# The Effect of D-penicillamine on the Survival of Cirrhosis Patients

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STAT 417 | Survival Analysis

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# Introduction

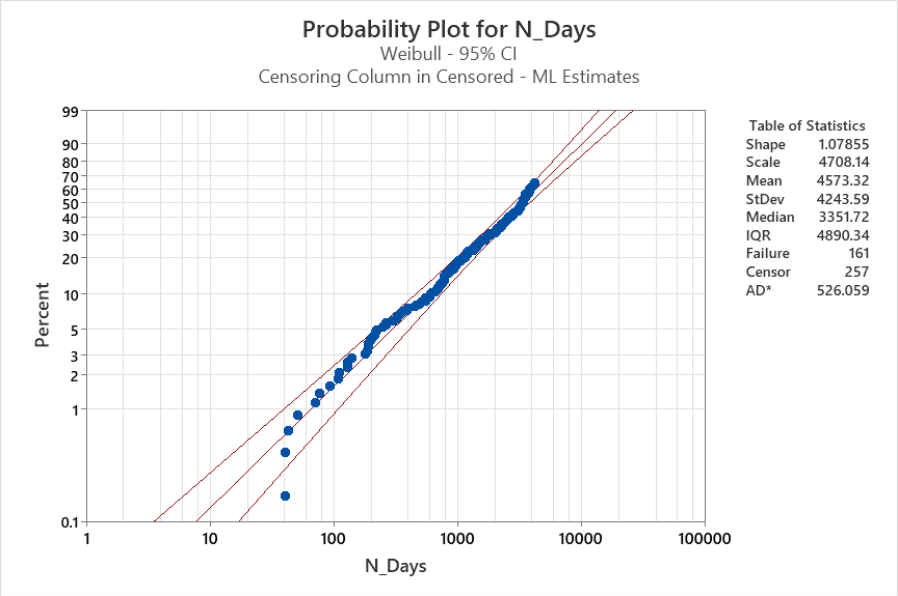
The dataset provided is a clinical study on primary biliary cirrhosis conducted by the Mayo Clinic from 1974 to 1984. The study aimed to find if D-penicillamine could extend the survival of an individual diagnosed with primary biliary cirrhosis. The dataset contains 20 columns with basic individual information such as ID, Age, and Sex. The other measurements in the dataset captured the liver and blood health of individuals. Of the 418 individuals recorded, 112 individuals agreed to have their health recorded but did not participate in the clinical trial. Several measurements such as ascites, hepatomegaly, spiders, cholesterol, copper, alkaline phosphatase, SGOT, and triglycerides were not recorded for these individuals. Because of this missing health data, these subjects were removed from the analysis.

The time-to-event variable is the number of days from enrollment in the program until death. There are two censoring variables in this dataset, one where individuals live beyond the study end and the other where individuals received a liver transplant and were ‘censored’ from the study. Our analysis’ particular interests are individuals’ age, sex, the drug given, and various blood health markers, such as albumin level and copper level.

In total, our reduced dataset without missing values had 124 complete event times and 186 censored events. A subject’s time was censored if they lived beyond the conclusion of the study, or if they had a liver transplant before they died. For the analysis, we combined these two types of censored times since they are functionally both a form of right censoring.

