

# 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+records>  
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- All 299 patients had left ventricular systolic dysfunction

Initial Variables:

- age: age of the patient (years)
- anaemia: decrease of red blood cells or hemoglobin since last measure (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 <- HF %>%
  mutate(EF_Condition = cut(HF$ejection_fraction, breaks = c(0, 30, 40, 52, Inf),
    labels = c("Severe", "Moderate", "Mild", "Normal"), include.lowest = TRUE))

HF <- select(HF, -high_blood_pressure)

skim(HF)
```

Data summary

Name	HF
Number of rows	299
Number of columns	14
Column type frequency:	
factor	7
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
EF_Condition	0	1	FALSE	4	Mod: 126, Sev: 93, Mil: 41, Nor: 39

**Variable type: numeric**

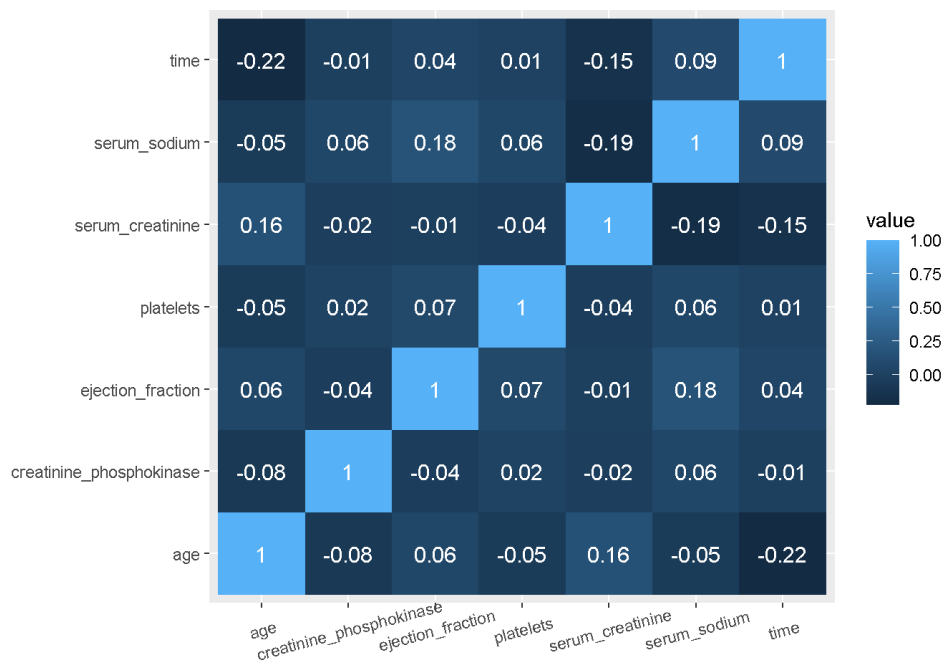
skim_variable	n_missing	complete_rate	mean	sd	p0	p25	p50	p75	p100	hist
age	0	1	60.83	11.89	40.0	51.0	60.0	70.0	95.0	
creatinine_phosphokinase	0	1	581.84	970.29	23.0	116.5	250.0	582.0	7861.0	
ejection_fraction	0	1	38.08	11.83	14.0	30.0	38.0	45.0	80.0	
platelets	0	1	263358.03	97804.24	25100.0	212500.0	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)

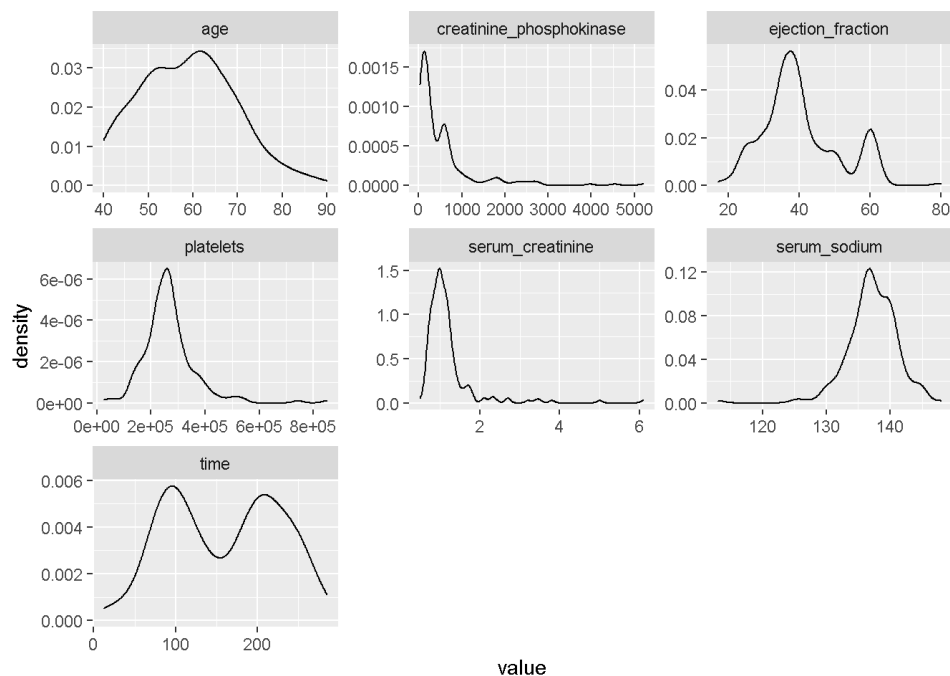
ggplot(data = melted_cormat, aes(x=Var1, y=Var2, fill=value)) +
  geom_tile() +
  geom_text(aes(Var2, Var1, label = value), color = "white", size = 4) +
  theme(axis.title.x=element_blank(),
        axis.title.y=element_blank(),
        axis.text.x = element_text(angle = 15, vjust = 0.8)
  )
```



