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COX PROPORTIONAL HAZARD AND EXPONENTIAL SURVIVAL ANALYSIS IN PATIENTS WITH END-STAGE CHRONIC KIDNEY FAILURE AT BOJONEGORO

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ABSTRACT

End-stage chronic renal failure is a condition that requires long-term treatment such as haemodialysis and poses a serious threat to patient survival. However, the survival time of each patient varies, depending on various clinical and demographic factors. Identifying variables that have a significant effect on survival time is important to help medical personnel prioritise patient care. Cox proportional hazard and exponential regression are statistical methods used to identify independent variables that affect the dependent variable, survival time. In this study, Cox proportional hazard and exponential regression survival analysis were modelled on end-stage chronic renal failure patients who were hospitalised in January-April 2024 at RSUD Dr. R. Sosodoro Djatikoesoemo Bojonegoro. This study aims to identify independent variables that have a significant influence on the survival rate of patients with end-stage chronic renal failure and the best model between Cox proportional hazard and exponential models. The Cox Proportional Hazard method is a semi-parametric method that analyses the influence of variables without having to know the specific shape of the failure time distribution. Meanwhile, the exponential model is a parametric model that assumes that the hazard function is constant over time. In this study, 10 variables were used to see their influence on the risk of occurrence. The results of Cox proportional hazard and exponential regression analysis obtained independent variables that have a significant effect, the variables of main complaint (X_3), urea (X_6), and diastolic blood pressure (X_8) on the survival time of patients with chronic renal failure. The hazard ratio value on significant variables, the variable that can increase the risk of death, is urea. Every additional 1 mg/dL urea value will increase the risk of death of chronic renal failure patients by 0.9%. The exponential model of 383.4526 is the best model based on the AIC value.

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1. INTRODUCTION

Survival analysis is an analysis that uses time data until the event to be studied occurs. This analysis is used to determine independent variables that are thought to have an influence on survival time. Survival analysis has three types of approaches, namely parametric, non-parametric, and semi-parametric survival analysis. Survival analysis with a parametric approach requires the assumption of a survival time distribution. Survival analysis that does not require the assumption of survival time distribution is a non-parametric model. The most popular non-parametric survival analysis is Kaplan-Meier. Kaplan-Meier provides an overview of the chances of an individual being alive at a certain time between categories in each variable.

Cox is a researcher who made the first Cox Proportional Hazard model in 1972. According to **[1]**, Cox Proportional Hazard regression is a popular method used to analyse survival data. Cox proportional hazard regression is used to determine the relationship between the independent variable and the dependent variable, with survival time as the dependent variable. The Cox PH regression model does not require the assumption of the distribution of the survival function. The model assumes that the hazard function for different individuals is proportional and independent of time.

Cox proportional hazard regression can be applied in the health sector. According to **[2]**, there were 1,501,016 cases of kidney failure. Kidney failure is a chronic disease with high treatment costs and is increasingly becoming a concern for the Indonesian government. According to **[2]**, there are eight diseases that require the highest costs in JKN Health services. One of the most costly diseases is kidney failure, which costs Rp 2,919,190,263,610 for the treatment of kidney failure. This includes the cost of medication, twice-weekly dialysis, supporting tests such as laboratory blood tests, and any hospitalisation that may be required.

On the 2nd Thursday in March, World Kidney Day was celebrated. This commemoration is a way to reduce the increasing number of chronic kidney failure diseases. Every date, Chronic Kidney Disease (CKD) screening is conducted for people with diabetes and hypertension. Screening is a programme that is in line with the government's 'Improving Equitable Access to Services and Optimal Treatment' programme **[3]**. The government created this programme because not all health services are able to provide proper treatment of chronic kidney disease according to its stage. Haemodialysis is one of the most commonly performed kidney replacement therapies. The quality of haemodialysis services greatly affects the quality of life of patients. Therefore, choosing the right health facility is very important.

Bojonegoro Regional General Hospital, one of the type B hospitals in East Java, has the potential to become a referral for kidney failure patients who need haemodialysis. This potential is based on several factors, including the availability of adequate haemodialysis facilities such as having a haemodialysis unit equipped with modern machines, a sufficient number of treatment rooms, and trained medical personnel. Chronic kidney disease at RSUD Dr R. Sosodoro Djatikoesoemo Bojonegoro is the number one disease causing death in 2023. There will be approximately 300 chronic kidney failure patients in 2024 who will need to undergo dialysis at RSUD Dr R. Sosodoro Djatikoesoemo. There are only 40 dialysis machines available in the haemodialysis room. The room operates every day except Sunday with three sessions. Each session lasts for 4-5 hours. RSUD Dr R. Sosodoro Djatikoesoemo Bojonegoro is a hospital that has few patients who use CAPD for the treatment of chronic renal failure; there are only 9 patients.

