**ID: 4934
Homework 04
BIOST 515/518**

Question 1

**Methods:** Descriptive statistics were computed using the distribution of censoring as well as the serum bilirubin levels. Censoring statistics included the minimum and maximum censoring times and the Kaplan-Meier-derived estimate of mean-follow-up time. Bilirubin statistics included minimum, maximum, percentiles, as well as the mean and standard deviation. For an initial description of survival, we categorized serum bilirubin into categories representing a roughly two fold difference between categories, that is, 0-2 mg/dl, 2-4 mg/dl, 4-8mg/dl, 8-16mg/dl, and 16-28 mg/dl. Within categories, we estimated survival at 2, 5, and 10 years using Kaplan-Meier methods as well as the 10th percentile of the observations. We also calculated the restricted mean survival given that all strata of bilirubin had participants remaining at risk around 6.00 years. Mean age and proportion female sex were included as they will be considered as potential confounders, effect modifiers, and precision variables.

**Descriptives:** The sample was comprised of 418 individuals evaluated over a mean of 8.35 years (median 9.30, range 3.87-13.13). A total of 161 deaths were observed over this period. All participants provided valid measures of serum bilirubin. Mean bilirubin was 3.22 mg/dl (SD 4.41, range 0.3-28, median 1.4).

As shown in the table below, groups with higher serum bilirubin showed decline in survival relative to groups with lower serum bilirubin. The two-year survival for the group with greater than 16 mg/dL bilirubin was less than 63%. The subgroup with the highest probability of two-year survival was the group with the lowest serum bilirubin (0-2 mg/dL). The average survival over the first six years of the study was 4.9 years overall. Among the serum bilirubin groups, six-year mean survival ranged from 2.19 to 5.65 years, with the group with the highest bilirubin having worst average survival (2.83 years).

A Kaplan-Meier plot of survival is shown in the figure below. Here we observe that the distribution of survival varies greatly with serum bilirubin level. In particular, groups with higher serum bilirubin having a more rapid decline in survival, while lower bilirubin groups show more modest decline.

|  |  |  |
| --- | --- | --- |
|  | All Participants | Serum bilirubin (mg/dL) |
|  | 0-1.99 | 2-3.99 | 4-7.99 | 8-15.99 | 16+ |
| N | 418 | 249 | 78 | 48 | 27 | 16 |
| Age (yrs)\* | 50.74 (10.45, 26-78)  | 50.92 (10.22, 26-77) | 50.16 (11.35, 30-72) | 50.91 (11.64,31-78) | 50.75 (10.14, 33-71) | 50.23 (6.37, 42-66) |
| % Female \*\* | 88.5% | 91.2% | 82.5% | 78.9% | 94.1% | 100% |
| *Survival* |
| Deaths | 161 | 50 | 44 | 32 | 20 | 15 |
| 2-year survival probability | 0.880 | 0.960 | 0.846 | 0.770 | 0.593 | 0.625 |
| 5-year survival probability | 0.703 | 0.905 | 0.525 | 0.330 | 0.309 | 0.0625 |
| 10-year survival probability | 0.442 | 0.670 | 0.0952 | 0.122 | -- | -- |
| 10th percentile survival (yrs) | 1.67 | 5.06 | 1.51 | 0.89 | 0.19 | 0.21 |
| Restricted mean survival, 6.00 years (yrs) | 4.90 | 5.65 | 4.45 | 3.70 | 2.83 | 2.19 |

\* Mean age (SD, min-max).
\*\* Sex was missing for 68 individuals in bilirubin 0-1.99 mg/dL group, 15 in bilirubin 2-3.99 mg/dL group, 10 in bilirubin 4-7.99 mg/dL group,10 in 8-15.99 mg/dL group, and 3 in bilirubin 16+ mg/dL group.
-- indicates sample size too small to estimate
Notes: Ten-year survival estimates were not available in the two highest bilirubin groups, as censoring occurred prior to this time in both groups. Restricted mean survival is an average of the years lived during the first 6.00 years after enrollment. This was estimated as the area under the Kaplan-Meier survival curve.



