Application of the Cox Proportional Hazards Model in Survival Analysis of Hypertensive Patients

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ABSTRACT – Hypertension is a global health problem and one of the leading causes of mortality in Indonesia, including the Bangka Belitung Islands Province. This study aims to analyze the factors affecting the time required for blood pressure to return to normal in hospitalized hypertension patients at Bakti Timah Hospital Pangkalpinang. The methods used were survival analysis with Kaplan–Meier estimation, the Log-rank test, and the Cox Proportional Hazard Model. The results of the Log-rank test showed that the survival functions of hypertensive patients aged less than 50 years and those aged more than 50 years were statistically significantly different, indicating a different effect on the time to blood pressure normalization. Similarly, the comparison of the survival functions between patients with comorbidities and those without comorbidities showed a statistically significant difference, indicating a different effect on the time to blood pressure normalization among hypertensive patients. The best model obtained was $h_i(t|X) = h_o(t)\exp(-2,82047_{hypertensive\ patients\ with\ comorbidities})$. Based on the Hazard Ratio (HR), hypertensive patients with comorbidities have a hazard of achieving normal blood pressure that is 0.06 times that of hypertensive patients without comorbidities

Keywords– Survival Analysis, Log-rank Test, Cox Proportional Hazard Model, Maximum Likelihood Estimation, Hypertension

I. INTRODUCTION

Hypertension is a global health problem that requires effective management. Hypertension is the most common cardiovascular disease. Increased arterial pressure causes pathological changes in vascular tissues and left ventricular hypertrophy. Hypertension is defined as a persistent increase in blood pressure of ≥ 140/90 mmHg, a criterion indicating that the risk of cardiovascular disease associated with hypertension is sufficiently high to require medical attention [1]. According to the World Health Organization (WHO) (2023), an estimated 1.28 billion adults aged 30–79 years worldwide have hypertension, with the majority (two-thirds) living in low- and middle-income countries. In addition, it is estimated that 46% of adults with hypertension are unaware that they have the disease, and less than half of adults (42%) with hypertension are diagnosed and treated.

Based on the 2018 Basic Health Research Data (Riskesdas), Indonesia has experienced an increase in the prevalence of non-communicable diseases, which have become the leading cause of mortality in the country. Hypertension ranks first among the leading causes of death. Evidence shows that the prevalence of hypertension increased from 25.8% in 2013 to 34.1% in 2018. This condition results in approximately 8 million deaths annually. Furthermore, the estimated number of hypertension cases in Indonesia is 63,309,620, while the number of deaths caused by hypertension is 427,218 (Riskesdas, 2018). Based on the 2021 Health Profile prepared by the Health Office of the Bangka Belitung Islands Province, hypertension ranks as the most prevalent disease among the population of the Bangka Belitung Islands Province.

Survival analysis is a statistical method that can be used to answer questions regarding whether and when an event of interest occurs [2]. The objective of survival analysis is to determine the relationship between time and explanatory variables measured during the study [3]. The time referred to in survival analysis is the waiting period or duration until a particular event occurs. In this study, the time considered was the period from hospital admission until the patient's blood pressure returned to normal. In these data, the observation of survival time was conducted only partially or did not continue until the occurrence of the failure event. In other words, termination occurred before the end of the observation period. This termination was associated with factors suspected of influencing blood pressure reduction in hypertensive patients, such as sex, age, obesity, family history, alcohol consumption, smoking, and the hypertensive patients with comorbidities.

Based on these considerations and the fundamental objective of survival analysis, this study aims to identify the explanatory variables that influence the time required for blood pressure to return to normal among hypertensive patients at Bakti Timah Hospital Pangkalpinang.

II. LITERATURE REVIEW

A. Survival Data

Survival data refers to the length of time until an event occurs or the time between events (time-to-event data). Survival data are often illustrated as a “matchstick” plot, where black dots represent events and horizontal straight lines represent the duration of time until the occurrence of an event. Survival data are realizations of a survival random variable, namely a non-negative random variable, (T), which forms the basis for the development of models and methods in survival data analysis [4].

If (T) is a non-negative random variable representing the survival time of an individual in a population, then the probability distribution of (T) can be expressed through the survival function, probability density function, and hazard function. The variable (T) may be either discrete or continuous.