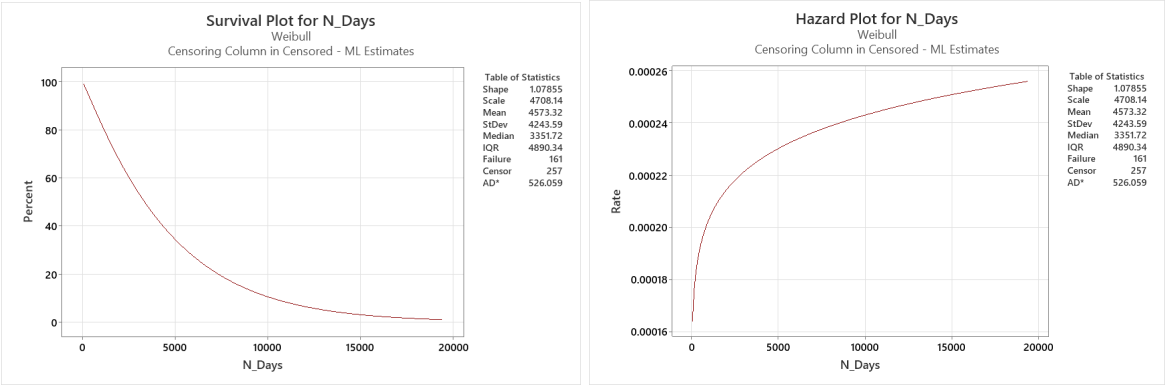
# Main Analysis

## Parametric



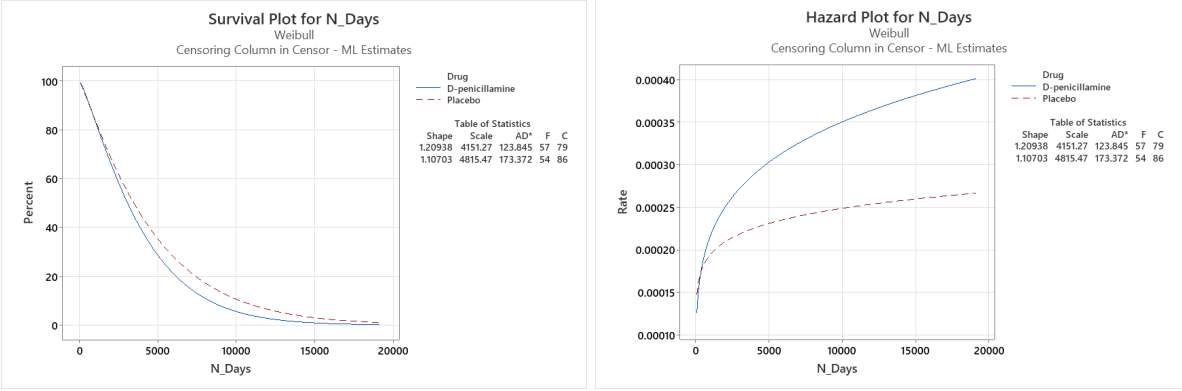

Graph 1: Probability Plot for all Individuals

The Weibull distribution fits the dataset the best. The other distributions were exponential, normal, lognormal, logistic, and log-logistic all fit the data, but the Weibull distribution was the best because it had the lowest Anderson-Darling score of 526.059 and many of its points fell along the diagonal line compared to the other distributions. The mean was 4,573.32 days and the median was 3,351.72 days. At this probability plot and more noticeably, the survival curves, we saw a drop off of surviving individuals before 100 days, then a slightly more consistent line as the number of days increased.



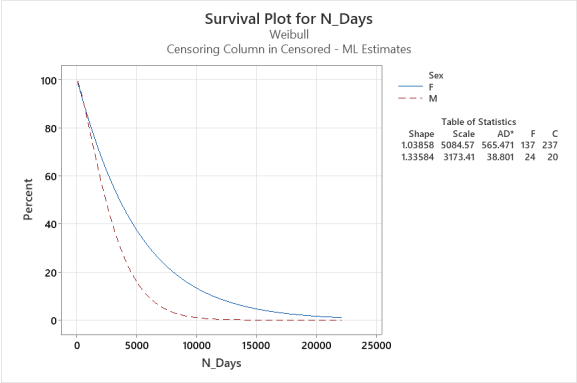

Graphs 2 and 3: Survival and Hazard Plot for all Individuals

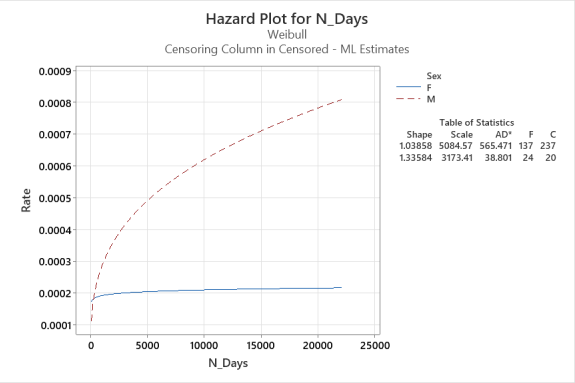
The survival curve has a very steep drop in the first 5,000 days where many individuals do die early on, going to around 30% survival. Although it starts to become flatter around 10,000 days. With a mean of 4,573.32 and a median of 3,351.72 days. Many individuals are predicted to survive for many years after enrolling in the study. Given that an individual has not died from cirrhosis on any day since enrolling in the study, the hazard of death up through around 3,000 days increases quickly. After around 5,000 days the hazard of dying increases slowly.




