EDA

Chen Liang

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Load data

```
cirrhosis <- read_csv("data/cirrhosis.csv")|>
  janitor::clean_names() |>
  mutate(age = round(age / 365),
         sex = if_else(sex == "M", "Male", "Female"),
         ascites = if_else(ascites == "N", "No", "Yes"),
         hepatomegaly = if_else(hepatomegaly == "N", "No", "Yes"),
         spiders = if_else(spiders == "N", "No", "Yes"),
         edema = if_else(edema == "N", "No", "Yes"))
```

```
## Rows: 418 Columns: 20
## -- Column specification --------------------------------------------------------
## Delimiter: ","
## chr  (7): Status, Drug, Sex, Ascites, Hepatomegaly, Spiders, Edema
## dbl (13): ID, N_Days, Age, Bilirubin, Cholesterol, Albumin, Copper, Alk_Phos...
##
## i Use `spec()` to retrieve the full column specification for this data.
## i Specify the column types or set `show_col_types = FALSE` to quiet this message.
```

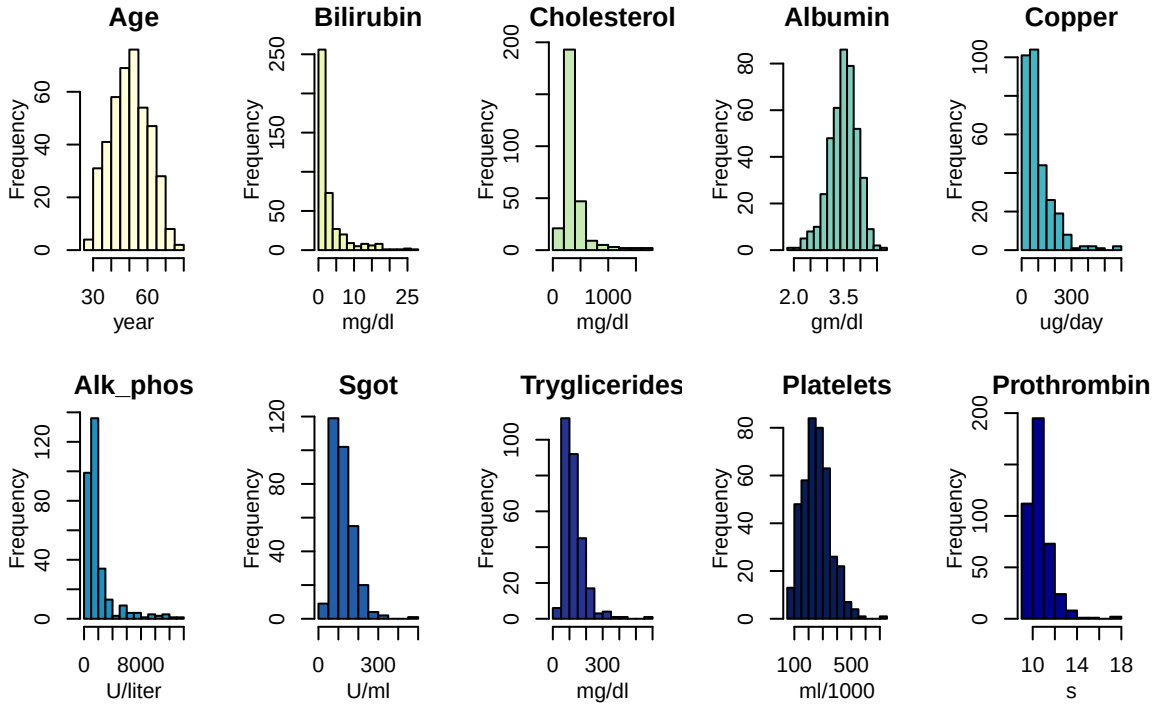
```
# Check for missing values
missing_data <- colSums(is.na(cirrhosis))
missing_data
```

```
##            id        n_days        status          drug           age
##             0             0             0           106             0
##           sex       ascites  hepatomegaly       spiders        edema
##             0           106           106           106             0
##     bilirubin   cholesterol       albumin        copper      alk_phos
##             0           134             0           108           106
##          sgot tryglicerides     platelets   prothrombin         stage
##           106           136            11             2             6
```

Historgram Plots for continuouse variables

```
conti_vars = cirrhosis |>
  select(age, bilirubin, cholesterol, albumin, copper, alk_phos, sgot, tryglicerides, platelets,prothro

par(mfrow = c(2, 5),  # 2 rows, 5 columns
    oma = c(2, 2, 3, 1),  # Outer margins
    mar = c(4, 4, 2, 1),  # Inner margins for individual plots
    mgp = c(2, 1, 0))     # Margins for axis labels and titles
```

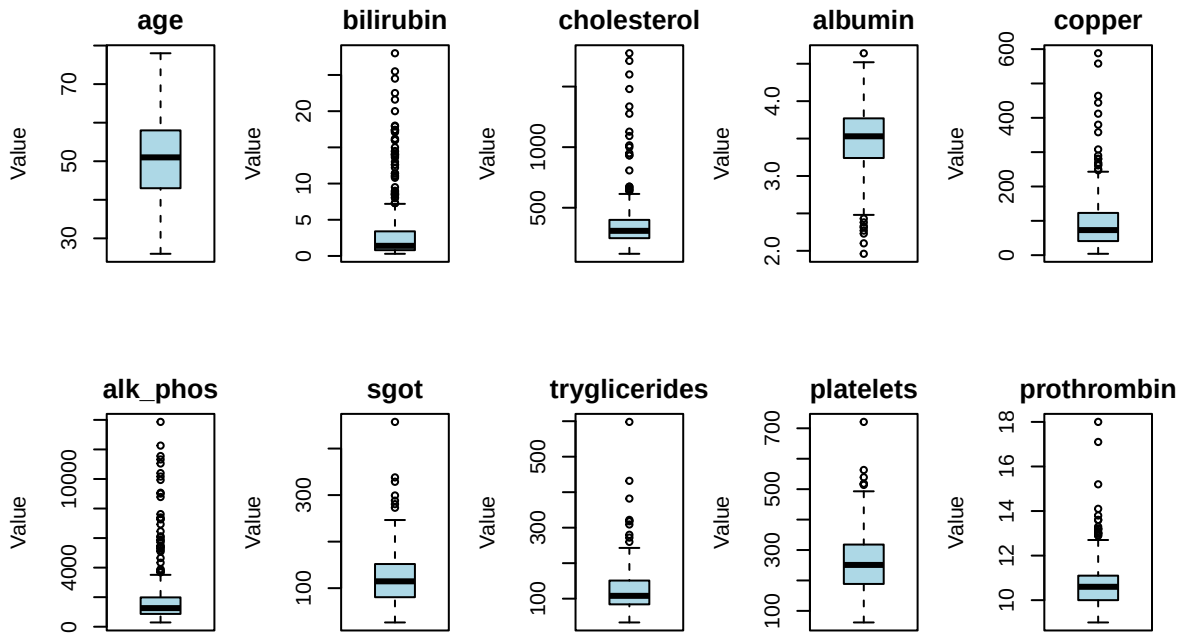
```r
colors <- c(brewer.pal(9, "YlGnBu"), "darkblue")

# Plot each histogram using a color from the Set3 palette
hist(conti_vars$age, main = "Age", xlab = "year", ylab = "Frequency", col = colors[1])
hist(conti_vars$bilirubin, main = "Bilirubin", xlab = "mg/dl", ylab = "Frequency", col = colors[2])
hist(conti_vars$cholesterol, main = "Cholesterol", xlab = "mg/dl", ylab = "Frequency", col = colors[3])
hist(conti_vars$albumin, main = "Albumin", xlab = "gm/dl", ylab = "Frequency", col = colors[4])
hist(conti_vars$copper, main = "Copper", xlab = "ug/day", ylab = "Frequency", col = colors[5])
hist(conti_vars$alk_phos, main = "Alk_phos", xlab = "U/liter", ylab = "Frequency", col = colors[6])
hist(conti_vars$sgot, main = "Sgot", xlab = "U/ml", ylab = "Frequency", col = colors[7])
hist(conti_vars$tryglicerides, main = "Tryglicerides", xlab = "mg/dl", ylab = "Frequency", col = colors
hist(conti_vars$platelets, main = "Platelets", xlab = "ml/1000", ylab = "Frequency", col = colors[9])
hist(conti_vars$prothrombin, main = "Prothrombin", xlab = "s", ylab = "Frequency", col = colors[10])
```



