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1. There were 418 subjects with primary biliary cirrhosis (PBC). Subjects were observed for a mean of 5.25 (median 4.74) years (range 1.46 to 13.13 years). Over that time, 161 patients were known to die. The table below shows the characteristics of the cohort as a whole, and those who were known to die during the study period. Data about race was unavailable for 106 subjects, for stage of disease in 106 subjects, and for treatment group in 108 patients. The patients were middle-aged and predominantly female, which is not surprising given that this is the demographic within PBC is most common. The majority of patients had more severe disease (stage 3 or 4) and were relatively equally distributed between treatment and placebo groups. Variables that appear to be associated with higher risk of death during the study period include older age, male gender, higher disease stage and higher serum bilirubin. The distribution of serum bilirubin is skewed to the right (as evidenced by the high mean: standard deviation ratio. The distribution of serum bilirubin is pictured below (Figure 1).

When considering the association between serum bilirubin and death, this relationship is potentially influenced by age, gender and stage of disease. Age and being male do not cause higher bilirubin but are both associated with higher risk of death, and can therefore be considered precision variables in this association. Higher stage of disease, on the other hand, does cause higher bilirubin and does increase risk for death, and should therefore be considered a possible confounder in the association between bilirubin and all-cause death.

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| **Table 1: Characteristics of all subjects and subjects who died during the study period** | | | |
|  |  | **All patients n=418** | **Died n=161** |
| **Age (years)** | Mean(SD) | 50.7 (10.4) | 53.9 (9.8) |
| **Female n=312** | N (%) | 276 (88.5%) | 103 (82.4%) |
| **Serum bilirubin (mg/dL)** | Mean (SD) | 3.22 (4.41) | 5.54 (5.84) |
| **Stage of disease n=312** | | | |
| **Stage 1** | N(%) | 16 (5.1%) | 1 (0.8%) |
| **Stage 2** | N(%) | 67 (21.5%) | 16 (12.8%) |
| **Stage 3** | N(%) | 120 (38.5%) | 43 (34.4%) |
| **Stage 4** | N(%) | 109 (34.9%) | 65 (52%) |
| **Treatment group n=310** | | | |
| **D-Penicillamine** | N(%) | 157 (50.7%) | 65 (52%) |
| **Placebo** | N(%) | 153 (49.4%) | 60 (48%) |

**Figure 1: Distribution of serum bilirubin**



1. Logistic regression is analogous to the Chi-square test, which is a test of proportions (or the mean of a binary variable). Given that this is right-censored data, a test of proportional survival or death is not appropriate because both the numerator and denominator are unknown due to right-censoring. If we wanted to use logistic regression we would have to limit our data to the time during which the first episode of censoring took place, which is at 533 days. This would require us to not use a large proportion of our data and thus lose precision in our attempt to describe the association between serum bilirubin and mortality. Finally, by shortening the analysis we might worsened the potential confounding by stage of disease.
2. Question 3
   1. Proportional hazards regression.
      1. Methods: Proportional hazards regression with robust standard errors was performed for the association between mean serum bilirubin and all-cause mortality. There was no missing data for either of these variables. A 95% confidence interval and 2-sided p-value were calculated for the difference in mean bilirubin between patients who died and those who survived.
      2. Results: For every increase of 1mg/dL in mean serum bilirubin, subjects had an average 15.2% higher instantaneous risk of death from any cause. With 95% confidence, we can say that this would not be unusual if the true population difference in risk of death were between 12.1% and 18.5% higher per 1 mg/dL increase in mean serum bilirubin. With a p-value of <0.0001, we can reject the null hypothesis that there is no difference in risk of instantaneous death in groups with different levels of serum bilirubin in favor of the alternative hypothesis that an increased bilirubin conveys an increased risk of death.
   2. See problem 6
3. Question 4
   1. Proportional hazards regression.
      1. Methods: Bilirubin was log (base 2) transformed to reflect its significance on a multiplicative scale in liver disease. The distribution of the log-transformed variable is shown in the histogram below (Figure 2). Proportional hazards regression with robust standard errors was performed for the association between mean log(2) bilirubin and all-cause mortality. There was no missing data for either of these variables. A 95% confidence interval and 2-sided p-value were calculated for the difference in mean log(2)bilirubin between patients who died and those who survived.

