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

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Dataset found at this link (https://archive.ics.uci.edu/ml/datasets/Heart+failure+clinical+record

· All 299 patients had left ventricular systolic dysfunction

Initial Variables:

- · age: age of the patient (years)
- · anemia: presence of critically low haematocrit levels (boolean)
- · high blood pressure: if the patient has hypertension (boolean)
- creatine 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 creatine: 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 is deceased during the follow-up period (boolean)

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

Loading in the data

```
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)</pre>

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	

```
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
```

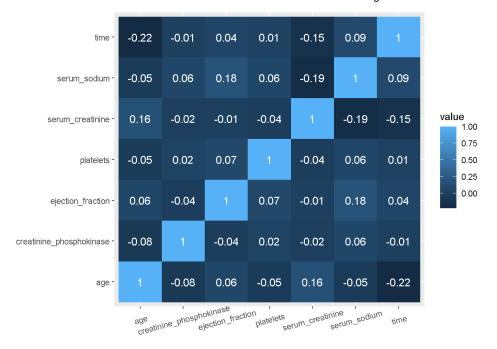
Exploratory Data Analysis

Correlation

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

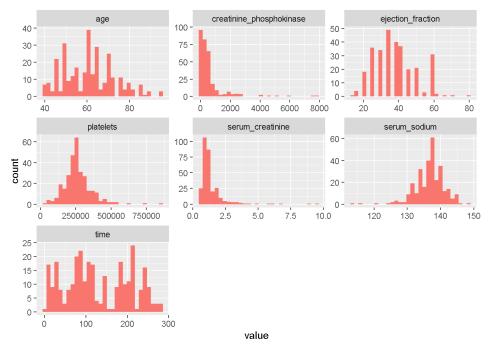
```
cormat <- HF %>% select(where(is.numeric)) %>% cor() %>% round(2)
melted_cormat <- reshape2::melt(cormat)

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.title.y=element_text(angle = 15, vjust = 0.8)
    )</pre>
```



· Histograms for all numeric variables





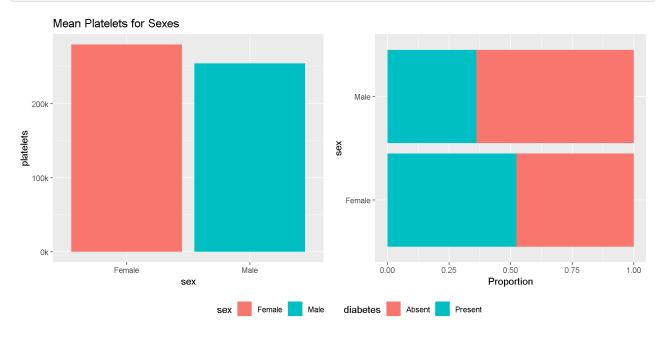
Comparing creatinine_phosphokinase to Men & Women— those who smoke and those who do not.

- Noticing that the average <code>creatinine_phosphokinase</code> is higher for non-smokers.
- Women, on average, have a higher platelets count.

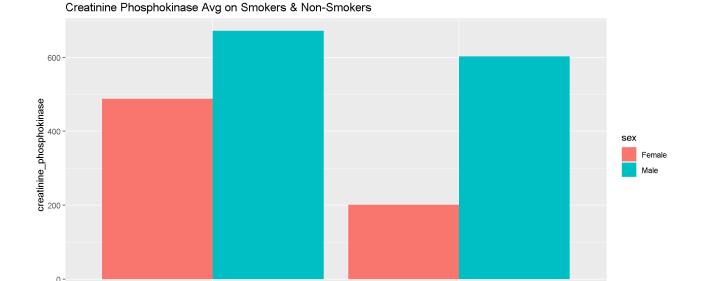
```
p1 <- ggplot(HF, aes(x=sex, y=platelets, fill=sex)) +
  geom_bar(position = "dodge", stat="summary", fun="mean") +
  scale_y_continuous(labels = scales::label_number(suffix = "k", scale = 1e-3)) +
  ggtitle("Mean Platelets for Sexes")

p2 <- ggplot(HF, aes(y=sex, fill=diabetes)) +
  geom_bar(position = "fill") + xlab("Proportion")

combined <- p1 + p2 & theme(legend.position = "bottom")
combined + plot_layout(guides = "collect")</pre>
```