To obtain survival data, three components related to the phenomenon of interest must be clearly defined, namely:

a. The definition of the event of interest.
b. The origin point used to measure the duration of time until an event occurs.
c. The unit of measurement used.

B. Survival Function

[5] The probability that an individual survives until time (t) is expressed by the survival function

$$\begin{aligned} S(t) &= P(T \geq t) \\ &= \int_t^{\infty} f(t)dt \end{aligned} \tag{1}$$

The function $S(t)$ is a non-increasing function with respect to time (t), with the properties $S(0) = 1$ and $\lim_{t\to\infty} S(t) = 0$. The survival function can be interpreted as the proportion of individuals who remain alive within a cohort. At the beginning of the cohort, the proportion surviving is high (close to one). As time progresses, the proportion of surviving individuals in the cohort decreases until eventually all individuals die (the proportion approaches zero) [6].

C. Hazard Function

[5] The hazard function is a function that represents the rate of death or failure within the interval [t, t+Δt], given that the individual has survived up to time (t), and is defined as:

$$h(t) = \lim_{t\to\infty} \frac{P(t \leq T \leq t + \Delta t | T \geq t)}{\Delta t} \tag{2}$$

which can be interpreted as the rate of occurrence of an event.

The hazard function is not a probability; therefore, it may take values greater than one. The only restriction imposed on the hazard function is that $h(t) \geq 0$.

D. Log-rank Test

The Log-rank test is one of the methods used to test or compare two or more survival curves for censored data.

The null hypothesis for the Log-rank test is $H_0: S_1(t) = S_2(t)$ with the alternative hypotheses [7]:

$$H_1: S_1(t) > S_2(t)$$
$$H_1: S_1(t) < S_2(t)$$
$$H_1: S_1(t) \neq S_2(t)$$

The Log-rank test is based on the number of observed and expected events at each event time. For a Log-rank test comparing two groups, the test statistic is:

$$W = \frac{(O_1 - E_1)^2}{E_1} + \frac{(O_2 - E_2)^2}{E_2} \tag{3}$$

Where $W - X^2(df = 1)$. The null hypothesis H_0 is rejected at the significance level (α) if $W > X^2(1 - \alpha, \mathrm{df} = 1)$.

E. Cox Regression Model

The Cox Regression Model is a proportional hazards regression model in which the baseline hazard function is modeled non-parametrically, while the independent variable function is modeled parametrically [8]. This model is also known as the Cox proportional hazards model (Cox, 1975; Cox, 1972) or the Cox semiparametric hazards model. The Cox regression model is expressed as follows:

$$h(t|x) = h_0(t)\varphi(x, \beta) \tag{4}$$

where $x = (x_1, \dots, x_p)$ is a vector of covariates (independent variables), and $\beta' = (\beta_1, \dots, \beta_p)$ β' is the vector of regression model parameters. The hazard for each individual is equal to the baseline hazard $h_0\,(t)$ when the effects of the independent variables are not considered, or when the values of $x = (x_1, \dots, x_p)$ are equal to zero.

The assumption of a constant hazard ratio is the fundamental assumption underlying Cox Regression. Under the proportional hazards assumption, all individuals are assumed to have the same baseline hazard, which is then modified according to the characteristics of each individual. The proportional hazards model can be modeled semi-parametrically and is commonly referred to as the Cox regression model. The hazard, survival, and cumulative hazard functions for the Cox regression model are given respectively as follows:

$$h(t|x) = h_0(t)exp(x\beta) \tag{5}$$
$$S(t|x) = S_0(t)exp(x\beta) \tag{6}$$
$$H(t|x) = H_0(t)exp(x\beta) \tag{7}$$

where X is the covariate vector (explanatory variables); β is the regression parameter to be estimated; h_0 is the baseline hazard; S_0 is the baseline survival function; and H_0 is the cumulative baseline hazard function.