Graphs 4 and 5: Survival and Hazard Plot for all Individuals in Drug Group

For any number of days since registration in the study, individuals who have taken the D-penicillamine drug have a lower probability of survival from cirrhosis beyond t days than individuals who took the placebo. The mean for individuals who have taken the drug is 3897.18 days while the mean for individuals who took the placebo was 4636.84 days. The drug median was 3065.94 days and the placebo median was 3458.23 days. The clinical trial had the opposite effect for D-penicillamine. Where more individuals who had taken the drug were predicted to have shorter survival times than individuals who took the placebo. The hazard plot also showed how individuals who take the graph have a higher hazard of death compared to the placebo. From the hazard plot, we can say the proportional hazards assumption was not violated.

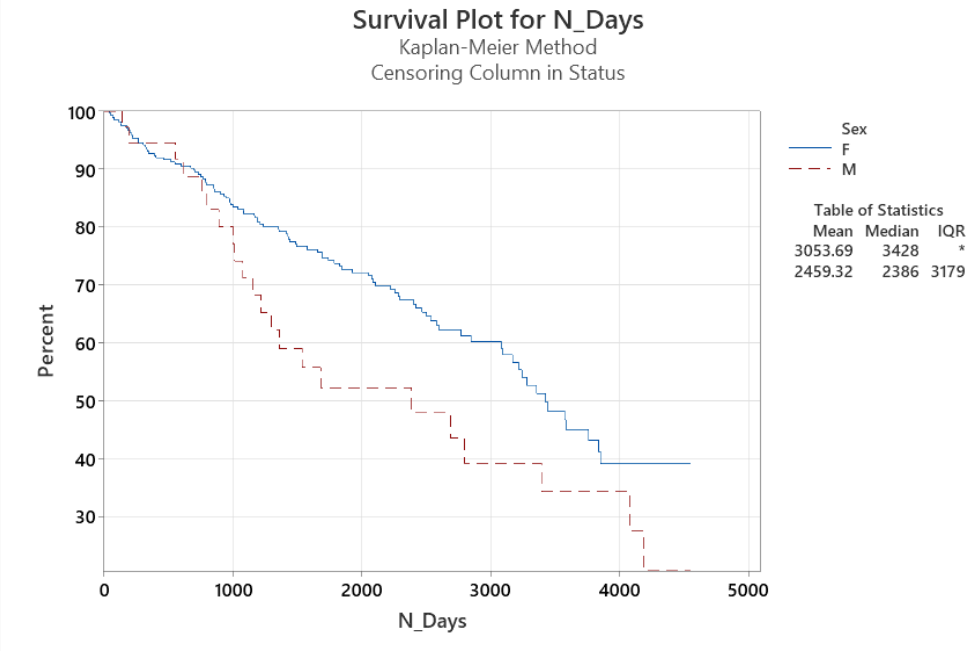



Graphs 6 and 7: Survival and Hazard Plot for all Individuals in Sex Group

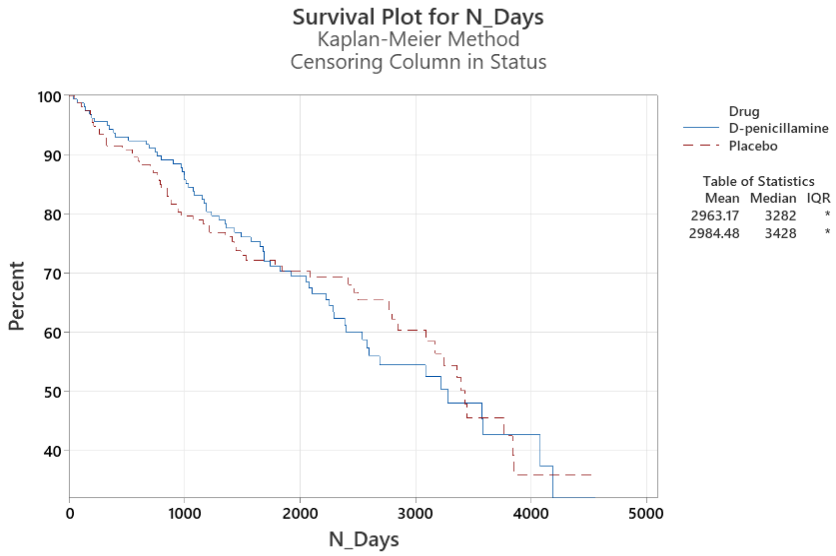
For any number of days since registration in the study, female patients have a higher probability of survival from cirrhosis beyond t days than male patients. Our initial analysis showed that sex was a somewhat contributing factor in the survival of cirrhosis. The initial graph shows a much lower survival rate for males, reaching a 0% survival probability at around 10,000 days, whereas at the same time, the female survival rate was at around 10%. The male survival mean was at 2,915.55 days and the female survival mean was at 5,007.58 days. Similarly, the hazard plot showed that given that a male has not died of cirrhosis, the hazard of death for males is significantly higher for all days compared to females. The proportional hazards assumption was also not violated for the group. Although the study took place in under 5000 days, because not every female died the estimated mean survival time is slightly above 5000 days.

## Nonparametric




Graph 8: Kaplan-Meier Survival Curve of Estimated Time to Death, by Sex

Starting from day 0 to about day 900 since diagnosis, the estimated probability of surviving liver cirrhosis for both males and females remained roughly the same. However, from about day 900 onwards, the estimated probability of surviving liver cirrhosis for both groups decreases rapidly, the decrease for males is more rapid than the decrease for females. The log-rank test statistic for the Sex predictor gives a Chi-Squared Statistic of 4.353 and a p-value