Heart Failure Survival Study

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Abstract

Heart failure (HF) results from weakened heart muscles, impairing blood pumping and causing symptoms like breathlessness (Ahmad et al., 2017). Statistics show HF affects 1-2% of adults, especially those over 70, potentially higher due to misdiagnosis (Jones et al., 2019). HF prevalence increased by 25% since 2002 due to aging, improved survival, and risk factors. This study utilizes data from the Institute of Cardiology and Allied Hospital in Faisalabad, Pakistan, which previously investigated the impact of key physiological and clinical factors on the prognosis of heart failure (HF) patients between April and December 2015. Our research employs a comprehensive range of statistical methodologies, including exploratory data analysis, non-parametric approaches, semi-parametric model, parametric models, hypothesis testing, model checking, and validation procedures, aiming to identify significant predictors and investigate their influences on heart failure. The significant factors identified in our study include creatinine levels, age, blood pressure, and serum sodium. Additionally, the model's discriminative ability across varied samples and conditions is validated using rigorous bootstrap validation methods such as c-index and calibration slope. Our findings contribute to refining risk assessment models, enhancing clinical decision-making, and optimizing patient care for heart failure in the future. The insights gained from our modeling process offer a deeper understanding of HF progression and its risk factors, paving the way for more personalized treatment approaches and preventive strategies that could profoundly impact patient outcomes and quality of life.

Contents

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).

In Pakistan, heart failure poses a significant health challenge, with the rate estimated to be 110 per million (Ahmad et al., 2017). The prevalence is driven by factors like coronary heart disease, diabetes, high blood pressure, and lifestyle factors such as poor diet and lack of exercise (Ahmad et al., 2017). The study conducted by (Ahmad et al., 2017) specifically focuses on patients from the Institute of Cardiology and Allied Hospital, Faisalabad, illustrating the local impact and importance of understanding heart failure in the Pakistani context.

Despite this alarming situation, reliable estimates of heart failure incidence and prevalence specific to this region are lacking. The need for localized data is particularly pressing in Pakistan, where diet and lifestyle factors differ significantly from Western countries and even other South Asian nations (Ahmad et al., 2017). Unlike India, Bangladesh, Nepal, and Sri Lanka, Pakistan exhibits distinct dietary patterns, which may influence heart failure progression differently (Ahmad et al., 2017). This difference necessitates a region-specific study to understand how different factors contribute to heart failure risk and progression.

Moreover, the scarcity of studies focusing on heart failure in Pakistan points to a critical research gap. Such a gap hinders the development of effective, region-specific heart failure management strategies. Our study aims to fill this void by providing data and insights relevant to the Pakistani population. By doing so, it contributes to a more nuanced understanding of heart failure in the region, paving the way for potential tailored prevention and treatment strategies that are attuned to the unique needs of the local population.

1.2 Objective

Our project aims to assess the influence of key physiological and clinical factors on the outcomes of heart failure patients admitted to the Institute of Cardiology and Allied Hospital, Faisalabad, Pakistan, from April to 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 analytic techniques including exploratory data analysis, nonparametric methods, hypothesis testing, semi-parametric modeling, parametric survival models, model checking, and validation procedures, our study is designed to identify crucial predictors of heart failure and to investigate their influences on patient outcomes. 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 echo-cardiogram 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 ≤ 30, Medium: $30 <$ EF ≤ 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.

Based on the descriptive table (**Table 1**), we observed that the mean survival time for deletions and events is 158 days and 70.9 days, respectively. Since the dataset is complete, we don't need to worry about missingness issue. The descriptive table also presents p-values for each variable, with some exhibiting relatively high values. However, we still need to check the distribution of each variable [1] and determine which variables need to be transformed.

Based on the histograms (**Figure 1.1**) and bar charts (**Figure 1.2**), we noticed the two continuous variables creatinine phosphokinase (`cpk`) and serum creatinine (`creatinine`) are heavily right-skewed. The right skewed covariates may have large outliers in Cox regression and violates the assumption of proportional hazards. To address this issue, we decided to log-transformed both of them for further model fitting. The new log-transformed variables follow a little more symmetric-like distribution and are stored as `logcre` and `logcpk`.

[1] Histograms for continuous variables and bar charts for categorical variables

Table 1: Descriptive Statistics Table for Variable Characteristic

	Censored	Event	Overall	P-value
	(N=203)	(N=96)	(N=299)	
Survival time (days)				
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]	
Age (years)				
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]	
Gender				
0	71 (35.0%)	34 (35.4%)	105 (35.1%)	1
1	132 (65.0%)	62 (64.6%)	194 (64.9%)	
Smoking status				
0	137 (67.5%)	66 (68.8%)	203 (67.9%)	0.932
1	66 (32.5%)	30 (31.3%)	96 (32.1%)	
Diabetes				
0	118 (58.1%)	56 (58.3%)	174 (58.2%)	1
1	85 (41.9%)	40 (41.7%)	125 (41.8%)	
Blood Pressure				
0	137 (67.5%)	57 (59.4%)	194 (64.9%)	0.214
1	66 (32.5%)	39 (40.6%)	105 (35.1%)	
Ejection Fraction (EF_cat)				
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%)	
Anemia				
0	120 (59.1%)	50 (52.1%)	170 (56.9%)	0.307
1	83 (40.9%)	46 (47.9%)	129 (43.1%)	
Serum Sodium (mEq/L)				
Mean (SD)	137 (3.98)	135 (5.00)	137 (4.41)	0.002
Median [Min, Max]	137 [113, 148]	136 [116, 146]	137 [113, 148]	
Serum creatinine (mg/dL)				
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]	
Creatinine phosphokinase (U/L)				
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]	
Plateletes (mcL)				
Mean (SD)	267000 (97500)	256000 (98500)	263000 (97800)	0.399
Median [Min, Max]	263000 [25100, 850000]	259000 [47000, 621000]	262000 [25100, 850000]	

Figure 1.1: Histograms of Continuous Variables

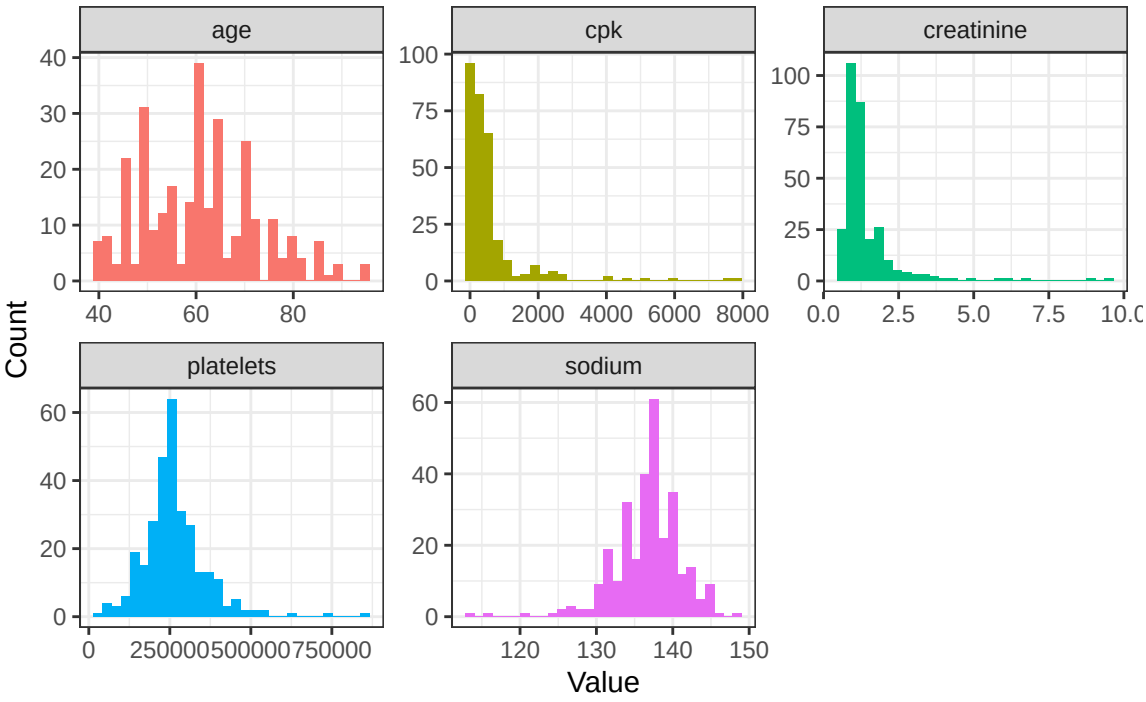
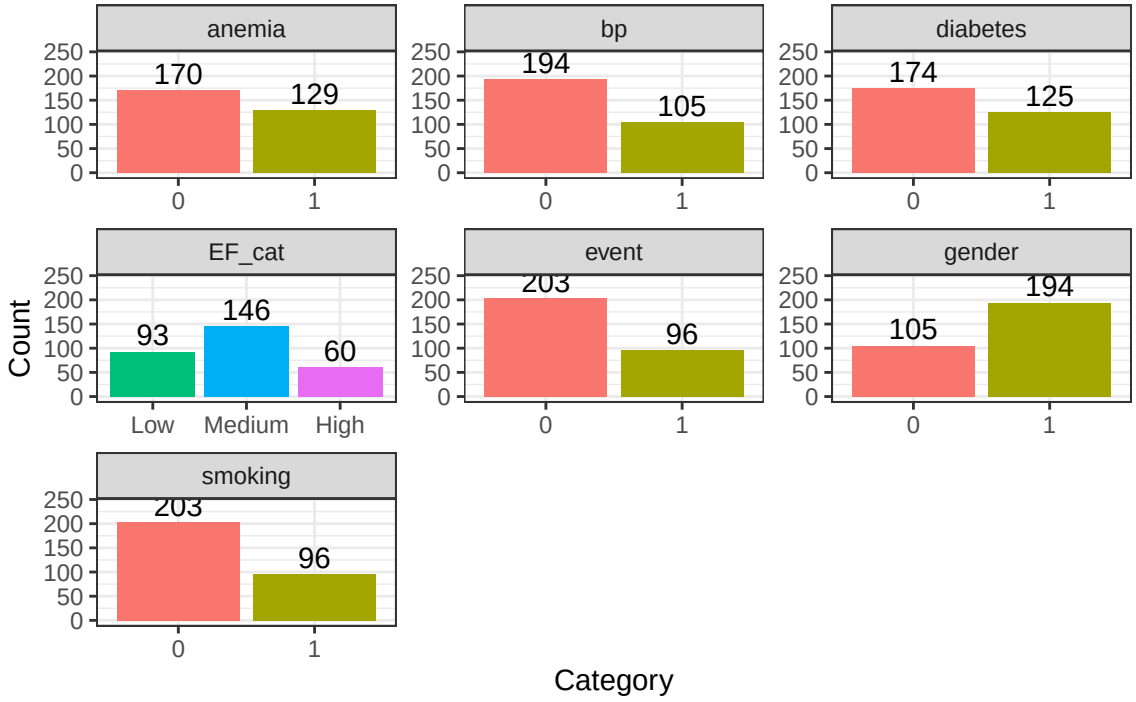


Figure 1.2: Bar Charts of Categorical Variables



2.2 Nonparametric Methods

In our analysis, we applied life table, Kaplan-Meier and Fleming-Harrington curves to estimate the survival function. All three approaches can handle censored data.

