

Biostatistics 140.623
Third Term, 2017-2018
Problem Set 2
Answer Key

2) Survival in Primary Biliary Cirrhosis

Introduction

Between January 1974 and May 1984 a double-blinded randomized trial on patients with primary biliary cirrhosis (PBC) of the liver was conducted at the Mayo clinic. A total of 312 patients were randomized to either receive the drug D-penicillimin (DPCA), or a placebo. Patients were followed until they died from PBC, or until censoring, either because of administrative censoring (withdrawn alive at end of study), death not attributable to PBC, liver transplantation, or loss to follow-up. At baseline clinical, biochemical, serological and histologic measurements were recorded on each patient. A sub-study was undertaken to test for increased survival amongst patients on the new treatment, and to investigate the association between survival and patients' age, gender, histologic stage of disease, and serum bilirubin level.

Methods

Descriptive statistics were calculated to investigate sample characteristics. Kaplan-Meier estimates of the survivor functions for various sample sub-groupings were calculated. Simple Cox regression models were used to evaluate univariate associations between patient characteristics and survival. Multivariable Cox regression was used to examine the association between survival and multiple patient characteristics simultaneously. Serum bilirubin was the only continuous covariate in the regression models. Age was modeled as a categorical variable, based on tertiles in the sample, to allow for a non-linear relationship between age and the log-hazard of death. Both Wald and likelihood ratio methods were used to test for the statistical significance of covariates in the final multiple proportional hazards model. Only predictors achieving statistical significance ($\alpha = .05$) were included in the final multivariable model.

Study Enrollees

The sample consists of 312 patients with primary biliary cirrhosis enrolled from 1974 to 1984 at the Mayo Clinic in Rochester, MN. The sample is majority female (276 patients, 88%) with only 36 male patients (12%). The average patient age at enrollment was 50 years, and the sample age range was from 26 to 78 years. The majority (75%) of the patients were in a later stage of the disease (Histologic Stage 3 or 4) at the time of enrollment. Average serum bilirubin level among participants at time of enrollment was 3.3 mg/dl. At the time of this analysis, 125 patients (40%) had died from causes related to primary biliary cirrhosis.

Results

Patients in the drug group had 6% greater hazard ("risk") of death than those in the placebo group, but this result was not statistically significant (95% CI, -25% - 50%, $p > .05$).

Serum bilirubin level, patients age, and histologic stage of disease all had statistically significant ($= .05$) positive univariate associations with the hazard of death. Females had 39% lower risk of

death than males (95% CI 2% - 62%, $p = .04$). In a multivariable analysis, serum bilirubin level, gender, and histologic stage of disease were found to have statistically significant associations with patient survival. The hazard ratio associated with a 1 mg/dl increase in serum bilirubin level was 1.16 (95% CI 1.13 – 1.19), indicating that a patient's risk of death increase by 16% for each 1 mg/dl increase in serum bilirubin after adjustment for gender, disease stage and age. The hazard ratio of death for females relative to males was 0.59 (95% CI 0.36 – 0.95), indicating that females had 41% reduction in the hazard of death than otherwise similar males. Those patients in the highest stage (stage 4) of disease had greater than 14 times the adjusted risk (95% CI 2.01 – 107.31) of dying when compared to patients in the earliest stage (stage 1).

Table 1 presents results from both the unadjusted and adjusted sets of analyses.

Conclusions

DPCA was not found to be statistically significantly associated with increased survival in either univariate or multivariable analyses. As this was a randomized trial with 312 patients, we conclude that DPCA does not appear to be efficacious in the treatment of patients with primary biliary cirrhosis. While primary biliary cirrhosis is a disease that primarily affects females, the prognosis is significantly worse for males. Similarly, the risk of death is much worse for patients in later stages of the disease relative to those in the earlier stages.

The results of this research suggest that improved screening techniques to identify the disease in affected patients early on, coupled with increased outreach to males at risk of developing PBC could result in a better overall prognosis for patients having this disease.