of 0.037. This means that the probability of surviving liver cirrhosis beyond any time is significantly different between the two sexes. The mean time to death for females is 3053.69 days and the median is 3428 days, while the mean time to death for males was 2459.32 days and the median is 2386 days. The standard error for males is 282.088 days and the standard error for females is 110.290




Graph 9: Kaplan-Meier Survival Curve of Estimated Time to Death, by Drug

Starting from day 0 to about day 1,900 since diagnosis, the estimated probability of surviving liver cirrhosis for the placebo is lower than for the D-penicillamine treatment. At 1,900 days, the probability of survival for the placebo levels out while the drop in survival for the D-penicillamine treatment keeps decreasing. Meaning for the time between 1,900 days after enrollment to about 3400 days after enrollment, the probability of surviving is higher for the placebo treatment than for the D-penicillamine treatment. From 3,400 days until the end of the study, the probability of survival between the two treatments is roughly the same. The results of the log-rank test for the drug predictor give a Chi-Square statistic of 0.0455 and a p-value of 0.831. This indicates that the probability of surviving liver cirrhosis between the two drug treatments is not significantly different for all time since diagnosis. The mean time to death for the placebo group is 2,984.48 days with a median of 3,428 days, while the mean time to death for the D-penicillamine group is 2,963.17 days with a median of 3,282 days. The standard error for the D-penicillamine group is 143.062 days and the standard error for the placebo group is 145.74 days.

These results are similar to the results from the parametric analysis. Both analyses found a large difference in the estimated mean survival times between males and females. The difference between parametric and non-parametric for females was 5,007.58 versus 3,053.69. For males that difference was 2,915.55 versus 2459.32. As stated before the parametric mean is strange since none of the individuals should reach past 5,000 days since the length of the study was less than 5,000. Furthermore, both analyses also found that there was a small difference in estimated mean survival time between the two drug groups, placebo and D-penicillamine. For placebo, the parametric mean is 4,636.84 versus the nonparametric mean of 2,984.48. For the D-penicillamine, the parametric mean is 3,897.18 versus the nonparametric mean of 2,963.17

