BIOST 518
Homework 4

1. **Methods**: The descriptive statistics reported below divide the study population into two groups based on treatment, as well as for the total study population. Descriptive statistics are presented as a mean for continuous variables (age, albumin, alkaline phosphatase, bilirubin, cholesterol, observation time, platelet count, prothrombin time, serum SGOT, triglycerides and urine copper) and as percentages for binary variables (presence of ascites, presence of edema, presence of hepatomegaly, sex and survival status). For continuous observations, in addition to the mean, the standard deviation, minimum and maximum are reported. Of the 310 patients with available data, many were missing several variables. Specifically, 28 were missing cholesterol levels, 4 were missing platelet levels, 30 were missing triglyceride data, and 2 were missing urine copper data. The numbers reported do not include any individuals that were missing data.

**Results**: In this sample study, there appear to be more women than men, regardless of which treatment group they belonged in. In the placebo group, the average participant age was 48.52 years and they were observed for 2003.42 days on average. 39.22% of the placebo group had known event times. In regards to their diagnostic test results, the average levels were as follows: albumin, 3.53 g/dL; alkaline phosphatase, 1948 U/L; bilirubin, 3.7 mg/dL; cholesterol, 374.7 mg/dL; platelet count, 265.43 x 103 cells/mm3; PT, 10.8 s; serum SGOT, 125 U/L; triglycerides, 125.6 mg/dL; urine copper, 98 µg/day. 6.5 % had ascites, 10.5 % experienced edema, and 56.9 % had hepatomegaly. In the treatment group, the average participant age was 51.35 years and they were observed for 2022.5 days on average. 41.4 % had known event times and the average levels of their diagnostic tests were as follows: albumin, 3.52 g/dL; alkaline phosphatase, 2023 U/L; bilirubin, 2.88 mg/dL; cholesterol, 364.5 mg/dL; platelet count, 258.9 x 103 cells/mm3; PT, 10.7 s; serum SGOT, 119.9 U/L; triglycerides, 124.3 mg/dL; urine copper, 98 µg/day. 8.9 % of participants had ascites, 13.4 % experienced edema and 46.5% had enlarged livers.

Based off the descriptive statistics, there do not appear to be many differences between treatment groups. When there are differences between the means of diagnostic tests, the standard deviations are so wide that the effects of the treatment do not appear to manifest as differences in the different diagnostic tests that were used. Additionally, the wide margins of observation times further confound any effects that may be observed. For example, mean bilirubin levels between treatment groups is suggestive of an association, however when you look at the standard deviation between placebo and D-penicillin groups (5.3 and 3.6 mg/dL, respectively), the observed difference appears to be spurious.

 **Table 1: Descriptive statistics by treatment status.**

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|  | **Treatment Status** |
|  | **Placebo****N=153** | **D-Penicillamine****N=157** | **Total****N=310** |
| **Age (years)** | 48.52 (9.96;30.57-74.52) | 51.35(11.01; 26.28-78.44) | 49.95(10.58; 26.28-78.44) |
| **Females (%)** | 90% | 86.62% | 88.39% |
| **Observation Time (days)** | 2003.42(1156.85; 51-4523) | 2022.48(1094.21; 41-4556) | 2013.07(1123.78; 41-4556) |
| **Survived** | 39.22% | 41.4% | 40.3% |
| **Albumin (g/dL)** | 3.5289(0.3921; 1.96-4.38) | 3.517(0.445; 2.1-4.64) | 3.5230(0.4188;1.96-4.64) |
| **Alkaline phosphatase (U/L)** | 1948.09(2107.64; 289-13862.4) | 2023.26(2190.28; 369-11552) | 1986.16(2146.74; 289-13862.4) |
| **Bilirubin (mg/dL)** | 3.6699(5.2927; 0.3-28) | 2.8809(3.6392; 0.3-20) | 3.27(4.54; 0.3-28) |
| **Cholesterol (mg/dL)** | 374.68(253.19; 120-1775) | 364.52(210.22; 127-1712) | 369.67(232.65; 120-1775) |
| **Platelet count (103 cells/mm3)** | 265.43(90.99; 71-487) | 258.91(100.63; 62-563) | 262.13(95.89; 62-563) |
| **Prothrombin time (PT in s)** | 10.8(1.14; 9.2-17.1) | 10.66(0.8533; 9-14.1) | 10.73(1.01; 9-17.1) |
| **Serum SGOT (U/L)** | 125.32(58.95; 28.38-457.25) | 119.89(54.54; 26.35-338) | 122.57(56.74; 26.35-457.25) |
| **Triglycerides (mg/dL)** | 125.56(58.61; 44-432) | 124.31(71.77; 33-598) | 124.94(65.31; 33-598) |
| **Urine Cu (µg/day)** | 98.03(80.62; 4-558) | 98.02(9.76; 9-588) | 98.02(85.76; 4-588) |
| **Ascites (%)** | 6.536% | 8.917% | 7.742% |
| **Edema (%)** | 10.46% | 13.38% | 11.93% |
| **Hepatomegaly (%)** | 56.86% | 46.50% | 51.61% |

**Continuous variable are presented as mean (standard deviation; min-max)**

1. Using logistic regression with this particular data set would not be advisable as there is a wide range of observation times. In past assignments, the time was limited to before and after a specific time, i.e. a continuous variable was transformed into a dichotomous variable (e.g. survivability before or after 4 years). Since logistic regression assesses risk, the outcome would need to be dichotomized in order to be meaningful. As our outcome is survivability in this case and we do not have any meaningful method for dichotomizing the survival data, logistic regression does not make sense with this analysis.
2. **Methods**: The st data was set such that observation time was set as the observation time and status was set as the event id. Estimated hazard ratios were calculated using simple proportional hazards regression analysis to assess the association between bilirubin and all-cause mortality by comparing the instantaneous risk (hazard) of death over the entire period of observation across groups defined by bilirubin modeled as a continuous variable. The confidence intervals calculated reported was from a robust analysis of the sample, and a two-sided P-value is reported.

