Conditional Inference Trees & Cox Regression to Predict Heart Failure Survival Time

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https://archive.ics.uci.edu/ml/datasets/Heart+failure+clinical+recorc (https://archive.ics.uci.edu/ml/datasets/Heart+failure+clinical+recor

- All 299 patients had left ventricular systolic dysfunction

Initial Variables:

- age: age of the patient (years)
- anaemia: presence of critically low haematocrit levels (boolean)
- high blood pressure: if the patient has hypertension (boolean)
- creatinine phosphokinase (CPK): level of the CPK enzyme in the blood (mcg/L)
- diabetes: if the patient has diabetes (boolean)
- ejection fraction: percentage of blood leaving the heart at each contraction (percentage)
- platelets: platelets in the blood (kiloplatelets/mL)
- sex: woman or man (binary)
- serum creatinine: level of serum creatinine in the blood (mg/dL)
- serum sodium: level of serum sodium in the blood (mEq/L)
- smoking: if the patient smokes or not (boolean)
- time: follow-up period (days)
- [target] death event: if the patient deceased during the follow-up period (boolean)

```
library(skimr)
library(ggplot2)
library(dplyr)
library(tidyr)
library(survival)
library(survminer)
library(partykit)
library(coin)
library(survminer)
library(flexsurv)
library(randomForestSRC)
library(broom)
library(gtsummary)
```

Loading in the data

Creating Left Ventricular Ejection Fraction Groups set by Cardiology Experts (https://www.ncbi.nlm.nih.gov/books/NBK459131/). Rounding for averages instead of only using data for men and women.

```
HF <- read.csv("heart_failure_clinical_records_dataset.csv")

HF$anaemia = as.factor(HF$anaemia)
HF$diabetes = factor(HF$diabetes,levels=c(0,1),labels=c("Absent","Present"))
HF$hypertension = factor(HF$high_blood_pressure,levels=c(0,1),labels=c("Absent","Present"))

HF$sex = factor(HF$sex,levels=c(0,1),labels=c("Female","Male"))
HF$smoking = as.factor(HF$smoking)
HF$DEATH_EVENT = as.factor(HF$DEATH_EVENT)


HF <- select(HF, -high_blood_pressure)

skim(HF)
```

Data summary

Name	HF
Number of rows	299
Number of columns	13

________________________	
Column type frequency:	
factor	6
numeric	7
________________________	
Group variables	None

Variable type: factor

skim_variable	n_missing	complete_rate	ordered	n_unique	top_counts
anaemia	0	1	FALSE	2	0: 170, 1: 129
diabetes	0	1	FALSE	2	Abs: 174, Pre: 125
sex	0	1	FALSE	2	Mal: 194, Fem: 105
smoking	0	1	FALSE	2	0: 203, 1: 96
DEATH_EVENT	0	1	FALSE	2	0: 203, 1: 96
hypertension	0	1	FALSE	2	Abs: 194, Pre: 105

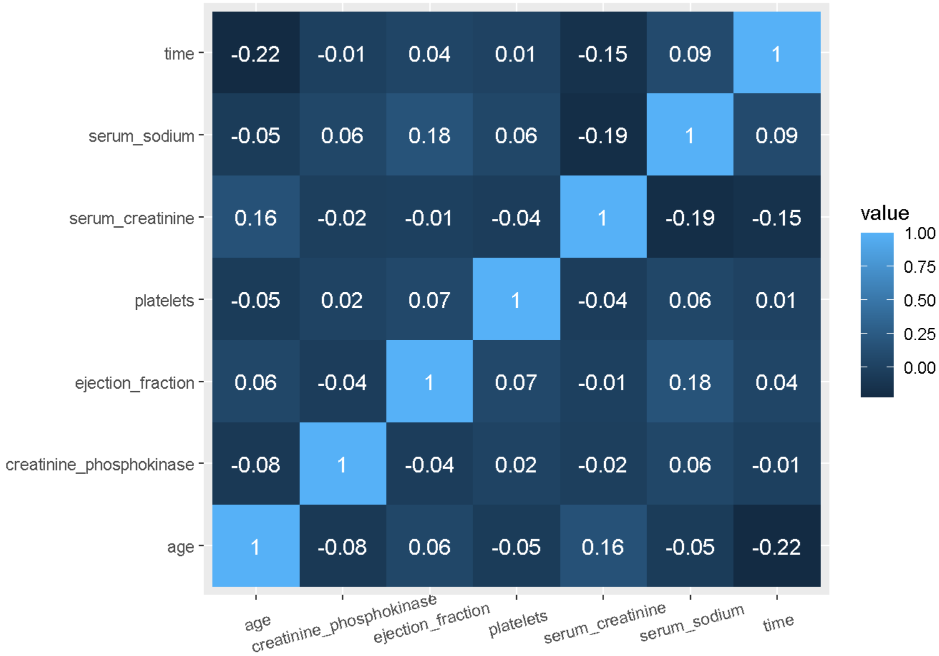
Variable type: numeric

skim_variable	n_missing	complete_rate	mean	sd	p0	p25	p50	p75	p100	hist
age	0	1	60.83	11.89	40.0	51.0	60.0	70.0	95.0	▆▇▇▂▁
creatinine_phosphokinase	0	1	581.84	970.29	23.0	116.5	250.0	582.0	7861.0	▇▁▁▁▁
ejection_fraction	0	1	38.08	11.83	14.0	30.0	38.0	45.0	80.0	▃▇▂▂▁
platelets	0	1	263358.03	97804.24	25100.0	212500.0	262000.0	303500.0	850000.0	▂▇▂▁▁
serum_creatinine	0	1	1.39	1.03	0.5	0.9	1.1	1.4	9.4	▇▁▁▁▁
serum_sodium	0	1	136.63	4.41	113.0	134.0	137.0	140.0	148.0	▁▁▃▇▁
time	0	1	130.26	77.61	4.0	73.0	115.0	203.0	285.0	▆▇▃▆▃

Correlation

Time and Serum_Creatinine have a correlation to Serum_Sodium of 0.15 & 0.19, respectively.