Boxplot for continuous variables

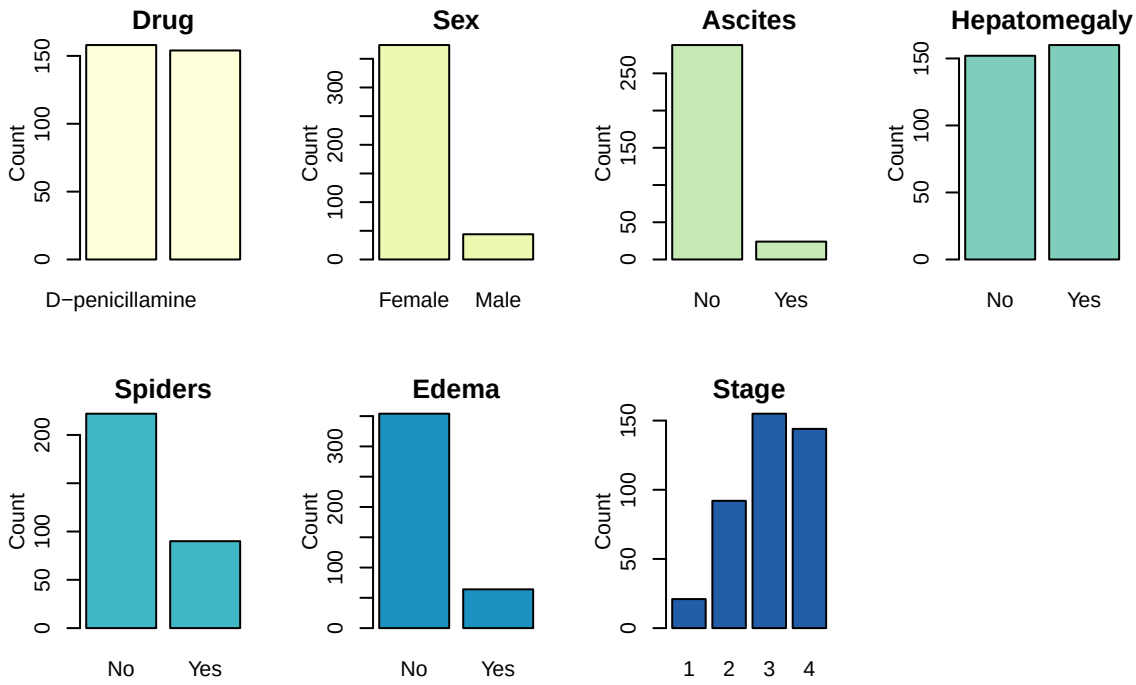
```r
# Boxplot for all continuous variables
par(mfrow = c(2, 5), oma = c(2, 2, 3, 1), mar = c(4, 4, 2, 1))
conti_names <- names(conti_vars)

for (i in seq_along(conti_names)) {
  boxplot(conti_vars[[conti_names[i]]],
          main = conti_names[i],
          ylab = "Value",
          col = "lightblue",
          outline = TRUE)  # Show outliers
}

# Add an overall title
```

```
mtext("Boxplots for Continuous Variables", outer = TRUE, cex = 1.5, line = 1)
```



Bar Plots for categorical vairables

```
cate_vars = cirrhosis |>
  select(drug, sex, ascites, hepatomegaly, spiders, edema, stage)

par(mfrow = c(2, 4),  # 2 rows, 5 columns
    oma = c(2, 2, 3, 1),  # Outer margins
    mar = c(4, 4, 2, 1),  # Inner margins for individual plots
    mgp = c(2, 1, 0))     # Margins for axis labels and titles

barplot(table(cate_vars$drug), main = "Drug", ylab = "Count", , col = colors[1])
barplot(table(cate_vars$sex), main = "Sex", ylab = "Count", , col = colors[2])
barplot(table(cate_vars$ascites), main = "Ascites", ylab = "Count", col = colors[3])
barplot(table(cate_vars$hepatomegaly), main = "Hepatomegaly", ylab = "Count", col = colors[4])
barplot(table(cate_vars$spiders), main = "Spiders", ylab = "Count", col = colors[5])
barplot(table(cate_vars$edema), main = "Edema", ylab = "Count", col = colors[6])
barplot(table(cate_vars$stage), main = "Stage", ylab = "Count", col = colors[7])
```



Correlation Plot

```
numeric_cirr <- cirrhosis |>
  select_if(is.numeric)

cor_matrix <- cor(numeric_cirr, use = "complete.obs")

corrplot(cor_matrix, method = "circle", type = "lower", order = "hclust")
```

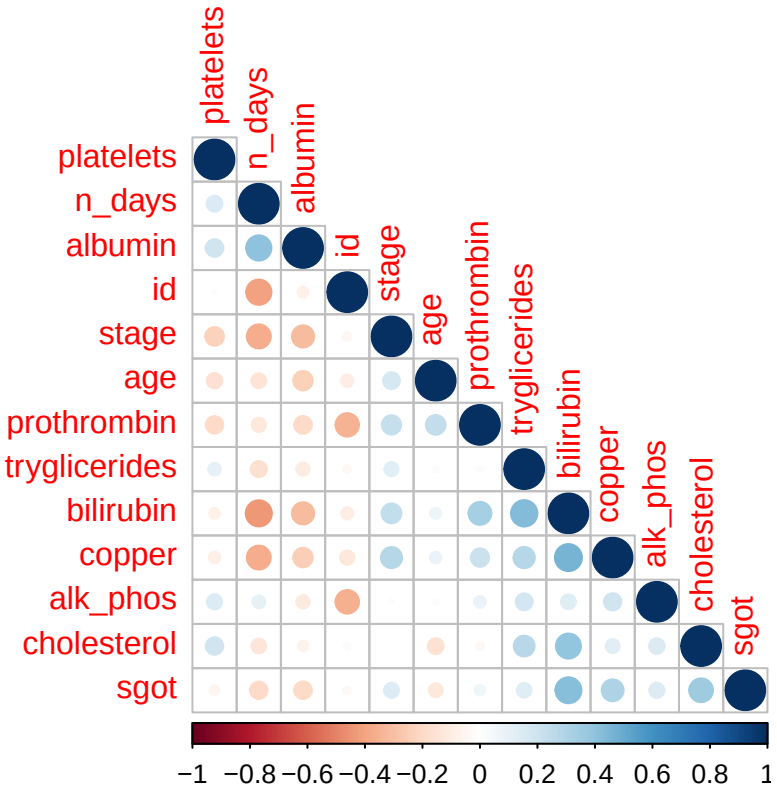


Table 1: Baseline Characteristics

```
theme_gtsummary_journal(journal = "nejm")
```

```
## Setting theme "New England Journal of Medicine"
```

```
cirrhosis_df <- cirrhosis |>
  mutate(
    status = case_when(
      status == "C" ~ "Censored",
      status == "CL" ~ "Censored due to liver tx",
      status == "D" ~ "Death",
      TRUE ~ status))

table_1 <- cirrhosis_df |>
  select(-id) |>
  tbl_summary(
    by = status,
    statistic = list(
      all_continuous() ~ "{mean} / {median} ({sd})",
      all_categorical() ~ "{n} ({p}%)"
    ),
    digits = all_continuous() ~ 1,
    missing = "no",
    label = list(
    n_days ~ "N_days",
    drug ~ "Drug",
    age ~ "Age",
```

```
    sex ~ "Sex",
    ascites ~ "Ascites",
    hepatomegaly ~ "Hepatomegaly",
    spiders ~ "Spiders",
    edema ~ "Edema",
    bilirubin ~ "Bilirubin",
    cholesterol ~ "Cholesterol",
    albumin ~ "Albumin",
    copper ~ "Copper",
    alk_phos ~ "Alk_phos",
    sgot ~ "SGOT",
    trygliceride ~ "Trygliceride",
    platelets ~ "Platelets",
    prothrombin ~ "Prothrombin",
    stage ~ "Stage"
  )) |>
  modify_caption("Baseline Characteristics") |>
  as_flex_table() |>
  line_spacing(space = 0, part = "body")

table_1
```

```
## Warning: fonts used in `flextable` are ignored because the `pdflatex` engine is
## used and not `xelatex` or `lualatex`. You can avoid this warning by using the
## `set_flextable_defaults(fonts_ignore=TRUE)` command or use a compatible engine
## by defining `latex_engine: xelatex` in the YAML header of the R Markdown
## document.
```