```
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")
```



Chi-Squared Inference Testing

Is there a statistically significant difference in the proportion of Males and Females that: have anemia, have hypertension, are diabetic?

smoking

- No statistically significant difference on sex & anemia / sex & hypertension.

Ó

 Yes, there is a statistically significant difference between proportion of males that are diabetic and females that are diabetic in the larger population from this hospital. Females hold the higher proportion in being diabetic.

```
HF %>% select(sex, anaemia) %>%
  table() %>% chisq.test()
```

```
##
## Pearson's Chi-squared test with Yates' continuity correction
##
## data:
## X-squared = 2.2995, df = 1, p-value = 0.1294
```

```
HF %>% select(sex, hypertension) %>%
table() %>% chisq.test()
```

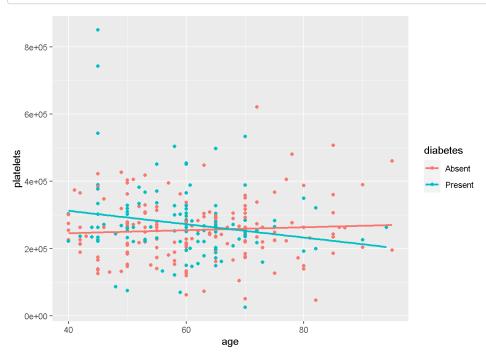
```
##
## Pearson's Chi-squared test with Yates' continuity correction
##
## data: .
## X-squared = 2.8293, df = 1, p-value = 0.09256
```

```
HF %>% select(sex, diabetes) %>%
  table() %>% chisq.test()
```

```
##
## Pearson's Chi-squared test with Yates' continuity correction
##
## data: .
## X-squared = 6.7839, df = 1, p-value = 0.009199
```

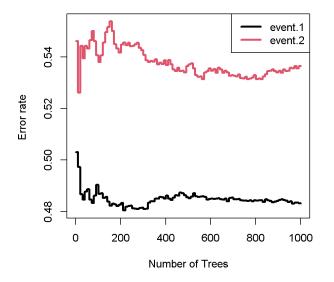
- Suggestion:
- For those diabetic, plateletes reduce as age increases.
- · For those who aren't diabetic, plateletes generally stay the same and potentially, increase by a marginal amount for an unknown reason.

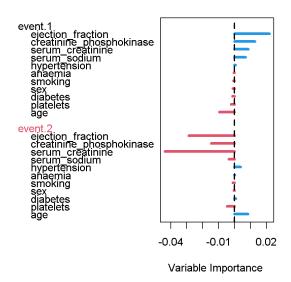
```
ggplot(HF, aes(x=age, y=platelets,color=diabetes)) + geom_point() +
geom_smooth(method='lm', se = FALSE)
```



Random Forest Survival

Used to get variable importance chart.



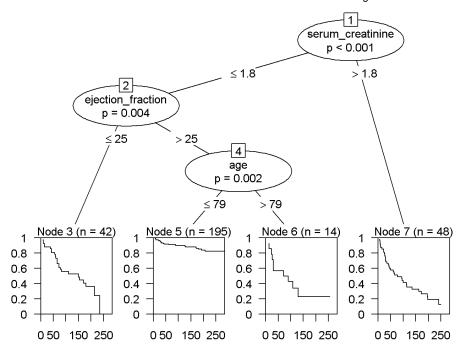