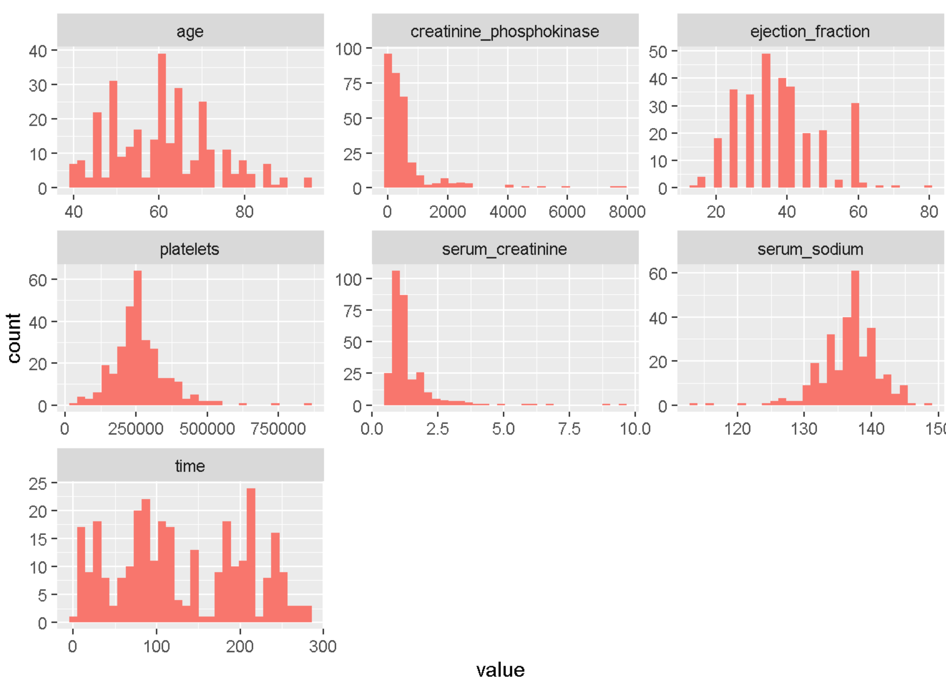
```
cormat <- HF %>% select(where(is.numeric)) %>% cor() %>% round(2)
melted_cormat <- reshape2::melt(cormat)

ggplot(data = melted_cormat, aes(x=Var1, y=Var2, fill=value)) +
  geom_tile() +
  geom_text(aes(Var2, Var1, label = value), color = "white", size = 4) +
   theme(axis.title.x=element_blank(),
        axis.title.y=element_blank(),
        axis.text.x = element_text(angle = 15, vjust = 0.8)
        )
```



Choosing to grab distributions based on having hypertension– what's traditionally seen as a good indicator of heart failure.

Doing so to look at, specifically, Ejection Fraction right after to see if there is correlation.

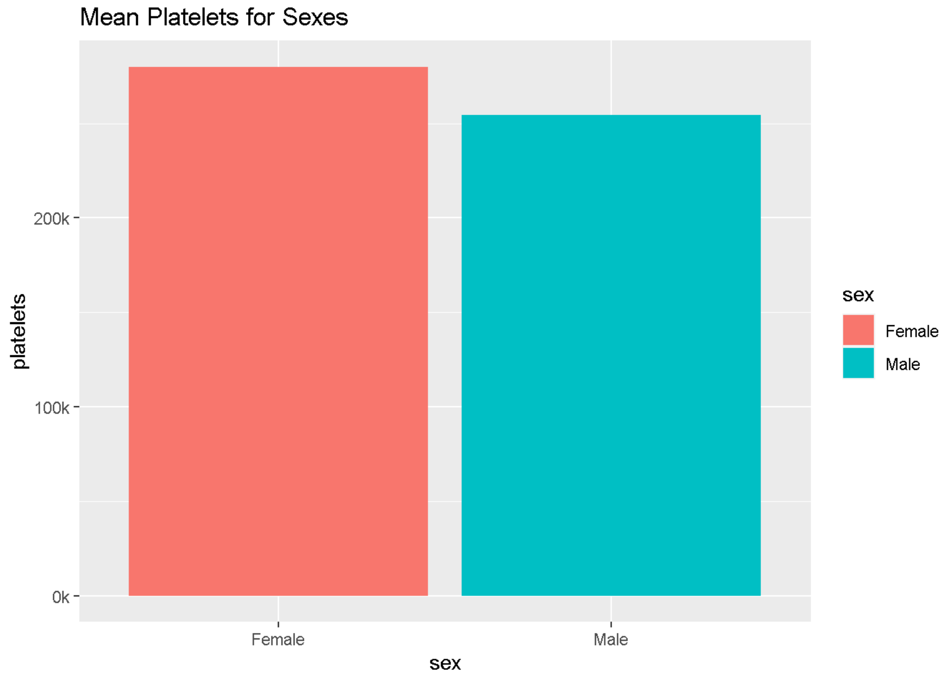
```
HF %>%
  purrr::keep(is.numeric) %>%
  gather() %>%
  ggplot(aes(value)) +
    facet_wrap(~ key, scales = "free") +
    geom_histogram(aes(fill="orange"), show.legend = FALSE)
```



Comparing `creatinine_phosphokinase` to Men & Women– those who smoke and those who do not.

- Noticing that the average `creatinine_phosphokinase` is higher for non-smokers.

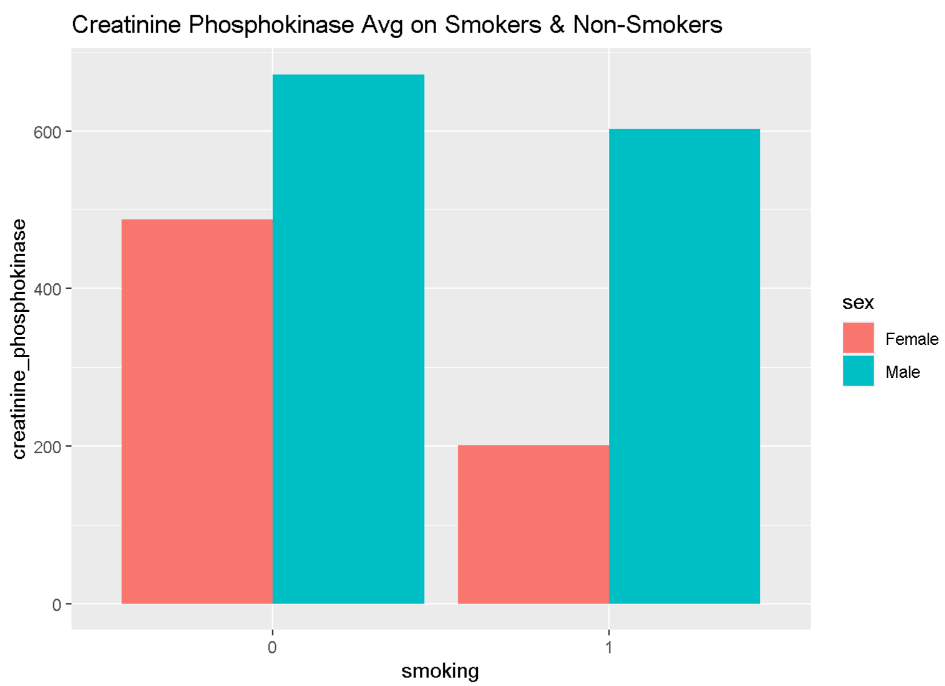
```
ggplot(HF, aes(x=sex, y=platelets, fill=sex)) +
  geom_bar(position = "dodge", stat="summary", fun="mean") +
  scale_y_continuous(labels = scales::label_number(suffix = "k", scale = 1e-3)) +
  ggtitle("Mean Platelets for Sexes")
```




```
HF %>% group_by(sex, DEATH_EVENT) %>%
  summarize(count = n(), .groups="drop")
```

```
## # A tibble: 4 × 3
##   sex    DEATH_EVENT count
##   <fct>  <fct>       <int>
## 1 Female 0              71
## 2 Female 1              34
## 3 Male   0             132
## 4 Male   1              62
```

