Biostats HW 4

1.)

**Methods:** I categorized serum bilirubin into <2.5 mg/dL, 2.5-5 mg/dL, and >5 mg/dL. Kaplan-Meier survival estimates were calculated for all 418 subjects in the study and plotted for each group categorized by bilirubin values. Then number of subjects, number of deaths, 1000 day survival probability, 3000 days survival probability, 25th percentile of survival, and 45th percentile of survival were calculated from Kaplan-Meier estimates and summarized in the following table. All subjects are included, as no subjects are missing bilirubin values.

**Results:** In the 418 subjects overall, there were 161 deaths observed. There were 257 total censored observations, with the earliest censoring time 533 days and the latest 4795 days. As can be seen in the following graph and table of Kaplan-Meier estimates, the probability of survival is lower at all times for those with higher bilirubin values.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Serum Bilirubin at Study Enrollment | | | All Subjects |
|  | < 2.5 mg/dL | 2.5-5 mg/dL | > 5 mg/dL |
| N Subjects | 278 | 65 | 75 | 418 |
| N Deaths | 65 | 41 | 55 | 161 |
| 1000 day survival probability | 93.5% | 65.6% | 51.0% | 81.7% |
| 3000 day survival probability | 73.5% | 31.3% | 12.1% | 56.9% |
| 25th percentile of survival | 2796 days | 786 days | 466 days | 1462 days |
| 45th percentile of survival | 4079 days | 1518 days | 971 days | 3170 days |



2.) A logistic regression analysis is not advisable with this data because it is censored data. If there is informative censoring, subjects that are censored may have characteristics that confound the observed measure of association between serum bilirubin and death. For example, if sicker subjects are censored more often, than an analysis of only non-censored subjects will attenuate the association between higher serum bilirubin and risk of death. Similarly, subjects that are censored may have characteristics that are precision variables for the association between serum bilirubin and death.

3.)

**Methods:** The hazard ratio and 95% CI were computed using Cox proportional hazard regression, with predictor variable serum bilirubin and response variable instantaneous risk of death over the entire period of observation. Wald based statistics were used to calculate the confidence interval. The Huber-White sandwich estimator was used to estimate the standard errors.

a.) **Results:** From proportional hazards regression on 418 subjects, I estimate that for each 1 mg/dl increase in serum bilirubin, the risk of death is 1.15 times higher in the group with the higher serum bilirubin. A 95% confidence interval suggests that our data would not be surprising if the true risk of death for groups differing in bilirubin by 1 mg/dL is between 1.12 and 1.18 times higher in the group with the higher bilirubin value. A two sided p value of <0.001 allows us to reject the null hypothesis of no difference in risk of death between groups with differing bilirubin values, in favor of the alternative hypothesis that the risk is higher in groups with higher bilirubin values.

b.) See graph in problem #6

4.)

**Methods:** The hazard ratio and 95% CI were computed using Cox proportional hazard regression, with predictor variable log base 2 of (serum bilirubin) and response variable instantaneous risk of death over the entire period of observation. Wald based statistics were used to calculate the confidence interval. The Huber-White sandwich estimator was used to estimate the standard errors. Subjects missing data for serum bilirubin were excluded from the analysis.

a.) This analysis might be preferred a priori because you might expect the association between serum bilirubin and risk of death to be on the multiplicative scale rather than the additive scale.

b.) **Results:** From proportional hazards regression on 418 subjects, I estimate that for each doubling in serum bilirubin, the risk of death is 1.98 times higher in the group with the higher serum bilirubin. A 95% confidence interval suggests that our data would not be surprising if the true risk of death for a group with twice the serum bilirubin level as another group is between 1.78 and 2.21 times higher in the group with the higher bilirubin value. A two sided p value of <0.001 allows us to reject the null hypothesis of no difference in risk of death between groups with differing bilirubin values, in favor of the null hypothesis that the risk is higher in groups with higher bilirubin values.

c.) See graph in problem #6

5.)

a.)

**Methods:** The log hazard ratio and 95% CI were computed using Cox proportional hazard regression, with predictor variables serum bilirubin and log base 2 of (serum bilirubin) and response variable instantaneous risk of death over the entire period of observation. Wald based statistics were used to calculate the confidence interval. The Huber-White sandwich estimator was used to estimate the standard errors.