## Regression

```
Call:
coxph(formula = Surv(N_Days, Censor) ~ Age + Sex * Bilirubin +
    Drug + Hepatomegaly + Copper + Albumin + SGOT, data = cirrhosis)

  n= 310, number of events= 124
   (108 observations deleted due to missingness)

                      coef  exp(coef)   se(coef)      z Pr(>|z|)
Age               1.205e-04  1.000e+00  2.877e-05  4.189 2.81e-05 ***
SexM              9.156e-01  2.498e+00  3.705e-01  2.471  0.01347 *
Bilirubin         1.036e-01  1.109e+00  1.674e-02  6.190 6.02e-10 ***
DrugD-penicillamine 4.628e-02  1.047e+00  1.876e-01  0.247  0.80518
HepatomegalyY     5.403e-01  1.716e+00  2.162e-01  2.499  0.01246 *
Copper            4.049e-03  1.004e+00  1.006e-03  4.025 5.71e-05 ***
Albumin          -1.172e+00  3.098e-01  2.364e-01 -4.958 7.13e-07 ***
SGOT              3.131e-03  1.003e+00  1.521e-03  2.059  0.03951 *
SexM:Bilirubin   -2.838e-01  7.529e-01  1.076e-01 -2.636  0.00838 **
```

Table 1: Final Cox Regression Model

$$h(t|X_1, ..., X_9) = h_0(t)exp(0.0001205(Age)+0.9156(Sex)+0.1036(Bilirubin)+ 0.0.04627(Drug)+0.5403(Hepatomegaly)+0.004049(Copper)-1.172(Albumin)+ 0.003131(SGOT) - 0.2838(Sex)(Bilirubin))$$

Note that there are 310 observations used for this model, with 108 observations that were truncated because of missing data. There were a total of 124 complete observations in the study; 124 participants died due to cirrhosis throughout the study.

The likelihood ratio test statistic is 176.3 with a p-value of < 2e-16 for the final model. The Wald test statistic is similar at 187.5 with a p-value of < 2e-16.

Hazard ratio tests for certain variables such as sex after adjusting for our key variables:

Male Hazard Ratio: $\widehat{HR} = e^{0.9156} = 2.4987$
95% CI for Sex: (1.2085, 5.1646).

The hazard of death from cirrhosis for males is 149.87% higher than for females after adjusting for the other variables. We are 95% confident that the hazard of males dying from cirrhosis is between 20.85% to 416.46% higher than for females, after adjusting for the other predictors.

Age Hazard Ratio: $\widehat{HR} = e^{0.001205} = 1.0012$
95% CI for Age: (1.0001, 1.0002)

The hazard of death from cirrhosis increases by 0.12% for every one day increase in age after adjusting for the other variables in the model. We are 95% confident that the hazard of death from cirrhosis increases between 0.1% to 0.2% for each increase of 1 day in age.

Drug Hazard Ratio: $\widehat{HR} = e^{0.04628} = 1.0474$
95% CI for Drug: (0.7251, 1.513)

The hazard of death for taking D-penicillamine is 4.74% higher than taking the placebo after adjusting for the other variables. We are 95% confident that the hazard of death from cirrhosis is between 27.49% lower to 51.3% higher for the D-penicillamine group than for the placebo group. From this interval, it is clear that the type of drug did not have a significant effect on the hazard of death from cirrhosis.

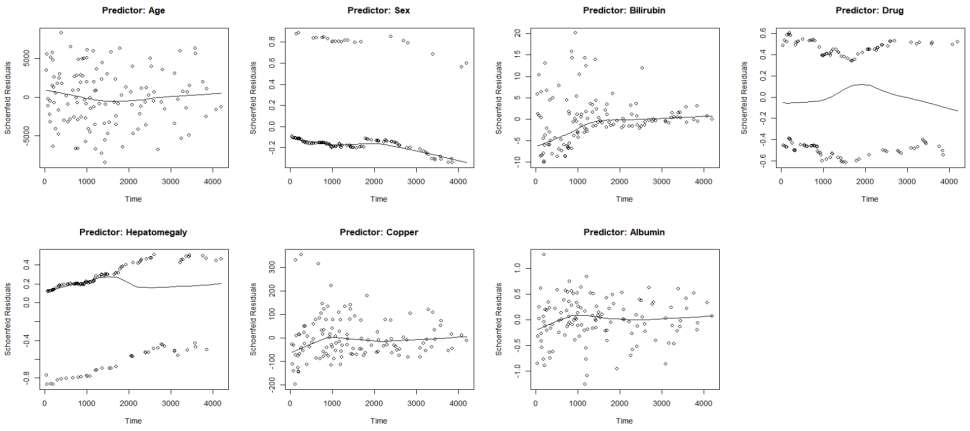



Figure 1: Schoenfeld Residual Plots

In addition, we did not find any influential observations or outliers in this dataset. Although the probability plot had one suspicious point in the dataset early in the N_Days, we could not find a strong enough reason to explore those points. We also ran a proportional hazard test and found that none of our explanatory variables violated the proportional hazard assumptions. Although the residual plots for drug and hepatomegaly do exhibit a slight curvature.