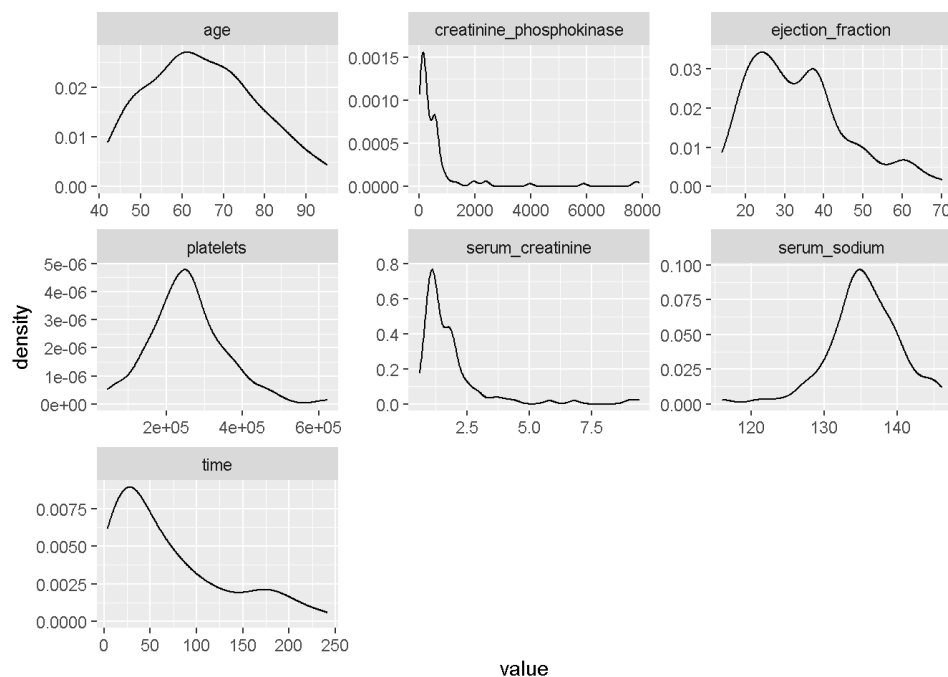
Choosing to grab distributions based on having hypertension– what's traditionally seen as a good indicator of heart failure.

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

```
HF %>% filter(DEATH_EVENT==0) %>%
  purrr::keep(is.numeric) %>%
  gather() %>%
  ggplot(aes(value)) +
    facet_wrap(~ key, scales = "free") +
    geom_density()
```



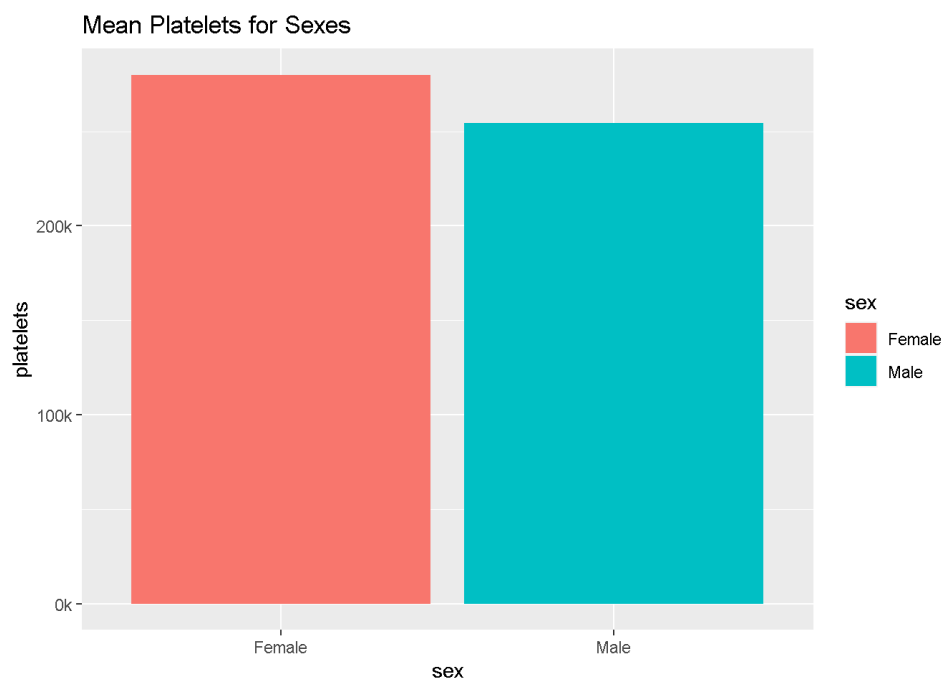
```
HF %>% filter(DEATH_EVENT==1) %>%
  purrr::keep(is.numeric) %>%
  gather() %>%
  ggplot(aes(value)) +
    facet_wrap(~ key, scales = "free") +
    geom_density()
```



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.