Previous research on survival analysis has been done. According to **[4]**, survival analysis of patients with kidney failure disease using the Kaplan-Meier method obtained the results of 106 data points with 90 censored patients and 16 uncensored patients, which showed a chance of survival of patients with kidney failure disease of 54%. The seriousness of the disease (chronic-acute), gender, and age each have an independent relationship with patients with kidney failure. According to **[5]**, survival analysis with the cox proportional hazard regression model on hemodialysis patient survival data obtained factors that affect the length of survival time for hemodialysis patients are systolic blood pressure, hemoglobin levels, and dialysis time. Research by **[6]** also strengthens these findings, where variables such as creatinine levels and treatment duration have a significant influence on the risk of death of chronic renal failure patients based on the exponential model.

Based on the description above, this study expands the scope of analysis by comparing the results of semi-parametric (Cox Proportional Hazard) and parametric (exponential regression) models to gain a more comprehensive understanding of the variables that affect the survival of chronic renal failure patients undergoing haemodialysis at RSUD Dr. R. Sosodoro Djatikoesoemo.

2. RESEARCH METHODS

2.1. Data

The data used are medical records data of 150 patients with end-stage chronic kidney failure from January to April 2024. This data was obtained from RSUD Dr. R. Sosodoro Djatikoesoemo Bojonegoro, which is located at Jl. Veteran No.36, Jambean, Sukorejo, Bojonegoro District, Bojonegoro Regency, East Java.

2.2. Research Variables

The dependent variable is the survival time of end-stage kidney failure patients undergoing hospitalisation (t). Patient status indicates whether the patient experienced the event of interest in the study, namely dying from end-stage renal failure at the time of the study (d).

1. Age (X_1)

   Age is an important factor to consider in the management of chronic renal failure. Between 40 and 80 years of age, there is generally a decrease in kidney function both anatomically and physiologically, which causes a kidney decline of up to 20% [7].

2. Gender (X_2)

   In a study conducted by Ningsih at Pertamina Bintang Amin Hospital in January 2021, there were 71 patients with chronic renal failure. Patients with the highest age frequency in the interval >71.8% aged 40 years to 60 years, with the highest gender 52.1% were male, who were registered at Pertamina Bintang Amin Hospital in January 2021 to 60 years of age, with the highest gender 52.1% were male, who were registered at Pertamina Bintang Amin Hospital, Bandar Lampung, with complete medical records [8].

3. Main Complaint (X_3)

   The main complaint is the condition felt by the patient, as described by symptoms, problems, and conditions. The patient's main complaint can determine the type of disease being experienced.

4. Secondary Diagnosis (X_4)

   Diagnosis is the determination of the type of disease by examining the symptoms. Secondary diagnosis is a diagnosis that accompanies the main diagnosis at the time of admission

5. Creatinine (X_5)

   Creatinine is a by-product of creatine catabolism in muscles. After the muscles contract, creatine is broken down into creatinine and phosphate, which are then excreted through urine. Damaged kidneys will affect creatinine levels, so that creatinine levels in the blood increase in patients with chronic renal failure. The creatinine value in chronic renal failure patients is more than 1.5 mg/dL. This value exceeds the normal limit, which should only be in the interval 0.6 - 1.3 mg/dL [9].

6. Urea (X_6)

   Urea is a chemical compound that indicates normal kidney function. If it is known that urea in the urine decreases, it will result in a decrease in the glomerular filtration rate, which results in increased urea levels in the blood. Therefore, the urea test is always used to determine kidney function in patients who are suspected of having kidney problems [10].

7. Blood Pressure

   Systolic blood pressure data after undergoing haemodialysis therapy showed an average value of 163.33 mmHg, while diastolic blood pressure data after undergoing haemodialysis therapy showed an average value of 100.53 mmHg [11].

8. Haemoglobin (X_9)

   Haemoglobin is a protein found in red blood cells and plays a role in carrying oxygen and carbon dioxide through the body. Anaemia in patients with CKD is caused by the lack of erythropoietin (EPO) produced

by the kidneys. A decrease in EPO can occur because, in patients with GHGK, there is chronic damage to the kidney organs. EPO has a function in the manufacture of haemoglobin, namely as a stimulant for the manufacture of erythrocytes. Damage to the kidneys in GGK can trigger impaired EPO production **[10]**.

9. Leukocytes (X_{10})

   The average number of leukocytes in routine and non-routine patients undergoing haemodialysis found that patients who do not routinely undergo haemodialysis tend to have a higher number of leukocytes than patients who routinely undergo haemodialysis, namely 13,700/µL and in patients who routinely undergo haemodialysis the average number of leukocytes is 6,295/µL **[8]**.