The life table is particularly useful for larger sample sizes and when the data are grouped into intervals. The survival probability at each interval is estimated as:

$$\hat{S}_L(t_i) = \prod_{t_{i-1}<t} (1 - \frac{d_i}{n_i'})$$

where d_i is the number of events in interval[2] $[t_{i-1}, t_i]$, n_i' is the average number at risk in the interval $[t_{i-1}, t_i]$.

The Kaplan-Meier curve allows for varying follow-up times and censored data, making it versatile for smaller samples and individual subject data. It provides a visual representation of the survival experience of the cohort over time. The Kaplan-Meier estimate of survival function can be mathematically expressed as:

$$\hat{S}_K(t) = \prod_{t_i \leq t} [1 - \frac{d_i}{n_i}]$$

where d_i is the number of events at time t_i and n_i is the number at risk at t_i^-, and c_i is the number of censored during the interval $[t_i, t_{i+1}]$

Unlike the Kaplan-Meier estimator, the Fleming-Harrington estimator[3] is designed to weight events differently over time in survival analysis. It focuses on estimating the cumulative hazard function. The estimated survival probability can be computed as:

$$\hat{S}_F(t) = \prod_{t_i \leq t} \exp[-\frac{d_i}{n_i}]$$

where the d_i, n_i and c_i conditions are the same as K-M estimator above, It is true that $\hat{S}_F(t) \geq \hat{S}_K(t)$ because $\exp[-\frac{d_i}{n_i}]$ is always great and equal to $1 - \frac{d_i}{n_i}$.

Both K-M and F-H survival curves are presented in the **Result** section for further comparison.

2.3 Hypothesis Testing

The Log-Rank test focuses on comparing the number of observed to expected events across the groups at each time point. The test statistic[4] is calculated as:

$$\frac{L}{\sqrt{\text{Var}(L)}} = \frac{\sum_{i=1}^{k}(d_{0i} - e_{0i})}{\sum_{i=1}^{k}\sqrt{\frac{n_{0i}n_{1i}d_i(n_i - d_i)}{n_i^2(n_i - 1)}}} \sim N(0,1)$$

The Gehan's Wilcoxon test[5] gives more weight to events at earlier time points. It achieves a greater sensitivity to differences in survival that manifest at the beginning of the observation period. The test statistic is calculated as:

$$\frac{L}{\sqrt{\text{Var}(L)}} = \frac{\sum_{i=1}^{k} n_i(d_{0i} - e_{0i})}{\sum_{i=1}^{k}\sqrt{\frac{n_{0i}n_{1i}d_i(n_i - d_i)}{n_i - 1}}} \sim N(0,1)$$

The Gehan's Wilcoxon test is actually a special case of weighted log-rank test for weight term equals n_i.

[2]This is the survival function at the end of interval. However, R often reports the survival function at the beginning of the interval

[3]Also known as Nelson-Aalen estimator

[4]This is the log-rank test statistics with tie

[5]Also known as the Breslow test

2.4 Proportional Hazards Models

The study also used two proportional hazards models to evaluate the effect of several factors on survival time. It allowed us to examine how specified factors influence the rate of the event that we are interested in at a particular time point. The "rate" here is the hazard rate. Proportional hazards model is the primary regression model to investigate the effectiveness of treatment X over survival time T, where the i_{th} patient at a time t
is:

$$h_i(t) = h_0(t) \exp[\beta_1 X_{i1} + \beta_2 X_{i2} + \ldots + \beta_p X_{ip}]$$

where

- $h_0(t)$ is the baseline hazard function
- $h_i(t)$ is the hazard function determined by a set of p covariates $(X_{i1},\ X_{i2},\ ...,\ X_{ip})$
- $(\beta_1,\ \beta_2,\ ...,\ \beta_p)$ are the coefficients which measure the impact of covariates.

The **proportional hazards** can be expressed as ratio of two hazard functions at time t in two individuals or groups with covariates X and X', and does not depend on t.

$$\frac{h(t|X = x)}{h(t|X = x')} = e^{\beta(x-x')}$$

There are different ways to formulate the baseline hazard function $h_0(t)$, corresponding with different models and estimations.

2.4.1 Cox Proportational Hazard Model

The Cox proportional hazards model is a **semi-parametric model** which does not assume a particular baseline hazard function $\tilde{h}_0(t)$. In contrast to parametric proportional hazards models which use the full likelihood, the Cox proportional hazards model is formulated by partial likelihood because there is very limited information on β beyond $L_p(\beta)$. The model is given by:

$$h_i(t) = \tilde{h}_0(t) \exp[\beta_1 X_{i1} + \beta_2 X_{i2} + \ldots + \beta_p X_{ip}]$$

2.4.2 Weibull Proportional Hazards Model

The Weibull proportional hazards model is a popular **parametric model** which assumes a specific functional form for the hazard rate, which can either increase or decrease over time. Its parameters are intuitively interpretable, with the shape parameter distinctly describing whether the hazard rate is increasing, decreasing, or constant.

$$h_i(t) = \lambda\gamma t^{\gamma-1} \exp[\beta_1 X_{i1} + \beta_2 X_{i2} + \ldots + \beta_p X_{ip}]$$

where λ is the scale parameter, and γ is the shape parameter.

2.5 Model Selection

Survival Tree

The survival tree method is a non-parametric approach used in survival analysis for model selection and identifying significant predictors of time-to-event outcomes. It involves segmenting the data into homogeneous subgroups based on the values of explanatory variables. The method constructs a tree structure where each node represents a subset of the dataset, and each split is based on the value of a predictor variable that best separates the data in terms of survival. Mathematically, this process involves recursively partitioning the

data to maximize a criterion like the log-rank statistic. At each node, the split is chosen to maximize the difference in survival between the resulting subgroups. This can be represented as:

$$\text{Max}_{v,s}[\chi^2_{LR}(v,s)]$$

where $\chi^2_{LR}(v,s)$ is the log-rank test statistic computed for a split s on variable v. The process continues until a stopping criterion is met, typically based on the minimum number of observations in a node or a minimum improvement in the survival difference. The result is a tree where the paths from the root to the leaves represent rules for predicting survival, offering a visual and interpretable model of the factors affecting the time to an event like death in this study.

Stepwise Selection

In model selection process, we incorporated bidirectional stepwise selection, alongside using various model assessment criteria such as Akaike Information Criterion (AIC), Corrected Akaike Information Criterion (AICc), and Schwarz Bayesian Criterion (SBC). This comprehensive approach enhanced our ability to identify the most appropriate model for our data.

We chose the final model based on AIC in our survival analysis due to its effective balance between model complexity and fit, particularly valuable in preventing overfitting in complex models. Additionally, given our sufficiently large sample size, AIC provided a more appropriate measure compared to AICc, and its less stringent penalty compared to SBC was better suited for our data's scale and complexity. The AIC for the survival model is as follows (Collett et al., 1999):

The formula for the Cox model being:

$$AIC_{cox} = -2\partial\mathcal{L}(\theta;x) + 2k$$

In this equation, k represents the number of parameters in the model. The term $2k$ serves as a penalty to discourage overfitting by complex models and $\mathcal{L}(\theta;x)$ indicates log-likelihood of parameter θ in the sample x.

For other survival models, the AIC adapts as follows with different penalty term:

$$AIC = -2\mathcal{L}(\theta;x) + 2(p+2+k)$$

where $k = 0$ for the exponential model, $k = 1$ for the Weibull, log-logistic and log-normal models, and $k = 2$ for the generalized gamma model.

2.6 Model Checking in the Proportional Hazards Model

Graphical Approach

The Cox proportional hazards model has two main assumptions. One is that the hazard functions of the survival curves of the different strata are proportional at time t. The other assumption is that the relationship between the $\log h(t)$ and each covariate is linear. We can compare the survival curves visually to check the PH assumption. One of the most commonly used plot is $\log(-\log \hat{S}(t|Z=z))$ over $\log t$. Since we know:

$$\log(-\log \hat{S}(t|Z=z)) - \log(-\log \hat{S}_0(t)) = \beta$$

where Z is a binary group indicator and the survival probability is usually estimated by K-M estimator. The parallel curves in the plot indicates the hazard ratio across the variable of interest is proportional at time t.

Another graphical method is to compare the differences between the fitted survival functions and observed K-M estimates from our proportional hazards models. If the fitted survival curves are closed to the observed K-M estimated survival curves, our PH assumption holds. In the parametric proportional hazards models, we can use both $-\log \hat{S}(t)$ plot and $\log(-\log \hat{S}(t))$ plot to confirm whether the hazard rate is constant. In other words, it can help us choose a proper distribution before fitting the models. For the $-\log \hat{S}(t)$ plot, a

straight line represents constant hazard rate and the distribution of time should be exponential. Otherwise, Weibull model is preferred. In the $\log(-\log \hat{S}(t))$ plot, if the slope of the straight line equals 1, the hazard rate should be constant which also means our survival time is exponentially distributed. And if it is not, the survival time should follows Weibull distribution.

Schoenfeld Residuals Test

The Schoenfeld residuals test evaluating the proportional hazards assumption in Cox regression models. It involves plotting the residuals against time; a lack of systematic trends in this plot generally indicates that the assumption holds. A smoothed curve can also be added to the plot to aid in interpretation. Conversely, if the residuals display a distinct trend over time, it suggests a violation of the proportional hazards assumption. Such a violation may occur if the effect of a covariate on the hazard rate changes over time, leading to non-constant hazard ratios. This could be attributed to time-varying covariates or time-dependent effects, which alter the relationship between the covariates and the survival outcome throughout the study period.

2.7 Model Validation

ROC Curves and AUC

In our analysis, we employed time-dependent Receiver Operating Characteristic (ROC) curves and Area Under the Curve (AUC) values to evaluate the discriminative ability of our Cox Proportional Hazards model over time. Specifically, we focused on two clinically relevant time points: 50 days and 250 days (Ahmad et al., 2017). The ROC curve is a graphical representation that illustrates the diagnostic ability of a binary classifier system by plotting the true positive rate (sensitivity) against the false positive rate (1 - specificity) at various threshold settings. AUC, a key summary measure of the ROC curve, quantifies the overall ability of the model to discriminate between individuals who will experience the event and those who will not, irrespective of the chosen probability threshold (Heagerty & Zheng, 2005). Generally, higher AUC values indicate better discriminative ability.