| | chisq | df | p |
|---|---|---|---|
| Age | 1.500 | 1 | 0.22 |
| Sex | 0.175 | 1 | 0.68 |
| Bilirubin | 2.421 | 1 | 0.12 |
| Drug | 0.153 | 1 | 0.70 |
| Hepatomegaly | 2.668 | 1 | 0.10 |
| Copper | 0.456 | 1 | 0.50 |
| Albumin | 1.324 | 1 | 0.25 |
| SGOT | 0.583 | 1 | 0.45 |
| Sex:Bilirubin | 0.415 | 1 | 0.52 |
| GLOBAL | 10.639 | 9 | 0.30 |

Table 2: Schoenfeld Residual Test Results

# Conclusion

Our analysis found that the survival time from cirrhosis depends on a multitude of variables. Variables such as age, sex, bilirubin, hepatomegaly, copper, albumin, SGOT, and the interaction between sex and bilirubin were all significant. Notably, the drug type was not a significant predictor. Because of this, we can conclude that the drug had no significant association with the hazard of death for an individual with cirrhosis. Though other predictors that pertain to the subject's overall health were much better predictors of death; the groups listed above such as age, sex, bilirubin level, copper level, SGOT, presence of hepatomegaly, and albumin level were all better predictors of death. Consequently, we can say that a person's overall health before coming into the study is a much better predictor for the hazard of dying from cirrhosis and that D-penicillamine was not an effective treatment.

## References

Arvidsson, J. (2023, November). *Cirrhosis Patient Survival Prediction*. kaggle. Retrieved March 19, 2024, from https://www.kaggle.com/datasets/joebeachcapital/cirrhosis-patient-survival-prediction/data

Zucker, S. D., Horn, P. S., & Sherman, K. E. (2004, October 4). *Serum bilirubin levels in the U.S. population: gender effect and inverse correlation with colorectal cancer*. PubMed. Retrieved March 19, 2024, from https://pubmed.ncbi.nlm.nih.gov/15382174/

# Appendix

## R Setup

```{r setup, include=FALSE}
library(tidyverse)
library(survival)
```

## Import the dataset into R

```{r}
cirrhosis <- read_csv(here::here("STAT 417 GROUP PROJECT", "cirrhosis.csv"))
cirrhosis <- cirrhosis |>
  mutate(Censor = ifelse(Status %in% c("C", "CL"), 0,
                         ifelse(Status == "D", 1, NA)))

# Make placebo be the reference group
cirrhosis$Drug <- relevel(as.factor(cirrhosis$Drug), ref = "Placebo")
```

*So in this case, we will combine censored "C" and censored due to liver transplantation "CL", due to censored due to liver transplantation only having 25 observations, with this type of censoring.*

```{r}
km.cirrhosis.sex <- survfit(Surv(N_Days,Censor)~Sex, data=cirrhosis)
plot(km.cirrhosis.sex,lty=1:2,xlab="Number of Days until Death",ylab="Survival
Probability", main="Kaplan-Meier Curves for Males and Females")
legend(30,.8, c("Females","Males"),lty=1:2)
```

**Note: This is redundant and not useful when not adjusting for other variables.**

```{r}
survdiff(Surv(N_Days,Censor)~Sex, data=cirrhosis)
```

*Interestingly, there are a total of 374 females and 44 males in the study. We also found that sex / gender doesn't have much of an effect in this study. Outside research found that women are more likely to cirrhosis. Research has found that females are more likely to develop cirrhosis than males. So adding sex/gender doesn't really help.*

*The log-rank test p-value also has a 0.08, so at a 0.05 significance level, we cannot conclude that the probability of surviving after being diagnosed with cirrhosis beyond any day t significanctly differs between males and females.*