Table 1: Baseline Characteristics

Characteristic	**Censored** N = 232[1]	**Censored due to liver tx** N = 25[1]	**Death** N = 161[1]
N_days	2,333.2 / 2,186.5 (994.7)	1,546.2 / 1,435.0 (753.1)	1,376.9 / 1,083.0 (1,0
Drug			
D-penicillamine	83 (49%)	10 (53%)	65 (52%)
Placebo	85 (51%)	9 (47%)	60 (48%)
Age	49.6 / 50.0 (10.4)	41.6 / 41.0 (6.3)	54.0 / 54.0 (9.8)
Sex			
Female	215 (93%)	22 (88%)	137 (85%)
Male	17 (7.3%)	3 (12%)	24 (15%)
Ascites	1 (0.6%)	0 (0%)	23 (18%)
Hepatomegaly	60 (36%)	12 (63%)	88 (70%)
Spiders	33 (20%)	5 (26%)	52 (42%)
Edema	16 (6.9%)	3 (12%)	45 (28%)
Bilirubin	1.6 / 0.9 (1.9)	3.6 / 3.1 (3.6)	5.5 / 3.2 (5.8)
Cholesterol	326.5 / 292.0 (165.8)	439.5 / 343.5 (335.5)	415.8 / 339.0 (275.

Table 1: Baseline Characteristics

Characteristic	Censored N = 232[1]	Censored due to liver tx N = 25[1]	Death N = 161[1]
Albumin	3.6 / 3.6 (0.4)	3.5 / 3.5 (0.5)	3.4 / 3.4 (0.5)
Copper	66.6 / 52.0 (57.1)	124.0 / 102.0 (100.1)	135.4 / 111.0 (98.5
Alk_phos	1,578.1 / 1,107.5 (1,633.1)	1,535.2 / 1,345.0 (837.7)	2,594.4 / 1,664.0 (2,67
SGOT	107.3 / 94.6 (52.8)	130.1 / 127.0 (36.9)	141.9 / 134.9 (58.4
Tryglicerides	111.8 / 104.0 (48.3)	133.9 / 124.0 (70.5)	140.5 / 122.0 (79.3
Platelets	261.2 / 256.0 (88.6)	309.6 / 304.0 (102.7)	242.5 / 224.0 (107.
Prothrombin	10.5 / 10.4 (0.9)	10.4 / 10.3 (0.5)	11.2 / 11.0 (1.0)
Stage			
1	19 (8.3%)	0 (0%)	2 (1.3%)
2	64 (28%)	5 (20%)	23 (15%)
3	97 (42%)	10 (40%)	48 (31%)
4	50 (22%)	10 (40%)	84 (54%)

[1]Mean / Median (SD); n (%)

Stratification

Note: To select variables for stratification, we used categorical variables that are more clinically relevent (recoded age, drug, stage) and variable that have similar sample size between each group (Hepatomegaly). We then perform logrank test, Gehan Wilcoxon test, and KM just for visualization/verification purpose.

Library (add this to the top)

```
library(MASS)
```

```
##
## Attaching package: 'MASS'
## The following object is masked from 'package:gtsummary':
##
##     select
## The following object is masked from 'package:dplyr':
##
##     select
```

```
library(survminer)
```

```
## Loading required package: ggpubr
##
## Attaching package: 'ggpubr'
## The following objects are masked from 'package:flextable':
##
##     border, font, rotate
```

```
##
## Attaching package: 'survminer'

## The following object is masked from 'package:survival':
##
##     myeloma
```

```
library(glmnet)
```

```
## Loading required package: Matrix

##
## Attaching package: 'Matrix'

## The following objects are masked from 'package:tidyr':
##
##     expand, pack, unpack

## Loaded glmnet 4.1-8
```

```
library(PHInfiniteEstimates)
```

```
## Loading required package: lpSolve

## Loading required package: coxphf

## Loading required package: nph
```

```
library(kableExtra)
```

```
##
## Attaching package: 'kableExtra'

## The following objects are masked from 'package:flextable':
##
##     as_image, footnote

## The following object is masked from 'package:dplyr':
##
##     group_rows
```

```
cirrhosis = cirrhosis |>
  mutate(
    status = case_when(
      status == "D" ~ 1,  # Event of interest (death)
      status == "C" | status == "CL" ~ 0,  # Censored data
      TRUE ~ as.numeric(status)))
```

```
## Warning: There was 1 warning in `mutate()`.
## i In argument: `status = case_when(...)`.
## Caused by warning:
## ! NAs introduced by coercion
```

Recoded age

```
# Age divide to 4 groups - seperated by quantile
age_quantile = cirrhosis |>
  pull(age) |>
  quantile(probs = c(0.25, 0.5, 0.75))
cirrhosis_age = cirrhosis |>
  mutate(age_ord = case_when(
```

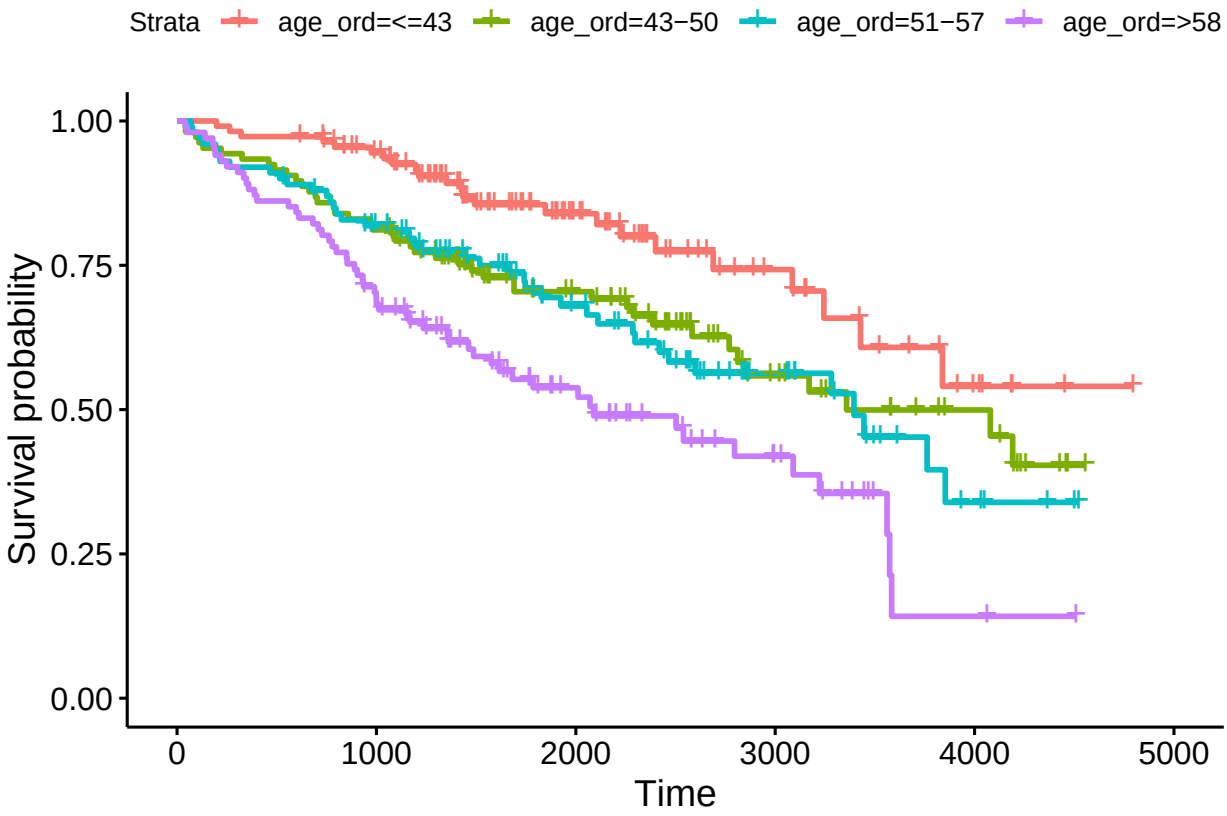
```
    age <= age_quantile[1] ~ paste0("<=", age_quantile[1]),
    age <= age_quantile[2] ~ paste0(age_quantile[1], "-", age_quantile[2]-1),
    age <= age_quantile[3] ~ paste0(age_quantile[2], "-", age_quantile[3]-1),
    .default = paste0(">", age_quantile[3])) |>
      factor( levels = c(paste0("<=", age_quantile[1]),
              paste0(age_quantile[1], "-", age_quantile[2]-1),
              paste0(age_quantile[2], "-", age_quantile[3]-1),
              paste0(">", age_quantile[3]),
              ordered = T))
    )

# Logrank
logrank_age_recoded_4 = survdiff(Surv(n_days, status) ~ age_ord, data = cirrhosis_age)
logrank_age_recoded_4
```

```
## Call:
## survdiff(formula = Surv(n_days, status) ~ age_ord, data = cirrhosis_age)
##
##                  N Observed Expected (O-E)^2/E (O-E)^2/V
## age_ord=<=43   111       23     44.2   10.1811   14.0679
## age_ord=43-50  106       42     45.0    0.1964    0.2756
## age_ord=51-57  100       41     39.3    0.0726    0.0962
## age_ord=>58    101       55     32.5   15.5766   19.6845
##
##  Chisq= 26.1  on 3 degrees of freedom, p= 9e-06
```

```
# Gehan Wilcoxon test
wilcoxon_age_recoded_4 = gehan.wilcoxon.test(Surv(n_days, status) ~ age_ord, data =
                                             cirrhosis_age)
wilcoxon_age_recoded_4
```

```
##
##  Gehan-Wilcoxon
##
## data:
## = 25.62, p-value = 1.146e-05
## alternative hypothesis: two-sided
```

```
# KM Curve
survfit(Surv(n_days, status) ~ age_ord, data = cirrhosis_age) |>
  ggsurvplot()
```




```
# divide quantile to 3 then
```

```
survdiff(Surv(n_days, status) ~ age_ord, data = cirrhosis_age)
```

```
## Call:
## survdiff(formula = Surv(n_days, status) ~ age_ord, data = cirrhosis_age)
##
##                  N Observed Expected (O-E)^2/E (O-E)^2/V
## age_ord=<=43   111       23     44.2   10.1811   14.0679
## age_ord=43-50  106       42     45.0    0.1964    0.2756
## age_ord=51-57  100       41     39.3    0.0726    0.0962
## age_ord=>58    101       55     32.5   15.5766   19.6845
##
##  Chisq= 26.1  on 3 degrees of freedom, p= 9e-06
```

```
# Age divide to 3 groups - seperated by quantile
age_quantile = cirrhosis |>
  pull(age) |>
  quantile(probs = c(1/3, 2/3))

cirrhosis_age = cirrhosis |>
  mutate(age_ord = case_when(
    age <= age_quantile[1] ~ paste0("<=", age_quantile[1]),
    age <= age_quantile[2] ~ paste0(age_quantile[1], "-", age_quantile[2]-1),
    .default = paste0(">", age_quantile[2])) |>
      factor( levels = c(paste0("<=", age_quantile[1]),
              paste0(age_quantile[1], "-", age_quantile[2]-1),
              paste0(">", age_quantile[2]),
              ordered = T))
```