C-Index

The concordance index (C-index) was calculated to assess the predictive accuracy of our model. This metric is a measure of the model's ability to correctly rank the survival times of pairs of individuals, considering censored data (Steyerberg & Vergouwe, 2014). The C-index is calculated through pairwise comparisons, where a pair is concordant if the individual predicted to have a shorter survival time indeed experiences the event earlier than the other individual in the pair (Steyerberg & Vergouwe, 2014). A C-index of 0.5 suggests no better predictive accuracy than random chance, while a value of 1 indicates perfect prediction.

Calibration Slope

To evaluate the calibration of our model, we focused on the calibration slope. Calibration reflects the agreement between observed outcomes and predicted probabilities and the calibration slope assesses whether the predicted risks are of the correct magnitude (Steyerberg & Vergouwe, 2014). A slope of 1 indicates perfect calibration, meaning the model's predicted probabilities are accurately scaled. We calculated the calibration slope using logistic regression within a bootstrap framework, which allowed us to robustly assess the scale of the predicted risks relative to the actual event occurrences. The bootstrap approach, involving resampling the dataset 400 times, provided a more comprehensive understanding of the model's calibration under varying sample conditions.

3 Results

3.1 Nonparametric Methods

3.1.1 Life Table

Table 2.1: Heart Failure Life Table (Male)

	tstart	tstop	nsubs	nlost	nrisk	nevent	surv	pdf	hazard	se.surv	se.pdf	se.hazard
0-30	0	30	194	1	193.5	23	1.0000000	0.0039621	0.0042125	0.0000000	0.0007755	0.0008766
30-60	30	60	170	4	168.0	12	0.8811370	0.0020979	0.0024691	0.0232651	0.0005862	0.0007123
60-90	60	90	154	25	141.5	9	0.8181986	0.0017347	0.0021898	0.0278070	0.0005626	0.0007295
90-120	90	120	120	20	110.0	5	0.7661577	0.0011608	0.0015504	0.0309802	0.0005094	0.0006932
120-150	120	150	95	18	86.0	2	0.7313323	0.0005669	0.0007843	0.0332571	0.0003970	0.0005546
150-180	150	180	75	2	74.0	5	0.7143246	0.0016088	0.0023310	0.0345899	0.0006991	0.0010418
180-210	180	210	68	26	55.0	3	0.6660594	0.0012110	0.0018692	0.0384014	0.0006834	0.0010787
210-240	210	240	39	16	31.0	2	0.6297289	0.0013543	0.0022222	0.0416431	0.0009305	0.0015705
240-270	240	270	21	16	13.0	1	0.5891013	0.0015105	0.0026667	0.0478504	0.0014564	0.0026645
270-300	270	300	4	4	2.0	0	0.5437858	0.0000000	0.0000000	0.0620201	NaN	NaN
300-Inf	300	Inf	0	0	0.0	0	0.5437858	NA	NA	0.0620201	NA	NA

Table 2.2: Heart Failure Life Table (Female)

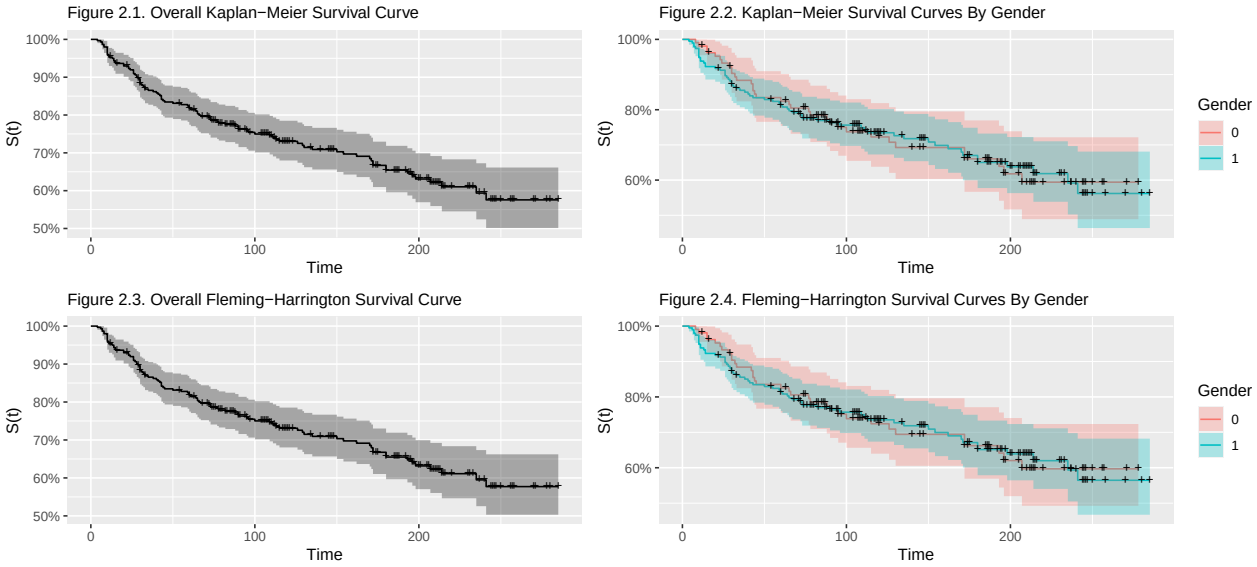
	tstart	tstop	nsubs	nlost	nrisk	nevent	surv	pdf	hazard	se.surv	se.pdf	se.hazard
0-30	0	30	105	3	103.5	8	1.0000000	0.0025765	0.0026801	0.0000000	0.0008750	0.0009468
30-60	30	60	94	0	94.0	9	0.9227053	0.0029448	0.0033520	0.0262504	0.0009372	0.0011159
60-90	60	90	85	10	80.0	6	0.8343612	0.0020859	0.0025974	0.0367098	0.0008241	0.0010596
90-120	90	120	69	15	61.5	4	0.7717841	0.0016732	0.0022409	0.0419136	0.0008140	0.0011198
120-150	120	150	50	5	47.5	2	0.7215868	0.0010128	0.0014337	0.0460937	0.0007039	0.0010135
150-180	150	180	43	3	41.5	2	0.6912042	0.0011104	0.0016461	0.0489040	0.0007700	0.0011636
180-210	180	210	38	12	32.0	3	0.6578931	0.0020559	0.0032787	0.0519106	0.0011416	0.0018907
210-240	210	240	23	10	18.0	0	0.5962156	0.0000000	0.0000000	0.0579853	NaN	NaN
240-270	240	270	13	11	7.5	0	0.5962156	0.0000000	0.0000000	0.0579853	NaN	NaN
270-300	270	300	2	2	1.0	0	0.5962156	0.0000000	0.0000000	0.0579853	NaN	NaN
300-Inf	300	Inf	0	0	0.0	0	0.5962156	NA	NA	0.0579853	NA	NA

Table 2.1 and **Table 2.2** represent the lifetable with a time break of 30 days (one month), stratified by gender. According to the table, we find that the last line (270-300 days) shows a survival probability larger than 0.5 for both genders (0.54 for male and 0.59 for female). This may indicate a high life expectancy and improved health care, where a significant proportion of individuals are expected to live longer than 300 days (10 months). Moreover, males have a relatively shorter survival time than females based on the life table. This hypothesis needs future testing in the following modeling fit.

3.1.2 The Kaplan-Meier Curve and Fleming-Harrington Test

From the survival curves in **Figure 2.1** and **Figure 2.3**, we noticed that the whole lines (as well as **confidence interval**) in both Kaplan-Meier and Fleming-Harrington are above 50%. In other words, more than half of the individuals in this study have not experienced the event in the study period, and the median survival time is longer than 300 days (10 months), with a certain level of significance.

Moreover, **Figure 2.2** and **Figure 2.4** have similar trends and show no significant difference between genders. Given that the p-value is relatively high (p-value = 0.95) for both Kaplan-Meier and Fleming-Harrington estimators, we can further make sure that no significant difference appears in the survival experience between males and females.



3.2 Hypothesis Testing

3.2.1 Log-Rank test and Gehan's Wilcoxon test

Figure 3.1: Comparison of Survival Experience Between Males and Females by Log-Rank Test

Gender	N	Observed	Expected	$\frac{(O-E)^2}{E}$	$\frac{(O-E)^2}{V}$
0	105	34	34.3	0.00254	0.00397
1	194	62	61.7	0.00141	0.00397

Figure 3.2: P-value for the Log-rank and Gehan's Wilcoxon Tests

Test	Chi square	df	p-value
Log Rank Test	0	1	0.950
Wilcoxon Test	0	1	0.765

The log-Rank test and Gehan's Wilcoxon test can be used to test for differences in survival experience between genders. Reviewing the results from the table, we find that both the Log-Rank test and the Gehan's Wilcoxon test have provided a similar result and provided a p-value greater than 0.05. This finding indicates that we failed to reject the null hypothesis at the significance level of 0.05, and we can state there is no statistically significant difference in survival experiences between males and females.

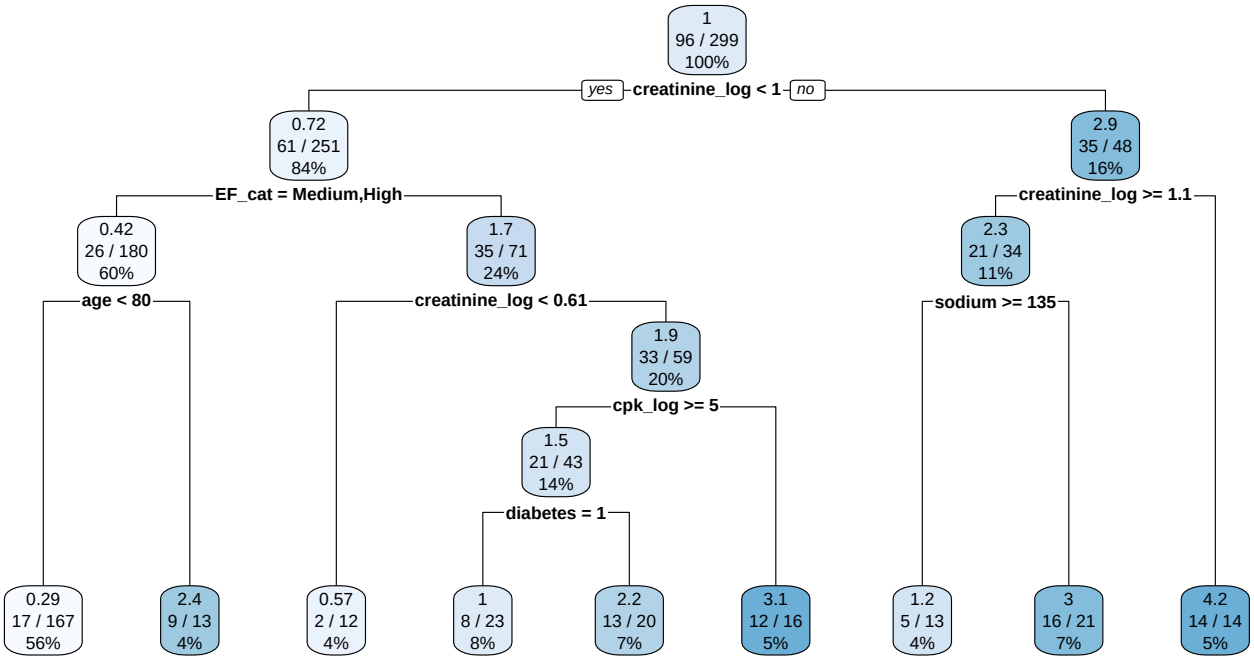
3.3 Model Selection

3.3.1 Survival Tree

The survival tree depicted in the **Figure 3** stratifies patients based on factors affecting survival. At the first level, patients are divided by `EF_cat` variable, suggesting that EF is a significant factor in survival. For patients with medium to high EF, age is the next discriminator, indicating its importance in survival for this subgroup. Among those with lower EF, log-transformed creatinine levels further split the cohort, underscoring renal function's role in survival. The tree branches into additional factors such as log-transformed creatinine phosphokinase levels (`logcpk`), the presence of diabetes, and sodium levels, highlighting their contribution to survival outcomes. Terminal nodes provide risk ratios and the proportion of patients experiencing the

event, illustrating the combined effect of these variables on patient survival. This tree model, therefore, offers a nuanced view of patient risk profiles, emphasizing the multifactorial nature of survival in this patient population.