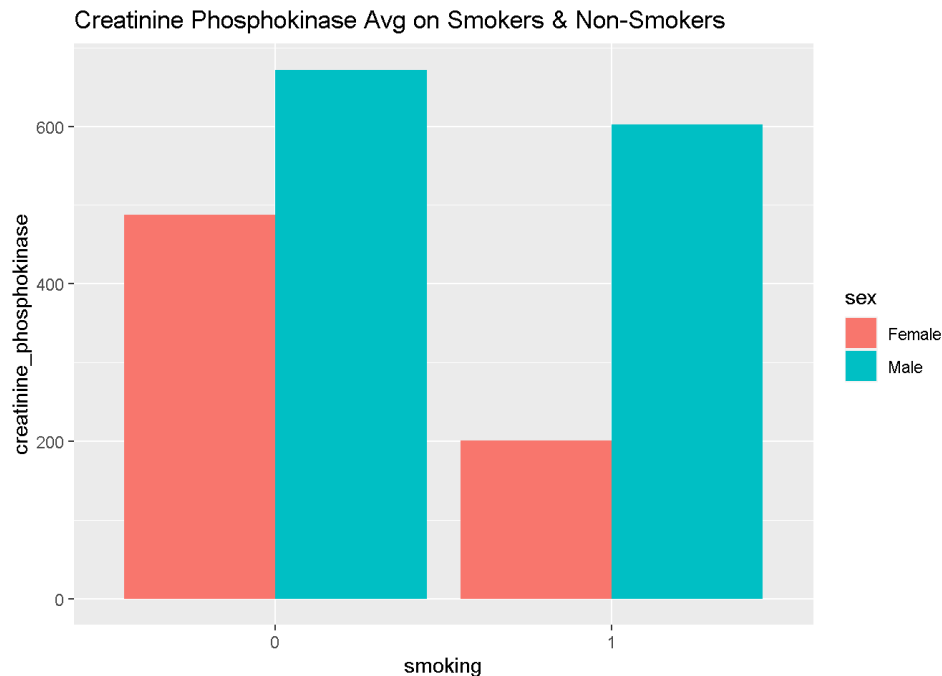
```
ggplot(HF, aes(x=sex, y=platelets, fill=sex)) +
  geom_bar(position = "dodge", stat="summary", fun="mean") +
  scale_y_continuous(labels = scales::label_number(suffix = "k", scale = 1e-3)) +
  ggtitle("Mean Platelets for Sexes")
```



```
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
```

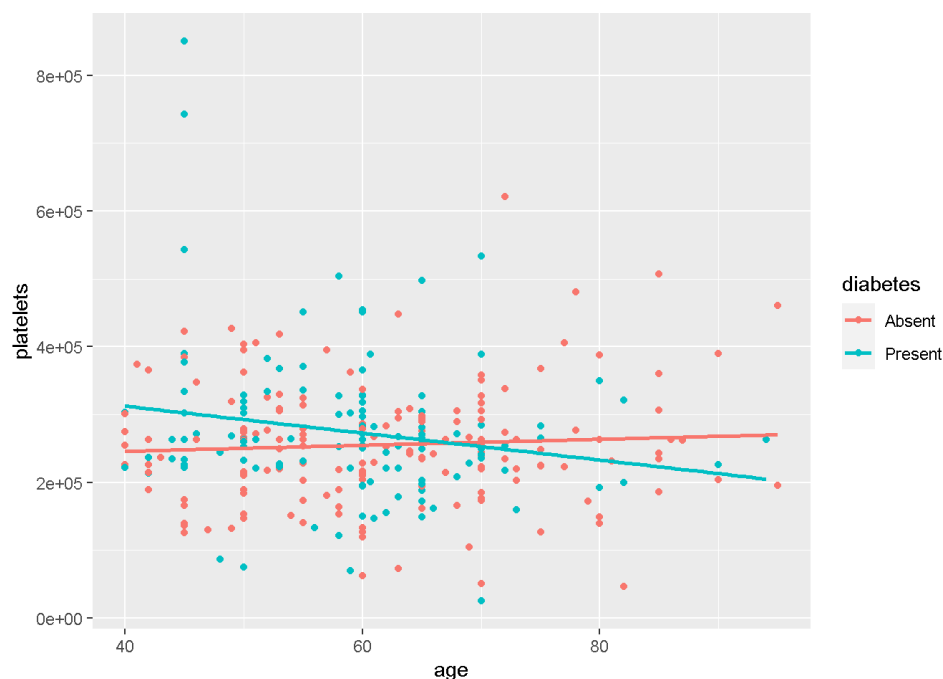
```
ggplot(HF, aes(x=smoking, y=creatinine_phosphokinase, fill=sex)) +
  geom_bar(position = "dodge", stat="summary", fun="mean") +
  ggtitle("Creatinine Phosphokinase Avg on Smokers & Non-Smokers")
```



