HOMEWORK #7
(Due Thursday, March 6 in class)

Reading:
Reread H&L: §7.3
Articles: Crowley and Hu JASA 1977 article on TDCs

Homework:

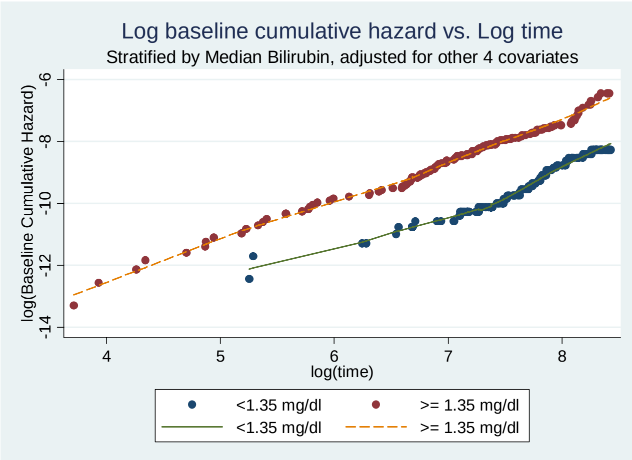
1. Use the data on the 312 randomized subjects (available from class website) to examine the influence of individual subjects and examine proportionality and influence in the "Mayo model" described in Dickson et al. (1989).
    a. Fit a series of models that extend the Mayo model by partitioning the time scale into three intervals with lower endpoints at 0, 800 and 1600 days. For each of the five terms in the original Mayo model (separately), fit a model with the interaction between that variable and time interval (as a factor, i.e. 2 additional model terms). What do you conclude about the constancy of relative risk over time? (Hint: use the STSPLIT command.)

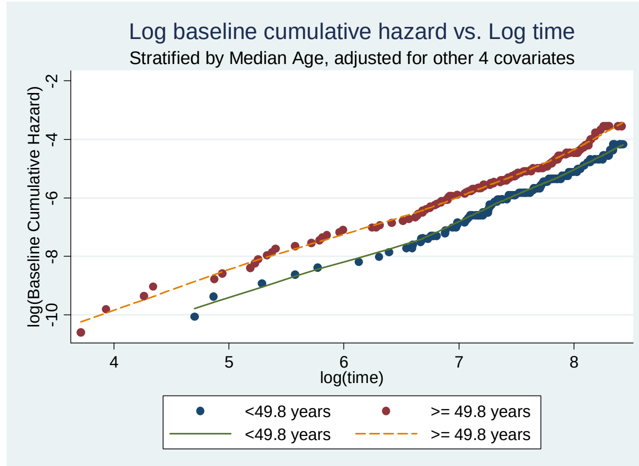
Table 1a: Associations of five variables from the Mayo model with survival, accounting for potential effect modification by follow-up time.

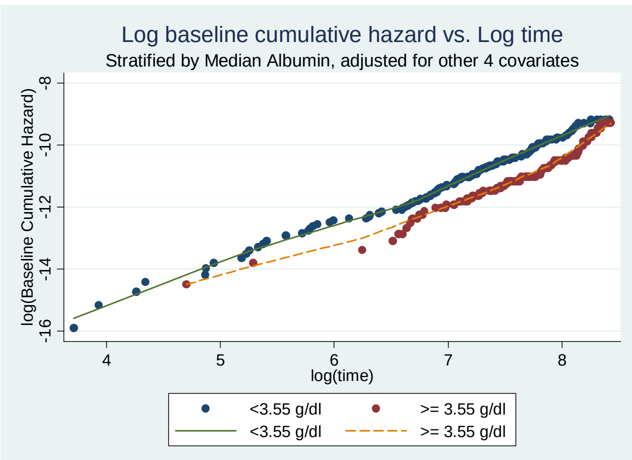
Independent Variable	**Coefficient for the independent variable (95% CI)**	**Coefficient for interaction term with time (95% CI)**		**Partial LRtest for both interaction coefficients = 0 (P – value)**
		800 – 1599 days vs < 800 days	**1600+ days vs < 800 days**	
Log-bilirubin (mg/dl)	0.716 (0.422, 1.011)	0.458 (0.023, 0.894)	0.129 (-0.337, 0.595)	0.1103
Log-albumin (g/dl)	-3.110 (-5.197, -1.024)	0.160 (-2.836, 3.155)	-0.200 (-3.724, 3.323)	0.9814
Log-prothrombin time (sec)	6.832 (3.742, 9.923)	-3.934 (-8.664, 0.797)	-6.983 (-11.645, -2.320)	0.0114
Age (yrs)	0.046 (0.023, 0.076)	-0.017 (-0.058, 0.024)	-0.021 (-0.063, 0.021)	0.5812
Edema (Yes vs No)	1.173 (0.506, 1.839)	-0.887 (-1.970, -0.196)	-1.814 (-3.155, -0.473)	0.0089