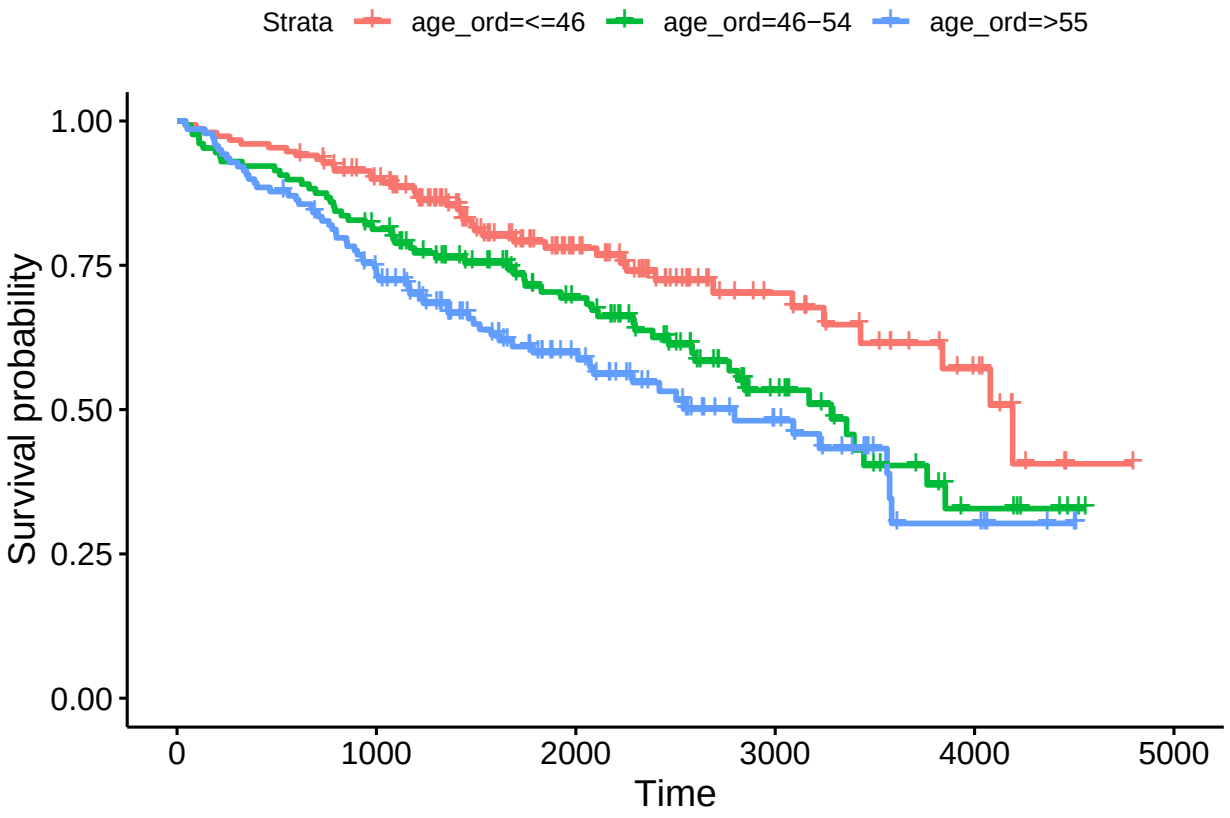
```
    )

# Logrank
logrank_age_recoded_3 = survdiff(Surv(n_days, status) ~ age_ord, data = cirrhosis_age)
logrank_age_recoded_3
```

```
## Call:
## survdiff(formula = Surv(n_days, status) ~ age_ord, data = cirrhosis_age)
##
##                  N Observed Expected (O-E)^2/E (O-E)^2/V
## age_ord=<=46   151       40     60.5     6.959    11.177
## age_ord=46-54  128       56     52.7     0.202     0.301
## age_ord=>55    139       65     47.7     6.242     8.914
##
##  Chisq= 13.4  on 2 degrees of freedom, p= 0.001
```

```
# Gehan Wilcoxon test
wilcoxon_age_recoded_3 = gehan.wilcoxon.test(Surv(n_days, status) ~ age_ord, data = cirrhosis_age)
wilcoxon_age_recoded_3
```

```
##
##  Gehan-Wilcoxon
##
## data:
## = 14.127, p-value = 0.0008559
## alternative hypothesis: two-sided
```

```
# KM Curve
survfit(Surv(n_days, status) ~ age_ord, data = cirrhosis_age) |>
  ggsurvplot()
```



Hepatomegaly

Hepatomegaly - enlarged liver Q: Does having hepatomegaly, a symptom of cirrhosis, affect survival probability?