2.3. Chronic Kidney Failure

Chronic Kidney Failure (CKD) is a chronic disease of the kidney nephrons that affects the body's fluid and electrolyte balance. The condition of end-stage renal disease (ESRD) or chronic kidney disease requires permanent kidney replacement by means of kidney transplantation, renal dialysis, or haemodialysis **[12]**. The decrease in glomerular filtration rate in chronic kidney disease is divided into 5 stages according to **[13]**.

Table 1. Classification of Kidney Damage

GFR Category	GFR	Terms
Stage 1	GFR $\geq$ 90 ml/min/1.73 m^2	Normal or high
Stage 2	GFR = 60 - 89 ml/min/1.73 m^2	Mildly decreased
Stage 3A	GFR = 45 - 59 ml/min/1.73 m^2	Mildly to moderately decreased
Stage 3B	GFR = 45 - 59 ml/min/1.73 m^2	Moderately to severely decreased
Stage 4	GFR = 15 - 29 ml/min/1.73 m^2	Severely decreased
Stage 5	GFR $<$ 15 ml/min/1.73 m^2	Kidney failure

2.4. Survival Analysis

Survival analysis has three types of approaches, namely parametric, non-parametric, and semi-parametric survival analysis **[1]**. The parametric approach assumes a certain distribution for the time until the occurrence of the event, while the nonparametric approach does not require the assumption of time distribution. The semi-parametric approach is a combination of parametric and non-parametric, an example of which is the Cox proportional hazards model.

Determining the survival time requires paying attention to several things **[1]**.

1. The initial time of the start of an event or time origin
2. The end time of all observed events must be clear, or the event time
3. The unit of time used.

Censored data is data on several objects whose survival time is not known with certainty, causing data from these objects to be censored (censored data). The causes of censored data are as follows **[1]**.

1. Study ends - no event, meaning that a person does not experience the event at the end of the study.
2. Lost to follow-up, is that a person cannot be followed up during the study period.
3. Withdraws from the study, is a patient who is given the treatment, drops out of the study for certain reasons, such as side effects on the patient, so that their health deteriorates, or the patient dies, not because of the disease being studied during the study period.

2.5. Survival Function

The survival function is a function used to determine the probability that an individual will survive at least until time t, where $t > 0$ **[1]**. The survival function can be expressed as follows.

$$S(t) = 1 - F(t) \tag{1}$$

where:

$S(t)$ = survival function

$F(t)$ = cumulative distribution function

The cumulative distribution function can be expressed as follows.

$$F(t) = \int_0^t f(t)\, dt \tag{2}$$

The odds density function can be expressed as follows.

$$f(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < (t + \Delta t))}{\Delta t} \tag{3}$$

Characteristics of the survival function $S(t)$ [1] :

1. The survival function $S(t)$ will decrease in value as the value of t increases.
2. At the beginning of the observation ($t = 0$), the survival function is 1, $S(t) = S(0) = 1$, which indicates that no individual has experienced the event.
3. At the end of the observation ($t = \infty$), the survival function is 0, $S(t) = S(\infty) = 0$, meaning that at the end of the study time, no individual can survive.

2.6. Hazard Function

The hazard function $h(t)$ is the rate of a person experiencing a certain risk or event, such as failure or death, at time t, provided that the person still survives until $T \geq t$ [1]. The hazard function can be expressed as follows.

$$h(t) = \frac{f(t)}{S(t)} \tag{4}$$

2.7. Kaplan Meier

According to [1], the Kaplan-Meier survival curve is a curve that describes the relationship between the survival function and the survival time. The survival function used to create a Kaplan-Meier survival curve can be expressed as follows.

$$\hat{S}(t_{(j)}) = \prod_{j=1}^{f} \left(\frac{n_j - m_j}{n_j} \right) \tag{5}$$

where:

n_j = number of individuals alive immediately before $t_{(j)}$ including those who died at $t_{(j)}$, $j = 1,2,\ldots,f$

m_j = the number of individuals who died at $t_{(j)}$

$t_{(j)}$ = survival time

$S(tj)$ = survival function at time-j

2.8. Log-Rank Test

The Log-Rank test is a non-parametric test used to compare Kaplan-Meier survival curves in different groups [1]. The hypothesis used in the Log-Rank test is as follows.

H_0 : $S_1(t) = S_2(t) = \cdots = S_G(t)$ (No difference in survival function curves between groups) vs.

H_1: $S_i(t) \neq S_G(t)$ (There is at least one difference in the survival function curves between groups.)

