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# 1 Introduction

## 1.1 Background

Heart failure (HF) occurs when the muscles in the heart wall weaken and enlarge, impairing the heart's ability to pump blood effectively. This condition can cause the heart's ventricles to become stiff, hindering their ability to fill properly between beats. Over time, the heart becomes less capable of meeting the body's demand for blood, leading to symptoms like difficulty in breathing as the heart struggles to function efficiently.(Ahmad et al., 2017).

According to the statistics, heart failure affects 1-2% of adults in the general population and is more common in older individuals, with over 10% of those aged over 70 years being diagnosed. The actual prevalence might be as high as 4%, as heart failure is often undiagnosed or misdiagnosed, especially in the elderly. Since 2002, the prevalence of heart failure has increased by nearly 25%, driven by factors such as an aging population, better survival rates post-coronary events, and a rise in risk factors like hypertension and atrial fibrillation. (Jones et al., 2019).

## 1.2 Objective

Our project aims to assess the influence of key physiological and clinical factors on the outcomes of heart failure patients at the Institute of Cardiology and Allied Hospital, Faisalabad, Pakistan, during April-December 2015. We will examine variables such as creatinine levels, gender, age, ejection fraction, blood pressure, anemia, and serum sodium to determine their impact on patient prognosis. Utilizing a range of analytical techniques including exploratory data analysis, nonparametric methods, Kaplan-Meier curves, Cox proportional hazards modeling, parametric survival models, and validation procedures, our study is designed to identify crucial predictors of patient outcomes and their interrelationships. The insights gained from this analysis are expected to contribute significantly to the development of tailored treatment strategies and improved risk stratification models, thereby enhancing clinical decision-making and patient care for heart failure management.

# 2 Methods

## 2.1 Exploratory Data Analysis (EDA)

The present study focuses on 299 heart failure patients, including 105 women and 194 men. All participants were over 40 years old and diagnosed with left ventricular systolic dysfunction, classified under NYHA classes III and IV. The follow-up duration ranged from 4 to 285 days, with an average of 130 days. Diagnosis of the disease was confirmed through cardiac echocardiogram reports or physician's notes. A brief description of variables in the dataset is shown below:

- **age**: Age in years
- **time**: Survival time in days
- **event**: Event binary indicator (0 = Censored, 1 = Event)
- **gender**: Sex binary indicator (0 = Female, 1 = Male)
- **smoking**: Smoking status (0 = No smoking, 1 = Smoking)
- **diabetes**: Diabetes status (0 = No diabetes, 1 = Diabetes)
- **bp**: Blood pressure status (0 = Normal, 1 = Hypertension)
- **anemia**: Anemia status (0 = No anemia, 1 = Anemia: patients with haematocrit  $< 36$ )
- **EF\_cat**: Ejection fraction (Low:  $EF \leq 30$ , Medium:  $30 < EF \leq 45$  and High:  $EF > 45$ )
- **sodium**: Sodium in mEq/L
- **creatinine**: Serum creatinine in mg/dL

- **platelets:** Platelets in mcL
- **cpk:** Creatinine phosphokinase in U/L

This study falls into the category of Overall Survival (OS), where event indicator equals 1 indicates the death of the subject and is the endpoint of survival. Specifically, 203 subjects were right-censored and 96 subjects have event. Detailed descriptive statistics table stratified by survival status are presented below.