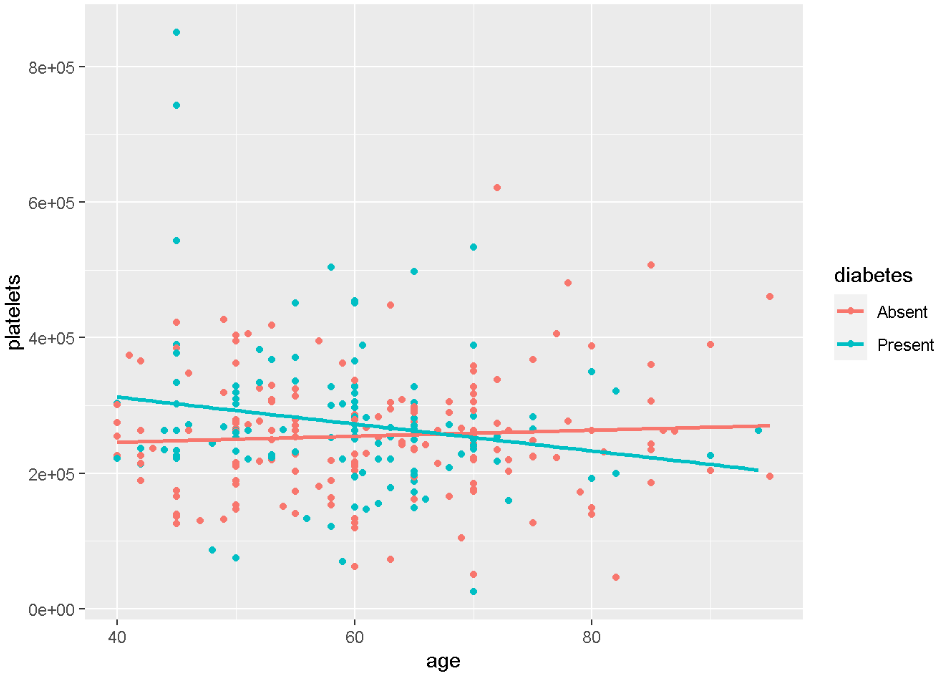
```
ggplot(HF, aes(x=smoking, y=creatinine_phosphokinase, fill=sex)) +
  geom_bar(position = "dodge", stat="summary", fun="mean") +
  ggtitle("Creatinine Phosphokinase Avg on Smokers & Non-Smokers")
```



- Finding out that for those diabetic, plateletes reduce as age increases.
- For those who aren't diabetic, plateletes generally stay the same and potentially, increase by a marginal amount.

Plateletes are incredibly important. Having too few plateletes can lead to internal bleeding in intestines or stroke.

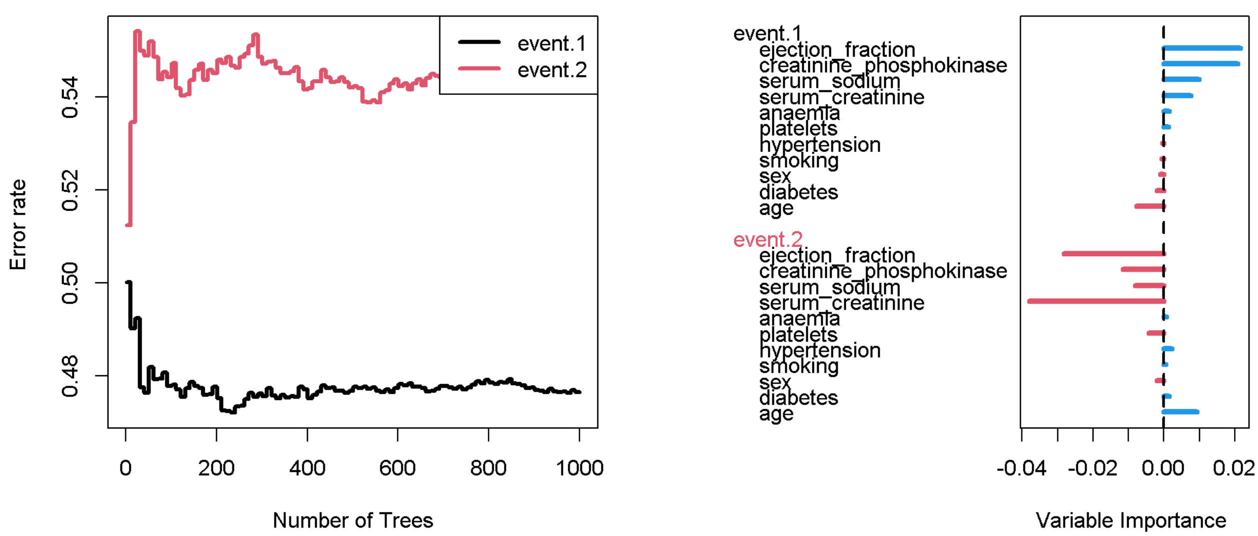
```
ggplot(HF, aes(x=age, y=platelets,color=diabetes)) + geom_point() +
  geom_smooth(method='lm', se = FALSE)
```



Random Forest Survival

Used to get variable importance chart.

```
# mtry means how many nodes at each split
fit <- rfsrc(Surv(time, DEATH_EVENT) ~ .,
             data = HF,
             ntree = 1000,
             importance = TRUE,
             nsplit = 5)

#fit
plot(fit)
```



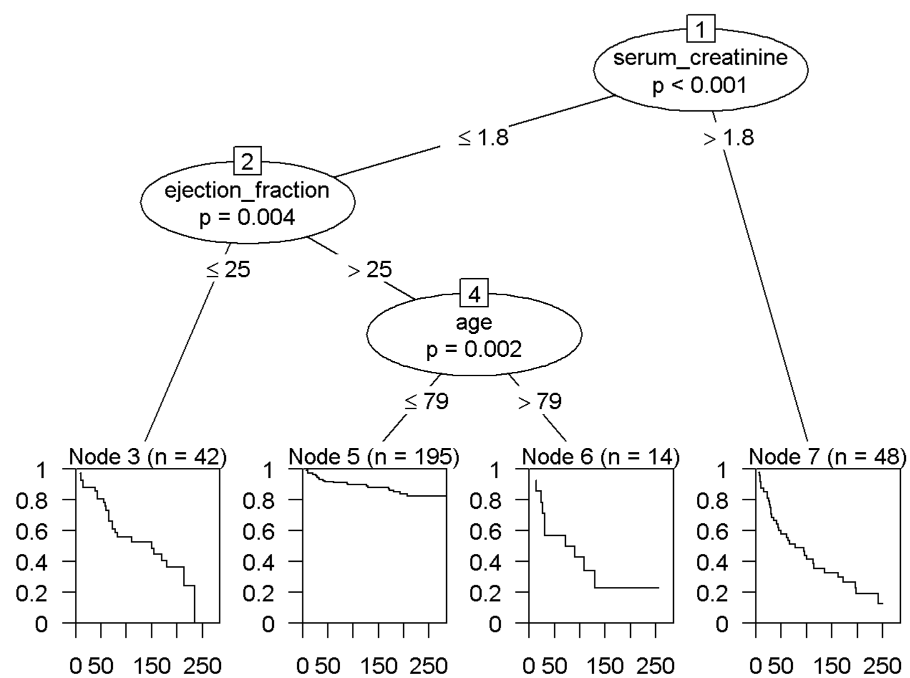
```
##
##                            event.1   event.2
## ejection_fraction           0.0216   -0.0282
## creatinine_phosphokinase    0.0209   -0.0115
## serum_sodium                0.0099   -0.0082
## serum_creatinine            0.0075   -0.0380
## anaemia                     0.0015    0.0006
## platelets                   0.0013   -0.0042
## hypertension               -0.0005    0.0023
## smoking                    -0.0007    0.0006
## sex                        -0.0010   -0.0020
## diabetes                   -0.0020    0.0014
## age                        -0.0078    0.0094
```

Conditional Inference Trees - Kaplan Meier Curves

We can see we have remaining cases in which the person did was not declared deceased due to the ending of the curve not dropping down to 0%.