The Log Rank test statistic can be expressed as follows.

$$\chi^2 = \sum_{i=1}^{G} \frac{(O_i - E_i)^2}{E_i} \tag{6}$$

where:

O_i = observation value of the i-th group

E_i = expectation value of the i-th group

i = number of groups, $i = 1,2,\ldots,G$

If $\chi^2 > \chi^2_{G-1,\alpha}$ then reject H_0 meaning there is at least one difference in the survival function between groups.

2.9. Proportional Hazard

The Proportional Hazard (PH) assumption is a test that must be met in the Cox proportional hazard regression model. This test is used to identify whether the hazard ratio value for each time is constant or independent of time. The Proportional Hazard assumption test can use the Goodness of Fit (GOF) test. The hypothesis for the proportional hazard assumption test is as follows.

H_0: $\rho = 0$ (There is no relationship between time and Schoenfeld residuals.) vs

H_1: $\rho \neq 0$ (There is a relationship between time and Schoenfeld residuals.)

Steps to use the Goodness of Fit (GOF) test **[14]**.

1. Obtain the Schoenfield residual value of the Cox proportional hazard regression model for each object that experienced the event.
2. Sort the survival time based on the event of interest or event from the smallest to the largest.
3. Pearson correlation test between Schoenfield residuals and survival times that have been sorted. The correlation formula can be expressed as follows.

$$r_{RT,PR_{ij}} = \frac{\sum_{i=1}^{r}\left(PR_{ij} - \overline{PR_j}\right)(RT_{ij} - \overline{RT_j})}{\sqrt{\sum_{i=1}^{r}(PR_{ij} - \overline{PR_j})^2 \sum_{i=1}^{r}(RT_{ij} - \overline{RT_j})^2}} \tag{7}$$

where:

$r_{RT,PR_{ij}}$ = correlation between RT and PR

PR_{ij} = Schoenfeld residuals of the i individual experiencing the event at time $t_{(j)}$ for the j variable

RT_j = rank of survival time for the j variable.

If the p-value of the Goodness of Fit (GOF) test is greater than 0.05, then the cox proportional hazard regression model fulfils the Proportional Hazard assumption and can be interpreted that there is no correlation between the Schoenfeld residual and the rank of survival time. Assumptions that have been met can be continued with parameter estimation of the Cox Proportional Hazard model. If the assumptions are not met, then the results of the Cox Proportional Hazard model are invalid, so that other models, such as the Cox extended model, can be used. This model can be used when one of the independent variables depends on time.

2.10. Cox Proportional Hazard

Cox Proportional Hazard regression is used to determine the relationship between the independent variable and the dependent variable, namely survival time, through the hazard function; therefore, the Cox

Proportional Hazard regression model is included as semi-parametric. The Cox proportional hazard model can be seen as follows.

$$h(t, \boldsymbol{X}) = h_0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_k X_k) \quad (8)$$

where:

$h(t, X)$ = hazard function

$h_0(t)$ = baseline hazard function

β_j = number of regression parameters, $j = 1,2,\ldots k$

X_j = number of predictor variables, $j = 1,2,\ldots k$

j = number of independent variables

Parameter estimation β_j with $j = 1,2,\ldots,k$ in the Cox Proportional Hazard model can be done using the Maximum Partial Likelihood Estimation (MPLE) method. The partial likelihood function of the Cox Proportional Hazard model can be seen as follows.

$$L(\boldsymbol{\beta}) = \prod_{j=1}^{r} \frac{\exp(\sum_{j=1}^{k} \boldsymbol{\beta}' X_j)}{\sum_{j \epsilon R(tj)} \exp(\sum_{j=1}^{k} \boldsymbol{\beta}' X_j)} \quad (9)$$

where:

X_j = observation value of the j-th independent variable

$R(t_{(j)})$ = group of surviving objects at time t_j

$\boldsymbol{\beta}'$ = vector of regression parameters

$t_{(j)}$ = time of death, $j = 1,2,..,r$

r = longest time of death

2.11. Exponential Model

Parametric survival analysis is an analysis in which survival time follows a certain distribution. Common distributions used in survival time are Weibull, exponential, log normal, logistic, and gamma **[1]**. Survival analysis with an exponential model is a model where the survival time is assumed to be exponentially distributed and can be written $T \sim exp(\lambda)$. The exponential model has only one parameter, which assumes that the hazard function $h(t)$ is constant. If the model has been formed, then the next process is to conduct a likelihood ratio test. The exponential model can be seen as follows.

$$h(t) = \lambda = \exp(\beta_0 + \beta_1 X_1 + \cdots + \beta_k X_k) \quad (10)$$

where:

$h(t)$ = hazard function

β_0 = intercept

β_j = regression parameter to $j, j = 1,2,\ldots k$

X_k = independent variable to $j, j = 1,2,\ldots,k$

j = number of independent variables

2.12. Value AIC

Akaike Information Criterion (AIC) is a method to determine the best model in relative terms by using maximum likelihood estimation as the corresponding calculation **[15]**. The best model is the one with the smallest AIC value. The following AIC formula can be seen as follows.

$$AIC = -2\log(L) + 2p \tag{11}$$

where:

L = likelihood value in the model formed

p = the number of parameters β in the model formed

3. RESULTS AND DISCUSSION

3.1. Descriptive Statistics of Chronic Renal Failure Patients

The results of descriptive statistics present the minimum, maximum, and average value of each variable used. The table below illustrates the length of stay of deceased and censored end-stage chronic renal failure patients at RSUD Dr Sosodoro Djatikoesoemo Bojonegoro.

Table 2. Results of Descriptive Statistics on the Dependent Variable

Status	Time			Number of Patients
	Minimum	Average	Maximum	
Death	1	6.17	22	52
Censored	1	6.45	17	98

Based on Table 2, it is known that end-stage chronic kidney failure CKD patients who died during the treatment period had an average length of stay of 6 days. Meanwhile, censored end-stage CKD patients (i.e., patients who are still alive or discharged from the hospital without the exact time of the event being known) also show the same average length of stay of 6 days. This shows that, in general, the length of hospitalisation did not show a significant difference between the deceased and censored patients within the observation period of this study.

3.2. Kaplan Meier Curve

Kaplan-Meier survival curves provide information on the survival probabilities of end-stage chronic renal failure patients based on variables thought to influence survival time. These curves provide a visual representation of how a patient's survival probability changes over time and allow comparison between groups of patients with different characteristics, such as gender, chief complaint, and secondary diagnosis.

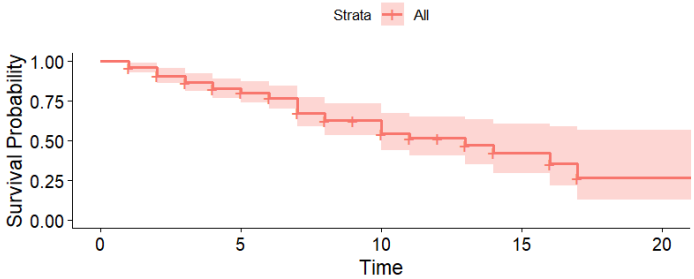

Figure 1. Kaplan Meier Survival Curve of Kidney Failure Patients

In Figure 1, it can be seen that the survival probability of end-stage chronic renal failure patients on day 10 of hospitalisation is 0.5. After the 10th day, the survival probability of patients with end-stage chronic renal failure decreases below 0.5. This means that the probability of survival time of patients with end-stage chronic renal failure will decrease with each increase in hospitalisation time.

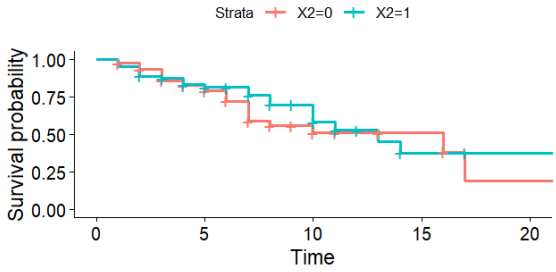

Figure 2. Kaplan Meier Survival Curve for Gender Variables

In **Figure 2**, it can be seen that the curves of the male and female groups coincide, meaning that there is no difference in survival curves between male and female patients. The probability of survival between male and female end-stage chronic kidney failure patients tends to be the same.

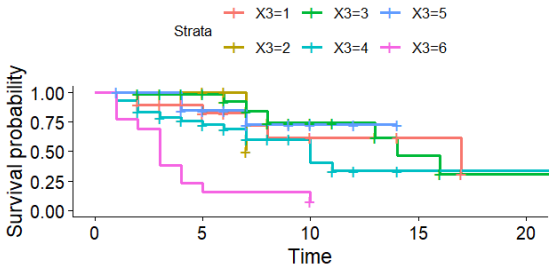

Figure 3. Kaplan Meier Survival Curve of the Main Complaint Variable

In **Figure 3**, it can be seen that the main complaint curves do not overlap, meaning that there are differences in survival curves in each group of main complaint variables. The probability of survival of patients with end-stage chronic kidney failure in each group of major complaints is different. For example, the probability of patients with the main complaint of nausea is different from patients with the main complaint of decreased consciousness.