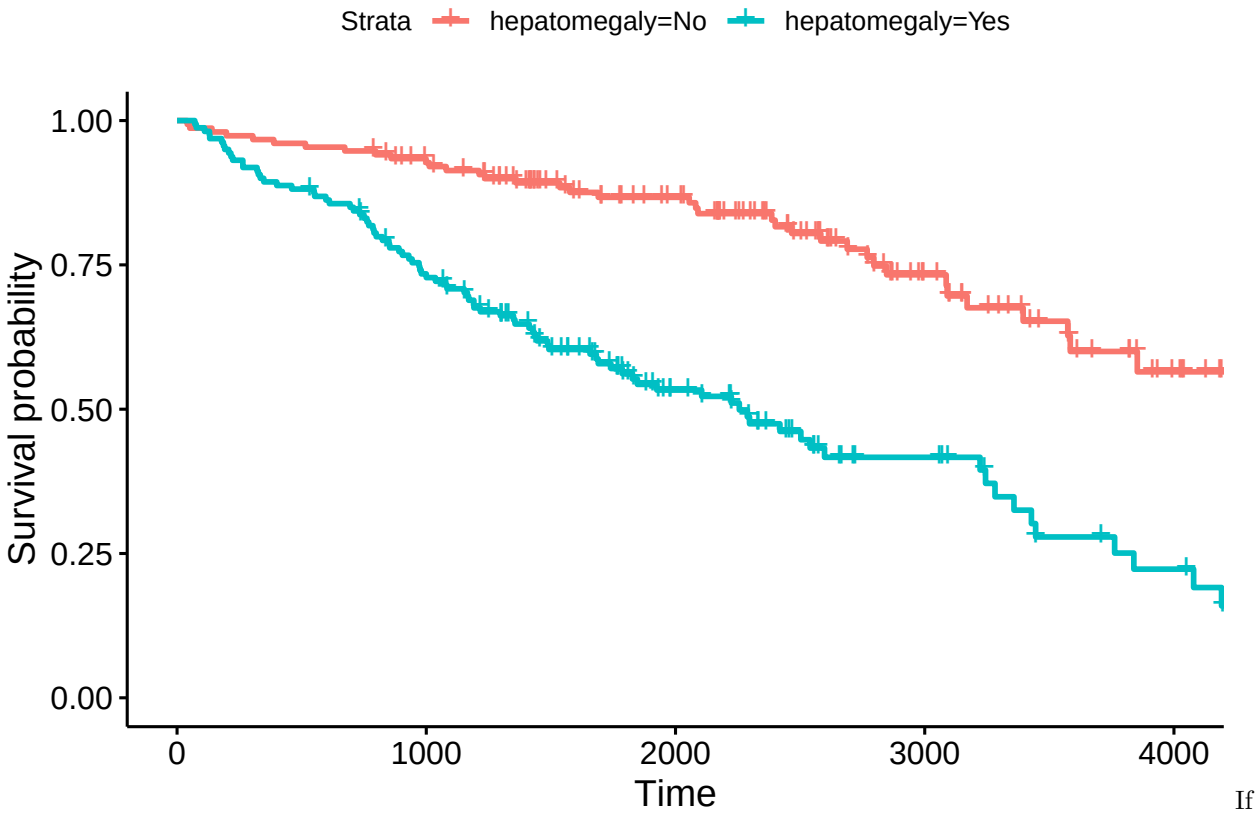
```
# Logrank
logrank_hepatomegaly = survdiff(Surv(n_days, status) ~ hepatomegaly, data = cirrhosis)
logrank_hepatomegaly
```

```
## Call:
## survdiff(formula = Surv(n_days, status) ~ hepatomegaly, data = cirrhosis)
##
## n=312, 106 observations deleted due to missingness.
##
##                     N Observed Expected (O-E)^2/E (O-E)^2/V
## hepatomegaly=No   152       37     71.7      16.8      40.2
## hepatomegaly=Yes 160       88     53.3      22.6      40.2
##
##  Chisq= 40.2  on 1 degrees of freedom, p= 2e-10
```

```
# Gehan Wilcoxon test
wilcoxon_hepatomegaly = gehan.wilcoxon.test(Surv(n_days, status) ~ hepatomegaly, data = cirrhosis)
wilcoxon_hepatomegaly
```

```
##
##  Gehan-Wilcoxon
##
## data:
## = 36.159, p-value = 1.818e-09
## alternative hypothesis: two-sided
```

```r
# KM Curve
survfit(Surv(n_days, status) ~ hepatomegaly, data = cirrhosis) |>
  ggsurvplot()
```



If the both logrank and Wilcoxon test are significant, having hepatomegaly significantly decreases survival probabilities.

Stage

Q: Does different stage of cirrhosis affect mortality?

```r
# Log rank test
logrank_stage = survdiff(Surv(n_days, status) ~ stage, data = cirrhosis)
logrank_stage
```

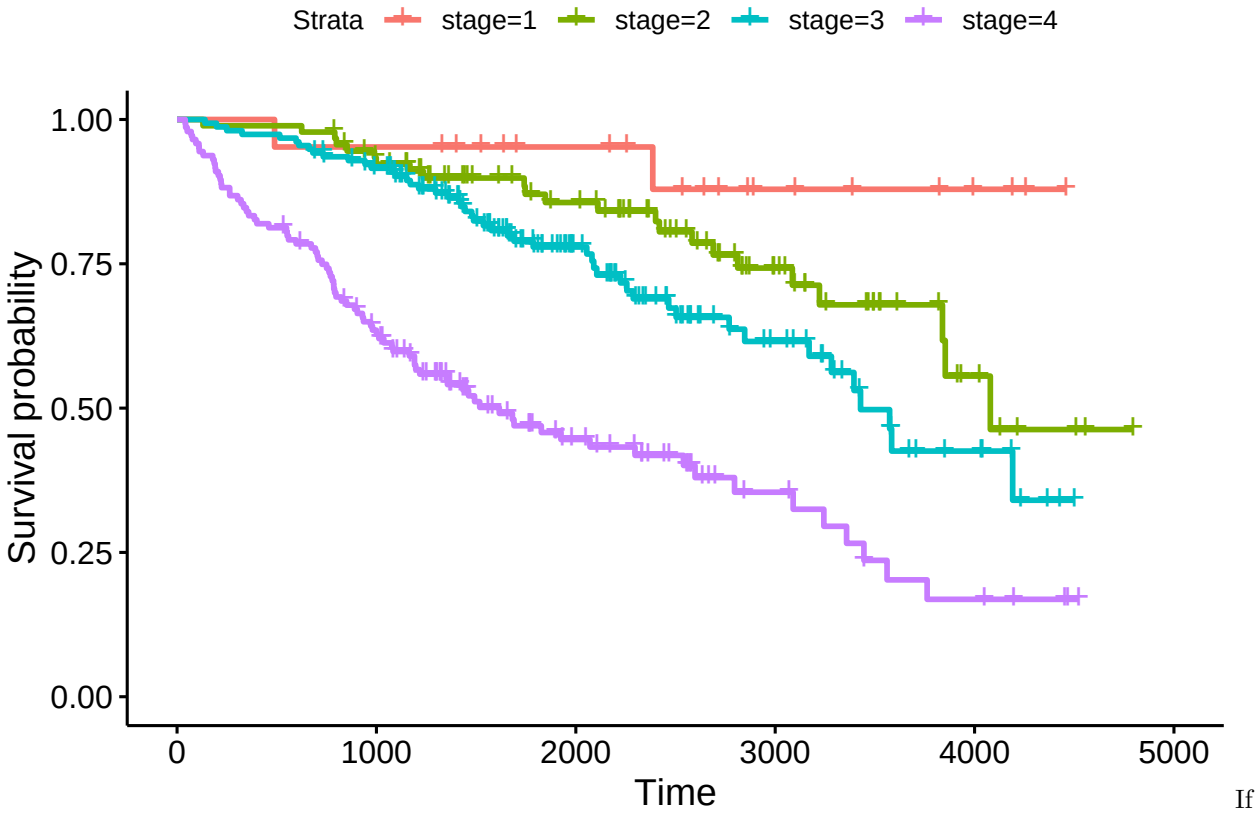
```
## Call:
## survdiff(formula = Surv(n_days, status) ~ stage, data = cirrhosis)
##
## n=412, 6 observations deleted due to missingness.
##
##           N Observed Expected (O-E)^2/E (O-E)^2/V
## stage=1  21        2     11.4      7.78      8.46
## stage=2  92       23     44.1     10.12     14.25
## stage=3 155       48     61.3      2.87      4.73
## stage=4 144       84     40.2     47.81     65.29
##
##  Chisq= 70.1  on 3 degrees of freedom, p= 4e-15
```

```r
# Gehan Wilcoxon test
wilcoxon_stage = gehan.wilcoxon.test(Surv(n_days, status) ~ stage, data = cirrhosis)
```

```
wilcoxon_stage
```

```
##
##  Gehan-Wilcoxon
##
## data:
## = 76.26, p-value = 2.22e-16
## alternative hypothesis: two-sided
```

```
# KM Curve
survfit(Surv(n_days, status) ~ stage, data = cirrhosis) |>
  ggsurvplot()
```



If the both logrank and Wilcoxon test are significant, having later stage of cirrhosis significantly lowers survival probabilities compared to earlier stage of cirrhosis.