Figure 3: Results of Survival Tree



3.3.2 Stepwise Selection

Our model selection applied bidirectional stepwise selection with a suite of model assessment criteria, AIC, AICc, and SBC. In the variable selection process, we adopted specific significance thresholds, setting the entry-level at 0.25 and the stay level at 0.15, to ensure a robust and relevant selection of predictors for our model.

The **Table 3** summarizes the Cox proportional hazards model selection process, indicating `logcre`, `age`, `EF` categories, and `BP` as persistent predictors across the top four models. The AIC favors `logcre` and `age` for their significant contributions to model fit relative to added complexity, emphasizing model fit over parameter count.

Table 3: Summary Table of Model Selection

Step	EnteredEffect	SL	AIC	AICc	SBC
1	logcre	0	993.05	991.09	995.61
2	age	0	975.5	971.62	980.62
3	EF_catMedium	2e-04	964.02	958.28	971.71
4	EF_catHigh	5e-04	953.71	946.15	963.97
5	bp	0.0185	950.16	940.83	962.98
6	sodium	0.1228	949.78	938.72	-
7	anemia	0.1922	-	937.35	-
8	logcpk	-	-	936.72	-
9	diabetes	-	-	936.33	-

However, with large sample size, the AICc modification slightly adjusts these values, shifting the preference toward other variables like `diabetes`, which shows the lowest AICc, suggesting a strong impact on the model when accounting for sample size. The SBC, with its more substantial penalty for complexity, particularly at larger sample sizes, selects `BP` as the best variable, underscoring its contribution to the model's explanatory power without excessive complexity.

We choose AIC for model selection, given its consistency with SL findings, which jointly highlight `logcre` and `age` as key predictors. This consistent identification underscores their substantial impact on model accuracy while maintaining simplicity, justifying their selection.

3.4 Semi-parametric Model

The Cox model obtained through the Stepwise Selection using Akaike Information Criterion (AIC) contains creatinine, age, ejection fraction, blood pressure status, sodium covariates, the model as follows:

$$h(t) = h_0(t) \exp[\beta_1 Age + \beta_2 EF_{Medium} + \beta_3 EF_{High} + \beta_4 BP + \beta_5 Sodium + \beta_6 \log(Creatinine + 1)]$$

3.4.1 Model Checking

Before fitting the Cox proportional hazards model, we need to check whether our variables hold the PH assumption[6]. The $\log(-\log \hat{S}(t|Z = z))$ over $\log t$ plot and observed survival versus estimated survival curves are provided below. We have multiple variables remained after model selection, so we randomly took two of them (`EF_cat` and `logcre`) for the PH assumption check. Since `logcre`[7] is continuous variable, we categorized it into two groups and recoded as "Low" and "High", respectively.

Figure 4.1: Log of Negative Log of Estimated Survival Functions

by EF Groups

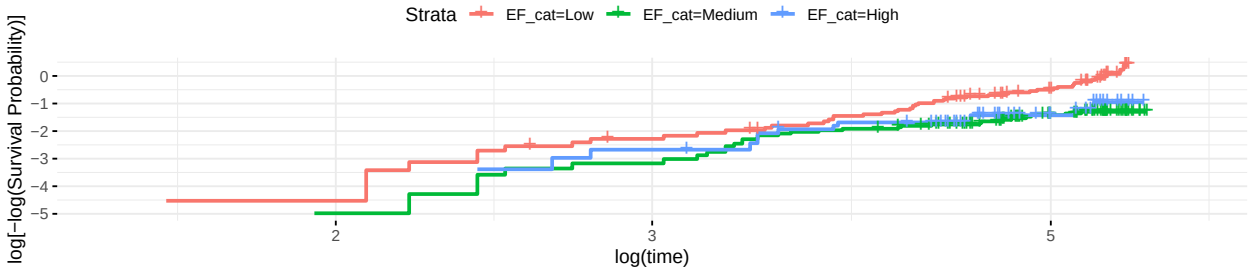
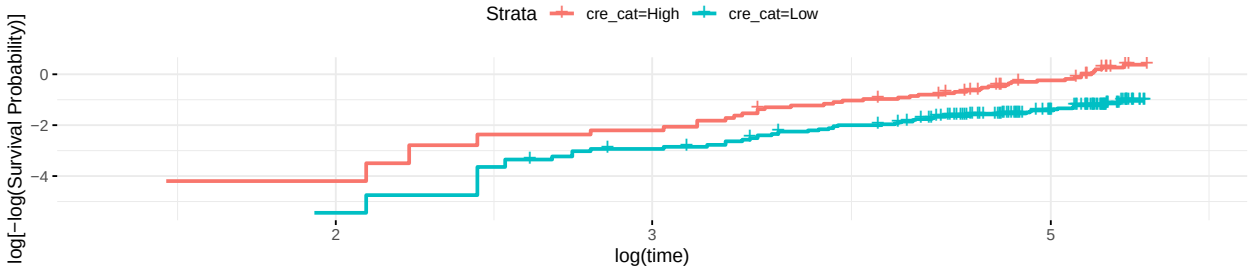


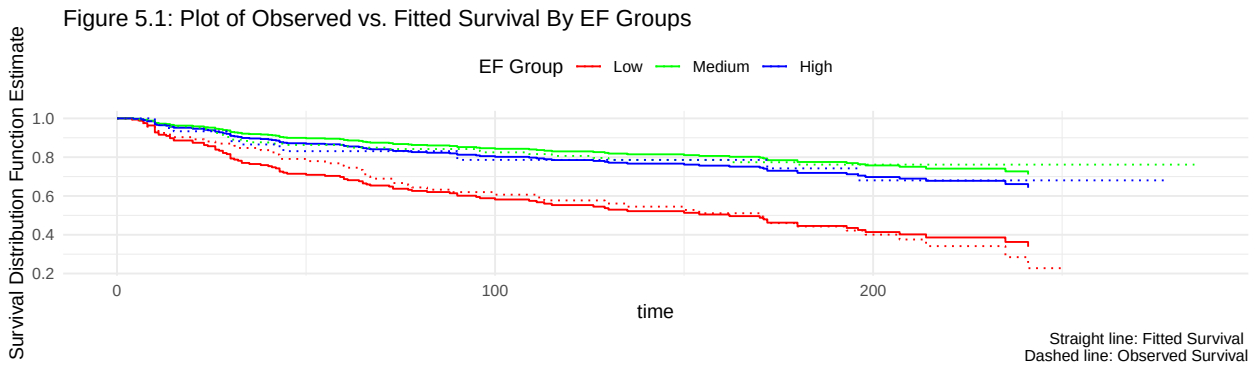
Figure 4.2: Log of Negative Log of Estimated Survival Functions

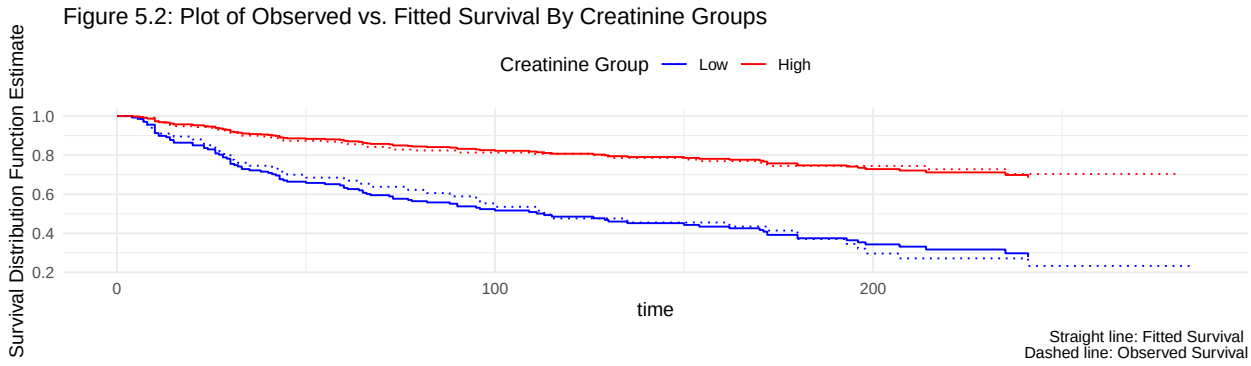
by Log−transformed Creatinine Groups



[6]See the Method Section for details

[7]Since 1.5 mg/dL is the clinical threshold of creatinine, so we categorized log(creatinine + 1) > log(2.5) as "High", otherwise, it's in "Low" group. And people in "High" group should be regarded as renal dysfunction.