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

Platelets are incredibly important. Having too few platelets 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)
```



## Conditional Inference Trees - Kaplan Maeier 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)

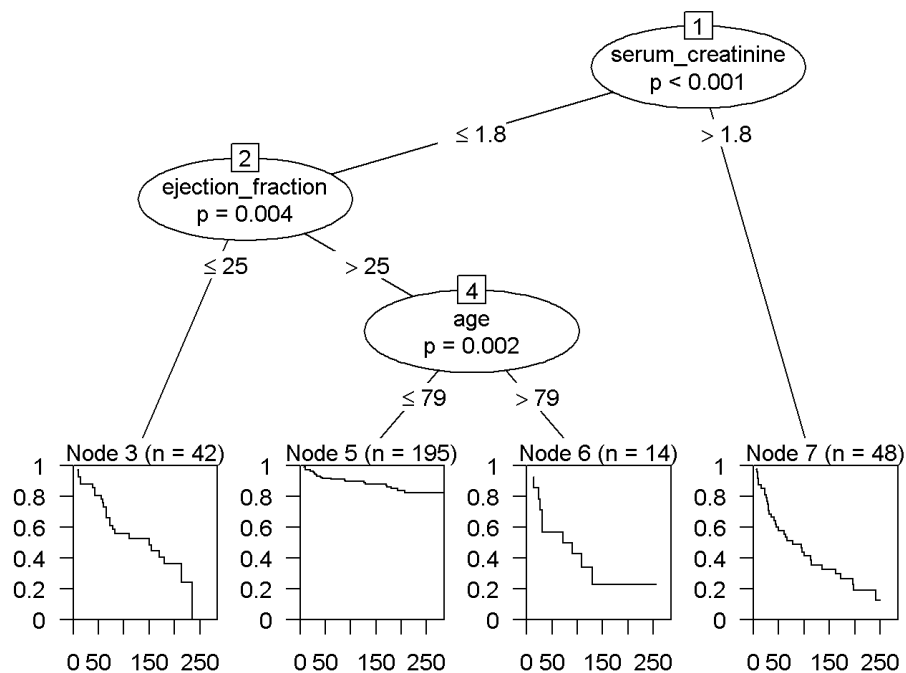
# Won't directly go from factor to numeric. Needed for Survival Analysis.
HF$DEATH_EVENT = as.numeric(as.character(HF$DEATH_EVENT))

# Dropping categorical Ejection Fraction.
HF <- HF %>% select(-EF_Condition)

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

plot(CondInfTree)

```



Plotting all node distributions/curves in one plot.

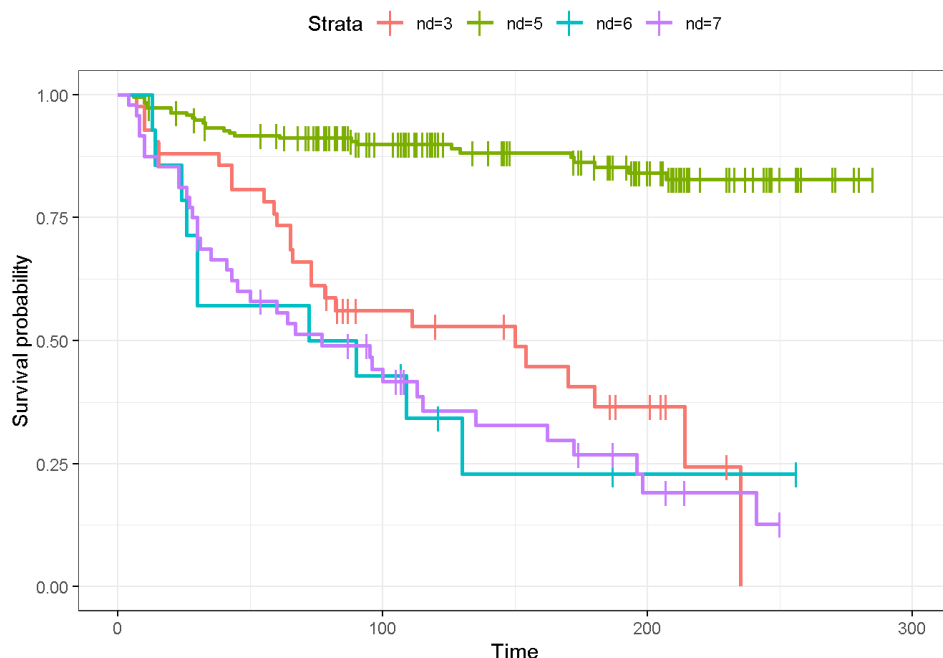
```

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())

```



EXTRACTING SURVIVAL CURVE FOR ONLY ONE OBSERVATION/PERSON FROM THE CTREE! PULL OUT AT LEAST ONE INSIGHT. THE 'X' DETERMINES WHICH OBSERVATION YOU'LL LOOK AT. PERHAPS LOOK AT AN OUTLIER TO TALK ABOUT A SPECIAL CASE.

```
#nd1 <- predict(CondInfTree, type = "prob")[[X]]
#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 creatinine, 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 of letting R know that we aren't using any x variables. Just time and whether event occurred which are both
# y variables.
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%.

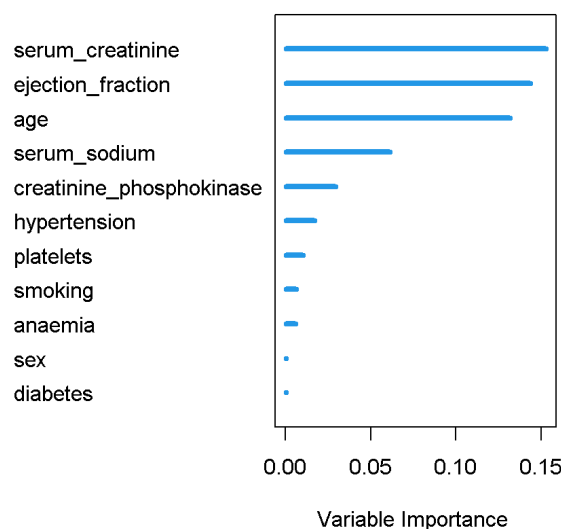
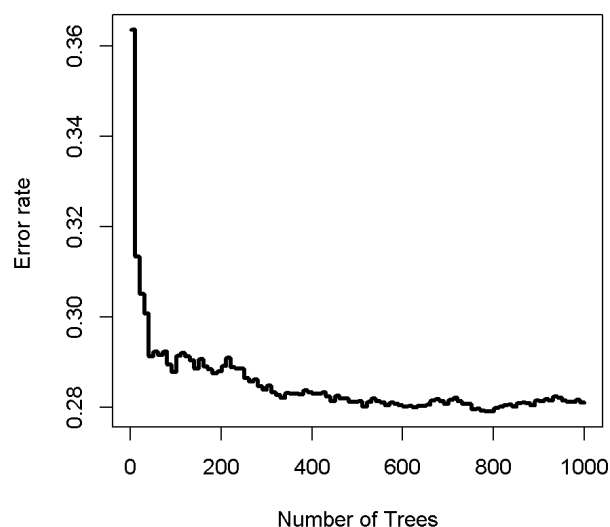
```
survfit(Surv(time, DEATH_EVENT) ~ 1, data = HF %>% filter(age <= 70)) %>%
  tbl_survfit(
    times = c(150, 200),
    label_header = "***{time} Day Survival (95% CI) For Those Younger Than 70***"
  )
```

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%)

## Random Forest Survival