**Figure 2: Distribution of Log (base2) – transformed serum bilirubin.**



* + 1. Results: For every doubling of mean serum bilirubin, there was a relative increase in the instantaneous risk of death of 98.4%. This result would not be unusual if the true population risk of instantaneous death was 1.78-2.21 times higher with every doubling of mean serum bilirubin. With a P value of <0.0001 we can reject the null hypothesis that there is no difference in instantaneous risk of death across groups defined by different levels of serum bilirubin if favor of the alternative hypothesis that risk of death increases with increase in serum bilirubin.
  1. See problem 6.

1. Question 5
   1. Methods: Proportional hazards regression was performed for the association between mean serum bilirubin and risk of instantaneous death from any cause when log(2) bilirubin is held constant across groups defined by a 1 mg/dL change in serum bilirubin. A 95% confidence interval and 2-sided p-value were calculated for the difference in risk of instantaneous death for 1 mg/dL change in serum bilirubin.
   2. Results: When adjusting for mean log(2)bilirubin, there was a 3.9% relative decrease in instantaneous risk of death per every mg/dL increase in mean serum bilirubin. With 95% confidence, this would not be unusual if the true population increase in instantaneous risk of death were between 8.9% lower and 1.4% higher per mg/dL increase in mean serum bilirubin. With a p-value of 0.148 we cannot reject the null hypothesis and therefore, when adjusting for mean log(2) bilirubin, we cannot with confidence say that there is a difference in instantaneous risk of death in groups that differ by 1 mg/dL in mean serum bilirubin. In this model, we cannot estimate that there is a linear relationship between mean serum bilirubin and instantaneous risk of death.
2. Figure 3 below displays the fitted values for each model. All three models predict an increase in relative hazard of death with increasing bilirubin. The linear-fit model is the greatest departure from a straight line, and predicts that risk will increase exponentially with increasing bilirubin. The fit from the log(2) transformed bilirubin and the combined model are very similar at levels of bilirubin less than approximately 12, and then the log(2) transformed values continue on a linear path while the combined model begins to approach a horizontal asymptote around a relative risk of 18.

**Figure 3: Fitted hazard ratios from problems 2-5**



1. Association between all-cause mortality and serum bilirubin after adjusting for age and sex.
   1. As seen in Table 1, the mean age of people who died is 3.7 years higher than the group as a whole and the proportion of women who died is 6.1% lower than the group as a whole. As stated in question one, I cannot think of a physiologic reason why age or gender should be associated with a difference in mean bilirubin, but it is well-accepted that both older age and being male(at any age included in this cohort) are associated with higher risk of death. Therefore, age and sex are most likely precision variables rather than confounders.
   2. See above
   3. Full statistical inference
      1. Methods: I performed a multivariable proportional hazards regression for the association between log(2) transformed serum bilirubin and instantaneous risk of death and included sex and age as covariates. There was missing sex and age data for 106 patients and those patients were not included in the analysis. I calculated a 95% confidence interval and 2-sided p-value for the difference in instantaneous risk of death across groups defined by log(2) transformed bilirubin.
      2. Results: When adjusting for age and sex, for every doubling of serum bilirubin the risk of instantaneous death increases by 2.11 times. With 95% confidence, we can say that these results would not be unusual of the true population increase in risk of death were between 1.84 and 2.42 times higher for every doubling of bilirubin. With a p-value of <0.0001 we can be confident in rejecting the null hypothesis that there is no difference in risk of death across groups defined by serum bilirubin in favor of the alternative that a doubling of serum bilirubin increases your instantaneous risk of death.
2. The impact of including the intervention arm in our analysis depends on the interaction between the treatment and serum bilirubin, and the treatment and death. Because serum bilirubin was measured prior to instituting treatment, treatment group is not a confounder. I performed proportional hazards regression for the association between bilirubin and risk of death, controlling for treatment group, and found only a small difference in the hazard ratio (increase to 2.12), so it seems unlikely that it is a significant effect-modifier or precision variable.