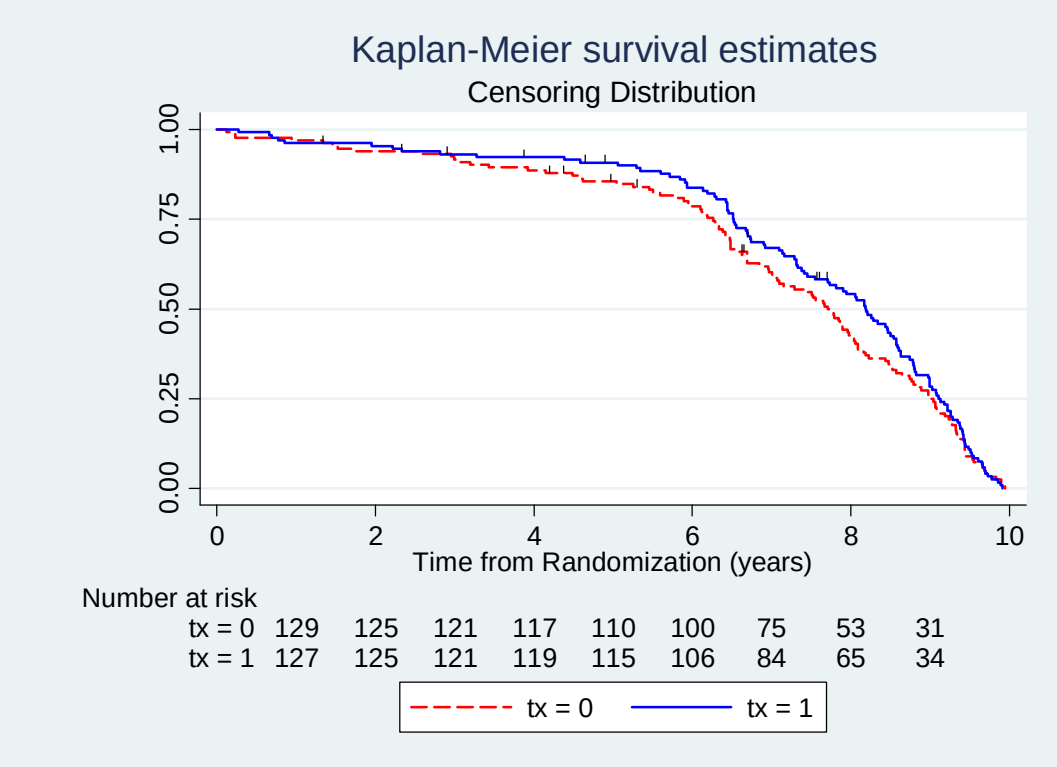
Biost 517: Applied Biostatistics I
Emerson, Fall 2009

Homework #7 Key
December 13, 2009

Questions for Biost 514 and Biost 517:

The written problems all refer to the data on outcomes from the clinical trial of methotrexate in patients with primary biliary cirrhosis as stored in the mtxotcm.txt data file 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 censoring distribution differed between the treatment arms. (For this problem we are interested in the censoring of observations of the primary endpoint of death.)