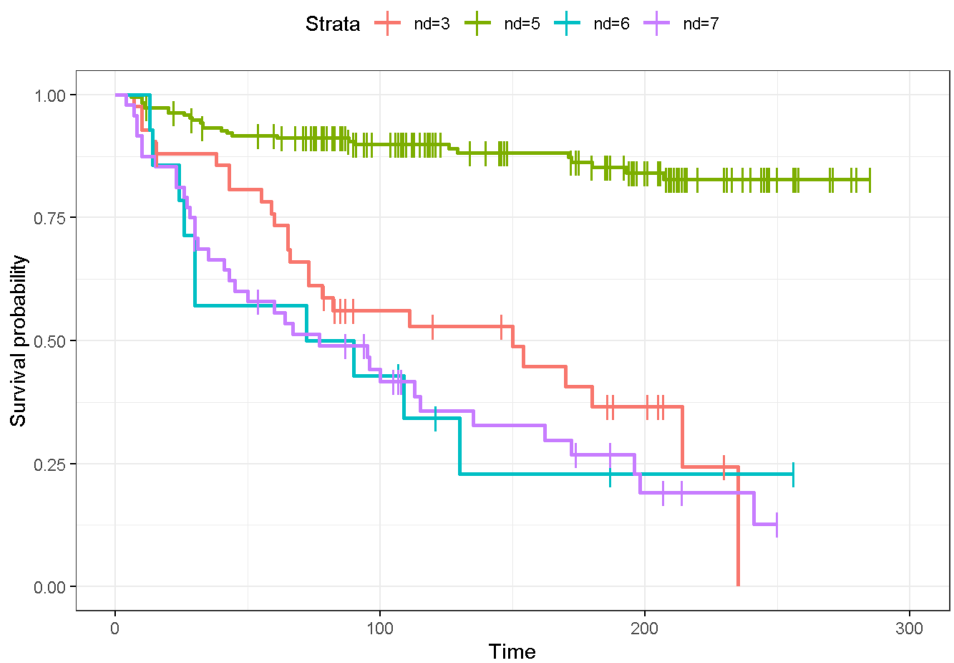
Insights from this graph include: * `Serum Creatinine` is highly significant with the showcased split at 1.8 for survival prediction.

```
set.seed(0)

# Won't directly go from factor to numeric. Needed for Survival Analysis.
HF$DEATH_EVENT = as.numeric(as.character(HF$DEATH_EVENT))

# Dropping categorical Ejection Fraction.


# Creating a Conditional Inference Tree for descriptive analytics
CondInfTree <- ctree(Surv(time, DEATH_EVENT) ~ .,
                     data = HF,
                     control = ctree_control(alpha = 0.05))


plot(CondInfTree)
```

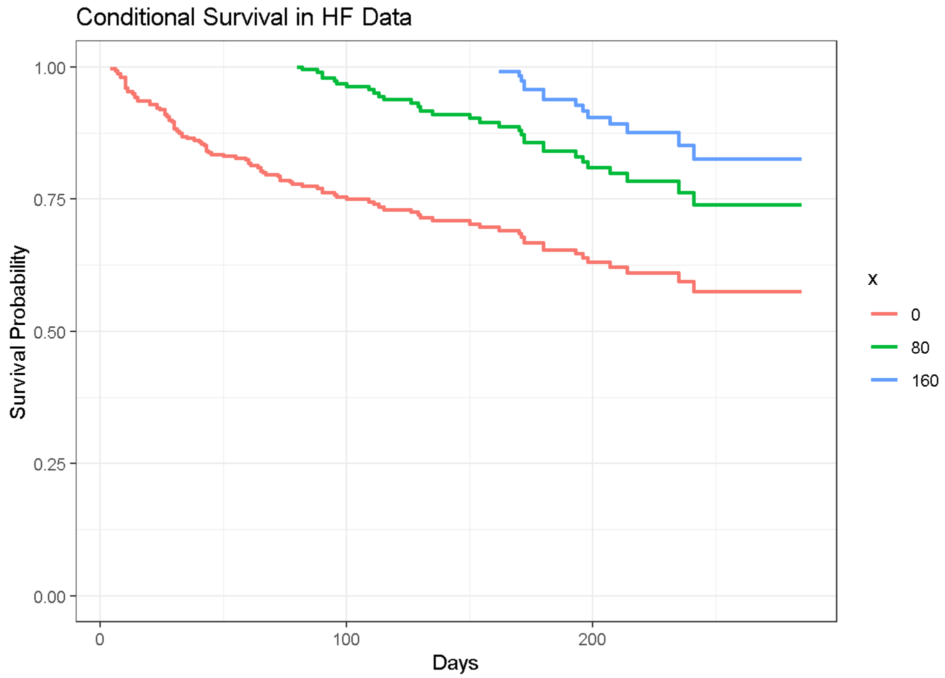


Plotting all node distributions/curves in one plot.

```
nd <- factor(predict(CondInfTree, type = "node"))

all_nd <- survfit(Surv(time, DEATH_EVENT) ~ nd, data = HF)

ggsurvplot(all_nd, data = HF,
           censor.shape="|",
           conf.int = FALSE, #surv.median.line = "hv",
           ggtheme = theme_bw())
```




```
remotes::install_github("zabore/condsurv")
library(condsurv)

fit1 <- survfit(Surv(time, DEATH_EVENT) ~ 1, data = HF)

gg_conditional_surv(
  basekm = fit1,
  at = seq(0, 160, 80),
  main = "Conditional Survival in HF Data",
  xlab = "Days",
  ylab = "Survival Probability"
  )
```




```
# Extracting survival curve for only one observation from the ctree. Perhaps an outlier.
#nd1 <- predict(CondInfTree, type = "prob")[[10]]
#summary(nd1, times=c(20, 45, 60, 80, 100, 10*(11:15)))
```

Constructing an exponential curve for previous graph's second node. * 24% probability of survival after t=130 days for patients older than 79, that have less than or equal to 1.8 in serum creatine, and an ejection fraction over 25.

```
K <- HF %>%
  filter(serum_creatinine <= 1.8, ejection_fraction > 25, age > 79)


# This one is best.
# The ~ 1 is our way ofletting R know that we aren't using any x variables. Just time and whether event occured which are both
 y variabes.
pred_k_surv <- survfit(Surv(time, DEATH_EVENT) ~ 1, data = K)

summary(pred_k_surv, times=c(20, 45, 60, 80, 100, 10*(11:15)))
```

```
## Call: survfit(formula = Surv(time, DEATH_EVENT) ~ 1, data = K)
##
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    20     12       2    0.857  0.0935       0.6921        1.000
##    45      8       4    0.571  0.1323       0.3630        0.899
##    60      8       0    0.571  0.1323       0.3630        0.899
##    80      7       1    0.500  0.1336       0.2961        0.844
##   100      6       1    0.429  0.1323       0.2341        0.785
##   110      4       1    0.343  0.1307       0.1624        0.724
##   120      4       0    0.343  0.1307       0.1624        0.724
##   130      3       1    0.229  0.1277       0.0765        0.683
##   140      2       0    0.229  0.1277       0.0765        0.683
##   150      2       0    0.229  0.1277       0.0765        0.683
```