```
# mtry means how many nodes at each split
fit <- rfsrc(Surv(time, DEATH_EVENT) ~ .,
            data = HF,
            ntree = 1000,
            importance = TRUE,
            nsplit = 3,
            mtry = 2)

#fit
plot(fit)
```



```
##
##              Importance  Relative Imp
## serum_creatinine      0.1527      1.0000
## ejection_fraction      0.1435      0.9399
## age                   0.1319      0.8635
## serum_sodium          0.0614      0.4020
## creatinine_phosphokinase 0.0295      0.1929
## hypertension          0.0170      0.1112
## platelets             0.0103      0.0674
## smoking               0.0062      0.0404
## anaemia               0.0059      0.0385
## sex                   0.0002      0.0014
## diabetes              0.0001      0.0006
```

## 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.



```
# diabetes isn't stat significant.
coxMod1 <- coxph(Surv(time, DEATH_EVENT) ~ diabetes, data=HF)
summary(coxMod1)
```

```
## Call:
## coxph(formula = Surv(time, DEATH_EVENT) ~ diabetes, data = HF)
##
##    n= 299, number of events= 96
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## diabetesPresent -0.04184   0.95902  0.20728 -0.202   0.84
##
##              exp(coef) exp(-coef) lower .95 upper .95
## diabetesPresent    0.959    1.043    0.6388    1.44
##
## Concordance= 0.502 (se = 0.027 )
## Likelihood ratio test= 0.04 on 1 df,  p=0.8
## Wald test               = 0.04 on 1 df,  p=0.8
## Score (logrank) test = 0.04 on 1 df,  p=0.8
```

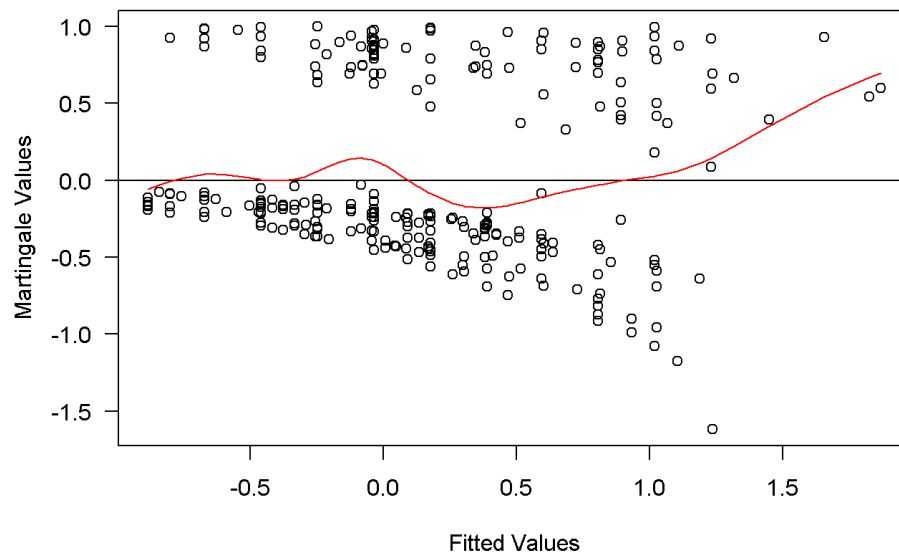
```
# hypertension useful bc tree didn't output it. i paired it w/ age bc why not? historia mejor.
coxMod2 <- coxph(Surv(time, DEATH_EVENT) ~ hypertension + age, data=HF)
summary(coxMod2)
```

```
## 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
```

```
# so long as most part of red doesn't stray, it's linear. This one strays a lot at end bc of less values overall so they hold more weight.
```

```
plot(predict(coxMod2), residuals(coxMod2, type = "martingale"), xlab = "Fitted Values",
     ylab = "Martingale Values", main = "Residual Plot", las = 1) +
  abline(h=0) +
  lines(smooth.spline(predict(coxMod2), residuals(coxMod2, type="martingale")), col="red")
```

Residual Plot



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

```
# Do the Likelihood-Ratio Test
# Try to find combination that may be insightful and make them "oh? interesting".
anova(coxMod1, coxMod2, test = "LRT")
```

```
## Analysis of Deviance Table
## Cox model: response is Surv(time, DEATH_EVENT)
## Model 1: ~ diabetes
## Model 2: ~ hypertension + age
##      loglik  Chisq Df P(>|Chi|)
## 1 -509.18
## 2 -495.52 27.322  1 1.722e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
# keep only variables that are significant. do manual stepwise, basically, and see what u get.
# boom, found it.
summary(coxph(Surv(time, DEATH_EVENT) ~ ., data=HF))
```