Drug

Q: Does D-penicillamine improve risk of mortality?

```
# Log rank test
logrank_drug = survdiff(Surv(n_days, status) ~ drug, data = cirrhosis)
logrank_drug
```

```
## Call:
## survdiff(formula = Surv(n_days, status) ~ drug, data = cirrhosis)
##
## n=312, 106 observations deleted due to missingness.
##
##                         N Observed Expected (O-E)^2/E (O-E)^2/V
```

```
## drug=D-penicillamine 158       65     63.2    0.0502     0.102
## drug=Placebo         154       60     61.8    0.0513     0.102
##
##  Chisq= 0.1  on 1 degrees of freedom, p= 0.7
```

```
# Gehan Wilcoxon test
wilcoxon_drug = gehan.wilcoxon.test(Surv(n_days, status) ~ drug, data = cirrhosis)
wilcoxon_drug
```

```
##
##  Gehan-Wilcoxon
##
## data:
## = 0.0017763, p-value = 0.9664
## alternative hypothesis: two-sided
```

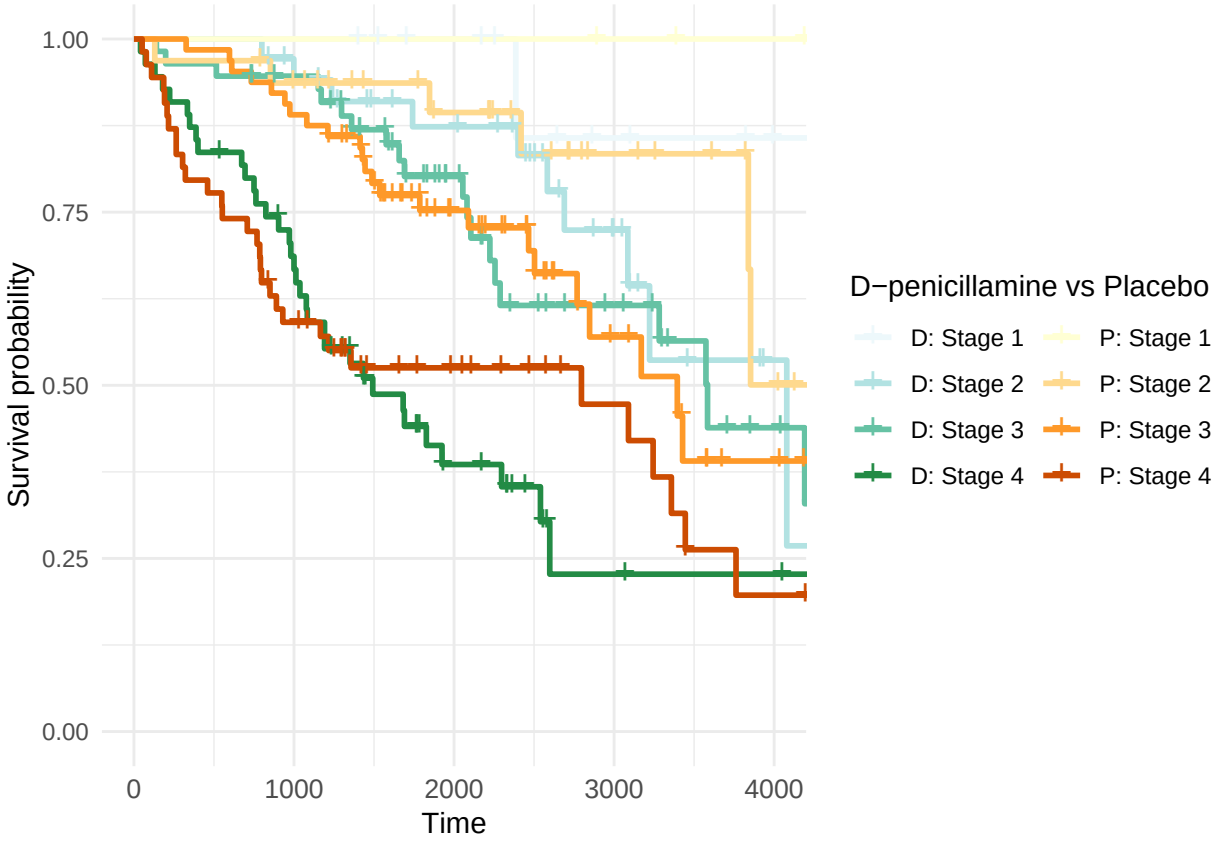
```
# KM Curve
custom_palette = c("#edf8fb", "#b2e2e2", "#66c2a4", "#238b45", # Similar shades for drug 1
                   "#ffffd4", "#fed98e", "#fe9929", "#cc4c02") # Similar shades for drug 2
survdiff(Surv(n_days, status) ~ drug, data = cirrhosis)
```

```
## Call:
## survdiff(formula = Surv(n_days, status) ~ drug, data = cirrhosis)
##
## n=312, 106 observations deleted due to missingness.
##
##                         N Observed Expected (O-E)^2/E (O-E)^2/V
## drug=D-penicillamine 158       65     63.2    0.0502     0.102
## drug=Placebo         154       60     61.8    0.0513     0.102
##
##  Chisq= 0.1  on 1 degrees of freedom, p= 0.7
```

```
legend_labels <- c(
  "D: Stage 1", "D: Stage 2",
  "D: Stage 3", "D: Stage 4",
  "P: Stage 1", "P: Stage 2",
  "P: Stage 3", "P: Stage 4"
)

km_plot = ggsurvplot(
  survfit(Surv(n_days, status) ~ drug + strata(stage), data = cirrhosis),
  palette = custom_palette,  # Apply the custom palette
  legend.title = "D-penicillamine vs Placebo",
  legend.labs = legend_labels
)

km_plot$plot = km_plot$plot +
  theme_minimal() +
  theme(axis.text.x = element_text(size = 10),
        legend.position = "right",
        plot.title = element_text(face="bold", size = 15),
        legend.labs = legend_labels) +
  guides(
    color = guide_legend(ncol = 2)  # Make the legend two columns
  )
```

```
print(km_plot)
```

```
## Warning in plot_theme(plot): The `legend.labs` theme element is not defined in the element hierarchy
## The `legend.labs` theme element is not defined in the element hierarchy.
```



If the both logrank and Wilcoxon test are not significant, D-penicillamine does not affect survival probabilities. Supporting argument: https://pmc.ncbi.nlm.nih.gov/articles/PMC8846335/

```
test_comparison = data.frame(
  Variable = c(
    "Age Recoded 4",
    "Age Recoded 3",
    "Hepatomegaly",
    "Stage",
    "Drug"
  ),
  Logrank = c(
    logrank_age_recoded_4$pvalue,
    logrank_age_recoded_3$pvalue,
    logrank_hepatomegaly$pvalue,
    logrank_stage$pvalue,
    logrank_drug$pvalue
  ),
  Wilcoxon = c(
    wilcoxon_age_recoded_4$p.value,
    wilcoxon_age_recoded_3$p.value,
    wilcoxon_hepatomegaly$p.value,
    wilcoxon_stage$p.value,
```

```
    wilcoxon_drug$p.value
  )
)
test_comparison |>
  knitr::kable(digits = 4,
               caption = "P-Values from Log-Rank and Wilcoxon Tests")
```

Table 2: P-Values from Log-Rank and Wilcoxon Tests

Variable	Logrank	Wilcoxon
Age Recoded 4	0.0000	0.0000
Age Recoded 3	0.0012	0.0009
Hepatomegaly	0.0000	0.0000
Stage	0.0000	0.0000
Drug	0.7498	0.9664

Feature Selection

Note: Also tried ChatGPT's R implementation of **Collett's Model Selection Approach** (involves p-value of log likelihood test. Gives the same thing as backward/stepwise selection. Since the implementation could be wrong and it's too lengthy. I won't put it there.

Performed forward, backward, and stepwise selection and LASSO to select relevant features.