- No pruning was done since most trees found revolve around the same 3 variables.
- Probability of survival after 150 days for those younger than 70 is 77%.
- Probability of survival after 200 days for those younger than 70 is 70%.

```
survfit(Surv(time, DEATH_EVENT) ~ 1, data = HF %>% filter(age <= 70)) %>%
  tbl_survfit(
    times = c(150,200),
    label_header = "**{time} Day Survival (95% CI) For Those Younger Than 70**"
    )
```

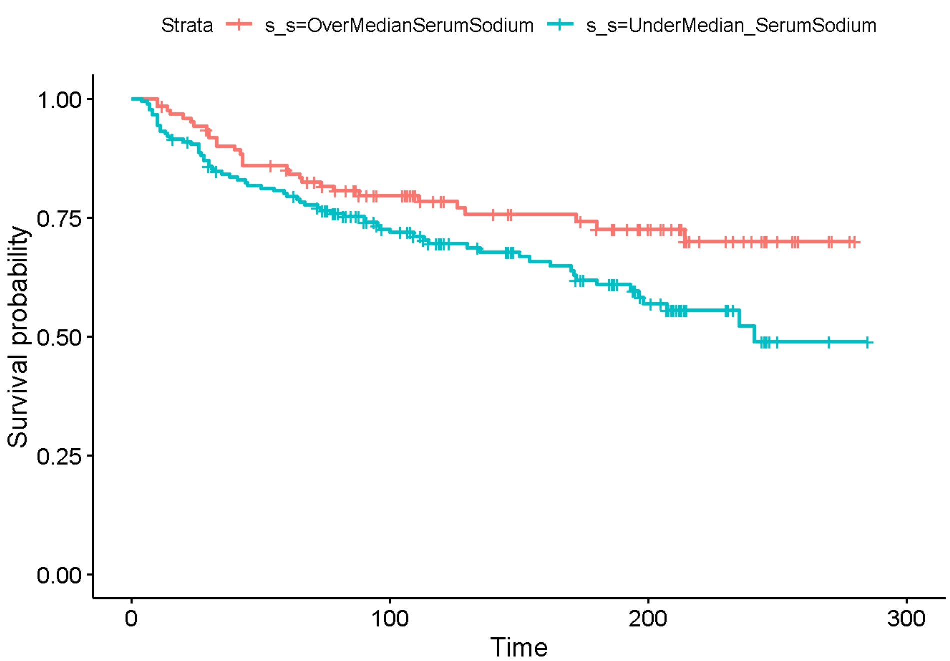
Characteristic	**150 Day Survival (95% CI) For Those Younger Than 70**	**200 Day Survival (95% CI) For Those Younger Than 70**
Overall	77% (71%, 82%)	70% (64%, 77%)

Looking at Serum Sodium Splitting at the median in case this dataset has any bias bc of outliers. * Finding that those with higher serum sodium have better survival rates, on average.

```
survfit(Surv(time, DEATH_EVENT) ~ 1, data = HF %>% filter(creatinine_phosphokinase <= 70)) %>%
  tbl_survfit(
    times = c(150,200),
    label_header = "**{time} Day Survival (95% CI) For Those Younger Than 70**"
    )
```

Characteristic	**150 Day Survival (95% CI) For Those Younger Than 70**	**200 Day Survival (95% CI) For Those Younger Than 70**
Overall	72% (57%, 90%)	72% (57%, 90%)

```
ss <- HF %>%
  mutate(s_s = ifelse((serum_sodium <= median(serum_sodium)), "UnderMedian_SerumSodium", "OverMedianSerumSodium"))

ss_fit <- survfit(Surv(time, DEATH_EVENT) ~ s_s, data=ss)

ggsurvplot(ss_fit, data = ss)
```




```
#CLEARLY, HAVING HIGHER SERUM_SODIUM MEANS HIGHER RATE OF SURVIVAL.
```

Cox Proportional Hazards Model (Cox Regression)

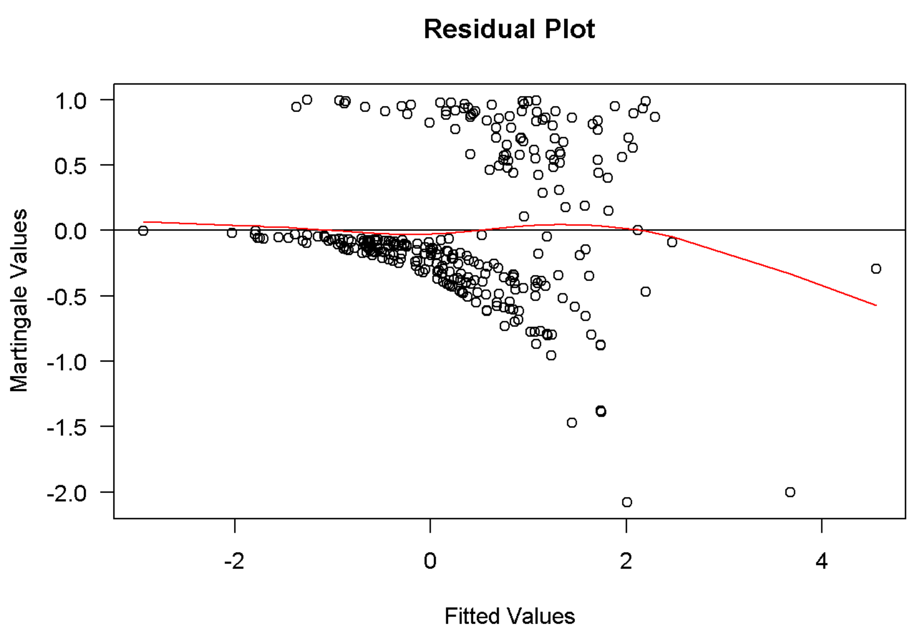
KM will make the curve based on event & time but that's all. We need to include the rest of the variables.

- At a given instance in time, someone who has hypertension is 0.42 times as likely to die as someone without hypertension adjusting for age.
- At any given instance in time, someone who does *not* have hypertension is 0.65 times as likely to die as someone who does, adjusting for age.
- Concordance: Goodness of fit for survival analysis.

```
# hypertension useful bc tree didn't output it. i paired it w/ age bc why not?
coxMod2 <- coxph(Surv(time, DEATH_EVENT) ~ hypertension + age, data=HF)
summary(coxMod2)
```

```
## Call:
## coxph(formula = Surv(time, DEATH_EVENT) ~ hypertension + age,
##     data = HF)
##
##   n= 299, number of events= 96
##
##                         coef exp(coef) se(coef)     z Pr(>|z|)
## hypertensionPresent 0.417717  1.518491 0.209708 1.992   0.0464 *
## age                 0.042424  1.043336 0.008693 4.880 1.06e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                     exp(coef) exp(-coef) lower .95 upper .95
## hypertensionPresent     1.518     0.6585     1.007     2.290
## age                     1.043     0.9585     1.026     1.061
##
## Concordance= 0.638  (se = 0.031 )
## Likelihood ratio test= 27.36  on 2 df,   p=1e-06
## Wald test            = 27.52  on 2 df,   p=1e-06
## Score (logrank) test = 28.25  on 2 df,   p=7e-07
```

```
# Deriving all significant variables, manually.
#summary(coxph(Surv(time, DEATH_EVENT) ~ ., data=HF))

FinalMod <- coxph(Surv(time, DEATH_EVENT) ~ age+anaemia+creatinine_phosphokinase+ejection_fraction+
                serum_creatinine+hypertension, data=HF)


# Red line didn't stray. Does so at end bc points hold more weight but overall, passes.
plot(predict(FinalMod), residuals(FinalMod, type = "martingale"), xlab = "Fitted Values",
     ylab = "Martingale Values", main = "Residual Plot", las = 1) +
  abline(h=0) +
  lines(smooth.spline(predict(FinalMod), residuals(FinalMod, type="martingale")), col="red")
```