Table 1: Descriptive Statistics Table

	Censored (N=203)	Event (N=96)	Overall (N=299)	P-value
<b>Survival time (days)</b>				
Mean (SD)	158 (67.7)	70.9 (62.4)	130 (77.6)	<0.001
Median [Min, Max]	172 [12.0, 285]	44.5 [4.00, 241]	115 [4.00, 285]	
<b>Age (years)</b>				
Mean (SD)	58.8 (10.6)	65.2 (13.2)	60.8 (11.9)	<0.001
Median [Min, Max]	60.0 [40.0, 90.0]	65.0 [42.0, 95.0]	60.0 [40.0, 95.0]	
<b>Gender</b>				
0	71 (35.0%)	34 (35.4%)	105 (35.1%)	1
1	132 (65.0%)	62 (64.6%)	194 (64.9%)	
<b>Smoking status</b>				
0	137 (67.5%)	66 (68.8%)	203 (67.9%)	0.932
1	66 (32.5%)	30 (31.3%)	96 (32.1%)	
<b>Diabetes</b>				
0	118 (58.1%)	56 (58.3%)	174 (58.2%)	1
1	85 (41.9%)	40 (41.7%)	125 (41.8%)	
<b>Blood Pressure</b>				
0	137 (67.5%)	57 (59.4%)	194 (64.9%)	0.214
1	66 (32.5%)	39 (40.6%)	105 (35.1%)	
<b>Ejection Fraction (EF_cat)</b>				
Low	42 (20.7%)	51 (53.1%)	93 (31.1%)	<0.001
Medium	115 (56.7%)	31 (32.3%)	146 (48.8%)	
High	46 (22.7%)	14 (14.6%)	60 (20.1%)	
<b>Anemia</b>				
0	120 (59.1%)	50 (52.1%)	170 (56.9%)	0.307
1	83 (40.9%)	46 (47.9%)	129 (43.1%)	
<b>Serum Sodium (mEq/L)</b>				
Mean (SD)	137 (3.98)	135 (5.00)	137 (4.41)	0.00187
Median [Min, Max]	137 [113, 148]	136 [116, 146]	137 [113, 148]	
<b>Serum creatinine (mg/dL)</b>				
Mean (SD)	1.18 (0.654)	1.84 (1.47)	1.39 (1.03)	<0.001
Median [Min, Max]	1.00 [0.500, 6.10]	1.30 [0.600, 9.40]	1.10 [0.500, 9.40]	
<b>Creatinine phosphokinase (U/L)</b>				
Mean (SD)	540 (754)	670 (1320)	582 (970)	0.369
Median [Min, Max]	245 [30.0, 5210]	259 [23.0, 7860]	250 [23.0, 7860]	
<b>Plateletes (mcL)</b>				
Mean (SD)	267000 (97500)	256000 (98500)	263000 (97800)	0.399
Median [Min, Max]	263000 [25100, 850000]	259000 [47000, 621000]	262000 [25100, 850000]	

Based on the descriptive table, we can observe that the mean survival time for deletions and events is 158 days and 70.9 days, respectively. Since we have the complete dataset, there is no need to worry about missingness issue. The table also lists the p-values for each variable. Some variables have relatively large p-values. However, we still need to check the distribution of each variable <sup>1</sup> and determine which variables need to be transformed.

<sup>1</sup>Histograms for continuous variables and bar charts for categorical variables