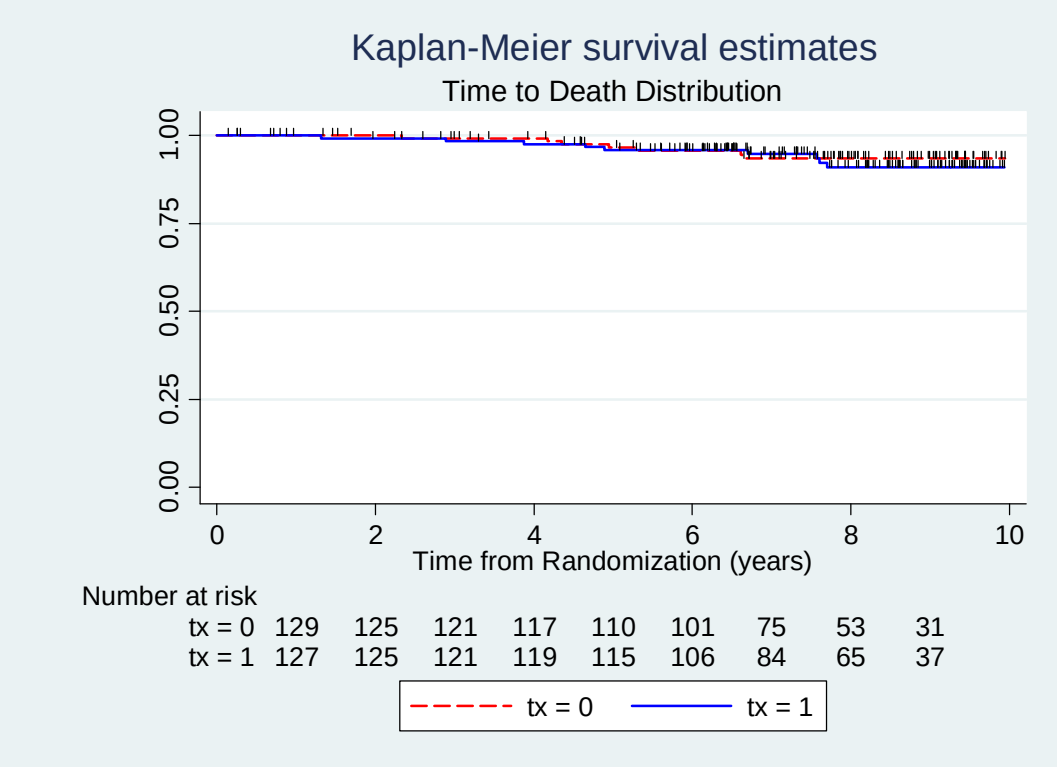


The above plot displays the Kaplan-Meier estimates of the probability of remaining under observation for the two treatment arms, where deaths were treated as censored observations of the potential follow-up time for each individual. The following table displays the mean time of observation, the 25th, 50th, and 75th percentiles of the observation time distribution, and the probability of remaining under observation by year since randomization. Apparent is a tendency toward slightly less observation time on average in the placebo group (7.52 years for the MTX group versus 7.14 years for the placebo group). The probability of having 8 years of follow-up was estimated at 54.2% for the MTX arm and 42.7% for the placebo arm. The difference between the treatment arms in the

distributions for the period of observation was not statistically significant when analyzed in a proportional hazards analysis using robust standard errors, however. Based on the estimated hazard ratio, the risk for study dropout on the MTX arm relative was 9.99% less on than that on the placebo arm (HR 0.901, 95% CI 0.702 to 1.16, P = 0.410).

	Placebo	Methotrexate
	n = 133	**n = 132**
Mean	7.14 (6.74, 7.53)	7.52 (7.15, 7.90)
Percentiles		
25th	6.26 (5.51, 6.48)	6.52 (6.19, 6.92)
50th	7.71 (7.02, 8.04)	8.19 (7.55, 8.57)
75th	8.99 (8.53, 9.28)	9.11 (8.80, 9.37)
Survival Probabilities		
1 year	0.970 (0.922, 0.989)	0.962 (0.911, 0.000)
2 years	0.940 (0.883, 0.970)	0.955 (0.902, 0.989)
3 years	0.917 (0.855, 0.953)	0.932 (0.873, 0.970)
4 years	0.887 (0.819, 0.930)	0.924 (0.863, 0.953)
5 years	0.856 (0.784, 0.906)	0.908 (0.844, 0.930)
6 years	0.786 (0.705, 0.847)	0.837 (0.761, 0.906)
7 years	0.604 (0.513, 0.682)	0.671 (0.582, 0.847)
8 years	0.427 (0.339, 0.511)	0.542 (0.451, 0.682)
9 years	0.250 (0.178, 0.328)	0.283 (0.206, 0.511)