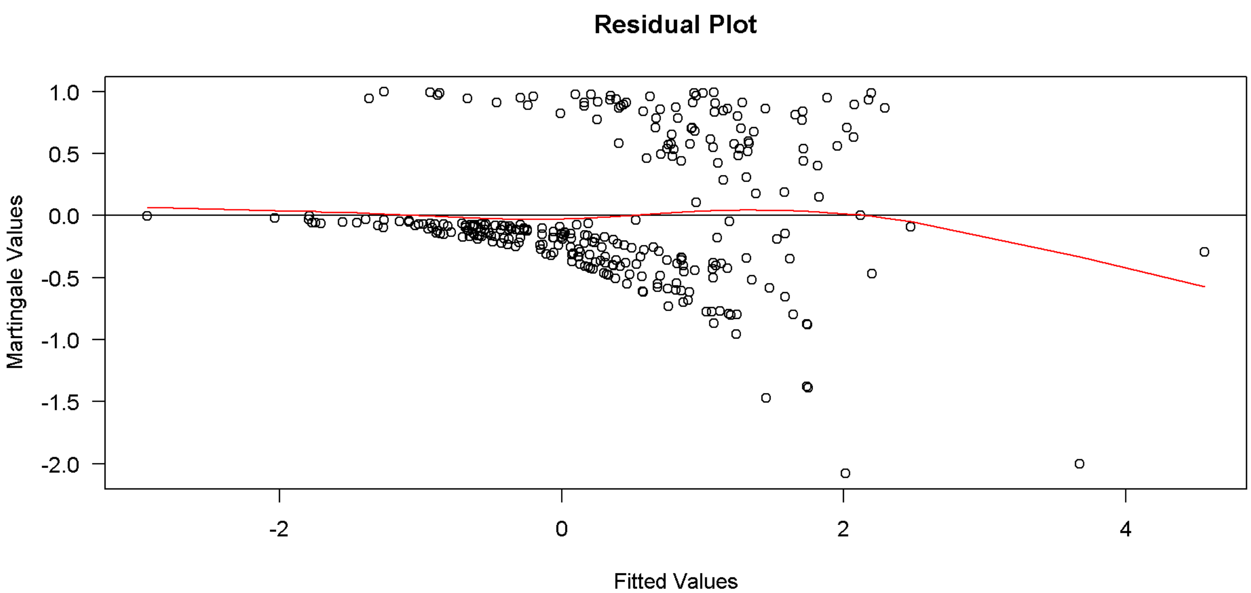

```
## integer(0)
```

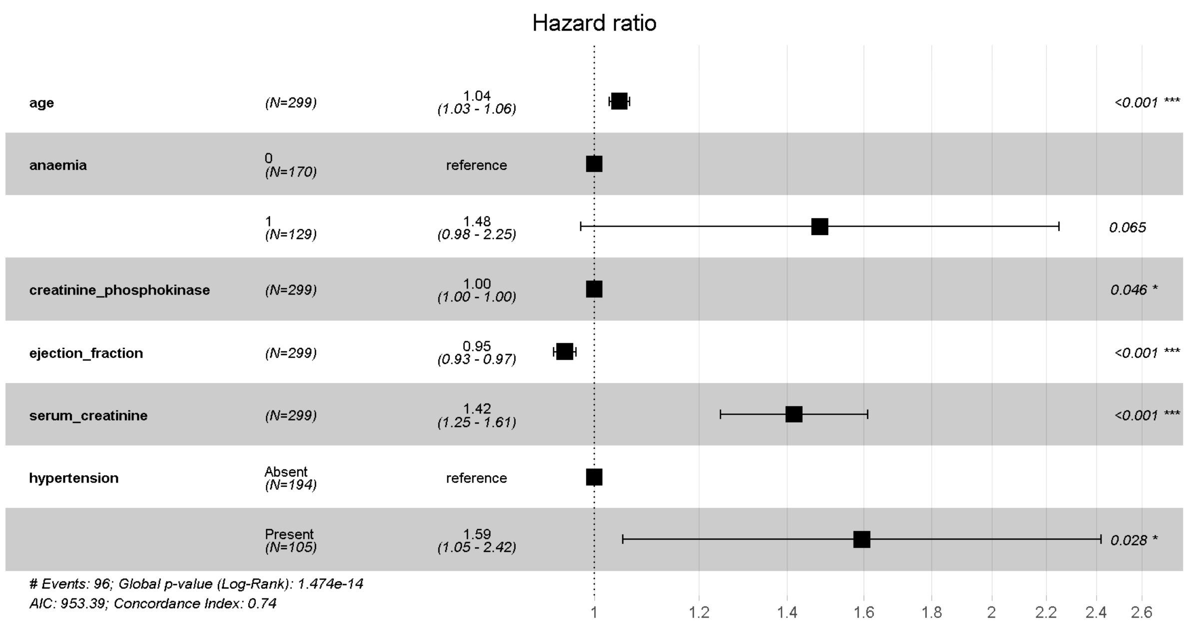
Checking Linearity of Model * Linearity of the final cox regression is sufficient. * `Anaemia` is not statistically significant.

```
sigMod = coxph(Surv(time, DEATH_EVENT) ~ age+anaemia+creatinine_phosphokinase+ejection_fraction+
                serum_creatinine+hypertension, data=HF)

plot(predict(sigMod), residuals(sigMod, type = "martingale"), xlab = "Fitted Values",
     ylab = "Martingale Values", main = "Residual Plot", las = 1) +
  abline(h=0) +
  lines(smooth.spline(predict(sigMod), residuals(sigMod, type="martingale")), col="red")
```

```
## integer(0)
```

```
ggforest(sigMod, data = HF)
```