Global Schoenfeld Test p: 0.0895

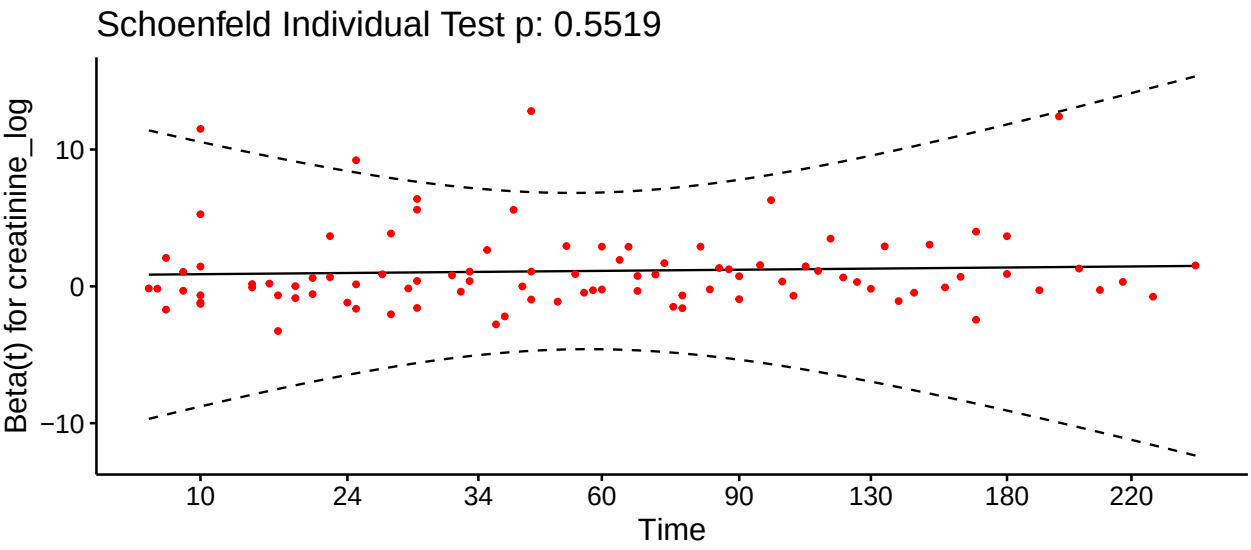


Figure 6.1: Schoenfeld Test For Log-transformed Creatinine

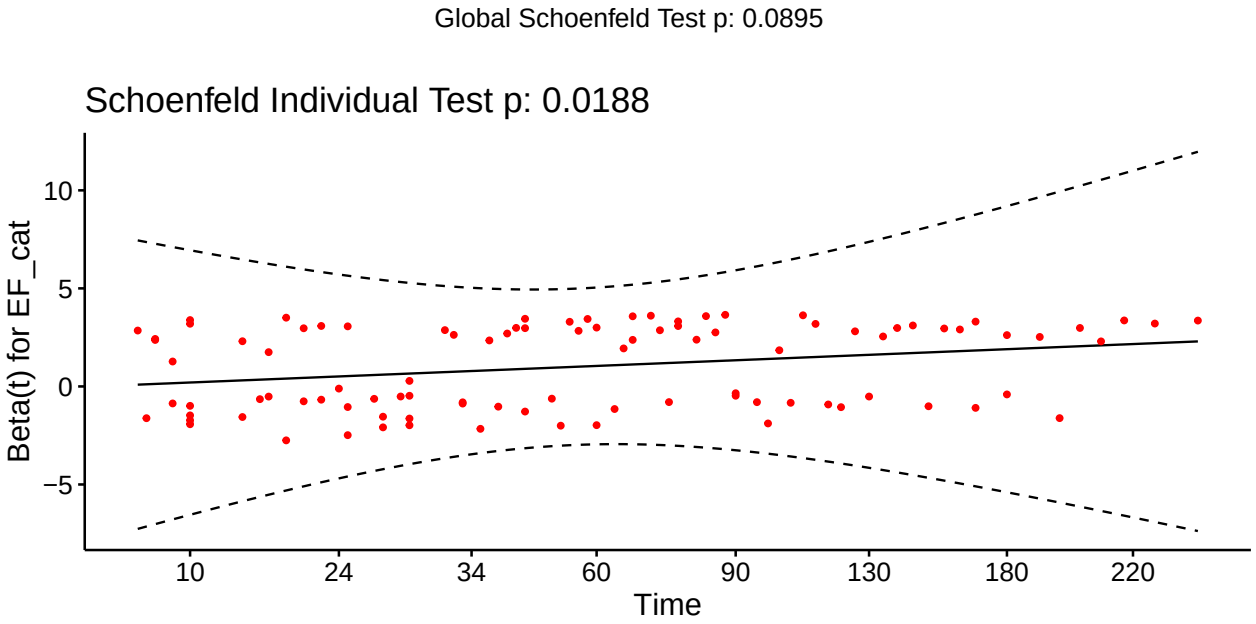


Figure 6.2: Schoenfeld Test For Categorized EF

Obviously, the curves in **Figure 4.2** are parallel with each other, indicating the proportional hazards assumption holds. For the observed survival versus estimated survival plot **Figure 5.2**, the solid curve and dashed curve are close to each other, which means the hazard ratio is proportional for creatinine groups. These findings are also consistent with what we observed in the Schoenfeld residual plots **Figure 6.1** of the fitted model. We chose to input `logcre` variables with resulted in a regression lines with a slope close to zero.

However, after examining the `EF_cat` variable, the curves in **Figure 4.1** are not parallel. The solid and dashed curves in **Figure 5.1** are not close to each other, especially at the beginning of the study. In **Figure 6.2**, we find that the slope of the regression line for the global Schoenfeld test is clearly non-zero. These findings violate the PH assumptions, and therefore we decided to remove `EF_cat` from the model and the subsequent analyses.

3.4.2 Cox Model Fitting and Results

Following the model checking in the Cox proportional hazards analysis, we excluded ejection fraction due to its violation of PH assumption. The final model thus includes the covariates: creatinine, age, blood pressure status, and sodium. This final model is as follows:

$$h(t) = h_0(t) \exp[\beta_1 Age + \beta_2 BP + \beta_3 Sodium + \beta_4 \log(Creatinine + 1)]$$

Table 4: Summary of Cox Proportional Hazards Model

	Variable	β	$exp(\beta)$	$SE(\beta)$	P-value
1	logcre	1.2654	3.5446	0.2602	0.0000
2	age	0.0399	1.0407	0.0088	0.0000
3	bp	0.4877	1.6286	0.2117	0.0213
4	sodium	-0.0528	0.9486	0.0214	0.0134

The sumamry table of Cox proportional hazards model **Table 4** indicates the first five variables are statistically significant at $\alpha = 0.05$. Among these, `logcre`, `age`, and `bp` exhibit positive hazard ratios, suggesting an

increased risk associated with higher values of these variables. On the other hand, `sodium` demonstrates a negative hazard ratio, indicating patient with high sodium value have a lower risk of mortality.

3.5 Parametric Models

3.5.1 Parametric Model Checking

Figure 7.1: Negative Log of Estimated Survival Functions For Age Groups

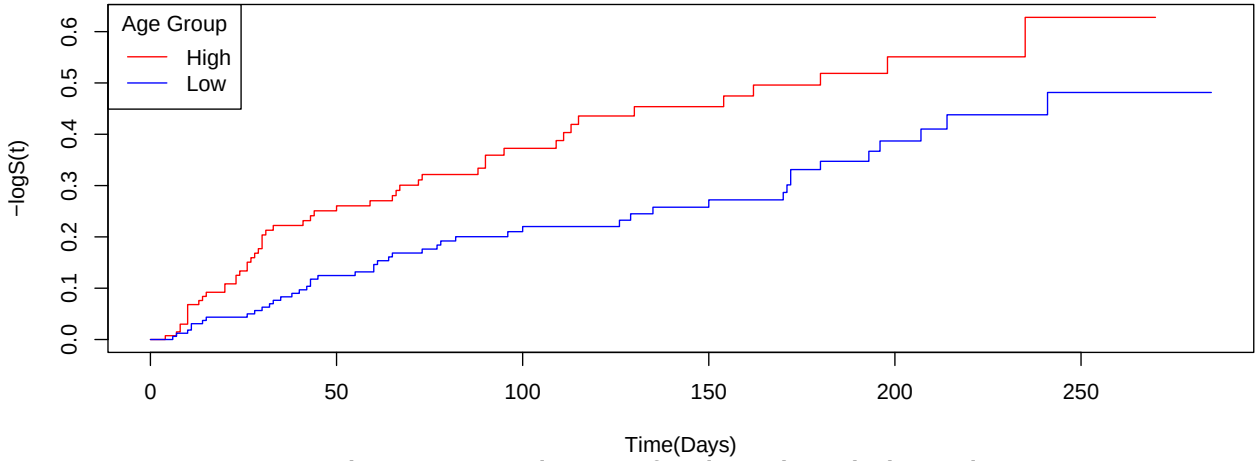
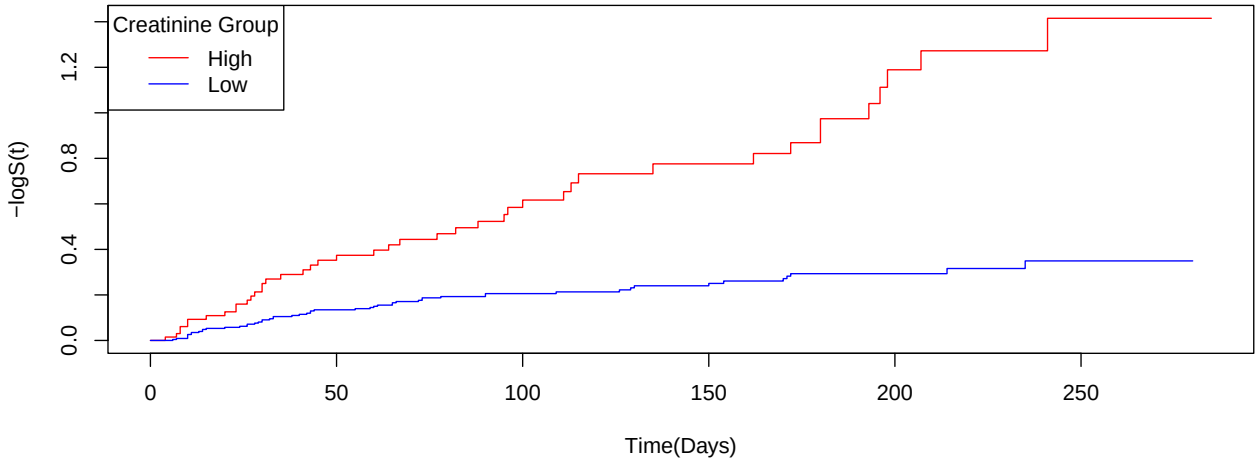


Figure 7.2: Negative Log of Estimated Survival Functions For Creatinine Groups



Since we have already created the $\log(-\log \hat{S}(t))$ (**Figure 4.1** and **Figure 4.2**) for `age` and `logcre`, and the slopes do not strictly equal to 1. In addition, we also check the $-\log \hat{S}(t)$ plot (**Figure 7.1** and **Figure 7.2**) for same variables, and the curves for both two plots seems not to be straight and linear. We then suggest fitting the survival time of the Weibull distribution in a parametric proportional hazards model.

3.5.2 Weibull Model Fitting and Results

The sumamry table of Weibull proportional hazards model **Table 5** demonstrates that in the, the four variables are statistically significant at $\alpha = 0.05$, which is the same as the significance variables in the Cox proportional hazards model. Additionally, the log scale value of 2.55 implies that the baseline hazard function is scaled by exp(2.55), influencing the time to event and indicating a higher baseline hazard rate. Meanwhile, the log shape value of -0.09, when exponentiated to approximately 0.92, suggests a decreasing hazard rate over time, meaning that the risk of the event occurring diminishes as time progresses.