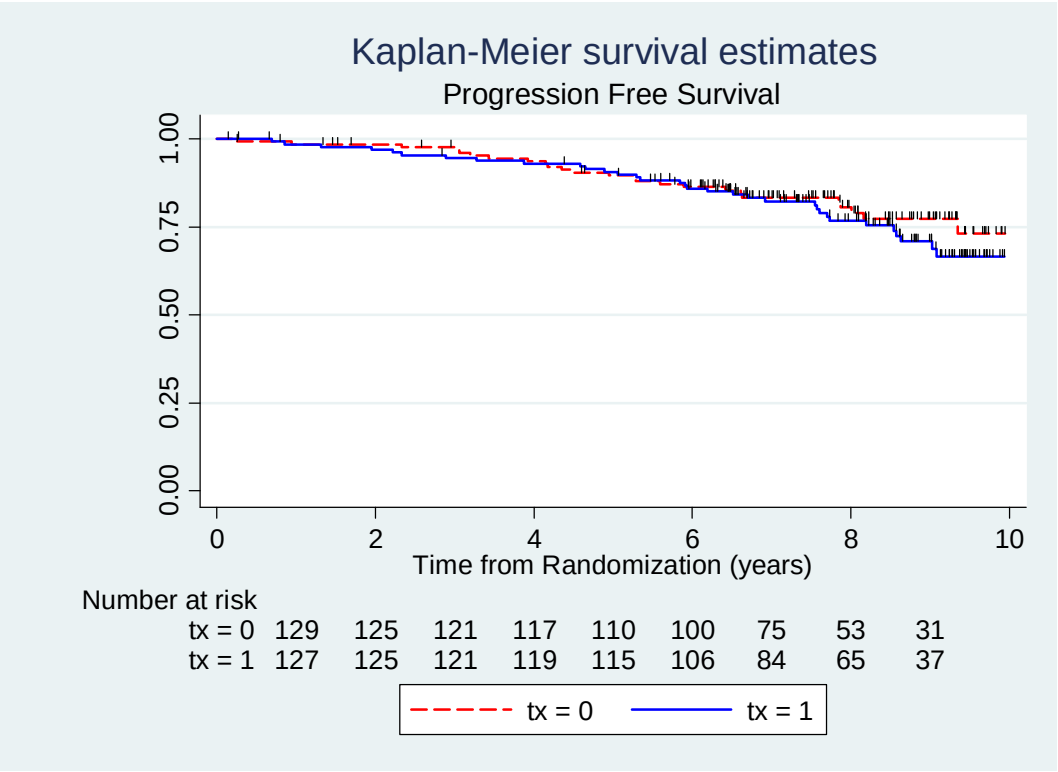
2. Perform an analysis to assess whether the risk of death (as measured by the hazard ratio) differs between the treatment arms.



The above plot displays the Kaplan-Meier estimates of the probability of survival for the two treatment arms. The following table displays the probability of survival by year since randomization. Overall, the survival rates were quite high with 93.4% of placebo patients and 91.0% of MTX patients estimated to survive for 8 years after beginning treatment. Based on the estimated hazard ratio from a proportional hazards regression using robust standard errors, the risk for death on the MTX arm was estimated to be 21.6% higher than that on the placebo arm (95% 54.6% lower to 226% higher, P = 0.697), however it should be noted that with only 16 observed deaths, this study had very little precision to estimate an effect of MTX on patient survival.

	Placebo	Methotrexate
	n = 133	n = 132
Survival Probabilities		
1 year	1.000 (., .)	1.000 (., .)
2 years	1.000 (., .)	0.992 (0.945, 0.999)
3 years	0.992 (0.945, 0.999)	0.984 (0.938, 0.996)
4 years	0.992 (0.945, 0.999)	0.976 (0.927, 0.992)
5 years	0.966 (0.912, 0.987)	0.959 (0.905, 0.983)
6 years	0.957 (0.900, 0.982)	0.959 (0.905, 0.983)
7 years	0.934 (0.866, 0.968)	0.949 (0.888, 0.977)
8 years	0.934 (0.866, 0.968)	0.910 (0.830, 0.953)