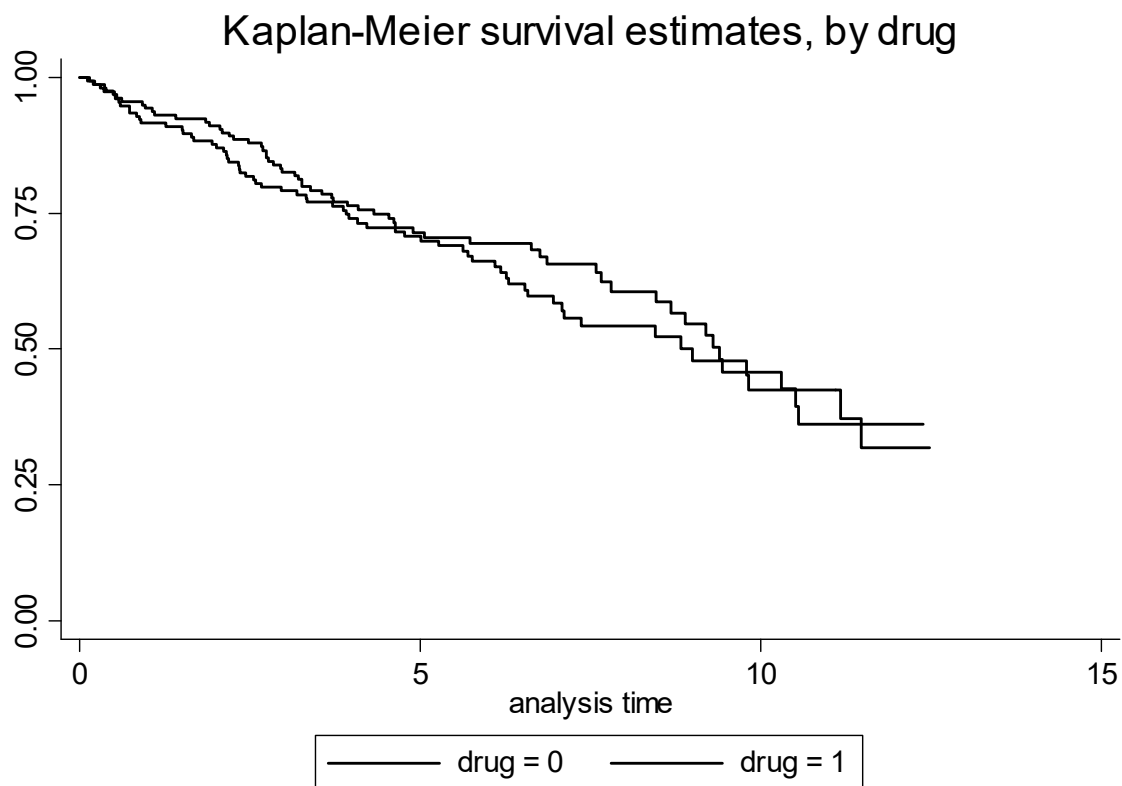


Table 1: Unadjusted and Adjusted Hazard Ratio Estimates of Death obtained from Proportional Hazards Regression

	Unadjusted Hazard Ratio Estimates		Adjusted Hazard Ratio Estimates	
Drug:				
Placebo	1.0		-	
DPCA	1.06	(0.75 – 1.50)	-	
Gender:				
Male	1.0		1.0	
Female	0.62	(0.39 – 0.98)	0.59	(0.36 – 0.95)
Serum Bilirubin (mg/dl)				
	1.16	(1.13 – 1.19)	1.16	(1.13 – 1.19)
Disease Stage				
Stage 1	1.0		1.0	
Stage 2	5.0	(0.67 – 37.63)	4.42	(0.59 – 33.62)
Stage 3	8.6	(1.18 – 62.40)	6.47	(0.88 – 47.67)
Stage 4	21.4	(2.96 – 154.44)	14.69	(2.01 –107.31)
Age Category				
< 45 yrs	1.0		1.0	
45-55 yrs	1.9	(1.17 – 3.00)	1.49	(0.92 – 2.42)
> 55 yrs	2.2	(1.40 – 3.56)		