F. Factors Causing Hypertension

Parameter estimation for a parametric survival model can be performed using the Maximum Likelihood Estimation (MLE) method [9]. The likelihood function is a function of the parameters constructed from the joint probability distribution, given the realizations or data obtained from the survival random variable T. If $f(t;\theta)$ is the joint probability function, where t is a realization of T, then the function of the parameter θ is defined as follows:

$$L(\theta|t) = f(t;\theta) \tag{8}$$

The function is called the likelihood function

For survival data that are assumed to be independent, identically distributed, and complete, if there are $t_1, t_2, \ldots\ t_n$ observations, then the likelihood function is given by:

$$L(\theta|t) = \prod_{i=1}^{n} f(t_i;\theta) \tag{9}$$

Meanwhile, for incomplete survival data, either due to censoring or truncation, the likelihood function for survival data with possible right censoring can be represented by a pair consisting of the observed survival time and its censoring status, namely $(t_i, \delta_i), i = 1,2, \ldots, n$, where

$$\delta_i = \begin{cases} 0, & if\ the\ i - th\ observation\ is\ censored \\ 1, & if\ the\ i - th\ observation\ experiences\ the\ event \end{cases}$$

Assuming that each (T_i, δ_i) is independent of the others, the likelihood function for right-censored data is:

$$L(\theta) \propto \prod_{i=1}^{n} f(t_i;\theta)^{\delta_i} S(t_i;\theta)^{1-\delta_i} \tag{10}$$

where $\theta = (\theta_1, \ldots, \theta_p$ denotes the p parameters to be estimated; $f(t_i;\theta)$ is the density function for the $i - th$ observation that experiences the event, and $S(t_1;\theta)$ is the survival function for the $i - th$ observation that does not experience the event. The log-likelihood function for right-censored data corresponding to the likelihood function in Equation (10) is:

$$\ell(\theta) \propto \sum_{i=1}^{n} (\delta_i)\, log\big(f(t_i;\theta)\big) + \sum_{i=1}^{n} (1-\delta_i)\, log\big(S(t_i;\theta)\big) \tag{11}$$

G. Factors Causing Hypertension

The factors causing hypertension are as follows:

1. Age Factor. Blood pressure in individuals over the age of 50 tends to be higher, resulting in a greater risk of developing hypertension (high blood pressure). Increasing age causes blood pressure to rise because the arterial walls undergo thickening due to the accumulation of collagen substances in the muscle layer, causing the blood vessels to gradually narrow [10].
2. Hereditary Factor. Hereditary factors always play an important role in the occurrence of diseases transmitted through family genes. If one family member or parent has high blood pressure, the offspring may have the same risk, and this risk may even be greater than that inherited from the parental genes [11]
3. Obesity. Obesity is not a direct cause of hypertension. However, the prevalence of hypertension among obese individuals is much higher. The relative risk of developing hypertension in obese individuals is five times higher than in individuals with normal body weight. In addition, approximately 20–33% of hypertensive patients are found to be overweight. Therefore, obesity should be controlled through weight reduction. To determine whether a person's body weight is ideal or classified as obese, the Body Mass Index (BMI) is used. BMI is a measure used to assess the proportionality between an individual's height and weight. BMI = Body Weight/(Height^2). In cases of obesity, an individual is classified as obese if the BMI value is greater than or equal to 30 [11].
4. High Salt Levels in the Body. Excessive salt consumption causes the kidneys, which function to process salt, to retain more fluid than necessary. The retention of excess fluid increases blood volume. This additional burden on the blood vessels causes an increase in blood pressure within the vessel walls. Attention should be paid to the dietary habits of patients. A drastic reduction in salt intake may be difficult to implement; therefore, salt consumption should be limited to less than 5 grams (one teaspoon) per day during food preparation [11].
5. Stress. The relationship between stress and hypertension is thought to occur through the sympathetic nervous system, which can increase blood pressure intermittently. If stress persists for a long period, it may result in a sustained increase in blood pressure. Although emotional stress can increase blood pressure over a short period, this reaction usually disappears as the cause of stress subsides. However, if stress becomes permanent and there appears to be no way to overcome or avoid it, individuals may experience persistent hypertension, making stress a risk factor [12].
6. Lack of Physical Exercise. Physical activity refers to movements performed by the body's muscles and supporting systems. During physical activity, muscles require energy beyond basic metabolism to move, while the heart and lungs require additional energy to deliver nutrients and oxygen throughout the body and remove waste products. Exercise can reduce the risk of coronary heart disease through several mechanisms, including reducing heart rate and blood pressure, decreasing sympathetic tone, increasing coronary artery diameter and collateral blood vessel systems, increasing HDL levels, and decreasing LDL levels. Through regular exercise, the heart can function more efficiently. Pulse rate decreases while cardiac pumping strength increases, oxygen demand of the heart at a given intensity decreases, body fat and body weight are reduced, and blood pressure decreases [13].
7. Alcohol Consumption. Excessive alcohol consumption significantly increases body weight because alcohol contains a high number of calories. Excess body fat places additional pressure on the arteries and consequently on the heart, indirectly causing an increase in blood pressure. Although alcohol consumption has not become a common lifestyle pattern in Indonesia, the number of alcohol consumers continues to increase along with changes in social interactions and lifestyles, particularly in large cities. Consuming more than two alcoholic drinks per day for men or more than one alcoholic drink per day for women can increase blood pressure [14].