```
## Call:
## coxph(formula = Surv(time, DEATH_EVENT) ~ ., data = HF)
##
##      n= 299, number of events= 96
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## age          4.641e-02  1.048e+00  9.324e-03  4.977 6.45e-07 ***
## anaemia1      4.601e-01  1.584e+00  2.168e-01  2.122  0.0338 *
## creatinine_phosphokinase 2.207e-04  1.000e+00  9.919e-05  2.225  0.0260 *
## diabetesPresent 1.399e-01  1.150e+00  2.231e-01  0.627  0.5307
## ejection_fraction -4.894e-02  9.522e-01  1.048e-02 -4.672 2.98e-06 ***
## platelets      -4.635e-07  1.000e+00  1.126e-06 -0.412  0.6806
## serum_creatinine 3.210e-01  1.379e+00  7.017e-02  4.575 4.76e-06 ***
## serum_sodium   -4.419e-02  9.568e-01  2.327e-02 -1.899  0.0575 .
## sexMale        -2.375e-01  7.886e-01  2.516e-01 -0.944  0.3452
## smoking1       1.289e-01  1.138e+00  2.512e-01  0.513  0.6078
## hypertensionPresent 4.757e-01  1.609e+00  2.162e-01  2.201  0.0278 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##              exp(coef) exp(-coef) lower .95 upper .95
## age          1.0475      0.9547      1.0285      1.067
## anaemia1      1.5843      0.6312      1.0358      2.423
## creatinine_phosphokinase 1.0002      0.9998      1.0000      1.000
## diabetesPresent 1.1501      0.8695      0.7427      1.781
## ejection_fraction 0.9522      1.0502      0.9329      0.972
## platelets      1.0000      1.0000      1.0000      1.000
## serum_creatinine 1.3786      0.7254      1.2014      1.582
## serum_sodium   0.9568      1.0452      0.9141      1.001
## sexMale        0.7886      1.2681      0.4816      1.291
## smoking1       1.1376      0.8790      0.6953      1.861
## hypertensionPresent 1.6092      0.6214      1.0534      2.458
##
## Concordance= 0.741 (se = 0.027 )
## Likelihood ratio test= 81.95 on 11 df,  p=6e-13
## Wald test              = 87.27 on 11 df,  p=6e-14
## Score (logrank) test = 88.39 on 11 df,  p=3e-14
```

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

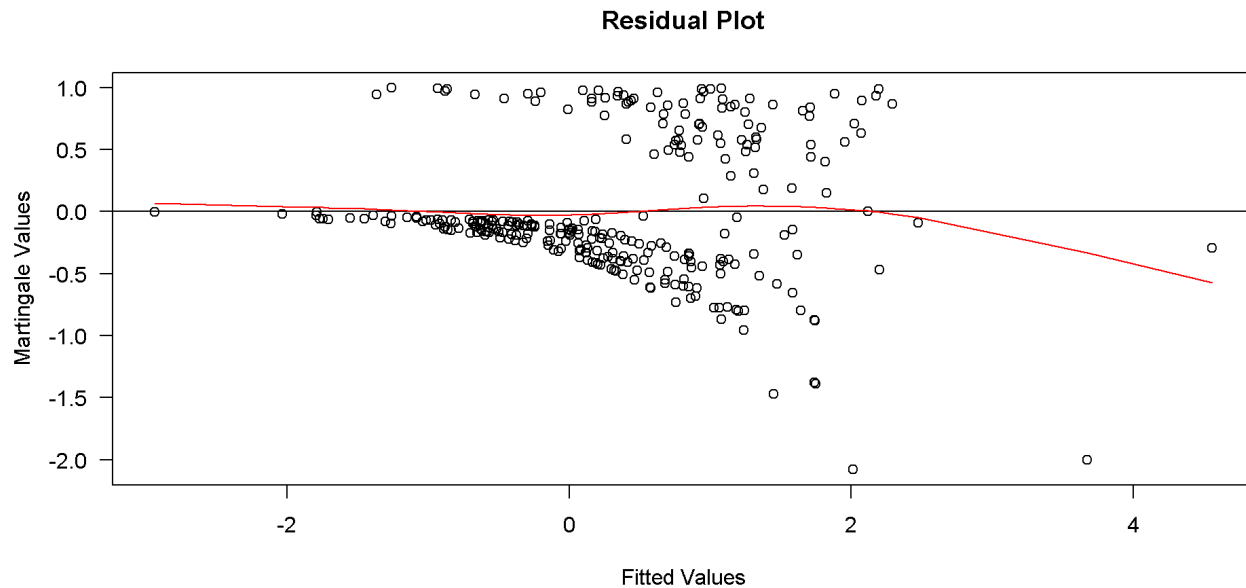
```
## Call:
## coxph(formula = Surv(time, DEATH_EVENT) ~ age + anaemia + creatinine_phosphokinase +
##      ejection_fraction + serum_creatinine + hypertension, data = HF)
##
##      n= 299, number of events= 96
##
##              coef exp(coef) se(coef)      z Pr(>|z|)
## age          4.361e-02  1.045e+00  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
## age          1.0446      0.9573      1.0266      1.0629
## 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      0.9684
## serum_creatinine 1.4167      0.7059      1.2460      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
```

Checking Linearity of Model \* Linearity of the final cox regression is sufficient.

## SAY SOMETHING ABOUT THE HAZARD RATIO PLOT