**Results:** From proportional hazards regression on 418 subjects, I estimate that the for every 1 mg/dL increase in serum bilirubin, the log hazard ratio of death decreased by 0.0394. A 95% confidence interval suggests that our data would not be surprising if the true change in log hazard ratio for each 1 mg/dL increase in serum bilirubin is between -0.0927 and 0.0140. A 2 sided p value of 0.148 does not allow us to reject the null hypothesis that there is no difference in log hazard ratios between groups with differing bilirubin values. Put another way, there is not statistical evidence of a linear association between log hazard ratio of death and serum bilirubin.

I also estimate that for every doubling of serum bilirubin, the log hazard ratio of death increases by 0.820. A 95% confidence interval suggests that our data would not be surprising if the true increase in log hazard ratio of death for every doubling of serum bilirubin value is between 0.603 and 1.037. A 2 sided p value of <0001 allows us to reject the null hypothesis of no difference in log hazard ratio of death between groups that differ in serum bilirubin by a factor of 2, in favor of the alternative hypothesis that the log hazard ratio of death is higher in groups with double the serum bilirubin value. As the beta coefficient for log2(bilirubin) is not 0, this provided further evidence against a linear relationship between serum bilirubin and log hazard ratio.

b.) See graph in problem #6 below

6.)



The above graph plots each model’s fitted Hazard Ratios (compared to the hazard when serum bilirubin is 1 mg/dL). As shown in the graph, all models predict an increase in HR with increasing bilirubin, but the actual HR estimated for each model is different, especially in the midrange of serum bilirubin values (and at the higher range when comparing fitted values from problem 4 and 5). For the fitted values from problems 3 and 4 (each of which includes a log transformed bilirubin predictor), the relationship between serum bilirubin and HR is fairly linear, whereas for the fitted values from problem 3 (which only includes the untransformed predictor serum bilirubin), there is a curvilinear increase in HR with increasing serum bilirubin.

7.)

a and b together.)

There is no evidence in our data set that age is associated with the predictor (serum bilirubin). For example, from linear regression on the 418 subjects, for each 1 year increase in age the serum bilirubin increases by 0.0009965 mg/dL. A 95% confidence interval suggests that this data would not be surprising if the true change in bilirubin per 1 year increase in age is between -0.0313 and 0.333. A p value of 0.95 does not allow us to reject the null hypothesis of no linear association between age and serum bilirubin.

In the general population, increasing age is generally associated with increased risk of death. This is true in our data set as well, as shown in the following Kaplan Meier curve of survival probabilities for those with age with age < 50 and those with age 50 or above.



As age is not associated with the predictor of interest (bilirubin) but is associated with the outcome (death), it is a precision variable.

Similarly, there is no evidence in our data set that sex is associated with the predictor (serum bilirubin). From linear regression on the 418 subjects with values for serum bilirubin, for females compared to males the average increase in serum bilirubin is 0.434 mg/dL. A 95% confidence interval suggests that this data would not be surprising if the true average difference in serum bilirubin between females and males is between -0.484 and 1.352. A p value of 0.35 does not allow us to reject the null hypothesis of no difference in average bilirubin between the sexes.

In the general population, male sex is generally associated with increased risk of death. This is true in our data set as well, as shown in the following Kaplan Meier curve of survival probabilities by sex.



As sex is not associated with the predictor of interest (serum bilirubin), but is associated with the outcome (death), it is a precision variable.

c.)

**Methods:** The hazard ratio and 95% CI were computed using Cox proportional hazard regression, with predictor variable log2 (serum bilirubin) and response variable instantaneous risk of death over the entire period of observation. Precision variables sex and age were also included as covariates in the cox regression model. Wald based statistics were used to calculate the confidence interval. The Huber-White sandwich estimator was used to estimate the standard errors.

**Results:** From proportional hazards regression on 418 subjects, I estimate that for each doubling in serum bilirubin, the risk of death adjusted for age and sex is 2.10 times higher in the group with the higher serum bilirubin. A 95% confidence interval suggests that our data would not be surprising if the true adjusted risk of death for a group with twice the serum bilirubin level as another group is between 1.84 and 2.42 times higher in the group with the higher bilirubin value. A two sided p value of <0.001 allows us to reject the null hypothesis of no difference in risk of death between groups with differing bilirubin values, in favor of the null hypothesis that the risk is higher in groups with higher bilirubin values.

8.) Ignoring treatment group should not confound our results. Since subjects were randomized, the distribution of serum bilirubin is expected to be the same in groups that received treatment and those that did not. If treatment group was associated with the outcome (death), then treatment group may be a precision variable (in which case our hazard ratio adjusted for treatment group should move farther from the null). I am not able to reliably tell if treatment group was associated with the outcome in our sample, because 108 of the 418 subjects are missing information about treatment group.