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8. Smoking. Smoking is a major risk factor for cardiovascular disease. Cigarettes can increase blood pressure while simultaneously narrowing the arterial walls. Hypertensive patients who smoke should receive additional counseling regarding the health risks associated with smoking. Furthermore, the potential benefits of smoking cessation should be explained to encourage quitting. Various smoking cessation programs, pharmacotherapy options, and support tools are available to assist patients [15].
9. Sex. In general, men suffer from hypertension more frequently than women, with a ratio of approximately 2.29% for increased systolic blood pressure. Men often experience signs of hypertension in their thirties. Men are believed to have lifestyles that tend to increase blood pressure more than women. However, after menopause or approaching the age of 60 years, the prevalence of hypertension among women increases. Women have a higher risk of developing hypertension because estrogen production decreases during menopause, causing women to lose its protective effects and resulting in increased blood pressure (Atriyaningrum, 2015). Female sex is more dominantly associated with the risk of hypertension, accounting for 82 cases (67.2%), compared to 40 cases (32.8%) among males [16].
10. Family History. In 70–80% of cases of essential hypertension, a family history of hypertension is present [16]. This family factor is also influenced by other environmental factors, which subsequently contribute to the development of hypertension. Genetic factors are also associated with salt metabolism regulation and membrane renin activity.

III. METHODOLOGY

A. Type and Source of Data

The type of data used in this study is secondary data. The data consist of the time required for blood pressure to return to normal among hospitalized patients with hypertension, obtained from the medical records of Bakti Timah Hospital Pangkalpinang during the period from January to July 2024. In addition, research data sources were obtained through a literature review relevant to survival analysis.

B. Data Analysis Technique

The data analysis technique used in this study is quantitative descriptive analysis. Descriptive analysis refers to describing or explaining the development of the research variables based on the data obtained. Meanwhile, the relationships among variables are explained using econometric tools commonly referred to as quantitative methods.

In this study, the relationship between the dependent variable, namely the time required for blood pressure to return to normal among hospitalized patients with hypertension at Bakti Timah Hospital Pangkalpinang and the explanatory variables, namely sex, age, hereditary status, and the hypertensive patients with comorbidities, was analyzed using the Cox Proportional Hazard Model approach, with the best model selected using the Maximum Likelihood Estimation (MLE) method. Furthermore, to compare two or more survival functions and hazard functions for each independent variable, this study employed Kaplan–Meier estimators graphically, and the Log-rank test statistically. In addition, the statistical software used in this study was R version 3.0.2.

IV. RESULTS AND DISCUSSIONS

A. Data Identification

This study used data from hospitalized patients with hypertension at Bakti Timah Hospital Pangkalpinang during the period from January to July 2024. A total of 72 patients were included in the study, of whom 44 had censored observations. The study employed Type I right censoring (time censoring) because the observation period was predetermined within a fixed time interval. Consequently, for patients whose blood pressure had not returned to normal by the end of the observation period, the exact time to recovery could not be determined, and these observations were therefore treated as censored data. The variables observed in this study were sex (jk), age (u), hereditary status (sk), and the hypertensive patients with comorbidities (mpl) as independent variables, while the status of blood pressure returning to normal was used as the dependent variable