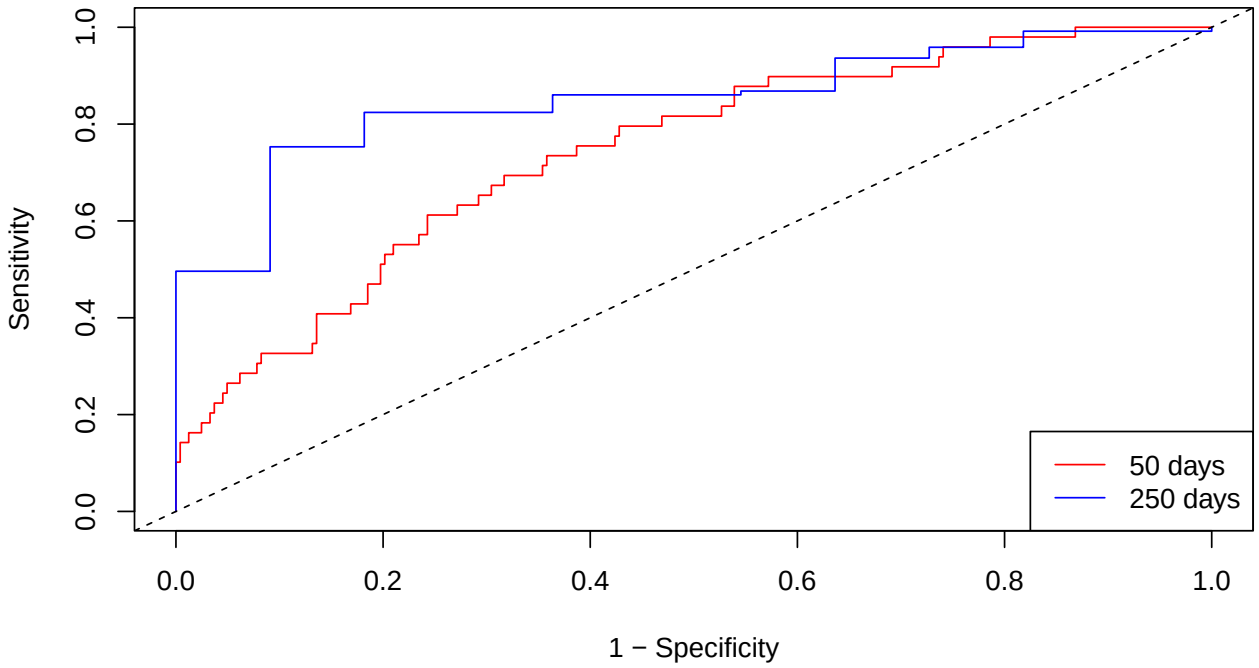
Table 5: Summary of Weibull PH Model Fitting

Variable	β	$exp(\beta)$	$SE(\beta)$	Wald P-value
bp	0.4907	1.6335	0.2110	0.0200
age	0.0409	1.0418	0.0089	0.0000
sodium	-0.0519	0.9494	0.0211	0.0140
logcre	1.2681	3.5539	0.2579	0.0000
log(scale)	2.5470	12.7691	3.2353	0.4311
log(shape)	-0.0875	0.9162	0.0891	0.3262

3.6 Model Validation

3.6.1 ROC Curves and AUC

Figure 8: Time−Dependent ROC Curves for 50 and 250 Days



Applying the Cox proportional hazards model with the five selected predictors, the time-dependent ROC analysis depicted in **Figure 8** reveals AUC is approximately 0.742, while at 250 days, the AUC is 0.851. These values indicate that the model's ability to discriminate between those who will experience the event and those who will not improves over time. The ROC curves further visually demonstrate this improvement, with the curve for 250 days being closer to the top left corner, indicating better performance.

3.6.2 C-Index

The average C-index calculated through bootstrapping (n = 400) was 0.703 This suggests that in about 70% of pairwise comparisons, our model correctly ranks the survival times. A C-index of around 0.70 is generally indicative of good predictive ability, especially in clinical settings where accurate risk stratification is crucial for treatment planning.

3.6.3 Calibration Slope

In our analysis, the calibration of the Cox proportional hazards model was evaluated using a bootstrap method with logistic regression. This model, incorporating `logcre`, `age`, `BP` , and `sodium` as predictors, was subjected to 400 bootstrap iterations to robustly assess its calibration slope. The average calibration slope, derived from these iterations, was approximately 0.627. This value suggests good calibration of the model, indicating a close alignment between the predicted risks and the observed outcomes in our dataset. The bootstrap method provided a comprehensive assessment by capturing the variability inherent in the model, thereby offering a reliable estimate of the model's calibration.

4 Discussion

Our comprehensive analysis, employing both semi-parametric and parametric models, has successfully achieved the objective of elucidating the predictors associated with heart failure prognosis. By integrating the Cox Proportional Hazards model and the Weibull proportional hazards model, we have identified key factors such as creatinine levels, age, blood pressure, and sodium, which play significant roles in the survival outcomes of heart failure patients. Our findings have not only underscored the importance of these established risk factors but have also shed light on how their impact evolves over time.

According to the non-parametric methods, we found that the median survival time is longer than 300 days (10 months), indicating that more than half of the individuals in this study have not experienced the event in the study period. Meanwhile, according to the life table, we find that there is a slight difference in survival probability between male and female. However, the hypothesis test and model selection show that there is actually no difference. Similarities in heart failure presentation, treatment regimen, and sample size may explain the absence of sex-based differences in survival. Specifically, if the severity of heart failure was not related to gender or if patients received appropriate gender-based treatment and the sample size or characteristics of the study limited gender-specific analyses, potential differences could be masked.

Both the **Cox proportional hazards model** and the **Weibull proportional hazards Model** reveals significant predictors of survival outcomes in heart failure patients. Key among these is `logcre`, with the Cox PH model showing a HR of 3.54, indicating a substantial risk increase with elevated levels. `Age` with the Cox PH model suggesting a 4 increase in risk per year, implies people with advancing age face higher hazard. `bp` similarly shows a significant impact on hazard, with a 62 increase in risk for higher levels in the Cox PH model, a finding mirrored in the Weibull analysis.

The Weibull PH model, in addition to confirming these findings, brings additional insights due to its parametric nature. The model emphasis on `bp`, `age`, and `logcre` with notably small p-values highlights their robustness as predictors. For `sodium`, the relationship with survival outcomes negative, a higher sodium value have lower risk of mortality. Both model shows this variable is statistically significant. The consistency between the Cox and Weibull models in identifying the key predictors provides credibility to these findings.

Supporting this, A study published in Frontiers in Cardiovascular Medicine found that postoperative serum creatinine is a significant prognostic factor for cardiac surgery patients (Zhong et al., 2021). This study showed that higher levels of postoperative serum creatinine were linked to increased hospital mortality and longer stays in the intensive care unit. Specifically, it found that patients who did not survive had significantly higher postoperative serum creatinine levels, and there was a positive correlation between these levels and lengths of ICU stay.

Building on the preceding discussion, our analysis further delved into the model's predictive capabilities using time-dependent ROC analysis and C-index evaluation. Our time-dependent ROC analysis revealed an Area Under the Curve (AUC) of approximately 0.742 at 50 days, which increased to 0.851 at 250 days. These AUC values signify the model's ability to effectively discriminate between patients at different risk levels, with an improvement observed over time. The increased AUC at 250 days suggests enhanced predictive accuracy for longer-term outcomes, a crucial aspect for patient management in heart failure. The calibration slope obtained from the bootstrap analysis (400 samples) was approximately 0.627. This value indicates a reasonable level of calibration, suggesting that the predicted risks generated by the model are in good alignment with the observed

outcomes. and demonstrating the model's reliability in risk prediction. Additionally, the average C-index, determined through bootstrapping, was 0.703. This indicates that in about 70% of pairwise comparisons, the model correctly ranks the survival times. A C-index of this magnitude reflects good predictive performance, especially important in clinical settings where accurate risk assessment is pivotal for treatment planning and patient care.

In concluding our discussion, it's important to recognize certain limitations inherent in our study. A key limitation of our model is linked to its adherence to the Proportional Hazards (PH) assumption, which influenced our selection of variables. This adherence necessitated a careful choice of variables, potentially limiting the breadth of predictors included in the model. As a result, this constraint may have impacted the model's overall predictive performance. By focusing exclusively on variables that satisfy the PH assumption, there's a possibility that other significant factors, which could have enhanced the model's predictive capacity, were not considered. This selective approach, while methodologically sound, may have inadvertently narrowed the scope of our analysis, potentially omitting crucial predictors.

Furthermore, while our study provides valuable insights into heart failure prognosis in the Pakistani context, it is based on a dataset from a single institution. This may limit the generalizability of our findings to other populations or regions. The demographic and clinical characteristics specific to the patient population at the Institute of Cardiology and Allied Hospital, Faisalabad, may not be fully representative of broader heart failure demographics.

Looking forward, we propose several directions for future research. To address the limitations of the Cox model, future studies could explore the use of alternative models that do not rely on the proportional hazards assumption. Such models might provide a more nuanced understanding of the risk factors over time. Additionally, expanding the study to include data from multiple institutions across different regions could enhance the generalizability of the findings. This would allow for a more comprehensive analysis of heart failure risk factors across diverse patient populations and enhance the applicability of the findings and continue to improve patient management strategies in heart failure.

5 Conclusions

In conclusion, our study, utilizing both the Cox Proportional Hazards and Weibull models, has effectively identified crucial predictors of survival outcomes in heart failure patients. The significant factors we highlighted include creatinine levels, age, blood pressure, and sodium levels.

While acknowledging certain methodological limitations, notably the adherence to the Proportional Hazards assumption and the study's reliance on data from a single institution, our findings provide valuable insights into heart failure management. They underscore the importance of these predictors in clinical decision-making and patient care. By enhancing our understanding of heart failure progression, this research contributes to the development of more effective, personalized treatment strategies, ultimately aiming to improve patient outcomes in heart failure.

Future research should aim to expand upon these findings, exploring a broader range of variables and including data from multiple institutions to increase the generalizability and applicability of the results. This approach will further refine our understanding of heart failure and aid in the continued advancement of patient care.

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. Collett, D. (1999). Modelling survival data in medical research. Chapman & Hall/CRC.