```
##
##
                               event.1
                                         event.2
## ejection_fraction
                                0.0220
                                         -0.0287
## creatinine_phosphokinase
                                0.0127
                                         -0.0145
## serum_creatinine
                                0.0085
                                         -0.0438
## serum_sodium
                                0.0068
                                         -0.0037
## hypertension
                                          0.0038
                                0.0005
## anaemia
                               -0.0005
                                          0.0002
## smoking
                               -0.0008
                                         -0.0010
                               -0.0010
                                         -0.0006
## sex
                               -0.0012
                                          0.0009
## diabetes
## platelets
                               -0.0021
                                         -0.0047
                                          0.0085
                               -0.0096
## age
```

Conditional Inference Trees - Kaplan Meier Curves

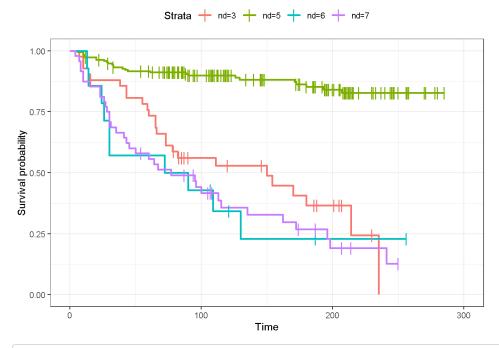
We can see we have remaining cases in which the person did was not declared deceased due to the ending of the curve not dropping down to 0%.

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



Plotting all node distributions/curves in one plot.

• Most notable is the second distribution (left to right) with a minimal survival rate of 82% at any given point in time.



```
# 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 first survival curve. * 48% probability of survival after t=150 days for patients older that have less than or equal to 1.8 in serum creatine, and an ejection fraction under 25.

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

# 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)))</pre>
```

```
## 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
           36
                   5
                         0.881 0.0500
                                             0.788
                                                         0.985
##
     45
            33
                         0.808 0.0612
                                             0.696
                                                         0.937
                    3
                        0.734 0.0688
                                                         0.882
##
     60
           31
                   3
                                            0.611
##
     80
           23
                    6 0.587 0.0768
                                            0.454
                                                         0.759
##
    100
           17
                  1 0.562 0.0776
                                            0.429
                                                         0.736
##
    110
           17
                    0
                        0.562 0.0776
                                            0.429
                                                         0.736
##
    120
                         0.529 0.0798
                                             0.393
                                                         0.711
           16
                    1
##
                                             0.393
                                                         0.711
    130
            14
                    0
                         0.529 0.0798
##
    140
            14
                    0
                         0.529 0.0798
                                             0.393
                                                         0.711
##
    150
           13
                    1
                         0.488 0.0834
                                             0.349
                                                         0.682
```

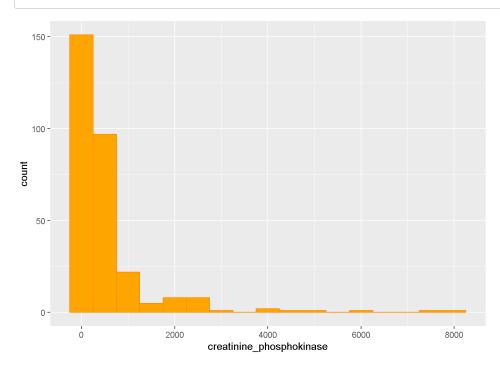
- No pruning was done since most trees found revolve around the same 3 variables.
- · Probability of survival after 150 days for those younger than 70 is 77%.
- Probability of survival after 200 days for those younger than 70 is 70%.

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

· Creatine Phosphokinase not being a split variable in the conditional inference tree lead me to look at in closer.