B. Data Analysis

1. Estimation of the Survival Function for the Sex Variable

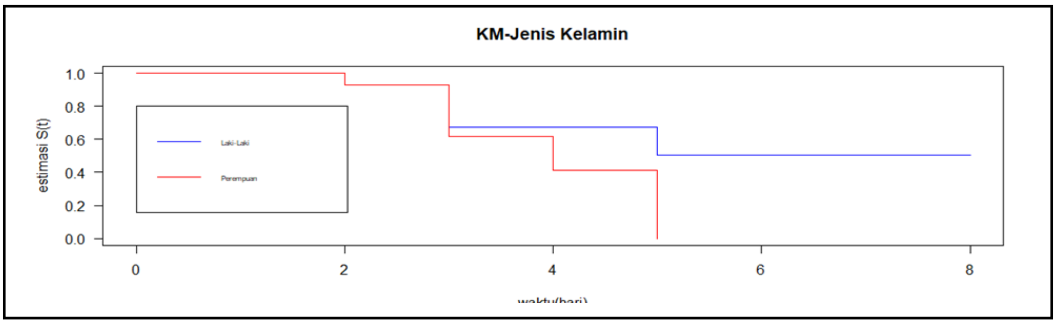

Figure 1 Estimation of the Survival Function for the Sex Variable

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```
> logrank.jk
Call:
survdiff(formula = Surv(datapasien4$WAKTU, datapasien4$STATUS.SENSOR) ~
    datapasien4$JENIS.KELAMIN, data = datapasien4)

                             N Observed Expected (O-E)^2/E (O-E)^2/V
datapasien4$JENIS.KELAMIN=0 14        5     6.52     0.354      1.03
datapasien4$JENIS.KELAMIN=1 14        7     5.48     0.421      1.03

 Chisq= 1  on 1 degrees of freedom, p= 0.3
```

2. Estimation of the Survival Function for the Age Variable

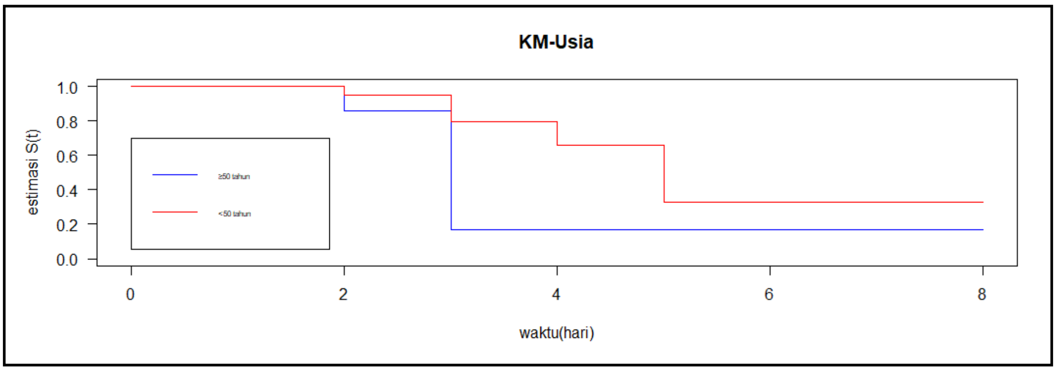

Figure 2 Estimation of the Survival Function for the Age Variable

```
> logrank.u
Call:
survdiff(formula = Surv(datapasien4$WAKTU, datapasien4$STATUS.SENSOR) ~
    datapasien4$USIA, data = datapasien4)

                    N Observed Expected (O-E)^2/E (O-E)^2/V
datapasien4$USIA=0  7        5     2.56     2.313      3.73
datapasien4$USIA=1 21        7     9.44     0.629      3.73