Question 2

To evaluate mortality in the previous CHS datasets we restricted to a time period over which we had full data on vital status. We were able to use logistic regression in those analyses where the vital status (0=alive, 1=death) was the main outcome and the predictors were other covariates. This would not advisable in the case of our dataset here. When we look at the first instance of censoring across all data we see that the minimum time of follow-up among the censored observations is 0.112 years. This is a fairly short period of time to evaluate survival over, so we would choose instead to use the full censoring dataset in proportional hazards regression. In this case, we would be evaluating the time to death as the main outcome and serum bilirubin as the continuous predictor of interest.

Question 3

**Methods:** We used proportional hazards model to evaluate the distribution of time to death across groups defined by a predictor, serum bilirubin. Serum bilirubin (mg/dL) was modeled as a continuous non-transformed variable. Death from any cause was a binary variable. A hazard ratio for the association between mortality and serum bilirubin was generated from the regression. P-values and confidence intervals were provided using the Wald statistic.

**Results:** A total of 418 participants with available serum bilirubin levels were included in proportional hazards regression for time to all-cause death. There were 161 deaths over a mean follow-up of 8.35 years. From proportional hazards regression, the estimated instantaneous risk of death is elevated by a relative 15.2% for each 1 mg/dL increase in serum bilirubin. With 95% confidence, the observed estimate is consistent with a relative increase between 12.1% and 18.4%. With two-sided p-value of p<0.001, we reject the null hypothesis that the risk of death is not associated with serum bilirubin level. All-cause mortality was increased with increased serum bilirubin.

Question 4

**Methods:** We used proportional hazards model to evaluate the distribution of time to death across groups defined by a predictor, serum bilirubin. Serum bilirubin (mg/dL) was modeled as a continuous base-2 logarithmically transformed variable. Death from any cause was a binary variable. A hazard ratio for the association between mortality and serum bilirubin was generated from the regression. P-values and confidence intervals were provided using the Wald statistic.

**Results:** A total of 418 participants with available serum bilirubin levels were included in proportional hazards regression for time to all-cause death. There were 161 deaths over a mean follow-up of 8.35 years. From proportional hazards regression, the estimated instantaneous risk of death is increased by a relative 98% for each doubling in serum bilirubin. With 95% confidence, the observed estimate is consistent with a relative increase between 78.1% and 121%. With two-sided p-value of p<0.001, we reject the null hypothesis that the risk of death is not associated with serum bilirubin level. All-cause mortality was increased with increased serum bilirubin.

Question 5

**Methods:** We used proportional hazards model to evaluate the distribution of time to death across groups defined by a predictor, serum bilirubin. Serum bilirubin (mg/dL) included in the model as both untransformed bilirubin and continuous base-2 logarithmically transformed bilirubin. Death from any cause was a binary variable. A log hazard ratio for the association between mortality and serum bilirubin was generated from the regression. We tested whether the coefficients of the regression were both equal to zero. P-values and confidence intervals were provided using the Wald statistic. Also, we evaluated linearity of the association between all-cause mortality and bilirubin using the Wald test where we tested whether the coefficient of the log bilirubin was zero.

**Results:** A total of 418 participants with available serum bilirubin levels were included in proportional hazards regression for time to all-cause death. There were 161 deaths over a mean follow-up of 8.35 years. From proportional hazards regression modeling both untransformed and transformed bilirubin, there was significant association between instantaneous hazard of death and bilirubin based on two-sided p=0.0001. A linearity test on the log-bilirubin term in the model suggests that association between all-cause mortality and serum bilirubin is not well-characterized by the log hazard function that is linear in bilirubin (p=0.001).