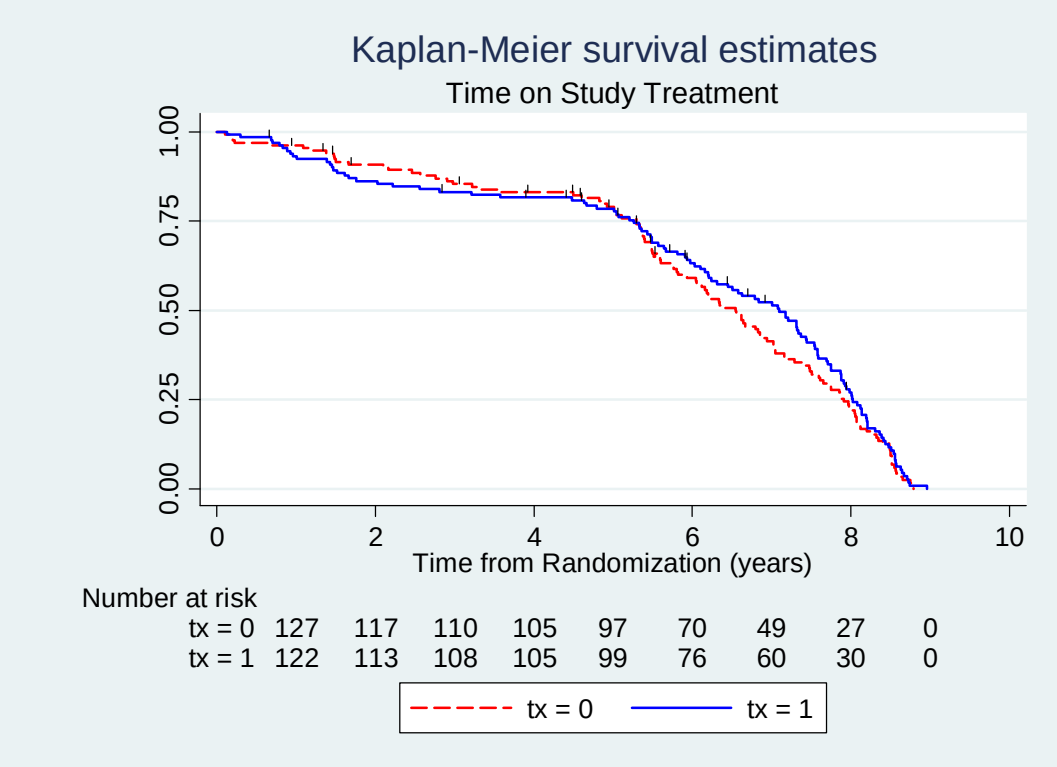
3. Perform an analysis to assess whether the risk of disease progression (as measured by the hazard ratio) differs between the treatment arms.



The above plot displays the Kaplan-Meier estimates of the probability of progression free survival for the two treatment arms. The following table displays the mean time alive progression free during the first 9.9 years of observation, the 25th, 50th, and 75th percentiles of the progression free survival time distribution, and the probability of remaining alive and progression free by year since randomization. Overall, the progression free survival rates were quite high with 89.7% of placebo patients and 90.7% of MTX patients estimated to survive for 5 years after beginning treatment and 80.5% of placebo patients and 76.7% of MTX patients estimated to survive for 8 years after beginning treatment. Based on the estimated hazard ratio from a proportional hazards regression using robust standard errors, the risk for death on the MTX arm relative was 22.8% higher than that on the placebo arm (95% CI 27.0% lower to 106% higher, P = 0.438), however it should be noted that with only 58 observed progressions or deaths, this study had very little precision to estimate an effect of MTX on patient survival.

	Placebo	**Methotrexate**
	n = 133	**n = 132**
Restricted Mean (9.9 year)	8.87 (8.47, 9.26)	8.68 (8.27, 9.08)
Percentiles		
25th	9.35 (7.85, .)	8.54 (6.92, .)
Survival Probabilities		
1 year	0.985 (0.941, 0.996)	0.985 (0.940, 0.996)
2 years	0.985 (0.941, 0.996)	0.969 (0.920, 0.988)
3 years	0.969 (0.919, 0.988)	0.946 (0.890, 0.974)
4 years	0.937 (0.878, 0.968)	0.930 (0.870, 0.963)
5 years	0.897 (0.829, 0.939)	0.907 (0.841, 0.946)
6 years	0.863 (0.789, 0.913)	0.859 (0.785, 0.909)
7 years	0.834 (0.753, 0.890)	0.823 (0.743, 0.880)
8 years	0.805 (0.716, 0.869)	0.767 (0.677, 0.835)

4. Perform an analysis to assess whether the probability of early termination of treatment with study drug differs between the treatment arms. (For this analysis directed toward patients' tolerance of the treatment, a patient who stopped treatment due to death is not considered early termination of therapy.)