```
ggplot(HF, aes(x=creatinine_phosphokinase)) + geom_histogram(binwidth = 500, fill = "orange", color = "darkorange")
```



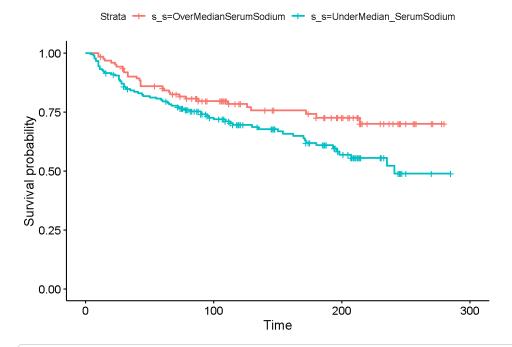
```
survfit(Surv(time, DEATH_EVENT) ~ 1, data = HF %>% filter(creatinine_phosphokinase <= 1000)) %>%
tbl_survfit(
times = c(150,200),
label_header = "**{time} Day Survival (95% CI) For Those with less than 1000 in Creatine Phosphokinase**"
)
```

150 Day Survival (95% CI) For Those with less than 200 Day Survival (95% CI) For Those with less than Characteristic 1000 in Creatine Phosphokinase 1000 in Creatine Phosphokinase

Overall 69% (64%, 76%) 62% (55%, 69%)

- · Looking at Serum Sodium Splitting at the median in case the lower-end outliers have too much weight.
- · Finding that those with higher serum sodium have better survival rates, on average.

```
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)</pre>
```



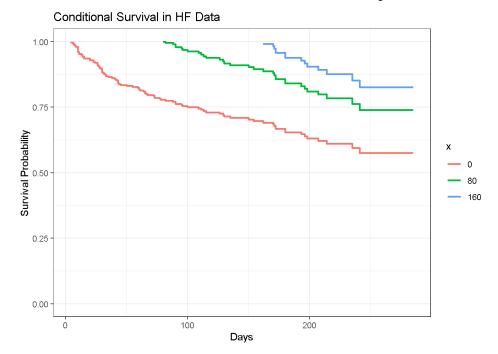
#CLEARLY, HAVING HIGHER SERUM_SODIUM MEANS HIGHER RATE OF SURVIVAL.

Conditional Survival: The probability of surviving further 't' years, given that a patient has already survived 's' years.

```
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"
   )</pre>
```



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.
- · 'Adjusting for age' meaning that this is true in a case where two people have the same 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)</pre>
```

```
## coxph(formula = Surv(time, DEATH_EVENT) ~ hypertension + age,
##
      data = HF)
##
##
    n= 299, number of events= 96
##
##
                         coef exp(coef) se(coef)
## hypertensionPresent 0.417717 1.518491 0.209708 1.992 0.0464
                     0.042424 1.043336 0.008693 4.880 1.06e-06 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
##
##
                     exp(coef) exp(-coef) lower .95 upper .95
## hypertensionPresent
                         1.518
                               0.6585
                                          1.007
                                                      2.290
                                  0.9585
                                             1.026
                                                      1.061
## age
                         1.043
##
## 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,
```

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

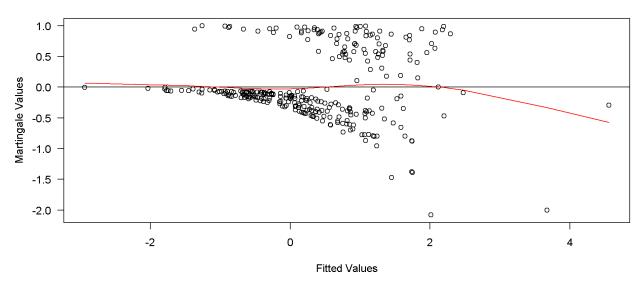
```
## Call:
## coxph(formula = Surv(time, DEATH_EVENT) ~ age + anaemia + creatinine_phosphokinase +
##
      ejection_fraction + serum_creatinine + hypertension, data = HF)
##
##
    n= 299, number of events= 96
##
##
                                                                 z Pr(>|z|)
                                 coef exp(coef) se(coef)
## age
                            4.361e-02 1.045e+00 8.853e-03 4.926 8.41e-07 ***
## anaemia1
                           3.933e-01 1.482e+00 2.129e-01 1.847 0.0648 .
## creatinine_phosphokinase 1.965e-04 1.000e+00 9.856e-05 1.993 0.0462 *
## ejection_fraction -5.179e-02 9.495e-01 1.005e-02 -5.152 2.57e-07 ***
## serum_creatinine 3.483e-01 1.417e+00 6.550e-02 5.318 1.05e-07 ***
## hypertensionPresent 4.668e-01 1.595e+00 2.129e-01 2.192 0.0284 *
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##
                           exp(coef) exp(-coef) lower .95 upper .95
                                                  1.0266
                                                            1.0629
## age
                              1.0446
                                         0.9573
## anaemia1
                              1.4818
                                         0.6749
                                                  0.9762
                                                            2.2493
## creatinine_phosphokinase 1.0002
                                         0.9998
                                                  1.0000
                                                            1.0004
## ejection_fraction 0.9495 1.0531 0.9310 ## serum_creatinine 1.4167 0.7059 1.2460
                                                            0.9684
                                                  0.9310
                                                           1.6108
## hypertensionPresent 1.5948 0.6270 1.0506 2.4209
## Concordance= 0.738 (se = 0.028)
## Likelihood ratio test= 77.02 on 6 df, p=1e-14
## Wald test = 85.82 on 6 df, p=2e-16
## Score (logrank) test = 83.51 on 6 df, p=7e-16
```