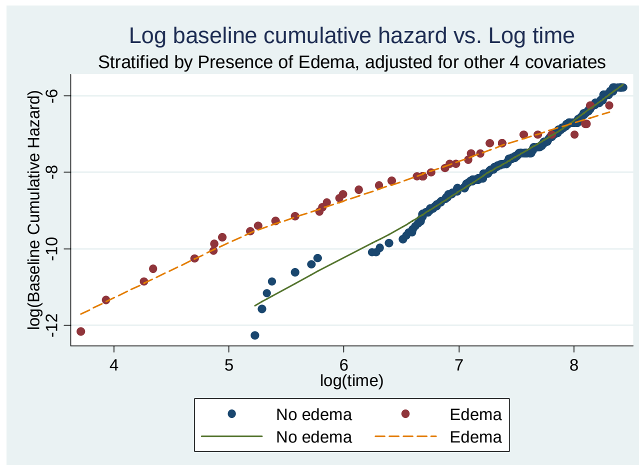
Variables for log-bilirubin, log-albumin, and age appear to have constant relative risks from 0-799 days, 800-1599 days and 1600+ days. Given the partitioned parameterization for time-dependence there is evidence of significant interaction between time and both prothrombin time (log-scale) and the presence of edema. These results suggest that the relative risks for these two covariates do not remain constant with varying time.

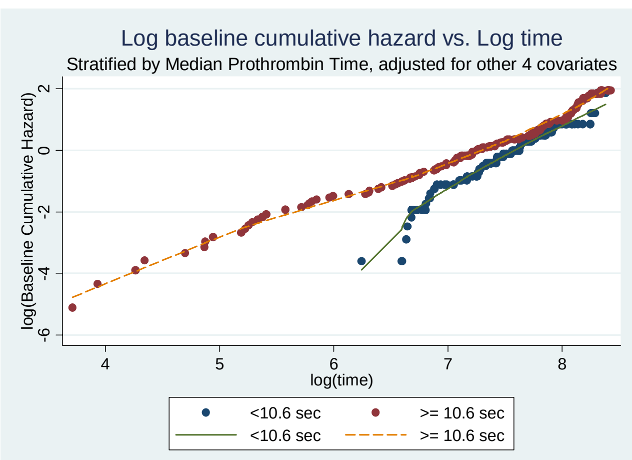
    b. By dichotomizing at the median for continuous covariates, plot log cumulative baseline hazard functions for the two levels of each (dichotomized) covariate from the Mayo model on the same plot, after covariate adjustment for the other variables in the Mayo model. Are the curves parallel?











Are each of the curves parallel?
The curves for bilirubin and age appear to be parallel for the sections of log-time where data is not sparse. The curves for albumin, prothrombin time, and edema demonstrate a tendency to converge at the upper end of the range of log-time values. These results are the same as those seen for Question 1 of Homework 6.

c. Compare the evidence for non-proportionality of hazards examined under a) and b). Are conclusions about the proportionality of the hazards for each variable the same according to the two methods? What do you conclude from this exercise about the adequacy of the Mayo model?

In 1a. we see evidence of non-proportionality for prothrombin time and presence of edema, and these conclusions are qualitatively supported by the plots for these variables in 1b, even after adjustment for the other 4 covariates in the Mayo model. In 1a we did not see evidence against proportionality for bilirubin, age, and albumin. The plots in 1b. qualitatively support the conclusion of proportionality for bilirubin and age. When looking at the plot for albumin in 1b, the curves start to converge at the extreme, high-end of the range of values for follow-up time, whereas for lower values of follow-up time the curves appear to be parallel. This phenomenon may not be captured by the regression in 1a, since follow-up time as it is parameterized in the interaction term is split into 3 relatively long periods (0-799, 800-1599, and 1600+ days). Therefore, the result of this coarse parameterization is residual confounding by time.

2. Read the article by Crowley and Hu
   a. Using the data presented in Table 1 of Crowley and Hu, and ignoring age, time and any other variables, form the single 2x2 table showing the association between transplant and death. Calculate the odds ratio estimate for this association and test whether it is one. What is the apparent effect of heart transplant according to this analysis?

```
. cci 45 30 24 4
                                                         Proportion
                 |   Transplant  No trans |      Total     Exposed
-----------------+------------------------+------------------------
            Dead |        45          30  |         75      0.6000
           Alive |        24           4  |         28      0.8571
-----------------+------------------------+------------------------
           Total |        69          34  |        103      0.6699
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
      Odds ratio |              .25       |    .0579606    .8427891 (exact)
 Prev. frac. ex. |              .75       |    .1572109    .9420394 (exact)
 Prev. frac. pop |         .6428571       |
                 +-------------------------------------------------
                               chi2(1) =     6.10  Pr>chi2 = 0.0135
```

Ignoring time, age, and any other variables, the odds ratio for death comparing individuals who received a transplant to individuals who did not receive a transplant was 0.25 (95% CI 0.06, 0.85) – or individuals receiving a transplant were 75% less likely to die than individuals not receiving a transplant, this difference was significantly different from 1.0.

b. Describe the potential biases that may influence the results obtained in a). How, in fact, do these results compare to those given by Model 1 of Table 2? What is the explanation for any differences you see?