3. Heagerty, P. J., & Zheng, Y. (2005). Survival Model Predictive Accuracy and ROC Curves. Biometrics, 61(1), 92–105. https://doi.org/10.1111/j.0006-341X.2005.030814.x

4. 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

5. Pavlou, M., Ambler, G., Seaman, S. R., Guttmann, O., Elliott, P., King, M., & Omar, R. Z. (2015). How to develop a more accurate risk prediction model when there are few events. BMJ, h3868. https://doi.org/10.1136/bmj.h3868

6. Steyerberg, E. W., & Vergouwe, Y. (2014). Towards better clinical prediction models: Seven steps for development and an ABCD for validation. European Heart Journal, 35(29), 1925–1931. https://doi.org/10.1093/eurheartj/ehu207

7. Zhong, J., Gao, J., Luo, J. C., Zheng, J. L., Tu, G. W., & Xue, Y. (2021). Serum creatinine as a predictor of mortality in patients readmitted to the intensive care unit after cardiac surgery: a retrospective cohort study in China. Journal of thoracic disease, 13(3), 1728–1736. https://doi.org/10.21037/jtd-20-3205

7 Appendix

7.1 Code

```
knitr::opts_chunk$set(echo = FALSE, message = FALSE, warning = FALSE)
# INSTALL PACKAGES
packages <- c("biostat3", "tidyverse", "knitr", "kableExtra", "survival",
                "survminer", "ggfortify", "ggsurvfit", "patchwork", "writexl",
                "readxl", "table1", "rmarkdown", "KMsurv", "StepReg", "ggplot2",
                "timeROC", "boot", "rms", "survivalROC", "rpart", "eha", "pec", "MASS")

# Install missing packages
installed_packages <- packages %in% rownames(installed.packages())
if (any(installed_packages == FALSE)) {
  install.packages(packages[!installed_packages], dependencies = TRUE)
}

# Load packages invisibly
invisible(lapply(packages, library, character.only = TRUE))

# Remove variables associated with package installation
rm(packages, installed_packages)
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)"
```

```r
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.
    # initial empty string places the output on the line below variable label
    c("", sub("<", "<", format.pval(p, digits = 3, eps = 0.001)))
}
caption = "Table 1: Descriptive Statistics Table for Variable Characteristic"

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)
t1kable(table1) |> kable_styling(font_size = 8, latex_options = "HOLD_position")
# Data contains the continuous vars only
cont_dat = dat |>
  dplyr::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 |>
  dplyr::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 = -0.3) +
  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))
nonpara_dat = dat_log |>
  dplyr::select(-c(EF, cpk, creatinine)) |>
  relocate(time, event, EF_cat, smoking, everything()) |>
  mutate(event = as.numeric(event) - 1)
nonpara_male = nonpara_dat |> filter(gender == 1)
nonpara_female = nonpara_dat |> filter(gender == 0)
life_table_male <- lifetab2(Surv(time, event) ~ 1, data = nonpara_male,
                            breaks = seq(0, 300, 30))
life_table_female <- lifetab2(Surv(time, event) ~ 1, data = nonpara_female,
                              breaks = seq(0, 300, 30))
life_table_male |> kable(booktabs = T,
                         caption =
                          "Table 2.1: Heart Failure Life Table (Male)") |>
  kable_styling(latex_options = c("HOLD_position"), font_size = 6)
life_table_female |> kable(booktabs = T,
                           caption =
                            "Table 2.2: Heart Failure Life Table (Female)") |>
  kable_styling(latex_options = c("HOLD_position"), font_size = 6)
km_overall = survfit(Surv(time, event) ~ 1, data = nonpara_dat)
km_overall_plot =
  km_overall |> autoplot() +
  labs(y = "S(t)",
       x = "Time",
       subtitle = "Figure 2.1. Overall Kaplan-Meier Survival Curve") +
  theme(legend.position = "none")

km = survfit(Surv(time, event) ~ gender, data = nonpara_dat)
km_plot =
  km |> autoplot() +
  labs(y = "S(t)",
       x = "Time",
       subtitle = "Figure 2.2. Kaplan-Meier Survival Curves By Gender",
       color = "Gender", fill = 'Gender')
fh_overall = survfit(Surv(time, event) ~ 1, data = nonpara_dat, type = "fh")
fh_overall_plot =
  fh_overall |> autoplot() +
  labs(y = "S(t)",
       x = "Time",
```

```
       subtitle = "Figure 2.3. Overall Fleming-Harrington Survival Curve") +
  theme(legend.position = "none")
fh <- survfit(Surv(time, event) ~ gender, data = nonpara_dat, type = "fh")
fh_plot =
  fh |> autoplot() +
  labs(y = "S(t)",
       x = "Time",
       subtitle = "Figure 2.4. Fleming-Harrington Survival Curves By Gender",
       color = "Gender", fill = 'Gender')
(km_overall_plot + km_plot) / (fh_overall_plot + fh_plot)
logrank_test <- survdiff(Surv(time, event) ~ gender, data = nonpara_dat)
wilcox_result <- wilcox.test(time ~ gender, data = nonpara_dat)
results1 <- tibble(
  Gender = c(0, 1),
  N = c(105, 194),
  Observed = c(34,62),
  Expected = c(34.3, 61.7),
  '11' = c(0.00254, 0.00141),
  '22' = c(0.00397, 0.00397)
)

results2 <- tibble(
  Test = c("Log Rank Test", "Wilcoxon Test"),
  "Chi square" = c(0, 0),
  df = c(1, 1),
  "p-value" = c(0.950, 0.765)
)

results_table1 <- kable(results1, align = "c", booktabs = T, escape = F,
caption =
  "Figure 3.1: Comparison of Survival Experience Between Males and Females
by Log-Rank Test",
col.names = c("Gender", "N", "Observed", "Expected", "$\\frac{(O-E)^2}{E}$",
              "$\\frac{(O-E)^2}{V}$")) |>
  kable_styling(latex_options = c("HOLD_position"))

results_table2 <- kable(results2, align = "c", booktabs = T,
caption = "Figure 3.2: P-value for the Log-rank and Gehan's Wilcoxon Tests") |>
  kable_styling(latex_options = c("HOLD_position"))

results_table1
results_table2
surv_obj <- Surv(time = nonpara_dat$time, event = nonpara_dat$event)
surv_tree <- rpart(surv_obj ~ gender + smoking + diabetes +
                     bp + anemia + age + EF_cat + sodium +
                     creatinine_log + platelets + cpk_log,
                   data = nonpara_dat, method = "exp")
rpart.plot::rpart.plot(surv_tree, main = "Figure 3: Results of Survival Tree")
# raw data
raw_data <- data |>
  arrange(TIME) |>
  janitor::clean_names() |>
  mutate(platelets = pletelets,
```

```
         anemia = anaemia)

# model data
model_data <- dat |>
  mutate(event = as.numeric(event))

## create dummy variable for categorical variable
heart_data <- model.matrix(EF~ EF_cat, data = model_data)[,-1] |>
  as.data.frame()

## create data frame for stepwiseCox
heart_data <- cbind(raw_data, heart_data)
stepwise_data <- heart_data |>
  mutate(logcre = log(creatinine + 1),
         logcpk = log(cpk + 1)) |>
  dplyr::select(-creatinine, -cpk, -ejection_fraction)
# Variable selection using stepwise Cox model using Sl
stepwise_model1 <- stepwiseCox(Surv(time, event) ~ gender + smoking +
                                 diabetes + bp + anemia + age + sodium +
                                 platelets + logcre + logcpk +
                                 EF_catMedium + EF_catHigh,
                               data = stepwise_data,
                               select = "SL",
                               # significant level for entry
                               sle = 0.25,
                               # significant level for stay
                               sls = 0.15,
                               method = "efron",
                               weights = NULL,
                               best = NULL)
# 7 variables are selected:
# logcre, age, EF_catMedium, EF_catHigh, bp, sodium, anemia

## Variable selection using stepwise Cox model using AIC
stepwise_model2 <- stepwiseCox(Surv(time, event) ~ gender + smoking +
                                 diabetes + bp + anemia + age + sodium +
                                 platelets + logcre + logcpk +
                                 EF_catMedium + EF_catHigh,
                               data = stepwise_data,
                               selection = "bidirection",
                               select = "AIC",
                               # significant level for entry
                               sle = 0.25,
                               # significant level for stay
                               sls = 0.15,
                               method = "efron",
                               weights = NULL,
                               best = NULL)
# 6 variables are selected: logcre, age, EF_catMedium, EF_catHigh, bp, sodium

### Variable selection using stepwise Cox model using AICc
stepwise_model3 <- stepwiseCox(Surv(time, event) ~ gender + smoking +
                                 diabetes + bp + anemia + age + sodium +
```

```
                                platelets + logcre + logcpk +
                                EF_catMedium + EF_catHigh,
                              data = stepwise_data,
                              selection = "bidirection",
                              select = "AICc",
                              # significant level for entry
                              sle = 0.25,
                              # significant level for stay
                              sls = 0.15,
                              method = "efron",
                              weights = NULL,
                              best = NULL)
# AICc 9 variables:
# logcre, age, EF_catMedium, EF_catHigh, bp, sodium, anemia, logcpk, diabetes

### Variable selection using stepwise Cox model using SBC
stepwise_model4 <- stepwiseCox(Surv(time, event) ~ gender + smoking +
                                diabetes + bp + anemia + age + sodium +
                                platelets + logcre + logcpk +
                                EF_catMedium + EF_catHigh,
                              data = stepwise_data,
                              selection = "bidirection",
                              select = "SBC",
                              # significant level for entry
                              sle = 0.25,
                              # significant level for stay
                              sls = 0.15,
                              method = "efron",
                              weights = NULL,
                              best = NULL)
# SBC 5 variables: logcre, age, EF_catMedium, EF_catHigh, bp
# Extract data from the models
steps2 <- stepwise_model3$`Process of Selection`[, "Step"]
enteredEffect1 <- stepwise_model3$`Process of Selection`[, "EnteredEffect"]
sl1 <- stepwise_model1$`Process of Selection`[, "SL"]
aic2 <- stepwise_model2$`Process of Selection`[, "AIC"]
aic3 <- stepwise_model3$`Process of Selection`[, "AICc"]
sbc4 <- stepwise_model4$`Process of Selection`[, "SBC"]

# Determine the maximum length
max_len <- max(sapply(list(steps2, enteredEffect1, sl1, aic2, aic3, sbc4),