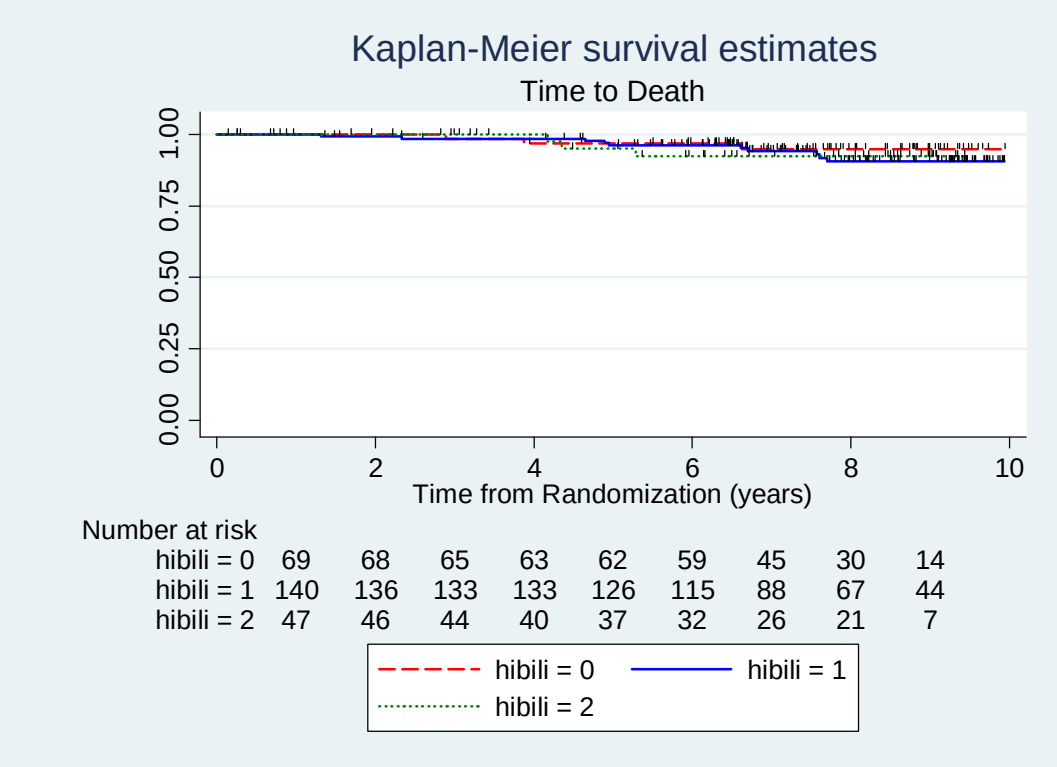


The above plot displays the Kaplan-Meier estimates of the probability of remaining on study drug for the two treatment arms, where deaths were treated as censored observations of the potential time for each individual. The following table displays the mean time on study drug, the 25th, 50th, and 75th percentiles of the distributions of time on study drug, and the probability of remaining on study drug by year since randomization. The average time on study drug in the placebo group is quite similar to that for the MTX group (6.13 years for the MTX group versus 6.04 years for the placebo group). Based on the estimated hazard ratio from a proportional hazards regression using robust standard errors, the risk for early discontinuation of study drug on the MTX arm was 10.7% lower than that on the placebo arm (95% CI 30.8% lower to 15.4% higher, P = 0.387). Although there was no significant difference in the distributions noted overall, it is of some interest to note that early in the clinical trial, there was a slight (nonsignificant) excess of patients on the MTX arm discontinuing their study drug, while later in the study, this trend reversed. *(I don't know that I would comment on this too much in a real manuscript due to its extreme imprecision, however, such a pattern would be consistent with early discontinuation due to adverse effects in the MTX group, and then late discontinuation to lack of effect in the placebo group. I always look for such possiblities, but given the lack of an overall effect due to MTX, it would be pretty hard to justify commenting on this.)*