If we do not account for the fact that some individuals did not survive long enough be matched with an appropriate donor, we will overestimate the relative risk for survival among heart transplant recipients versus non-recipients. This would occur because deaths among those who don't survive long enough but would have received a transplant will be falsely assigned to the non-transplant group. In addition, the time from acceptance until transplant for the recipients will be free, "immortal time", thereby further biasing survival for transplant recipients toward greater values.

In contrast, the fact that we aren't even considering the existence of censored observations means that estimates for risk ratios will be biased. The direction of this bias will depend on the reasons for censorship and their association with the probability of failure, which generally will not be measureable from the data.

The results from Model 1 of Table 2 (Crowley et al. 1977) indicate a hazard ratio of 1.04 (Wald 95% CI: 0.58, 1.86). These results indicate a non-significantly increased risk of death among transplant recipients, which is in opposition to the conclusions from 2a.

It is likely that the differences between the risk ratio estimates from Part A and Model 1 are the result of accounting for the existence of censored data through the use of Cox PH regression. We can exclude "immortal time" bias as the reason for the difference; because Model 1's fundamental time variable is the time from acceptance until outcome or censorship.

c. Using the Stanford heart transplant data available from the class web page, reproduce (as closely as possible) the results shown in lines 7-9, Table 2, of Crowley and Hu. Write out a detailed model formula for each of the three models. Interpret (explain) the <u>change</u> in the coefficient of Z_6 depending on whether or not Z_5 is in the model.

Table 1c. Coefficient (SE) and [p-value] corresponding to models 7-9 of Crowley and Hu.

	z0 (post) tvc: transplant	z4 tvc:age@transplant	z5 (prior) non tvc: prior surg.	z6 (post*prior) tvc: prior surgery
model 7	-2.41 (1.1) [0.026]	0.05 (0.02) [0.014]	-0.72 (0.36) [0.046]	---
model 8	-2.32 (1.1) [0.033]	0.05 (0.02) [0.014]	---	-0.81 (0.45) [0.070]
model9	-2.37 (1.08) [0.029]	0.05 (0.02) [0.014]	-0.54 (0.61) [0.372]	-0.26 (0.76) [0.728]

$$Model7: \lambda(t) = \lambda_0(t)\exp\left[-2.41 * post(t) + 0.05 * age@trans * post(t) - 0.72 * prior\right]$$
$$Model8: \lambda(t) = \lambda_0(t)\exp\left[-2.32 * post(t) + 0.05 * age@trans * post(t) - 0.81 * prior * post(t)\right]$$
$$Model9: \lambda(t) = \lambda_0(t)\exp\left[-2.37 * post(t) + 0.05 * age@trans * post(t) - 0.54 * prior - 0.26 * prior * post(t)\right]$$

In model 7, we observe that after adjusting for transplant status and its interaction with age at transplant, individuals who began this study with a history of open heart surgery had a decreased risk of death (with borderline statistical significance, (HR = 0.49, p = 0.046).

In model 8, we observe that after adjusting for transplant status (including its interaction with age at transplant), individuals who began this study with a history of open heart surgery have a decreased risk of death (HR 0.44, p = 0.07). This comparison is restricted, however, to individuals who received transplants, after they have received the transplant (since "post*prior" equals zero otherwise). The problem with this model is that it leads to a misinterpretation of the result because of their failure to obey the rule that you (almost) always include the main effect term in models with interactions. The -0.80 is carrying much of the weight that is captured by the main effect term for pre-transplant effects of prior surgery. Crowley and Hu make the statement "Previous surgery also seemed to be an important factor… but as an indicator of pre-transplant health, not as a post-transplant factor."

In model 9, we examine whether the association between "prior" surgery and risk of death **depends on** whether one has received a transplant or not. The model contains a main effects term for "prior" and an interaction term. The nonsignificance of the interaction term, Z_6, implies that the association between "prior" surgery and risk of death does not depend on whether one has received a transplant.

Notice that to get the log RR for the post period in Model 9, we would add together the -0.54 and -0.26, which gives -0.80, is identical to what is estimated for the post-transplant period in Model 8. This identity is not at all surprising: the estimates for the pre- and post-transplant periods are practically independent since they are based on completely different risk sets.