 Chisq= 3.7  on 1 degrees of freedom, p= 0.05
```

3. Estimation of the Survival Function for the Hereditary Status Variable

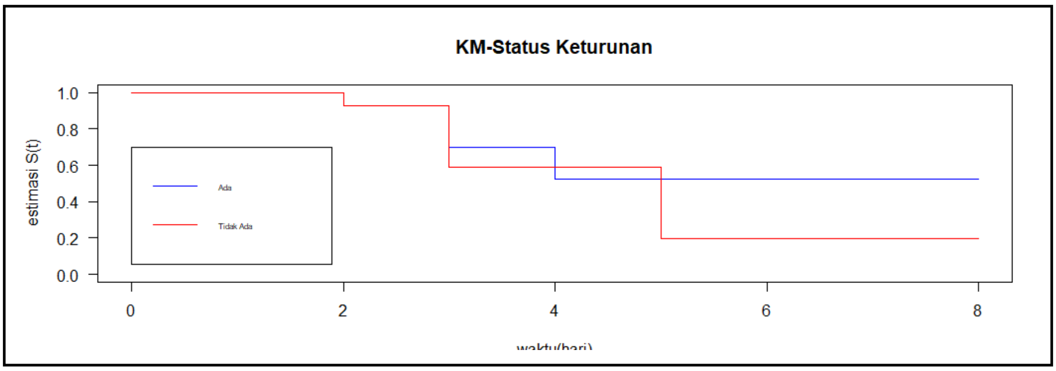

Figure 3 Estimation of the Survival Function for the Hereditary Status Variable

```
> logrank.sk
Call:
survdiff(formula = Surv(datapasien4$WAKTU, datapasien4$STATUS.SENSOR) ~
    datapasien4$STATUS.KETURUNAN, data = datapasien4)

                                N Observed Expected (O-E)^2/E (O-E)^2/V
datapasien4$STATUS.KETURUNAN=0 14        5     6.02     0.174     0.445
datapasien4$STATUS.KETURUNAN=1 14        7     5.98     0.175     0.445

 Chisq= 0.4  on 1 degrees of freedom, p= 0.5
```

4. Estimation of the Survival Function for the Hypertensive patients with comorbidities Variable

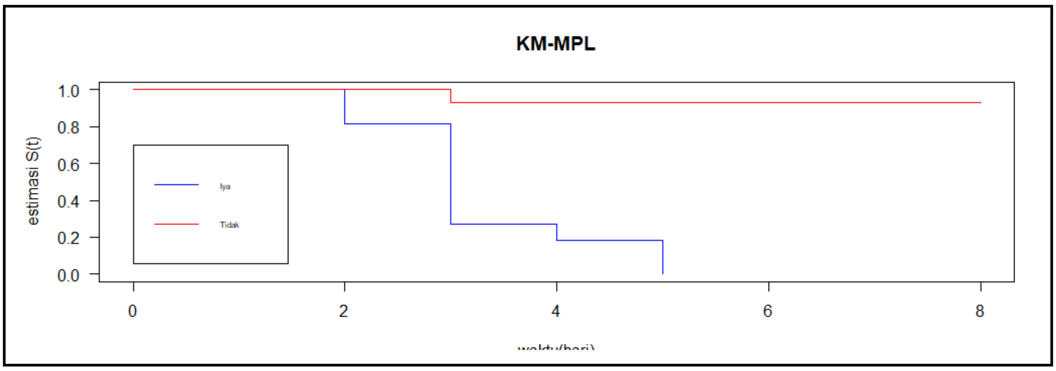

Figure 4 Estimation of the Survival Function for the Hypertensive patients with comorbidities Variable

```
> logrank.mpl
Call:
survdiff(formula = Surv(datapasien4$WAKTU, datapasien4$STATUS.SENSOR) ~
    datapasien4$MENDERITA.PENYAKIT.LAIN, data = datapasien4)

                                       N Observed Expected (O-E)^2/E (O-E)^2/V
datapasien4$MENDERITA.PENYAKIT.LAIN=0 11       11     4.75      8.21      17.1
datapasien4$MENDERITA.PENYAKIT.LAIN=1 17        1     7.25      5.38      17.1