Figure 1.1: Histograms of Continuous Variables

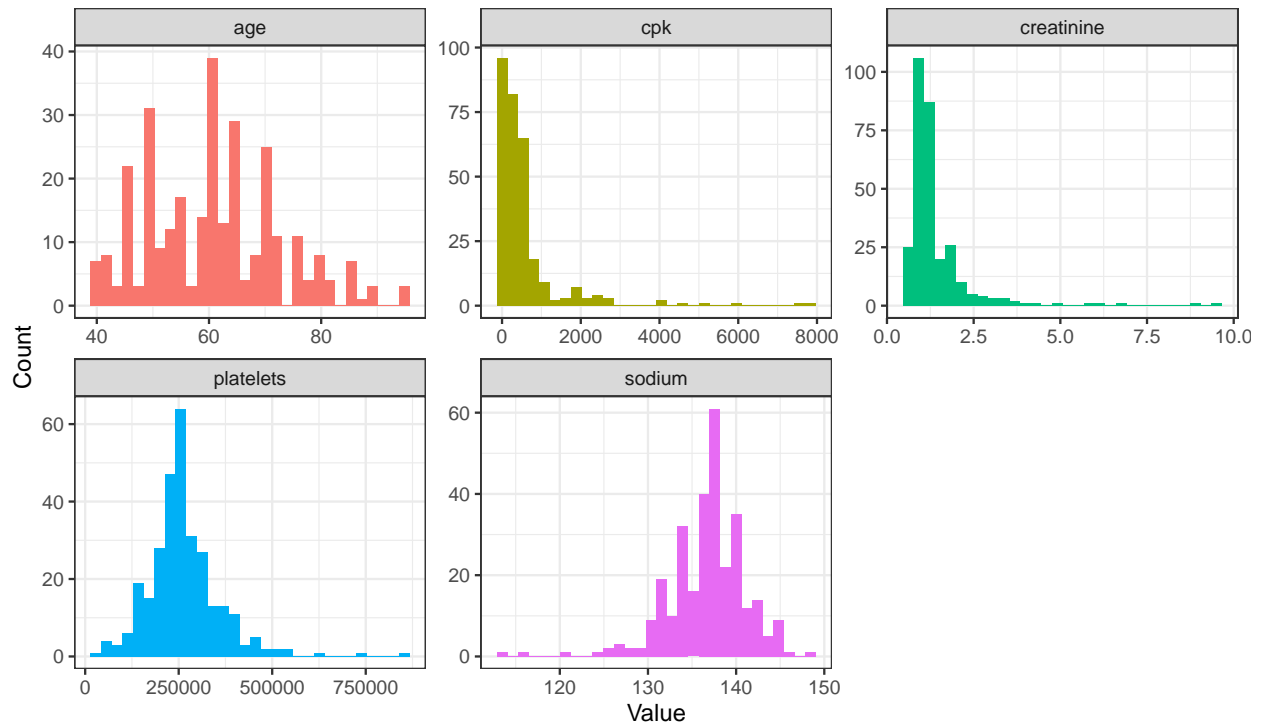
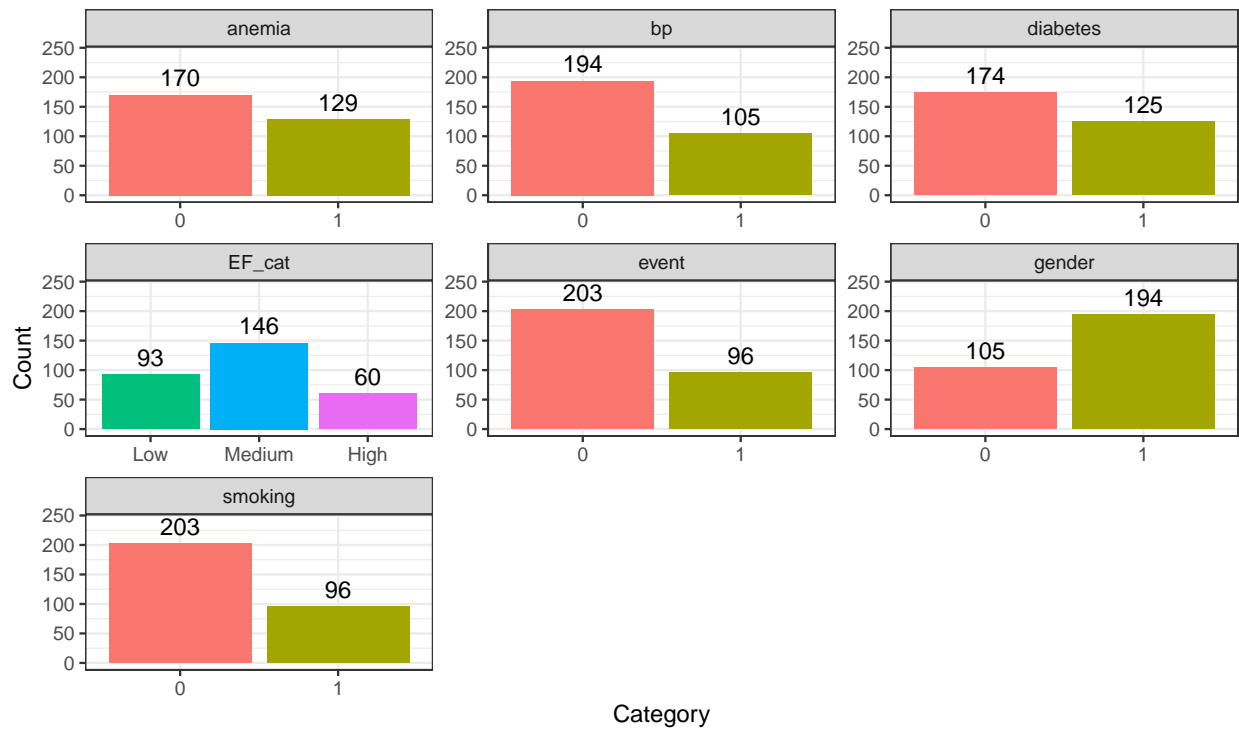


Figure 1.2: Bar Charts of Categorical Variables



After checking the histograms, two continuous variables creatinine phosphokinase (cpk) and serum creatinine are right-skewed. We decide to log-transformed both of them for further model fitting.

## **2.2 Nonparametric Estimate**

(Life table separated by gender, KM and FH comparing)

## **2.3 Hypothesis Testing**

(Log-Rank test and Wilcoxon test)

## **2.4 Semi-parametric Estimate**

(model selection (survival tree - optional), and model checking???, fitting the model)

## **2.5 Parametric Estimate**

(Model checking, fitting the model)

## **2.6 Model Validation**

()

## **3 Results**

## **4 Discussion**

## **5 Conclusions**

## 6 References

1. Ahmad, T., Munir, A., Bhatti, S. H., Aftab, M., & Raza, M. A. (2017). Survival analysis of heart failure patients: A case study. PLOS ONE, 12(7), e0181001. <https://doi.org/10.1371/journal.pone.0181001>
2. Jones, N., Ak, R., Adoki, I., Fdr, H., & Cj, T. (2019). Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. European Journal of Heart Failure, 21(11), 1306–1325. <https://doi.org/10.1002/ejhf.1594>