*So we won't look at this variable as much.*

```{r}
km.cirrhosis.stage <- survfit(Surv(N_Days,Censor)~as.factor(Stage), data=cirrhosis)
plot(km.cirrhosis.stage,lty=1:4,xlab="Number of Days until Death",ylab="Survival
Probability", main="Kaplan-Meier Curves for Different Stages of Cirrhosis")
legend(30,.8, c("1", "2", "3", "4"),lty=1:4)
```

**Testing Cancer Stages**

```{r}
km.cirrhosis.stage <- survfit(Surv(N_Days,Censor)~as.factor(Stage), data=cirrhosis)
plot(km.cirrhosis.stage,lty=1:4,xlab="Number of Days until Death",ylab="Survival
Probability", main="Kaplan-Meier Curves for Different Stages of Cirrhosis")
legend(30,.8, c("1", "2", "3", "4"),lty=1:4)
```

**Log-Rank Test Individually for the stages of cancer**

```{r}
survdiff(Surv(N_Days,Censor)~as.factor(Stage), data=cirrhosis)
```

**Another individual test**

```{r}
km.cirrhosis.drug <- survfit(Surv(N_Days,Censor)~Drug, data=cirrhosis)
plot(km.cirrhosis.drug,lty=1:2,xlab="Number of Days until Death",ylab="Survival
Probability", main="Kaplan-Meier Curves for the Different Drug Treatments")
legend(30,.8, c("D-penicillamine", "Placebo"),lty=1:2)
```

```{r}
survdiff(Surv(N_Days,Censor)~Drug, data=cirrhosis)
```

**Testing first model**

*First model with all variables in place*

```{r}
cr.cir <- coxph(Surv(N_Days,Censor)~as.factor(Stage)+Sex, data=cirrhosis)
summary(cr.cir)
```

*Note that we did not include sex in our models. We found that we have a low number of males in our sample so we decided we won't get an accurate result. We kept the drug variables the blood testing and other testing variables are effected by the drug treatment. Including urine cystine levels, metal poisoning, copper metabolism. So we next test copper with an interaction with drug.*

**More Model testing**

```{r}
cr.cir2 <- coxph(Surv(N_Days,Censor)~as.factor(Stage)+Drug*Copper, data=cirrhosis)
summary(cr.cir2)
```

*What about including age?*

```{r}
cr.cir3 <- coxph(Surv(N_Days,Censor)~as.factor(Stage)+Drug*Copper+Age, data=cirrhosis)
summary(cr.cir3)
```

```{r}
cr.cir4 <- coxph(Surv(N_Days,Censor)~as.factor(Stage)+Drug*Tryglicerides+Age+Edema,
data=cirrhosis)
summary(cr.cir4)
```

```{r}
cr.cir5 <- coxph(Surv(N_Days,Censor)~as.factor(Stage)+Drug+Tryglicerides, data=cirrhosis)
summary(cr.cir5)
```

```{r}
cr.cir6 <- coxph(Surv(N_Days,Censor)~as.factor(Stage)+Albumin*Drug+Sex+Tryglicerides,
data=cirrhosis)
summary(cr.cir6)
```

```{r}
```

```
cr.cir7 <- coxph(Surv(N_Days,Censor)~as.factor(Stage)+Bilirubin*Drug+Sex+Tryglicerides,
data=cirrhosis)
summary(cr.cir7)
```

```{r}
cr.cir8 <-
coxph(Surv(N_Days,Censor)~as.factor(Stage)+Bilirubin+Albumin+Cholesterol+Edema+Drug+
Sex+Tryglicerides, data=cirrhosis)
summary(cr.cir8)
```

**Included all variables to test out significance after adjusting for all.**

```{r}
cr.cir9 <-
coxph(Surv(N_Days,Censor)~Age+Sex+Ascites+Hepatomegaly+Spiders+Edema+Bilirubin+Ch
olesterol+Albumin+Copper+Alk_Phos+SGOT+Tryglicerides+Platelets+Prothrombin+as.factor(
Stage), data=cirrhosis)
summary(cr.cir9)
```