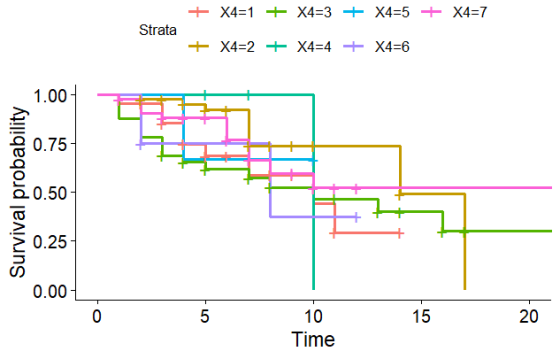

Figure 4. Kaplan Meier Survival Curve Secondary Diagnosis Variables

In **Figure 4**, it can be seen that the secondary diagnosis curves overlap, meaning that there is no difference in survival curves in each group of secondary diagnosis variables. The survival probability of end-stage chronic renal failure patients in each secondary diagnosis group tends to be the same. For example, the probability of patients with a secondary diagnosis of ALO tends to be the same as that of patients whose secondary diagnosis is anemia.

3.3. Log Rank Test Results

The log-rank test is used to determine whether there is a significant difference in the Kaplan-Meier curve between different categories in each observed variable. This test compares survival functions between groups to determine whether the chances of survival of end-stage chronic renal failure patients are statistically different based on certain variables, such as gender, chief complaint, and secondary diagnosis. The complete log-rank test results are presented in **Table 3**, which shows which variables have significant differences in

survival function between categories. This study uses a significance level (α) of 5%. This means that the statistical test results are considered statistically significant if the p-value < 0.05.

Table 3. Log Rank Test Results

Variable	Chi-square	df	p-value	Decision
Age	124	50	$3x10^{-8}$	Reject H_0
Gender	0.5	1	0.5	Accept H_0
Main Complaint	46.1	5	$9x10^{-9}$	Reject H_0
Secondary Diagnosis	6.1	6	0.4	Accept H_0
Creatinine	359	144	$<2\ x10^{-16}$	Reject H_0
Urea	216	112	$1\ x10^{-8}$	Reject H_0
Systolic Blood Pressure	169	78	$1\ x10^{-8}$	Reject H_0
Diastolic Blood Pressure	128	62	$2\ x10^{-6}$	Reject H_0
Hemoglobin	194	64	$6\ x10^{-15}$	Reject H_0
Leucocyte	265	106	$1\ x10^{-15}$	Reject H_0

Table 3 shows that two variables were obtained whose p-value $> \alpha$, these variables were gender and secondary diagnosis, so we accept H_0. This means that there is no difference between groups on the variables of gender and secondary diagnosis. Comparison of the results of the Kaplan-Meier survival curve with the results of the log-rank test showed the same results.

3.4. Cox Proportional Hazard Assumption Test

The Cox Proportional Hazard regression model has a key assumption that the hazard ratio between two groups or individuals is constant over time (proportional hazard assumption). To ensure that the model meets this assumption, one method used is the goodness of fit test, which evaluates the fit of the model to the data analysed. This is usually done through residual analysis, such as Schoenfeld residuals, which are used to examine the relationship between time and covariates in the model. The results of the goodness of fit test are shown in **Table 4**, which provides information on whether the proportional hazard assumption is met for each variable in the Cox regression model used in this study.

Table 4. PH Assumption Test Results

Variable	p-value	Decision	Conclusion
Age (X_1)	0.419	Accept H_0	Assumptions met
Gender (X_2)	0.519	Accept H_0	Assumptions met
Main Complaint (X_{31})	0.772	Accept H_0	Assumptions met
Main Complaint (X_{32})	0.208	Accept H_0	Assumptions met
Main Complaint (X_{33})	0.095	Accept H_0	Assumptions met
Main Complaint (X_{34})	0.350	Accept H_0	Assumptions met
Main Complaint (X_{35})	0.736	Accept H_0	Assumptions met
Secondary Diagnosis (X_{41})	0.111	Accept H_0	Assumptions met
Secondary Diagnosis (X_{42})	0.103	Accept H_0	Assumptions met
Secondary Diagnosis (X_{43})	0.034	Reject H_0	Assumptions not met
Secondary Diagnosis (X_{44})	0.058	Accept H_0	Assumptions met
Secondary Diagnosis (X_{45})	0.529	Accept H_0	Assumptions met
Secondary Diagnosis (X_{46})	0.968	Accept H_0	Assumptions met
Creatinine (X_5)	0.077	Accept H_0	Assumptions met
Urea (X_6)	0.102	Accept H_0	Assumptions met
Systolic Blood Pressure (X_7)	0.564	Accept H_0	Assumptions met
Diastolic Blood Pressure (X_8)	0.343	Accept H_0	Assumptions met
Hemoglobin (X_9)	0.224	Accept H_0	Assumptions met
Leucocyte (X_{10})	0.221	Accept H_0	Assumptions met

Based on **Table 4** with alpha = 5%, it was found that only the secondary diagnosis variable (X_{43}) did not fulfill the proportional hazard assumption. Cox proportional hazard and exponential models can still be used because there is only one dummy variable that does not meet the assumptions in one secondary diagnosis variable. Dummy variables that do not fulfil the proportional hazard assumption will not affect the results of the Cox proportional hazard and exponential models.