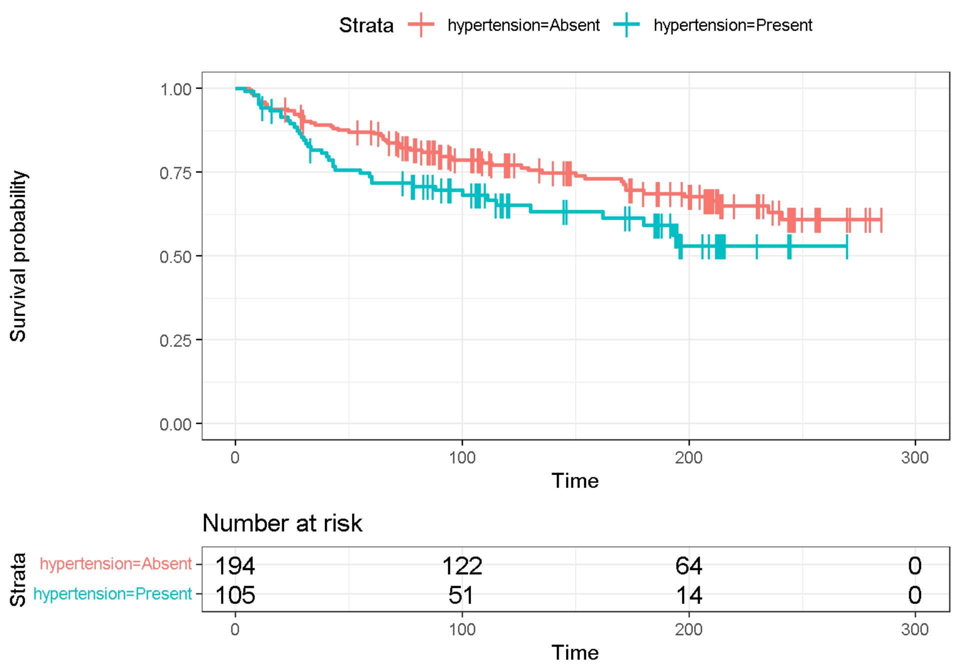




```
library(ggthemes)
finMod <- sigMod %>% tidy()

# finMod %>%  mutate(upper = estimate + 1.96 * std.error,
#          lower = estimate - 1.96 * std.error) %>%
#   mutate(across(all_of(c("estimate", "lower", "upper")), exp)) %>%
#   ggplot(aes(estimate, term, color = estimate > 1)) +
#   geom_vline(xintercept = 1, color = "gray75") +
#   geom_linerange(aes(xmin = lower, xmax = upper), size = 2.25, alpha = 0.28) +
#   geom_point(size = 4) +
#   theme_gdocs(base_size = 16) +
#   scale_color_manual(values = c("green4", "red3"), guide = "none") +
#   xlim(c(0, 3)) +
#   labs(title = "Hazard Ratios for Significant Variables", y = NULL,
#        x = "Hazard Ratio Estimates (95% C.I.)") +
#   theme(axis.text.y = element_text(hjust = 0, size = 18)) +
#     geom_text(label = exp(finMod$estimate) %>% round(2),
#               nudge_y = .2, nudge_x = .15)
```

Performing the Log-Rank Test on select variables to extract significance.

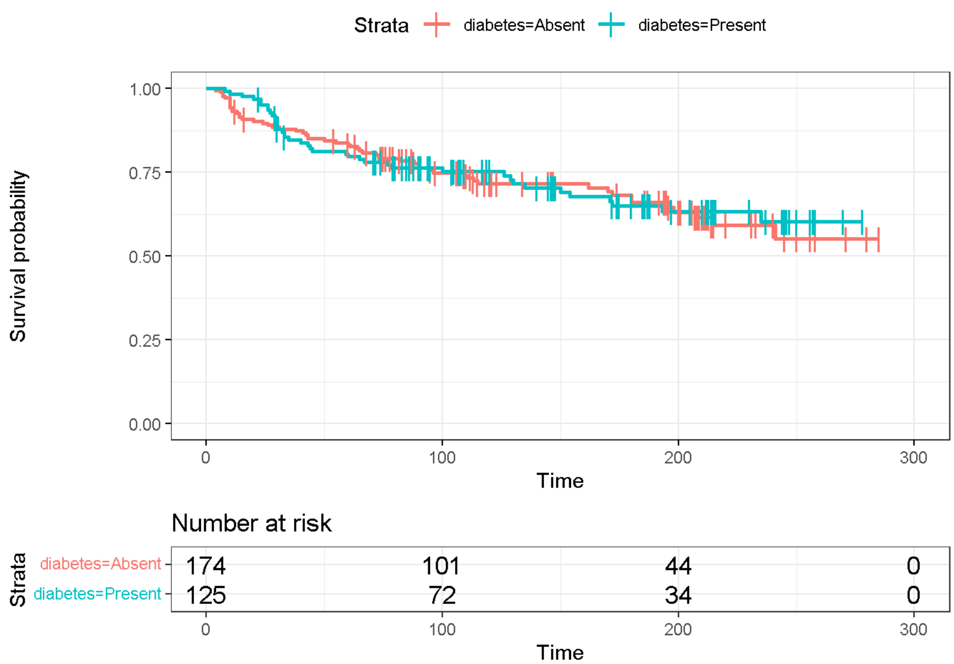
```
#Hypertension
ggsurvplot(survfit(Surv(time,DEATH_EVENT) ~ hypertension, data=HF),
           data = HF,
           censor.shape="|",
           conf.int = FALSE, #surv.median.line = "hv",
           risk.table = TRUE,
           ggtheme = theme_bw())
```




```
survdiff(Surv(time,DEATH_EVENT) ~ hypertension, data=HF)
```

```
## Call:
## survdiff(formula = Surv(time, DEATH_EVENT) ~ hypertension, data = HF)
##
##                         N Observed Expected (O-E)^2/E (O-E)^2/V
## hypertension=Absent  194       57     66.4      1.34      4.41
## hypertension=Present 105       39     29.6      3.00      4.41
##
##  Chisq= 4.4  on 1 degrees of freedom, p= 0.04
```

```
#Diabetes
ggsurvplot(survfit(Surv(time,DEATH_EVENT) ~ diabetes, data=HF),
           data = HF,
           censor.shape="|",
           conf.int = FALSE, #surv.median.line = "hv",
           risk.table = TRUE,
           ggtheme = theme_bw())
```




```
survdiff(Surv(time,DEATH_EVENT) ~ diabetes, data=HF)
```

```
## Call:
## survdiff(formula = Surv(time, DEATH_EVENT) ~ diabetes, data = HF)
##
##                    N Observed Expected (O-E)^2/E (O-E)^2/V
## diabetes=Absent  174       56       55    0.0172    0.0405
## diabetes=Present 125       40       41    0.0231    0.0405
##
##  Chisq= 0  on 1 degrees of freedom, p= 0.8
```

Binary Logistic Regression

Creating category variables for `Serum Creatinine` & `Creatinine Phosphokinase` due to their heavy right skewness.

Using 1 (https://labs.selfdecode.com/blog/creatine-kinase/#:~:text=The%20low%20normal%20limit%20for,3%2C%204%2C%205%5D./) and 2 (https://www.mayoclinic.org/tests-procedures/creatinine-test/about/pac-20384646#:~:text=The%20typical%20range%20for%20serum,52.2%20to%2091.9%20micromoles%2FL).

```
HF <- HF %>%
  mutate(SC_Condition = cut(HF$serum_creatinine, breaks = c(0, 0.7, 1.25, Inf),
         labels = c("Low", "Normal", "High"), include.lowest = TRUE),
        CPK_Condition = cut(HF$creatinine_phosphokinase, breaks = c(0, 30,200, 300, Inf),
         labels = c("Low", "Normal", "High", "Severely High"), include.lowest = TRUE)) %>%
  select(-serum_creatinine, -creatinine_phosphokinase)
```

```
set.seed(0)
library(caTools)

split_log <- sample.split(HF, SplitRatio = 0.7)
train_log <- subset(HF, split_log == TRUE) %>% select(-time)
test_log <- subset(HF, split_log == FALSE)


logit1 <- glm(DEATH_EVENT~., family = binomial,data = train_log)
summary(logit1)$coefficients[,4] %>% round(digits = 5)
```

```
##               (Intercept)                      age
##                   0.90491                  0.00005
##                  anaemia1           diabetesPresent
##                   0.24233                  0.78826
##         ejection_fraction                platelets
##                   0.00002                  0.58928
##              serum_sodium                  sexMale
##                   0.73230                  0.20661
##                  smoking1       hypertensionPresent
##                   0.97265                  0.10369
##        SC_ConditionNormal          SC_ConditionHigh
##                   0.37492                  0.01592
##       CPK_ConditionNormal         CPK_ConditionHigh
##                   0.60066                  0.27251
## CPK_ConditionSeverely High
##                   0.46066
```