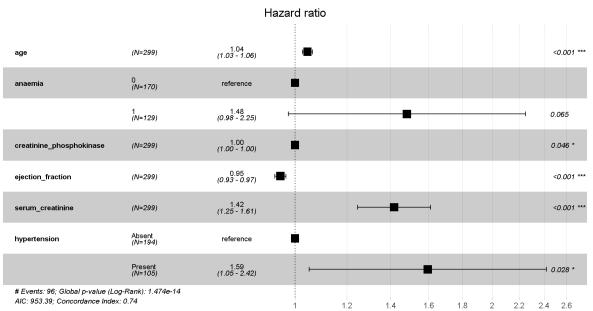
```
plot(predict(sigMod), residuals(sigMod, type = "martingale"), xlab = "Fitted Values",
   ylab = "Martingale Values", main = "Residual Plot", las = 1) +
   abline(h=0) +
   lines(smooth.spline(predict(sigMod), residuals(sigMod, type="martingale")), col="red")
```

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

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

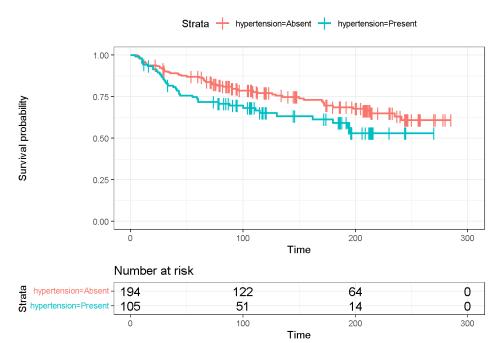
Residual Plot





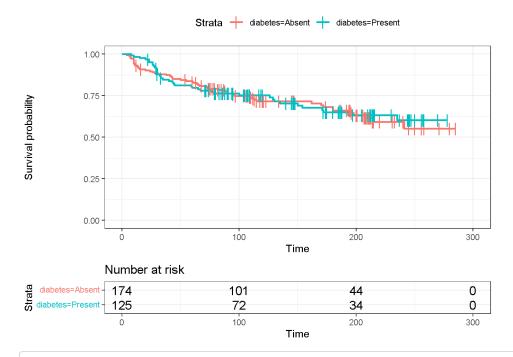
```
library(ggthemes)
finMod <- sigMod %>% tidy()
# finMod %>% mutate(upper = estimate + 1.96 * std.error,
           Lower = estimate - 1.96 * std.error) %>%
   mutate(across(all_of(c("estimate", "lower", "upper")), exp)) %>%
   ggplot(aes(estimate, term, color = estimate > 1)) +
   geom_vline(xintercept = 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") +
   x lim(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 between those with hypertension & age and those without those variables



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