3.5. Cox Proportional Hazard Model

In this study, the Cox Proportional Hazard regression model was used to identify variables that affect the survival time of patients with end-stage chronic renal failure. This model allows for the determination of how much influence each independent variable has on the patient's risk of death during the treatment period. The parameter estimation results of the Cox Proportional Hazard regression model are presented in **Table 5**, which shows the regression coefficient values, hazard ratio (HR) values, and the significance level of each variable on survival time.

Table 5. Cox Proportional Hazard Regression Model Parameter Estimates

Variable	Estimator	Exp(Estimator)	Chi-square	*p-value*
Age (X_1)	0.017	1.017	1.072	0.284
Gender (X_2)	-0.695	0.499	-1.897	0.058
Main Complaint (X_{31})	-0.231	0.794	-0.353	0.724
Main Complaint (X_{32})	-1.512	0.22	-1.349	0.177
Main Complaint (X_{33})	-1.559	0.21	-2.861	0.004*
Main Complaint (X_{34})	-0.453	0.636	-0.896	0.37
Main Complaint (X_{35})	-1.838	0.159	-2.468	0.014*
Secondary Diagnosis (X_{41})	0.295	1.343	0.597	0.551
Secondary Diagnosis (X_{42})	0.147	1.158	0.292	0.77
Secondary Diagnosis (X_{43})	-0.057	0.944	-0.119	0.905
Secondary Diagnosis (X_{44})	0.341	1.407	0.28	0.779
Secondary Diagnosis (X_{45})	0.718	2.051	0.639	0.523
Secondary Diagnosis (X_{46})	-0.059	0.943	-0.057	0.954
Creatinine (X_5)	-0.028	0.973	-0.566	0.571
Urea (X_6)	0.009	1.009	3.304	0.001*
Systolic Blood Pressure (X_7)	0.012	1.012	1.541	0.123
Diastolic Blood Pressure (X_8)	-0.035	0.965	-2.344	0.019*
Hemoglobin (X_9)	0.064	1.066	0.903	0.366
Leucocyte (X_{10})	0.044	1.045	1.698	0.09
Likelihood Ratio			73,230	$2{,}65\text{x}10^{-8}$

Based on **Table 5**, the Cox Proportional Hazard model is obtained as follows.

$$h(t,x) = h_0(t)\exp\,(0.017X_1 - 0.695X_2 - 0.231X_{31} - 1.512X_{32} - 1.559X_{33} - 0.453X_{34} - 1.838X_{35} + 0.295X_{41} + 0.147X_{42} - 0.057X_{43} + 0.341X_{44} + 0.718X_{45} - 0.059X_{46} - 0.028X_5 + 0.009X_6 + 0.012X_7 - 0.035X_8 + 0.064X_9 + 0.044X_{10} \quad (12)$$

After obtaining the Cox PH model, it is continued with a simultaneous test using the Likelihood Ratio test and obtained a chi-squared value of $73.230 > 19.675$ and a p-value of $2.65 \times 10^{-8} < 0.05$, so the decision rejects H_0. This means that at least one independent variable has a significant effect on the Cox proportional hazard model. The significant independent variables are the main complaint variable (X_{33}), main complaint (X_{35}), urea (X_6), and dystolic blood pressure (X_8) because the p-value < 0.05, so reject H_0. This means that these variables have a significant effect on the survival time of patients with end-stage chronic renal failure.

3.6. Hazard Ratio

Hazard ratio is used to determine the comparison of hazard values in different categories of one variable.

Table 6. Hazard Ratio Value for Cox PH Model

Variable	Estimator	*Hazard Ratio* = *exp*(estimator)	1-HR
Main Complaint (X_{33})	-1,559	0,210	0,79
Main Complaint (X_{35})	-1,838	0,159	0,841
Urea (X_6)	0,009	1,009	0,009
Diastolic Blood Pressure (X_8)	-0,035	0,965	0,035

Based on **Table 6**, the hazard ratio value for the dummy variable (X_{33}) is 0.210. This means that patients with the main complaint of weakness have a 79% lower risk of death than patients with the main complaint of decreased consciousness. The hazard ratio value for the dummy variable (X_{35}) is 0.159. This means that patients with the main complaint of chest pain have a risk of death 84.1% less than patients with the main complaint of decreased consciousness.