**Most significant and interesting variables remaining**

```{r}
cr.cir10 <-
coxph(Surv(N_Days,Censor)~Age+Sex+Edema+Bilirubin+Albumin+Copper+SGOT+Trygliceri
des+Prothrombin+as.factor(Stage), data=cirrhosis)
summary(cr.cir10)
```

```{r}
cr.cir11 <-
coxph(Surv(N_Days,Censor)~Age+Drug+Sex*Bilirubin+Copper+Albumin+SGOT+as.factor(St
age), data=cirrhosis)
summary(cr.cir11)
```

**Ran an ANOVA to test whether or not an interaction would have an effect for drug and copper. Since the drug does affect the amount of copper in a persons' body.**

```{r}
cr.cir12 <- coxph(Surv(N_Days,Censor)~Age+Drug+Copper+Sex*Bilirubin+Albumin+SGOT,
data=cirrhosis)
summary(cr.cir12)
cr.cir12a <- coxph(Surv(N_Days,Censor)~Age+Drug*Copper+Sex*Bilirubin+Albumin+SGOT,
data=cirrhosis)
```

```
summary(cr.cir12a)
anova(cr.cir12, cr.cir12a)
```

**Final Model**

```{r}
cr.cir.final <-
coxph(Surv(N_Days,Censor)~Age+Sex*Bilirubin+Drug+Hepatomegaly+Copper+Albumin+SGOT, data=cirrhosis)
summary(cr.cir.final)
```

```{r}
cirrhosis_na <- cirrhosis |>
  na.omit()
```

**Created a reduce file here**

```{r}
write.csv(cirrhosis_na, file = here::here("STAT 417 GROUP PROJECT","cirrhosis_reduced.csv"))
```

**Created the residual plots up in the regression analysis**

```{r}
schoen <- residuals(cr.cir.final, type="schoenfeld")
cirrhosis.na2 <- cirrhosis |>
  select(Age, Sex, Bilirubin, Drug, Hepatomegaly, Copper, Albumin, SGOT, N_Days, Censor) |>
  na.omit()
complete.times <- sort(cirrhosis.na2[cirrhosis.na2$Censor != 0,]$N_Days)
par(mfrow=c(2,4))

#Predictor 1
plot(complete.times,schoen[,1],xlab="Time",ylab="Schoenfeld Residuals", main="Predictor: Age")
smooth.sres <- lowess(complete.times,schoen[,1])
lines(smooth.sres$x,smooth.sres$y,lty=1)
#Predictor 2
plot(complete.times,schoen[,2],xlab="Time",ylab="Schoenfeld Residuals", main="Predictor: Sex")
smooth.sres <- lowess(complete.times,schoen[,2])
lines(smooth.sres$x,smooth.sres$y,lty=1)
#Predictor 3
```

```
plot(complete.times,schoen[,3],xlab="Time",ylab="Schoenfeld Residuals", main="Predictor:
Bilirubin")
smooth.sres <- lowess(complete.times,schoen[,3])
lines(smooth.sres$x,smooth.sres$y,lty=1)
#Predictor 4
plot(complete.times,schoen[,4],xlab="Time",ylab="Schoenfeld Residuals", main="Predictor:
Drug")
smooth.sres <- lowess(complete.times,schoen[,4])
lines(smooth.sres$x,smooth.sres$y,lty=1)
#Predictor 5
plot(complete.times,schoen[,5],xlab="Time",ylab="Schoenfeld Residuals", main="Predictor:
Hepatomegaly")
smooth.sres <- lowess(complete.times,schoen[,5])
lines(smooth.sres$x,smooth.sres$y,lty=1)
#Predictor 6
plot(complete.times,schoen[,6],xlab="Time",ylab="Schoenfeld Residuals", main="Predictor:
Copper")
smooth.sres <- lowess(complete.times,schoen[,6])
lines(smooth.sres$x,smooth.sres$y,lty=1)
#Predictor 7
plot(complete.times,schoen[,7],xlab="Time",ylab="Schoenfeld Residuals", main="Predictor:
Albumin")
smooth.sres <- lowess(complete.times,schoen[,7])
lines(smooth.sres$x,smooth.sres$y,lty=1)
#Predictor 8
plot(complete.times,schoen[,8],xlab="Time",ylab="Schoenfeld Residuals", main="Predictor:
SGOT")
smooth.sres <- lowess(complete.times,schoen[,8])
lines(smooth.sres$x,smooth.sres$y,lty=1)
```