```
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")
```

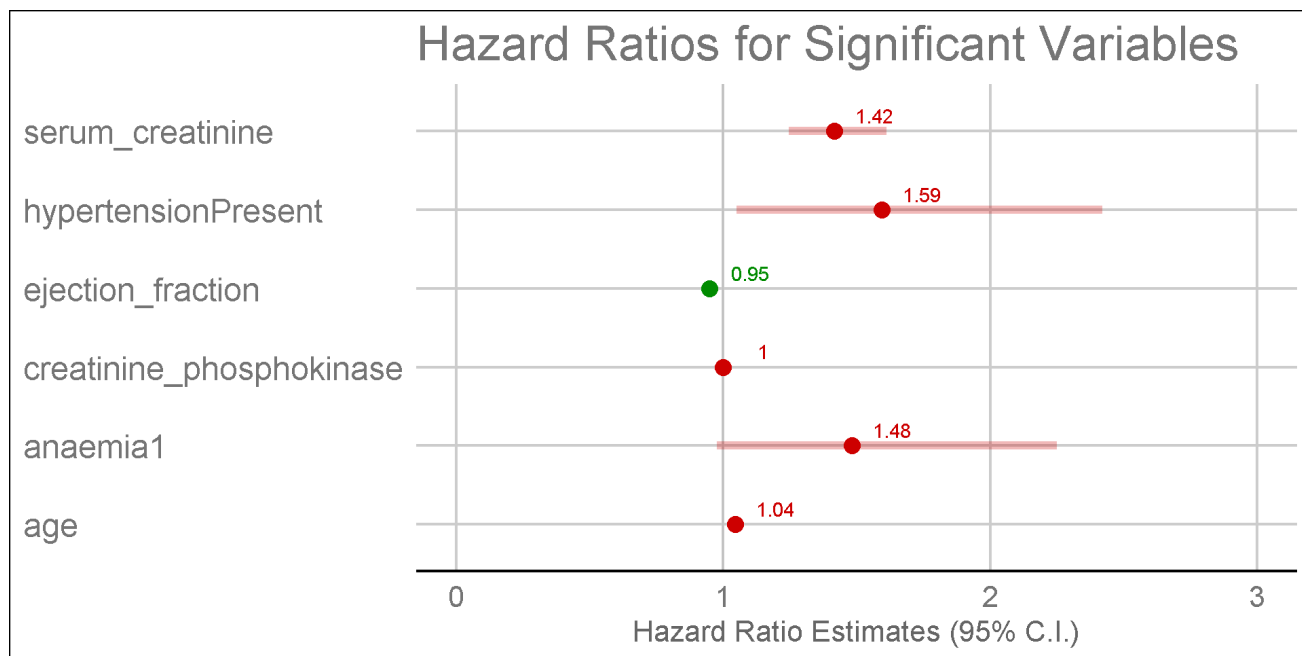


```
## integer(0)
```

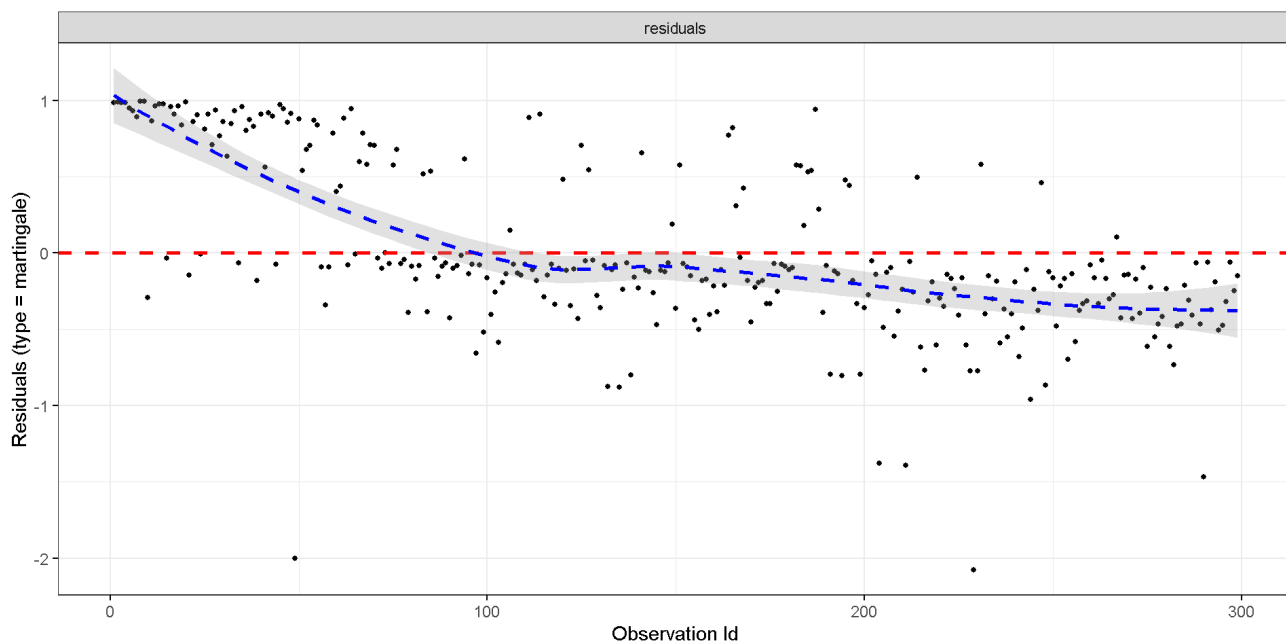
```
#ggforest(sigMod, data = HF)
```