Each additional 1 mg/dL urea value will slightly increase the risk of death by 0.9%. This means that patients with high urea have a higher risk of death than patients with lower urea. Every 1 mmHg increase in diastolic blood pressure value will reduce the risk of death by 3.5%. This means that patients with high diastolic blood pressure have a lower risk of death than patients with lower diastolic blood pressure.

Based on the hazard ratio value of significant variables, the further the Hazard Ratio value is from 1, either smaller or larger, the greater the influence of the variable on the risk of events. The main complaint of chest pain (X_{35}) is the most influential variable in reducing the risk of death, followed by the main complaint variable of weakness, and diastolic blood pressure, which also reduces the risk of death. While urea is a variable that increases the risk, but with a small influence compared to other variables.

3.7. Exponential Model

Hazard value and time are two parameters that describe the exponential change in survival probability.

Table 7. Survival Model Parameter Estimator Exponential Distribution

Variable	Estimator	Chi-square	*p-value*
Intercept	3.488	2.18	0.029
Age (X_1)	-0.012	-0.78	0.434
Gender (X_2)	0.563	1.65	0.1
Main Complaint (X_{31})	0.221	0.36	0.723
Main Complaint (X_{32})	1.476	1.35	0.176
Main Complaint (X_{33})	1.323	2.55	0.011*
Main Complaint (X_{34})	0.407	0.86	0.388
Main Complaint (X_{35})	1.7	2.34	0.019*
Secondary Diagnosis (X_{41})	-0.148	-0.31	0.755
Secondary Diagnosis (X_{42})	0.006	0.01	0.99
Secondary Diagnosis (X_{43})	-0.046	-0.1	0.917
Secondary Diagnosis (X_{44})	-0.202	-0.17	0.866
Secondary Diagnosis (X_{45})	-0.47	-0.43	0.668
Secondary Diagnosis (X_{46})	-0.11	-0.12	0.908
Creatinine (X_5)	0.022	0.52	0.606
Urea (X_6)	-0.007	-2.98	0.003*
Systolic Blood Pressure (X_7)	-0.009	-1.39	0.164
Diastolic Blood Pressure (X_8)	0.031	2.35	0.019*
Hemoglobin (X_9)	-0.04	-0.62	0.538
Leucocyte (X_{10})	-0.039	-1.6	0.11

Based on **Table 7**, the exponential model is obtained as follows.

$$h(t,x) = \exp\,(3.448 - 0.012X_1 + 0.563X_2 + 0.221X_{31} + 1.476X_{32} + 1.323X_{33} + 0.407X_{34} + 1.700X_{35} - 0.148X_{41} + 0.006X_{42} - 0.046X_{43} - 0.202X_{44} - 0.470X_{45} - 0.110X_{46} + 0.022X_5 - 0.007X_6 - 0.009X_7 + 0.031X_8 - 0.040X_9 - 0.039X_{10} \quad (13)$$

After obtaining the exponential model, it is continued with the parameter significance test and obtained four independent variables, namely the main complaint variable (X_{33}), main complaint (X_{35}), urea (X_6), and dystolic blood pressure (X_8), because the p-value < 0.05, then reject H_0. This means that these variables have a significant effect on the survival time of patients with end-stage chronic renal failure.

3.8. Value AIC

The following is the AIC value.

Table 8. Comparison of Two Models

Model	Value AIC
Cox Proportional Hazard	390.3385
Exponential	383.4526

In this study, there are two models, the Cox proportional hazard model and the exponential model. The best model to model the survival of end-stage chronic renal failure patients is the model with the lowest AIC value. The results of the comparison of the AIC values of the two models in **Table 8**, the exponential model is the best model because the AIC value is the smallest at 383.4526.

4. CONCLUSIONS

Based on the analysis of data on patients with end-stage chronic renal failure at RSUD Dr. Sosodoro Djatikoesoemo Bojonegoro, the following conclusions were obtained. Significant variables in patients with end-stage chronic renal failure at Sosodoro Djatikoesoemo Hospital on survival time based on Cox proportional hazard and exponential models obtained four independent variables, namely the main complaint variable (X_{33}), main complaint (X_{35}), urea (X_6), and dystolic blood pressure (X_8) which have a significant effect on the survival time of patients with end-stage chronic renal failure. The AIC (Akaike Information Criterion) value is used as a criterion for selecting the best model, where the smaller the AIC value, the better the model is in describing the data without overfitting. In this study, the exponential model has the lowest AIC value, which is 383.4526, so it is considered the most optimal model to analyse the survival time of end-stage chronic renal failure patients.

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