Forward Selection

```
forward_model = stepAIC(coxph(Surv(n_days, status) ~ ., data = cirrhosis |>
                                dplyr::select(-id) |> na.omit()),
                        direction = "forward",
                        trace = F)

forward_model_interact = stepAIC(
  coxph(Surv(n_days, status) ~ 1, data = cirrhosis |>
                                dplyr::select(-id) |> na.omit()),
  scope = list(lower = ~ 1, upper = as.formula(paste(
    "~ . +", paste0("drug:", cirrhosis |> dplyr::select(-id, -n_days, -status, -drug) |> colnames(), co
  ))),
  tract = F,
  direction = "forward"
)
```

```
## Start:  AIC=1100.38
## Surv(n_days, status) ~ 1
##
##                       Df    AIC
## + drug:bilirubin       2 1028.4
## + drug:copper          2 1052.9
## + drug:albumin         2 1056.4
## + drug:ascites         3 1059.5
## + drug:stage           2 1060.5
## + drug:edema           3 1070.5
## + drug:prothrombin     2 1078.2
```

```
## + drug:hepatomegaly   3 1078.6
## + drug:age            2 1082.2
## + drug:spiders        3 1082.6
## + drug:sgot           2 1087.1
## + drug:tryglicerides  2 1091.4
## + drug:cholesterol    2 1094.3
## + drug:platelets      2 1098.9
## + drug:alk_phos       2 1099.4
## + drug:sex            3 1100.0
## <none>                  1100.4
##
## Step:  AIC=1028.38
## Surv(n_days, status) ~ drug:bilirubin
##
##                      Df     AIC
## + drug:stage          2  999.77
## + drug:albumin        2 1003.36
## + drug:copper         2 1007.57
## + drug:ascites        2 1010.16
## + drug:age            2 1014.06
## + drug:prothrombin    2 1019.03
## + drug:edema          2 1021.27
## + drug:hepatomegaly   2 1022.68
## + drug:spiders        2 1023.94
## + drug:sex            2 1025.63
## + drug:platelets      2 1026.21
## <none>                  1028.38
## + drug:sgot           2 1029.22
## + drug:alk_phos       2 1030.17
## + drug:tryglicerides  2 1031.79
## + drug:cholesterol    2 1032.31
##
## Step:  AIC=999.77
## Surv(n_days, status) ~ drug:bilirubin + drug:stage
##
##                      Df     AIC
## + drug:albumin        2  985.02
## + drug:copper         2  986.22
## + drug:ascites        2  992.54
## + drug:age            2  993.10
## + drug:prothrombin    2  993.26
## + drug:sgot           2  995.06
## + drug:edema          2  996.52
## + drug:sex            2  997.04
## + drug:platelets      2  999.60
## <none>                   999.77
## + drug:alk_phos       2 1000.30
## + drug:tryglicerides  2 1000.60
## + drug:spiders        2 1001.78
## + drug:hepatomegaly   2 1003.08
## + drug:cholesterol    2 1003.72
##
## Step:  AIC=985.02
## Surv(n_days, status) ~ drug:bilirubin + drug:stage + drug:albumin
```

```
##
##                       Df    AIC
## + drug:copper          2 974.52
## + drug:sex             2 979.11
## + drug:prothrombin     2 980.15
## + drug:age             2 980.35
## + drug:sgot            2 982.98
## + drug:tryglicerides   2 983.63
## <none>                   985.02
## + drug:ascites         2 985.43
## + drug:edema           2 986.47
## + drug:platelets       2 986.97
## + drug:spiders         2 987.25
## + drug:alk_phos        2 988.02
## + drug:hepatomegaly    2 988.31
## + drug:cholesterol     2 988.76
##
## Step:  AIC=974.52
## Surv(n_days, status) ~ drug:bilirubin + drug:stage + drug:albumin +
##     drug:copper
##
##                       Df    AIC
## + drug:prothrombin     2 970.36
## + drug:age             2 971.75
## + drug:tryglicerides   2 973.20
## <none>                   974.52
## + drug:sex             2 974.86
## + drug:sgot            2 975.26
## + drug:edema           2 975.52
## + drug:platelets       2 976.76
## + drug:ascites         2 976.89
## + drug:alk_phos        2 977.63
## + drug:spiders         2 977.71
## + drug:hepatomegaly    2 977.81
## + drug:cholesterol     2 978.29
##
## Step:  AIC=970.36
## Surv(n_days, status) ~ drug:bilirubin + drug:stage + drug:albumin +
##     drug:copper + drug:prothrombin
##
##                       Df    AIC
## + drug:age             2 968.83
## + drug:sgot            2 970.14
## + drug:sex             2 970.31
## <none>                   970.36
## + drug:tryglicerides   2 970.83
## + drug:hepatomegaly    2 972.58
## + drug:platelets       2 973.03
## + drug:edema           2 973.36
## + drug:spiders         2 973.66
## + drug:alk_phos        2 973.99
## + drug:ascites         2 974.20
## + drug:cholesterol     2 974.23
##
```

```
## Step:  AIC=968.83
## Surv(n_days, status) ~ drug:bilirubin + drug:stage + drug:albumin +
##     drug:copper + drug:prothrombin + drug:age
##
##                       Df    AIC
## + drug:sgot            2 966.29
## <none>                   968.83
## + drug:tryglicerides   2 970.15
## + drug:sex             2 970.55
## + drug:hepatomegaly    2 971.24
## + drug:edema           2 971.33
## + drug:platelets       2 971.50
## + drug:spiders         2 971.61
## + drug:cholesterol     2 971.97
## + drug:ascites         2 972.64
## + drug:alk_phos        2 972.66
##
## Step:  AIC=966.29
## Surv(n_days, status) ~ drug:bilirubin + drug:stage + drug:albumin +
##     drug:copper + drug:prothrombin + drug:age + drug:sgot
##
##                       Df    AIC
## <none>                   966.29
## + drug:edema           2 967.81
## + drug:tryglicerides   2 967.97
## + drug:hepatomegaly    2 968.80
## + drug:spiders         2 968.96
## + drug:sex             2 969.38
## + drug:platelets       2 969.64
## + drug:cholesterol     2 969.77
## + drug:ascites         2 969.79
## + drug:alk_phos        2 970.19
```

```
forward_model_interact  |>
  tbl_regression(exponentiate = TRUE) |>
  modify_caption("Cox Model From Forward Selection")
```

Backward Selection

```
backward_model = stepAIC(coxph(Surv(n_days, status) ~ ., data = cirrhosis |>
                               dplyr::select(-id) |> na.omit()),
                         direction = "backward",
                         trace = F)
backward_model_interact = stepAIC(coxph(as.formula(paste("Surv(n_days, status) ~ . +", paste0("drug:", c
                               dplyr::select(-id) |> na.omit()),
                         direction = "backward",
                         trace = F)

backward_model_interact |>
  tbl_regression(exponentiate = TRUE) |>
  modify_caption("Cox Model From Backward Selection")
```

Table 3: Cox Model From Forward Selection

Characteristic	HR[1]	95% CI[1]	p-value
drug * bilirubin			
D-penicillamine * bilirubin	1.07	1.00 to 1.14	0.048
Placebo * bilirubin	1.12	1.07 to 1.17	<0.001
drug * stage			
D-penicillamine * stage	1.47	0.99 to 2.20	0.059
Placebo * stage	1.79	1.20 to 2.68	0.004
drug * albumin			
D-penicillamine * albumin	0.39	0.20 to 0.73	0.004
Placebo * albumin	0.45	0.24 to 0.87	0.017
drug * copper			
D-penicillamine * copper	1.00	1.00 to 1.01	0.075
Placebo * copper	1.00	1.00 to 1.01	0.029
drug * prothrombin			
D-penicillamine * prothrombin	1.44	1.09 to 1.91	0.010
Placebo * prothrombin	1.27	1.02 to 1.59	0.035
drug * age			
D-penicillamine * age	1.03	1.00 to 1.05	0.037
Placebo * age	1.03	1.00 to 1.07	0.049
drug * sgot			
D-penicillamine * sgot	1.01	1.00 to 1.01	0.018
Placebo * sgot	1.00	1.00 to 1.01	0.18

[1]HR = Hazard Ratio, CI = Confidence Interval

Stepwise Selection

```
stepwise_model = stepAIC(coxph(Surv(n_days, status) ~ ., data = cirrhosis |>
                               dplyr::select(-id) |> na.omit()),
                         direction = "both",
                         trace = F)

stepwise_model_interact = stepAIC(coxph(as.formula(paste("Surv(n_days, status) ~ . +", paste0("drug:", 
                               dplyr::select(-id) |> na.omit()),
                         direction = "both",
                         trace = F)

stepwise_model_interact |>
  tbl_regression(exponentiate = TRUE) |>
  modify_caption("Cox Model From Stepwise Selection")
```

LASSO

```
x = model.matrix(Surv(n_days, status) ~ . - id, cirrhosis |> na.omit())[, -1]
y = Surv(cirrhosis |>
```