```
## Call:
## survdiff(formula = Surv(time, DEATH_EVENT) ~ hypertension, data = HF)
##
##
                         N Observed Expected (0-E)^2/E (0-E)^2/V
## hypertension=Absent 194
                                 57
                                         66.4
                                                   1.34
                                                             4.41
## hypertension=Present 105
                                         29.6
                                                   3.00
                                                             4.41
##
## Chisq= 4.4 on 1 degrees of freedom, p= 0.04
```



```
## Call:
## call:
## survdiff(formula = Surv(time, DEATH_EVENT) ~ diabetes, data = HF)
##
##
##

N Observed Expected (0-E)^2/E (0-E)^2/V
## diabetes=Absent 174 56 55 0.0172 0.0405
## diabetes=Present 125 40 41 0.0231 0.0405
```

Binary Logistic Regression

Chisq= 0 on 1 degrees of freedom, p= 0.8

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

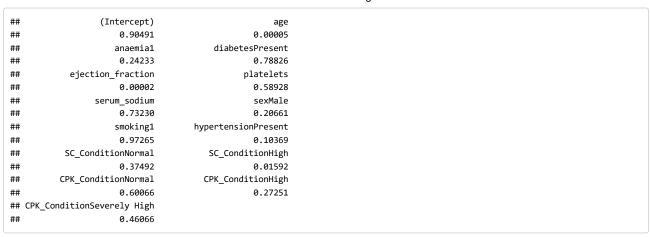
Using sources One (https://labs.selfdecode.com/blog/creatine-

 $kinase/\#: \sim : text = The \%20low \%20 normal \%20 limit \%20 for, 3\%2C\%204\%2C\%205\%5D./) \ and \ Two \ (https://www.mayoclinic.org/tests-procedures/creatinine-test/about/pac-20384646\#: \sim : text = The \%20 typical \%20 range \%20 for \%20 serum, 52.2 \%20 to \%20 91.9 \%20 micromoles \%2FL).$

```
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)
```



summary(logit1)\$aic

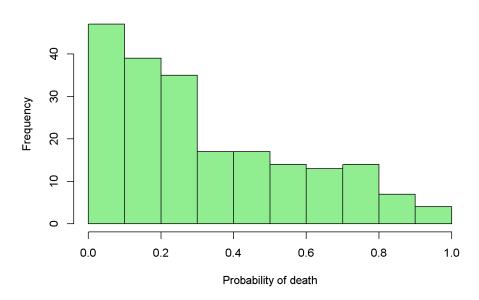
[1] 217.2686

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

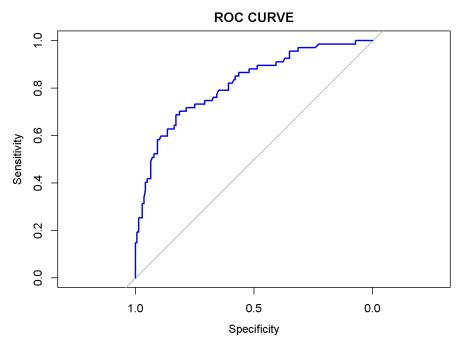
## 0.00349 0.00003 0.00010 0.04829 ## SC_ConditionNormal SC_ConditionHigh ## 0.40556 0.01190	##	(Intercept)	age	ejection_fraction	hypertensionPresent
	##	0.00349	0.00003	0.00010	0.04829
## 0.40556 0.01190	##	SC_ConditionNormal	SC_ConditionHigh		
	##	0.40556	0.01190		

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

Histogram



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



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

efficiency

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

Findings:

- There is a statistically significant difference between proportion of males that are diabetic and females that are diabetic in the larger population from this hospital. Females hold the larger proportion in being diabetic.
- 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.
- Suggestion: For those diabetic, plateletes seem to reduce as age increases. [Regressions may not be statistically significant].
- 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.
- anemia, smoking, sex status, and diabetes, and are the fields that contribute the least to survival rates, in that order (greatest contribution to least).