```
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)
```



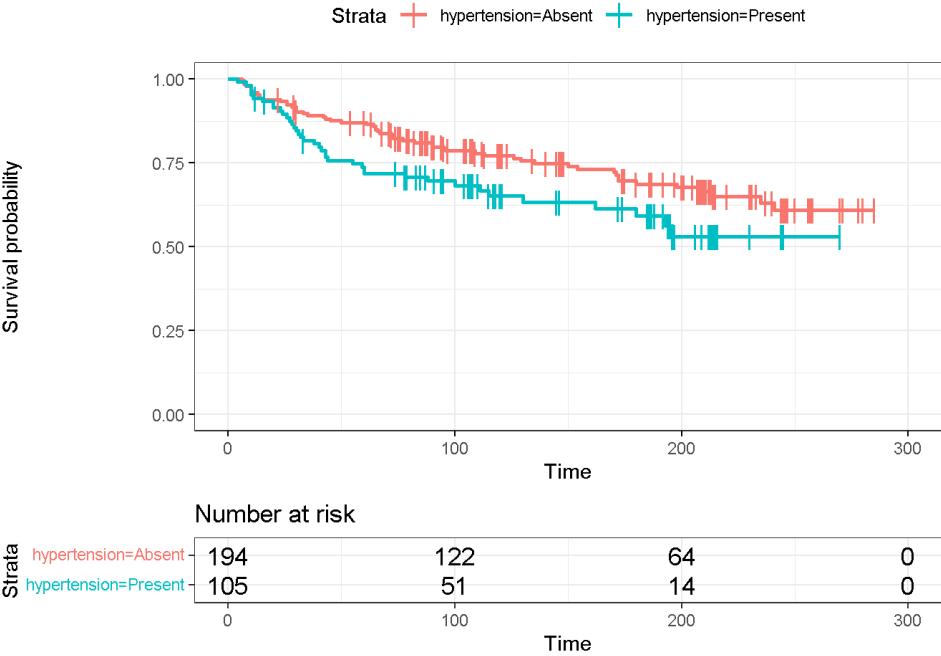
```
ggcoxdiagnostics(sigMod, type = "martingale",
  linear.predictions = FALSE,
  ggtheme = theme_bw(),
)
```



Performing the Log-Rank Test on the hypertension & diabetes .

- Finding out that the distribution of present hypertension is statistically significant when compared against the distribution of the absence of it.
- The presence of diabetes, however, does not impact survival rate.

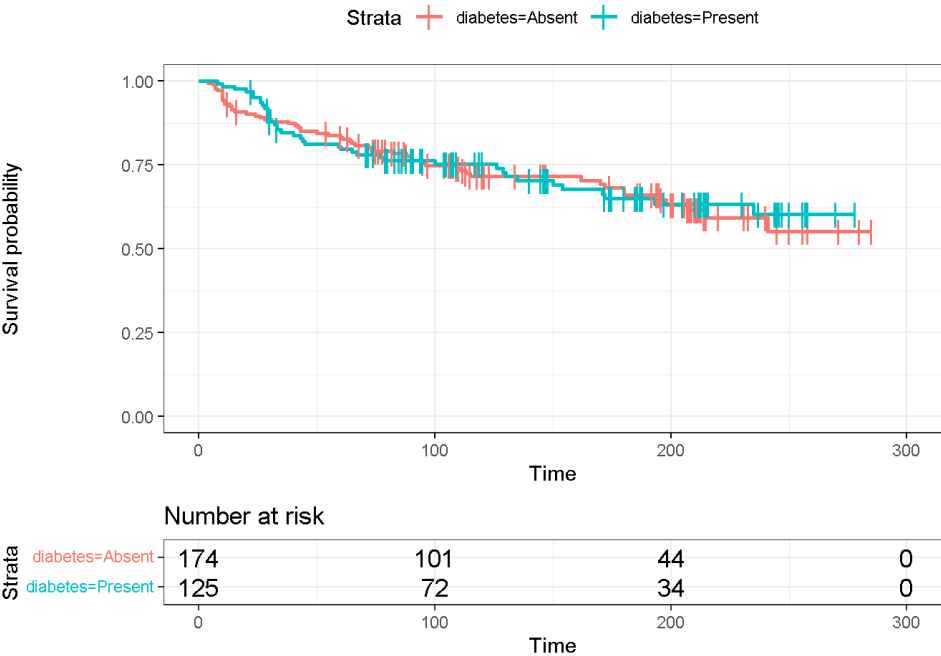
```
#Hypertension
ggsurvplot(survfit(Surv(time,DEATH_EVENT) ~ hypertension, data=HF),
  data = HF,
  censor.shape="|",
  conf.int = FALSE, #surv.median.line = "hv",
  risk.table = TRUE,
  ggtheme = theme_bw())
```



```
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())
```



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

```
## Call:
## survdifff(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
```

## QUESTIONS TO ASK:

- Probability that person survives longer than time = x? CHECK
- Typical survival rate for person in a certain region? N/A
- Out of 10 random observations, how many do we expect to be deceased after 60 days?

## NEXT STEPS: BUILD A LOGISTIC MODEL FOR PREDICITONS RIGHT AFTER, PERHAPS.

### Findings:

- Diabetes isn't a statistically significant predictor of survival time.
- 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.
- 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 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.