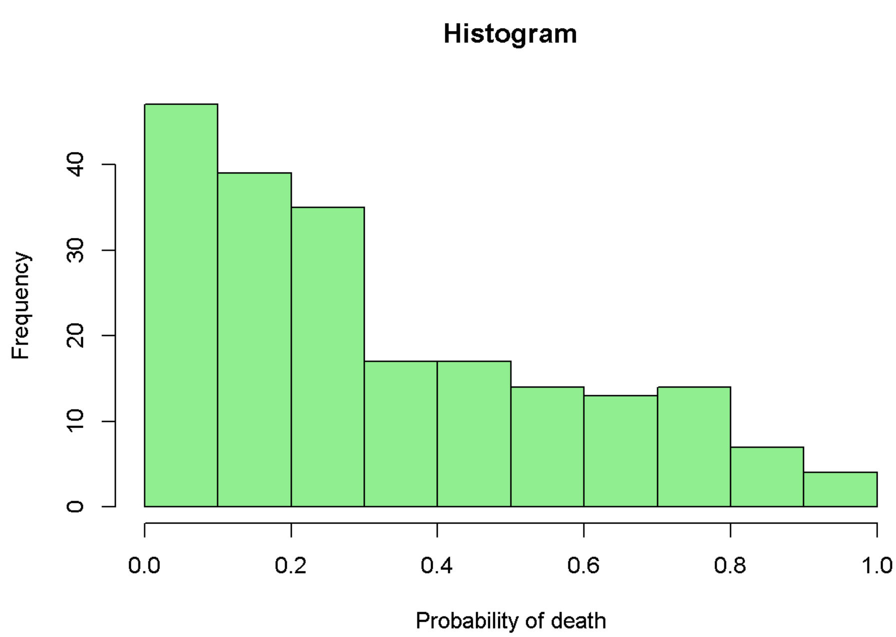
```
summary(logit1)$aic
```

```
## [1] 217.2686
```

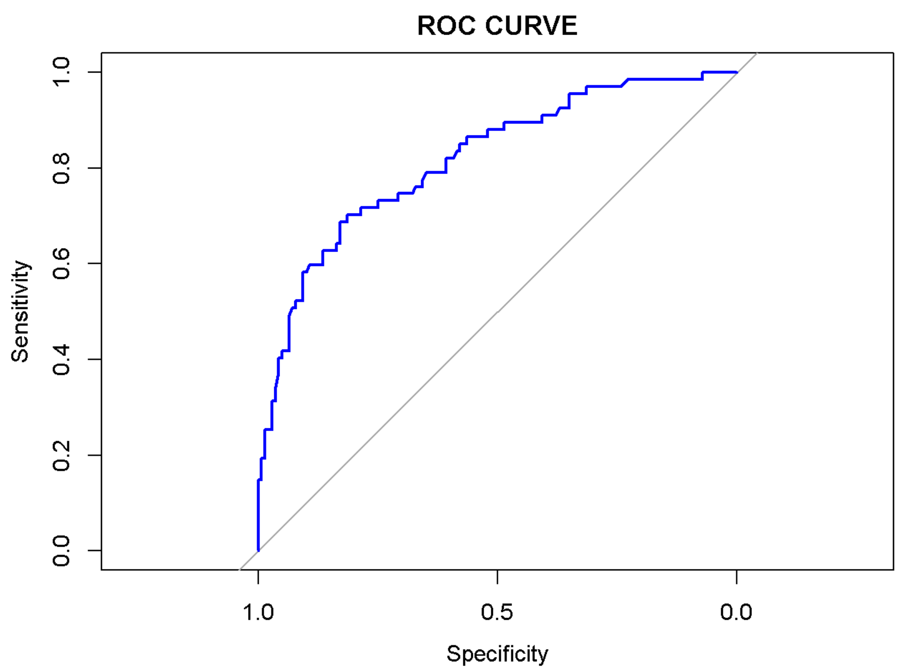
```
logit2 <- step(logit1, direction = "backward", trace = FALSE)
summary(logit2)$coefficients[,4] %>% round(digits = 5)
```

```
##        (Intercept)                age   ejection_fraction hypertensionPresent
##            0.00349            0.00003             0.00010             0.04829
##  SC_ConditionNormal    SC_ConditionHigh
##            0.40556            0.01190
```

```
hist(logit2$fitted.values, main=" Histogram ",xlab="Probability of death", col='light green')
```



```
r <- pROC::roc(DEATH_EVENT~logit2$fitted.values, data = train_log, plot = TRUE, main = "ROC CURVE", col= "blue")
```




```
optimal_roc <- r$thresholds[which.max(r$sensitivities + r$specificities)]


test_predicted_data <- test_log %>%
      mutate(p1=predict(logit2, newdata=test_log, type="response")) %>%
              mutate(Predict=ifelse(p1 < optimal_roc,0,1))


cm <- table(test_predicted_data$DEATH_EVENT,test_predicted_data$Predict) %>% prop.table()
rownames(cm) <- c("Obs. neg","Obs. pos")
colnames(cm) <- c("Pred. neg","Pred. pos")

ERROR.RESULTS <- tibble(
  Sensitivity=c(cm[1,1]/sum(cm[1,])),
  Specificity=c(cm[2,2]/sum(cm[2,])),
  FalsePositives=c(cm[2,1]/sum(cm[2,])),
  FalseNegatives=c(cm[1,2]/sum(cm[1,]))
)

efficiency <- sum(diag(cm))/sum(cm)

ERROR.RESULTS
```

```
## # A tibble: 1 × 4
##   Sensitivity Specificity FalsePositives FalseNegatives
##         <dbl>       <dbl>          <dbl>          <dbl>
## 1       0.698       0.586          0.414          0.302
```

```
efficiency
```

```
## [1] 0.6630435
```

Findings:

- At a given instance in time, someone who has `hypertension` is 0.42 times as likely to die as someone without hypertension adjusting for age.
- Probability of survival after 150 days for those younger than 70 is 77%.
- Probability of survival after 200 days for those younger than 70 is 70%.

- 24% probability of survival after t=130 days for patients older than 79, that have less than or equal to 1.8 in serum creatine, and an ejection fraction over 25.
- For those diabetic, plateletes seem to reduce as age increases.
- On average, `creatinine_phosphokinase` is higher for non-smokers.
- Men, on average, have higher `creatinine_phosphokinase`.
- Women, on average, have a higher `platelets` count.
- `age`, `ejection fraction`, the presence of `hypertension`, and a value of `serum creatinine` greater than 1.25 are the variables that contribute most to an accurate prediction of mortality.
- `age`, `creatinine_phosphokinase`, `ejection_fraction`, `serum_creatinine`, and the presence of `hypertension` are what most impact the survival rate probability.
- `sex`, `smoking` status, `diabetes`, and `anemia` are the fields that contribute the least to survival rates.