio measuring treatment effect is that the observed results are not incompatible with a treatment effect in males that is 34.8% lower (so only 0.652 as high) or 257% higher (so 3.57 times higher) than the treatment effect in females.