Question 6



A plot of the fitted values for relative hazards from the previous three proportional hazards models is shown above. All three fitted models show a positive upward trend, ie, that higher values of bilirubin are associated with greater relative hazards. The linear fit (shown in blue) is most different from the other two with a u-shape and greatest differences from the others over the range of bilirubin from approximately 7-20 mg/dL. The log fit (green) and log-linear fit (red) show great similarity until approximately bilirubin 17 mg/dL, in which case the log-linear fit levels off and log fit continues on.

Question 7

*Part A*As shown in the descriptive statistics table, there do not appear to be large differences in age across groups determined by serum bilirubin (mean age approximately 50), which suggests that age is not related to serum bilirubin. Thus, we do not consider age to be a confounder in the relationship between bilirubin and all-cause mortality.

As shown in the descriptive statistics table, there are some differences in proportion of females across groups determined by serum bilirubin. However, it is important to note that the numbers of individuals in the groups with higher bilirubin are very small (<20) so small shifts in counts reflect larger changes in proportion females. Thus, we do not consider female sex to be a confounder in the relationship between bilirubin and all-cause mortality.

*Part B*

As we presume that age and sex are not confounders, we can evaluate whether age and sex might be precision variables. We can judge this by looking at the HRs and 95%CIs of the analysis stratified by age and gender. Age was cut into three groups. The bulk of the data lie in the 40-60 age group, and the estimated HR is higher than the crude estimate. As a rule, omission of precision variables in PH regression attenuates the association toward the null. Thus, because we saw an increased effect in the subgroup, we might anticipate de-attentuation when we adjust for age. In the case of age, we see that the bulk of the data are for females, where we see that the HR is again higher than the crude estimate. Thus, adjusting for female sex will de-attentuate our association (i.e. move it further away from the null).

|  |  |  |
| --- | --- | --- |
| Group | HR | SE |
| Crude | 1.98  | 0.110 |
| 28-40 (n=69) | 2.14 | 0.560 |
| 40-60 (n=261) | 2.16 | 0.157 |
| 60+ (n=88)  | 1.70  | 0.201 |
| Females (n=276) | 2.20 | 0.149 |
| Males (n=36) | 1.39 | 0.244 |

*Part C*

**Methods:** We used proportional hazards model adjusted for age and sex to evaluate the distribution of time to death across groups defined by a predictor, serum bilirubin. Serum bilirubin (mg/dL) was modeled as a continuous base-2 logarithmically transformed variable. Death from any cause was a binary variable. A hazard ratio for the association between mortality and serum bilirubin was generated from the regression. P-values and confidence intervals were provided using the Wald statistic.

**Results:** A total of 418 participants with available serum bilirubin levels were included in proportional hazards regression for time to all-cause death. There were 161 deaths over a mean follow-up of 8.35 years. From proportional hazards regression, the estimated instantaneous risk of death is increased by a relative 2.1-fold for each doubling in serum bilirubin. With 95% confidence, the observed estimate is consistent with a relative increase between 1.8- and 2.4-fold. With two-sided p-value of p<0.001, we reject the null hypothesis that the risk of death is not associated with serum bilirubin level. All-cause mortality was increased with increased serum bilirubin.

Question 8

Intervention could serve as an effect modifier or precision variable because in being randomized it is not associated with our predictor of interest bilirubin. The intervention may have some potential effect on all-cause mortality. Thus, for effect modification, we would expect that a stratified analysis on treatment might show differences in the estimate of the association between bilirubin and all-cause mortality. For precision, in an adjusted analysis we would expect the estimates would be quite similar but possibly the SE would be smaller and the 95% CI would be narrower. In the cases observed below, we see a tiny difference between placebo and treatment in stratified analysis, where the crude estimate is a weighted average of the stratum-specific. Thus, the adjusted model may be more precise, but is quite similar to the crude in the estimate.

|  |  |  |
| --- | --- | --- |
| Group | HR (age-sex adjusted) | SE |
| Crude | 2.11 | .147 |
| Treatment=placebo | 2.15 | 0.181 |
| Treatment=drug  | 2.03 | 0.208 |
| Adjusted for treatment  | 2.10 | 0.145 |