                      length))

# Function to pad vectors with NA to make their length equal to max_len
pad_vector <- function(vec, max_len) {
  length(vec) <- max_len
  return(vec)
}

# Apply the function to each vector
steps2 <- pad_vector(steps2, max_len)
enteredEffect1 <- pad_vector(enteredEffect1, max_len)
sl1 <- pad_vector(sl1, max_len)
```

```r
aic2 <- pad_vector(aic2, max_len)
aic3 <- pad_vector(aic3, max_len)
sbc4 <- pad_vector(sbc4, max_len)

# Create the data frame
model_selection <- data.frame(
  Step = steps2,
  EnteredEffect = enteredEffect1,
  SL = round(as.numeric(sl1),4),
  AIC = round(as.numeric(aic2), 2),
  AICc = round(as.numeric(aic3), 2),
  SBC = round(as.numeric(sbc4), 2)
)
model_selection[is.na(model_selection)] <- c("-")

# Create table using kable
model_selection |> kable(booktabs = T,
                         caption = "Table 3: Summary Table of Model Selection",
                         digits = 4) |>
  kable_styling(latex_options = c("HOLD_position"), font_size = 10)
mc_dat = nonpara_dat %>% mutate(age_cat =
                                  case_when(age <= mean(age) ~ "Low",
                                            age > mean(age) ~ "High")) %>%
  mutate(cre_cat = case_when(creatinine_log <= log(2.5) ~ "Low",
                             creatinine_log > log(2.5) ~ "High")) %>%
  mutate(age_cat = factor(age_cat)) %>%
  mutate(cre_cat = factor(cre_cat)) %>%
  mutate(EF_cat = factor(EF_cat, levels = c("Low", "Medium", "High"))) %>%
  as.data.frame()
mc_surv_ef = survfit(Surv(time, event == 1) ~ EF_cat, data = mc_dat)
mc_surv_cre = survfit(Surv(time, event == 1) ~ cre_cat, data = mc_dat)
mc_ef_surv_log = survfit(Surv(log(time + 1), event == 1) ~ EF_cat,
                         data = mc_dat)
mc_cre_surv_log = survfit(Surv(log(time + 1), event == 1) ~ cre_cat,
                          data = mc_dat)

g1 = ggsurvplot(mc_ef_surv_log, data = mc_dat, fun = "cloglog",
                risk.table = FALSE,
                xlab = "log(time)", ylab = "log[-log(Survival Probability)]",
                ggtheme = theme_minimal(), xlim = c(1.5, 6)) +
  labs(title =
         "Figure 4.1: Log of Negative Log of Estimated Survival Functions
       \nby EF Groups")
g2 = ggsurvplot(mc_cre_surv_log, data = mc_dat, fun = "cloglog",
                risk.table = FALSE,
                xlab = "log(time)", ylab = "log[-log(Survival Probability)]",
                ggtheme = theme_minimal(), xlim = c(1.5,6)) +
  labs(title =
         "Figure 4.2: Log of Negative Log of Estimated Survival Functions
       \nby Log-transformed Creatinine Groups")
gridExtra::grid.arrange(g1$plot, g2$plot, nrow = 2)

g3.1 = ggsurvplot(mc_surv_ef, data = mc_dat, risk.table = FALSE,
```

```
                  ggtheme = theme_minimal())
g3.2 = ggadjustedcurves(coxph(Surv(time, event == 1) ~ EF_cat, data = mc_dat),
                        variable = "EF_cat",
                        data = mc_dat, ggtheme = theme_minimal())
km_fit = g3.1$plot$data
cox_fit = g3.2$data
cox_fit$EF_cat = cox_fit$variable

g3 = ggplot(cox_fit, aes(x = time, y = surv, group = EF_cat, color = EF_cat)) +
  geom_step() +
  geom_step(data = km_fit,
            aes(x = time, y = surv, group = EF_cat, color = EF_cat), lty = 3) +
  labs(title = "Figure 5.1: Plot of Observed vs. Fitted Survival By EF Groups",
       y = "Survival Distribution Function Estimate",
  caption = "Straight line: Fitted Survival \nDashed line: Observed Survival") +
  theme_minimal() +
  theme(legend.position = "top") +
  scale_color_manual(
    name = "EF Group",
    values = c("red", "green","blue"),
    labels = c("Low", "Medium","High")
  )


g4.1 = ggsurvplot(mc_surv_cre, data = mc_dat, risk.table = FALSE,
                  ggtheme = theme_minimal())
g4.2 = ggadjustedcurves(coxph(Surv(time, event == 1) ~ cre_cat, data = mc_dat),
                        variable = "cre_cat",
                        data = mc_dat, ggtheme = theme_minimal())
km_fit = g4.1$plot$data
cox_fit = g4.2$data
cox_fit$cre_cat = cox_fit$variable

g4 = ggplot(cox_fit,
            aes(x = time, y = surv, group = cre_cat, color = cre_cat)) +
  geom_step() +
  geom_step(data = km_fit,
            aes(x = time, y = surv, group = cre_cat, color = cre_cat), lty = 3) +
  labs(title =
         "Figure 5.2: Plot of Observed vs. Fitted Survival By Creatinine Groups",
       y = "Survival Distribution Function Estimate",
  caption = "Straight line: Fitted Survival \nDashed line: Observed Survival") +
  theme_minimal() +
  theme(legend.position = "top") +
  scale_color_manual(
    name = "Creatinine Group",
    values = c("blue", "red"), # Change these colors based on your data
    labels = c("Low", "High") # Custom labels for the legend
  )

g3 / g4
scho <- coxph(Surv(time, event == 1) ~ EF_cat + bp + creatinine_log + age +
                sodium, data = mc_dat)
```

```r
ggcoxzph(cox.zph(scho), var = c("creatinine_log"), df = 2, nsmo = 1000)
ggcoxzph(cox.zph(scho), var = c("EF_cat"), df = 2, nsmo = 1000)
# final model
cox_model <- coxph(Surv(time, event) ~ logcre + age + bp + sodium,
                   data = stepwise_data)

cox_summary <- summary(cox_model)

model_summary <- tibble(Variable = base::rownames(cox_summary$coefficients),
                        as.data.frame(cox_summary$coefficients)) |>
  dplyr::select(-z)

model_summary |> kable(booktabs = T, escape = F,
      caption = "Table 4: Summary of Cox Proportional Hazards Model",
      digits = 4, row.names = TRUE,
      col.names = c("Variable",
                    "$\\beta$", "$exp(\\beta)$", "$SE(\\beta)$",  "P-value")) |>
  kable_styling(latex_options = c("HOLD_position"), font_size = 10)
mc_surv_age = survfit(Surv(time, event == 1) ~ age_cat, data = mc_dat)
mc_surv_cre = survfit(Surv(time, event == 1) ~ cre_cat, data = mc_dat)

plot(mc_surv_age, col = c("red", "blue"),
     fun = "cumhaz", xlab = "Time(Days)", ylab = "-logS(t)",
     main =
       "Figure 7.1: Negative Log of Estimated Survival Functions For Age Groups")
legend("topleft", legend = c("High", "Low"),
       title = "Age Group", col = c("red", "blue"), lty = 1)

plot(mc_surv_cre, col = c("red", "blue"),
     fun = "cumhaz", xlab = "Time(Days)", ylab = "-logS(t)",
     main =
       "Figure 7.2: Negative Log of Estimated Survival Functions
     For Creatinine Groups")
legend("topleft", legend = c("High", "Low"),
       title = "Creatinine Group", col = c("red", "blue"), lty = 1)
final_weibull <- eha::phreg(formula = Surv(time, event) ~ bp + age + sodium +
                              logcre, data = stepwise_data, dist = "weibull")

# Extract relevant information
weibull_summary <- tibble(
  Variable = c("bp", "age", "sodium", "logcre", "log(scale)", "log(shape)"),
  Coef = round(as.vector(final_weibull$coefficients),4),
  `Exp(Coef)` = round(exp(as.vector(final_weibull$coefficients)),4),
  `se(Coef)` = round(sqrt(as.vector(diag(final_weibull[["var"]]))),4),
  `Wald p` = round(1 - pchisq((as.vector(final_weibull$coefficients) /
                                 sqrt(as.vector(
                                   diag(final_weibull[["var"]]))))^2,1),4))

# Create table using kable
weibull_summary |> kable(booktabs = T, escape = F,
                         caption = "Table 5: Summary of Weibull PH Model Fitting",
                         digits = 4,
                         col.names = c("Variable", "$\\beta$", "$exp(\\beta)$",
```

```
                                        "$SE(\\beta)$", "Wald P-value")) |>
  kable_styling(latex_options = c("HOLD_position"), font_size = 10)
step_model_final <- coxph(Surv(time, event == 1) ~  + logcre + age + sodium + bp,
                          data = stepwise_data)

# Calculate predicted risks
predicted_risks <- predict(step_model_final, newdata = stepwise_data,
                           type = "risk")
 # Time points for ROC analysis
time_points <- c(50, 250)

# Calculate ROC curves at specified times
roc_50 <- timeROC(T = stepwise_data$time, delta = stepwise_data$event,
                  marker = predicted_risks, times = 50, cause = 1)
roc_250 <- timeROC(T = stepwise_data$time, delta = stepwise_data$event,
                   marker = predicted_risks, times = 250, cause = 1)

# Extract AUC values
auc_50 <- roc_50$AUC
auc_250 <- roc_250$AUC

# Print AUC values
#print(paste("AUC at 50 days:", auc_50))
#print(paste("AUC at 250 days:", auc_250))

# Plot ROC curves
plot(roc_50$FP, roc_50$TP, type = "l", col = "red", xlab = "1 - Specificity",
     ylab = "Sensitivity",
     main = "Figure 8: Time-Dependent ROC Curves for 50 and 250 Days")
lines(roc_250$FP, roc_250$TP, type = "l", col = "blue")
legend("bottomright", legend = c("50 days", "250 days"),
       col = c("red", "blue"), lty = 1)
abline(0, 1, col = "black", lty = 2)
# Define the function for calculating C-statistic
boot_c_statistic <- function(original_data, indices) {
 # Creating a bootstrap sample
  boot_data <- original_data[indices, ]

 # Fit the Cox model to the bootstrap sample
 fit <- coxph(Surv(time, event == 1) ~  + logcre + age + sodium + bp,
              data = stepwise_data)

   # Calculate the concordance statistic using the updated function
   concordance <- concordance(fit)$concordance
   return(concordance)
 }

 # Perform bootstrapping for C-statistic
 set.seed(123) # for reproducibility
 boot_results_c_stat <- boot(data = stepwise_data, statistic =
                               boot_c_statistic, R = 400)

 # Calculate the average C-statistic
```

```r
 mean_c_stat <- mean(boot_results_c_stat$t)
 #print(mean_c_stat)
 # Define the bootstrap function for calibration metrics using logistic regression
boot_calibration_logistic <- function(original_data, indices) {
 boot_data <- original_data[indices, ]
 fit <- coxph(Surv(time, event == 1) ~  + logcre + age + sodium+bp,
              data = stepwise_data)


  # Predicted risks for the original dataset
   predicted_risks <- predict(fit, newdata = original_data, type = "risk")

  # Fit a logistic model for calibration
   calibration_model_logistic <- glm(event ~ predicted_risks,
                                     data = original_data, family = "binomial")

   # Calibration slope (coefficient of predicted_risks)
   calibration_slope_logistic <-
     coef(calibration_model_logistic)["predicted_risks"]

   return(calibration_slope_logistic)
 }

 # Perform bootstrap
 set.seed(123)
 boot_results_logistic <- boot(data = stepwise_data,
                               statistic = boot_calibration_logistic, R = 400)

 # Calculate the average calibration slope
mean_calibration_slope_logistic <- mean(boot_results_logistic$t)
#print(mean_calibration_slope_logistic)
```