 Chisq= 17.1  on 1 degrees of freedom, p= 3e-05
```

5. Log-rank Test

The Log-rank test was conducted to compare the survival distributions of two or more survival functions for censored data. The following are the results of the Log-rank test on data from hospitalized patients with hypertension.

Table 1 Log-rank Test

Variabel	Log Rank	df	p-value	Decision
Sex	1	1	0.3	Not Significant
Age	3.7	1	0.05	Significant
Hereditary Status	0.4	1	0.5	Not Significant
Hypertensive patients with comorbidities	17.1	1	0.00003	Significant

Based on Table 1, the comparison of the survival functions for each variable is as follows:

1. Sex
   Based on the results of the Log-rank test, with a $p-value\ >\ \alpha\ =\ 0.05$, the statistical comparison of the survival functions between male and female patients did not show a different effect on the status of blood pressure returning to normal among hypertensive patients
2. Age
   Based on the results of the Log-rank test, with a $p-value\ \leq\ \alpha\ =\ 0.05$, the statistical comparison of the survival functions between patients aged $<$ 50 years and patients aged $\geq$ 50 years showed a different effect on the status of blood pressure returning to normal among hypertensive patients.
3. Hereditary Status
   Based on the results of the Log-rank test, with a $p-value\ >\ \alpha\ =\ 0.05$, the statistical comparison of the survival functions between patients with a family history of hypertension and patients without a family history of hypertension did not show a different effect on the status of blood pressure returning to normal among hypertensive patients.
4. Hypertensive patients with comorbidities
   Based on the results of the Log-rank test, with a $p-value\ \leq\ \alpha\ =\ 0.05$, the statistical comparison of the survival functions between patients with comorbidities and patients without comorbidities showed a different effect on the status of blood pressure returning to normal among hypertensive patients.

6. Cox Proportional Hazard Model

```
mcoxph4
Call:
coxph(formula = Surv(datapasien4$WAKTU, datapasien4$STATUS.SENSOR) ~
    datapasien4$MENDERITA.PENYAKIT.LAIN, data = datapasien4,
    method = "breslow")

                                        coef exp(coef) se(coef)    z       p
datapasien4$MENDERITA.PENYAKIT.LAIN -2.82047   0.05958  1.04453 -2.7 0.00693

Likelihood ratio test=14.5  on 1 df, p=0.0001399
n= 28, number of events= 12
```

Based on the R output for likelihood estimation, the p-value of the variable hypertensive patients with comorbidities is less than the significance level (α) of 0.05. In other words, the variable hypertensive patients with comorbidities has a significant effect on the hazard function of the status of blood pressure returning to normal among hypertensive patients. The Cox Proportional Hazard Regression Model for hypertensive patient data is as follows:

$$\boldsymbol{h_i(t|X) = h_0(t)exp\left(-2,82047_{hypertensive\ patients\ with\ comorbidities}\right)}$$

7. Hazard Ratio

$$HR = \exp(-2{,}82047) = 0{,}06$$

The parameters in the Cox Proportional Hazard Regression can be interpreted as the Hazard Ratio (HR). Based on the Hazard Ratio (HR), hypertensive patients with comorbidities have a hazard of achieving normal blood pressure that is 0.06 times that of hypertensive patients without comorbidities. In other words, the hazard of achieving normal blood pressure is 94% lower among hypertensive patients with comorbidities compared with those without comorbidities.

V. CONCLUSIONS AND SUGGESTIONS

1. Based on the results of the Log-rank test, the variables that showed statistically different effects on the status of blood pressure returning to normal among hypertensive patients were age and hypertensive patients with comorbidities.
2. The Cox Proportional Hazard Regression Model for hypertensive patient data is given as follows:
$$\boldsymbol{h_i(t|X) = h_0(t)exp\left(-2,82047_{hypertensive\ patients\ with\ comorbidities}\right)}$$
3. The parameters in the Cox Proportional Hazard Regression can be interpreted as the Hazard Ratio (HR). Based on the Hazard Ratio (HR), hypertensive patients with comorbidities have a hazard of achieving normal blood pressure that is 0.06 times that of hypertensive patients without comorbidities. In other words, the hazard of achieving normal blood pressure is 94% lower among hypertensive patients with comorbidities compared with those without comorbidities

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1. One limitation of this study is the incompleteness of the data variables due to the limited information obtained from the hospitals. Therefore, future studies are expected to include more complete data variables.
2. The completeness of data variables requires support from the hospitals, as the data management system has not yet been fully organized and systematically recorded. Therefore, it is expected that the hospitals improve their patient data entry system, from the time of admission until discharge.

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