	1. **Inference**: From proportional hazards regression analysis, it is estimated that the risk of death is 15.24% higher for each 1 mg/dL increase in bilirubin levels. From the calculated confidence intervals, this estimate would not be judged to be unusual if the true increase in risk of death for each 1 mg/dL increase in bilirubin was between 12.09% and 18.47%. This observation is significant at a statistical level of 0.05 (P<0.0001).
	2. The hazard ratios relative to a group having serum bilirubin of 1 mg/dL were computed and used in problem 6 (fithrA).
3. **Methods**: A variable describing the log transformed (base 2) bilirubin variables were created. Estimated hazard ratios were calculated using simple proportional hazards regression analysis to assess the association between bilirubin and all-cause mortality by comparing the instantaneous risk (hazard) of death over the entire period of observation across groups defined by bilirubin modeled as a log transformed variable. The confidence intervals calculated reported was from a robust analysis of the sample, and a two-sided P-value is reported.

	1. This analysis might be preferred because bilirubin may have multiplicative effects on the instantaneous risk of survival.
	2. **Inference**: From proportional hazards regression analysis, it is estimated that the risk of death increases 98.45% for each two-fold increase of serum bilirubin concentrations. From calculated confidence intervals, this observation would not be deemed unusual if the true increase risk of death for each two-fold increase of serum bilirubin was between 78.06% and 121.17%. This observation is statistically significant at a significance level of 0.05 (P<0.0001).
	3. The hazard ratio relative to a group having serum bilirubin levels of 1 mg/dL was computed and used in problem 6 (fithrB). For this analysis, the log transformed bilirubin levels utilized base e, rather than base 2 as was described above.
4. **Methods**: Estimated hazard ratios were calculated using simple proportional hazards regression analysis to probe the association between bilirubin and all-cause mortality by comparing the instantaneous risk of death over the entire observation time across groups defined by bilirubin modeled as both an untransformed variable as well as a log transformed variable. Linearity was then assessed for the model containing bilirubin as both an untransformed and a log-transformed variable.

	1. **Inference**: The hazard ratios obtained from simple proportional hazards regression analysis including bilirubin as both an untransformed and log-transformed variable was tested for linearity. The results indicate that the association between bilirubin and the log hazard ratio is linear. The predictor of interest in this case is adequately modeled by an untransformed continuous variable. This observation was significant at a level of 0.05 (P<0.0001).
	2. The hazard ratios using both untransformed and log-transformed bilirubin relative to a group having bilirubin levels of 1 mg/dL were computed for use in problem 6 (fithrC and fithrD).
5. 
In the plot above, the predictive hazard ratios compared to groups with serum bilirubin levels of 1 mg/dL are displayed. The blue curve (fithrA) appears to be the only curved plot, which indicates that serum bilirubin as a predictor of interest is multiplicative. In order to better predict hazard ratios, then the log transformed values of bilirubin should be used in constructing the predictive model. It is interesting that when both untransformed and log-transformed bilirubin values are combined in a single model, the hazard does not appear different if using the HR obtained for the untransformed bilirubin levels (fithrC), however, when using the HR obtained for the log-transformed values (fithrD), it is much more drastic of an effect in the combined model than in the solo model (fithrB, i.e. modeling log-transformed bilirubin and all-cause mortality without untransformed bilirubin).
6. **Methods**: The association between all-cause mortality and serum bilirubin adjusted for age and sex was estimated using simple proportional hazards regression analysis. The confidence intervals calculated reported was from a robust analysis of the sample, and a two-sided P-value is reported.

	1. Based on the data, sex may have confounded the association between death and bilirubin. According to the data file, the disease in question (and therefore risk of death from the disease) is more prevalent in women. Indeed, the data support that as more women than men were enrolled in the study. Additionally, when looking at bilirubin levels, the women in this study had higher mean bilirubin levels than the men. Lastly, as sex is not in the causal pathway of interest, it is likely that sex is a confounder within this data set, at least in so far as an association between bilirubin levels and all-cause mortality is concerned.
	2. A cursory glance of the data suggests that there is no association between serum bilirubin and age. There is, however, an obvious link between age and risk of death in that those who are older are likely to be at higher risk of dying than those who are younger. This could be confounded by many things, however, as age brings about some other factors that need to be considered when looking at associations between age and risk of death. Given an association with the outcome but not the predictor, age appears to be a precision variable in this data set.
	3. **Inference**: When comparing two groups that differ by 1 mg/dL of serum bilirubin levels but have the same age and are of the same sex, it is estimated that there is 16.15% higher risk of all-cause mortality among those with the higher serum bilirubin levels. This estimate would not be judged to be unusual if the increase in risk of all-cause mortality were truly between 12.50% and 19.92% for groups that have 1 mg/dL higher serum bilirubin. This observation is statistically significant at a level of 0.05 (P<0.0001).
7. Given that the drug is reported to prolong the life expectancy by aiding in Cu excretion and auto-immune suppression, it is not likely to affect bilirubin levels. The drug, based on the explanation provided in the data file, does not reverse any damage already done which means that bilirubin levels would stay elevated since liver repair is not an effect of the drug. Additionally, based on the descriptive statistics presented above, mean observation times were similar for both treatment groups. This implies that the intervention is not associated with either the POI or the response and therefore is an irrelevant variable – the effect of which is a loss of precision when we perform the proportional hazards regression analysis.