Table 4: Cox Model From Backward Selection

Characteristic	HR[1]	95% CI[1]	p-value
drug			
D-penicillamine	—	—	
Placebo	2.92	0.56 to 15.4	0.21
age	1.04	1.01 to 1.06	0.001
edema			
No	—	—	
Yes	2.29	1.26 to 4.16	0.007
bilirubin	1.07	1.02 to 1.13	0.004
cholesterol	1.00	1.00 to 1.00	0.062
albumin	0.48	0.28 to 0.84	0.009
copper	1.00	1.00 to 1.01	0.003
sgot	1.01	1.00 to 1.01	0.003
tryglicerides	1.00	0.99 to 1.00	0.046
platelets	1.00	1.00 to 1.00	0.27
prothrombin	1.20	0.98 to 1.47	0.078
stage	1.73	1.28 to 2.35	<0.001
drug * sgot			
Placebo * sgot	0.99	0.99 to 1.00	0.034
drug * tryglicerides			
Placebo * tryglicerides	1.01	1.00 to 1.01	0.007
drug * platelets			
Placebo * platelets	1.00	0.99 to 1.00	0.072

[1]HR = Hazard Ratio, CI = Confidence Interval

```
            na.omit() |>
            pull(n_days),
          cirrhosis |>
            na.omit() |>
            pull(status))
cv_model = cv.glmnet(x, y, family = "cox", alpha = 1)
best_lambda = cv_model$lambda.min
selected_coefficients = coef(cv_model, s = best_lambda)
selected_var_name = rownames(selected_coefficients)[which(selected_coefficients != 0)]
selected_var_name = map(selected_var_name, str_remove_all, "Yes") |> unlist()
lasso_model = coxph(as.formula(paste0("Surv(n_days, status) ~ ", paste(selected_var_name, collapse = "+
                              dplyr::select(-id) |> na.omit())
lasso_model |>
  tbl_regression(exponentiate = TRUE) |>
  modify_caption("Cox Model From LASSO")
```

Table 5: Cox Model From Stepwise Selection

Characteristic	HR[1]	95% CI[1]	p-value
drug			
D-penicillamine	—	—	
Placebo	2.92	0.56 to 15.4	0.21
age	1.04	1.01 to 1.06	0.001
edema			
No	—	—	
Yes	2.29	1.26 to 4.16	0.007
bilirubin	1.07	1.02 to 1.13	0.004
cholesterol	1.00	1.00 to 1.00	0.062
albumin	0.48	0.28 to 0.84	0.009
copper	1.00	1.00 to 1.01	0.003
sgot	1.01	1.00 to 1.01	0.003
tryglicerides	1.00	0.99 to 1.00	0.046
platelets	1.00	1.00 to 1.00	0.27
prothrombin	1.20	0.98 to 1.47	0.078
stage	1.73	1.28 to 2.35	<0.001
drug * sgot			
Placebo * sgot	0.99	0.99 to 1.00	0.034
drug * tryglicerides			
Placebo * tryglicerides	1.01	1.00 to 1.01	0.007
drug * platelets			
Placebo * platelets	1.00	0.99 to 1.00	0.072

[1]HR = Hazard Ratio, CI = Confidence Interval

Model Comparison

```
model_comparison = data.frame(
  Model = c(
    "Forward",
    "Forward with Interaction",
    "Backward",
    "Backward with Interaction",
    "Stepwise",
    "Stepwise with Interaction",
    "LASSO"
  ),
  Log_Lik = c(
    logLik(forward_model),
    logLik(forward_model_interact),
    logLik(backward_model),
    logLik(backward_model_interact),
    logLik(stepwise_model),
    logLik(stepwise_model_interact),
    logLik(lasso_model)
```

Table 6: Cox Model From LASSO

Characteristic	HR[1]	95% CI[1]	p-value
age	1.03	1.01 to 1.05	0.003
ascites			
No	—	—	
Yes	1.01	0.50 to 2.03	0.98
edema			
No	—	—	
Yes	1.52	0.92 to 2.51	0.10
bilirubin	1.09	1.05 to 1.13	<0.001
albumin	0.47	0.27 to 0.83	0.010
copper	1.00	1.00 to 1.01	0.003
sgot	1.00	1.00 to 1.01	0.012
prothrombin	1.28	1.05 to 1.56	0.013
stage	1.55	1.17 to 2.07	0.003

[1]HR = Hazard Ratio, CI = Confidence Interval

```
  ),
  AIC = c(
    AIC(forward_model),
    AIC(forward_model_interact),
    AIC(backward_model),
    AIC(backward_model_interact),
    AIC(stepwise_model),
    AIC(stepwise_model_interact),
    AIC(lasso_model)
  ),
  Kept_Variable = c(
    str_replace_all(paste(forward_model$formula[[3]][2]), " \\+", ","),
    str_replace_all(paste(forward_model_interact$formula[[3]][2]), " \\+", ","),
    str_replace_all(paste(formula(backward_model)[3]), " \\+", ","),
    str_replace_all(paste(formula(backward_model_interact)[3]), " \\+", ","),
    str_replace_all(paste(formula(stepwise_model)[3]), " \\+", ","),
    str_replace_all(paste(formula(stepwise_model_interact)[3]), " \\+", ","),
    str_replace_all(paste(formula(lasso_model)[3]), " \\+", ",")
  )
)
model_comparison |>
  knitr::kable() |>
  kable_styling(full_width = TRUE) |>
  column_spec(1, width = "2cm") |>
  column_spec(2, width = "2cm") |>
  column_spec(3, width = "2cm") |>
  column_spec(4, width = "7cm")
```

Model	Log_Lik	AIC	Kept_Variable

Forward	-467.8089	969.6179	drug, age, sex, ascites, hepatomegaly, spiders, edema, bilirubin, cholesterol, albumin, copper, alk_phos, sgot, tryglicerides, platelets, prothrombin
Forward with Interaction	-469.1465	966.2930	drug:bilirubin, drug:stage, drug:albumin, drug:copper, drug:prothrombin, drug:age
Backward	-469.6056	955.2111	age, edema, bilirubin, albumin, copper, sgot, prothrombin, stage
Backward with Interaction	-463.5469	957.0937	drug, age, edema, bilirubin, cholesterol, albumin, copper, sgot, tryglicerides, platelets, prothrombin, stage, drug:sgot, drug:tryglicerides, drug:platelets
Stepwise	-469.6056	955.2111	age, edema, bilirubin, albumin, copper, sgot, prothrombin, stage
Stepwise with Interaction	-463.5469	957.0937	drug, age, edema, bilirubin, cholesterol, albumin, copper, sgot, tryglicerides, platelets, prothrombin, stage, drug:sgot, drug:tryglicerides, drug:platelets
LASSO	-469.6052	957.2104	age, ascites, edema, bilirubin, albumin, copper, sgot, prothrombin, stage

Since stepwise model have the lowest AIC and best log likelihood statistics, "age + edema + bilirubin + albumin + copper + sgot + prothrombin + stage" will be used for the following models.

Precaution: ChatGPT said we need to choose a variable of interest before variable selection (forcing the variable in). From the context of the data, it seems like they are testing the effect of drug. However, by test statistics and unadjusted association between drug and survival probability. There is no apparent link. Maybe this could be the central topic of the following parts?

Multivariate analysis

```
cirrhosis <- cirrhosis |>
  mutate(
    status = case_when(
      status == "D" ~ 1,  # Event of interest (death)
      status == "C" | status == "CL" ~ 0,  # Censored data
      TRUE ~ as.numeric(status)))

# Fit the Cox proportional hazards model
cox_model <- coxph(Surv(n_days, status) ~ age + sex + bilirubin + albumin + copper + prothrombin + stage
                   data = cirrhosis)

# Summarize the results
cox_summary <- tbl_regression(cox_model, exponentiate = TRUE) %>%
  modify_caption("Multivariate Cox Proportional Hazards Analysis")

cox_summary
```

Table 8: Multivariate Cox Proportional Hazards Analysis

Characteristic	**HR**[1]	**95% CI**[1]	**p-value**
age	1.02	1.00 to 1.04	0.019
sex			
Female	—	—	
Male	1.30	0.75 to 2.26	0.35
bilirubin	1.12	1.08 to 1.16	<0.001
albumin	0.35	0.22 to 0.56	<0.001
copper	1.00	1.00 to 1.01	0.002
prothrombin	1.32	1.12 to 1.57	0.001
stage	1.46	1.13 to 1.88	0.003

[1]HR = Hazard Ratio, CI = Confidence Interval