## 7 Appendix

### 7.1 Code

```
knitr::opts_chunk$set(echo = FALSE, message = FALSE, warning = FALSE)
library(tidyverse)
library(knitr)
library(kableExtra)
library(survival)
library(survminer)
library(writexl)
library(readxl)
library(table1)
library(rmarkdown)
library(KMsurv)
library(StepReg)
data = read_csv("../data/heart_failure.csv")
dat <- data %>%
  arrange(TIME) %>% janitor::clean_names() %>%
  mutate(ejection_fraction_cat = case_when(ejection_fraction <= 30 ~ "Low",
                                           ejection_fraction > 30 & ejection_fraction <= 45 ~ "Medium",
                                           ejection_fraction > 45 ~ "High")) %>%

  mutate(gender = factor(gender),
         smoking = factor(smoking),
         diabetes = factor(diabetes),
         bp = factor(bp),
         event = factor(event),
         anaemia = factor(anaemia),
         ejection_fraction_cat = factor(ejection_fraction_cat, levels = c("Low", "Medium", "High"))) %>%
  rename(platelets = pletelets,
         anemia = anaemia,
         EF = ejection_fraction,
         EF_cat = ejection_fraction_cat)

# Calculate the number of right-censored:
number_censored <- sum(dat$event == 0)
# Calculate the number of event:
number_event <- sum(dat$event == 1)
dat_table = dat
label(dat_table$time) = "Survival time (days)"
label(dat_table$gender) = "Gender"
label(dat_table$smoking) = "Smoking status"
label(dat_table$diabetes) = "Diabetes"
label(dat_table$bp) = "Blood Pressure"
label(dat_table$anemia) = "Anemia"
label(dat_table$age) = "Age (years)"
label(dat_table$EF_cat) = "Ejection Fraction (EF_cat)"
label(dat_table$sodium) = "Serum Sodium (mEq/L)"
label(dat_table$creatinine) = "Serum creatinine (mg/dL)"
label(dat_table$platelets) = "Plateletes (mcL)"
label(dat_table$cpk) = "Creatinine phosphokinase (U/L)"
dat_table$event <- factor(dat$event, levels = c(0, 1), labels = c("Censored", "Event"))
```



```

pvalue <- function(x, ...) {
  # Remove the "overall" column
  x <- x[names(x) != "overall"]
  # Construct vectors of data y, and groups (strata) g
  y <- unlist(x)
  g <- factor(rep(1:length(x), times = sapply(x, length)))
  if (is.numeric(y)) {
    # For numeric variables, perform a standard 2-sample t-test
    p <- t.test(y ~ g)$p.value
  } else {
    # For categorical variables, perform a chi-squared test of independence
    p <- chisq.test(table(y, g))$p.value
  }
  # Format the p-value, using an HTML entity for the less-than sign.
  # The initial empty string places the output on the line below the variable label.
  c("", sub("<", "<", format.pval(p, digits = 3, eps = 0.001)))
}

caption = "Table 1: Descriptive Statistics Table"

table1 = table1(~ time + age + gender + smoking + diabetes + bp + EF_cat +
  anemia + sodium + creatinine + cpk + platelets | event,
  data = dat_table, extra.col = list(`P-value` = pvalue), caption = caption)
tikable(table1) %>% kable_styling(font_size = 8, latex_options = "HOLD_position")
# Data contains the continuous vars only
cont_dat = dat %>%
  select(age, sodium, creatinine, platelets, cpk)
# Long format
cont_dat.long = cont_dat %>%
  pivot_longer(cols = c(age, sodium, creatinine, platelets, cpk))
# Plot the continuous variable histograms
cont_hist = ggplot(data = cont_dat.long, aes(x = value)) +
  geom_histogram(aes(fill = name), bins = 30) +
  facet_wrap(~name, scales = "free") +
  labs(x = "Value", y = "Count", title = "Figure 1.1: Histograms of Continuous Variables") +
  theme_bw() +
  theme(legend.position = "none")
cont_hist

# Data contains the categorical vars only
cate_data = dat %>%
  select(event, gender, smoking, diabetes, bp, anemia, EF_cat)
# Long format
cate_dat.long = cate_data %>%
  pivot_longer(cols = c(event, gender, smoking, diabetes, bp, anemia, EF_cat))
# Plot the categorical variable barplots
cate_barplot = ggplot(cate_dat.long, aes(x = value, fill = value)) +
  geom_bar() +
  geom_text(stat = 'count', aes(label = ..count..), vjust = -0.5) +
  facet_wrap(~name, scales = "free") +
  labs(x = "Category", y = "Count", fill = "Category", title = "Figure 1.2: Bar Charts of Categorical Variables") +
  theme_bw() +
  theme(legend.position = "none") +
  ylim(0, 240)

```

```
cate_barplot
dat_log = dat %>%
  mutate(cpk_log = log(cpk + 1),
         creatinine_log = log(creatinine + 1))
```