	Placebo	**Methotrexate**
	n = 133	**n = 132**
Mean	6.04 (5.65, 6.44)	6.13 (5.70, 6.56)
Percentiles		
25th	5.29 (4.49, 5.49)	5.26 (3.21, 5.64)
50th	6.55 (5.93, 6.95)	7.10 (6.21, 7.45)
75th	7.92 (7.48, 8.12)	8.02 (7.75, 8.21)

Survival Probabilities		
1 year	0.962 (0.912, 0.984)	0.931 (0.872, 0.964)
2 years	0.909 (0.845, 0.947)	0.863 (0.791, 0.911)
3 years	0.854 (0.781, 0.905)	0.832 (0.756, 0.886)
4 years	0.831 (0.755, 0.885)	0.817 (0.739, 0.873)
5 years	0.791 (0.710, 0.851)	0.785 (0.704, 0.846)
6 years	0.591 (0.499, 0.672)	0.633 (0.542, 0.710)
7 years	0.414 (0.326, 0.500)	0.523 (0.432, 0.607)
8 years	0.228 (0.158, 0.307)	0.270 (0.194, 0.352)

5. Perform an analysis to assess whether the risk of death (as measured by the hazard ratio) differs according to the bilirubin level at time of randomization.



The above plot displays the Kaplan-Meier estimates of the probability of survival for strata defined by baseline bilirubin less than 0.5 mg/dl, between 0.5 and 1.0 mg/dl, or equal to or above 1.0 mg/dl. The following table displays the probability of survival by year since randomization. Overall, the survival rates were quite high and similar across the strata with 95.0% of patients with low bilirubin, 90.6% of patients with moderate bilirubin, and 92.4% of patients with high bilirubin estimated to survive for 8 years after beginning treatment.

	Bili < 0.5	**0.5 <= Bili < 1**	**1 <= Bili**
	n = 70	**n = 144**	**n = 51**
Survival Probabilities			
1 year	1.000 (., .)	1.000 (., .)	1.000 (., .)
2 years	1.000 (., .)	0.993 (0.950, 0.999)	1.000 (., .)

3 years	0.985 (0.897, 0.998)	0.986 (0.943, 0.996)	1.000 (., .)
4 years	0.970 (0.884, 0.992)	0.986 (0.943, 0.996)	1.000 (., .)
5 years	0.970 (0.884, 0.992)	0.963 (0.912, 0.984)	0.950 (0.815, 0.987)
6 years	0.970 (0.884, 0.992)	0.963 (0.912, 0.984)	0.924 (0.781, 0.975)
7 years	0.950 (0.851, 0.984)	0.943 (0.883, 0.973)	0.924 (0.781, 0.975)
8 years	0.950 (0.851, 0.984)	0.906 (0.829, 0.949)	0.924 (0.781, 0.975)

(I would actually do only one of the following analyses. Based on my prior experience, I would have tended to perform the analysis using log(bili).)

Based on the estimated hazard ratio from a proportional hazards regression using robust standard errors, the hazard for death among patients having a baseline bilirubin greater than or equal to 1 mg/dl was 14.6% higher than that for patients having bilirubin levels below 1 mg/dl (estimated HR 1.146, 95% CI 0.323 to 4.07, P = 0.833). It should be noted that there is very little precision with which to judge a true association between bilirubin and death, as evidenced by the very wide confidence interval.

Based on the estimated hazard ratio from a proportional hazards regression using robust standard errors, when comparing two groups differing in their bilirubin levels, we estimate the hazard of death to be 23.8% for each 1 mg/dl difference in bilirubin levels, with the worse survival in the group with the higher bilirubin (95% CI 51.7% lower to 3.17 times higher for each 1 mg/dl difference, P = 0.387). It should be noted that there is very little precision with which to judge a true association between bilirubin and death, as evidenced by the very wide confidence interval.

Based on the estimated hazard ratio from a proportional hazards regression using robust standard errors, when comparing two groups differing in their bilirubin levels, we estimate the hazard of death to be 28.5% for each doubling of bilirubin levels, with the worse survival in the group with the higher bilirubin (95% CI 28.4% lower to 2.30 times higher for each doubling of bilirubin, P = 0.84). It should be noted that there is very little precision with which to judge a true association between bilirubin and death, as evidenced by the very wide confidence interval.