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Survival Analysis of Chronic Kidney Disease Patients using Stratified Cox Regression in Arifin Achmad Hospital, Pekanbaru, Riau

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ABSTRACT

Chronic Kidney Disease (CKD) is a clinical condition characterized by decreased kidney function requiring renal replacement therapy were fixed, in the form of dialysis. The mortality rate caused by CKD increases significantly each year and needs to be reduced. The purpose of this study to determine the factors that affect patients from CKD in hospitals Arifin Achmad, Pekanbaru, Riau in 2015-2017. The sample of this study amounted to 230 samples. One of the tools to analyze the longer survival of patients with CKD is cox proportional hazards regression. In the long survival data of patients with CKD there is a possibility of ties, so there is one method in determining the partial likelihood estimation parameters, that is exact. Based on the analysis results obtained the factors that most influence with the best parameter estimation is the exact approach are diastolic blood pressure, respiratory rate, urea levels, and action. There is a variable that does not meet the proportional hazard assumption, is the action variable. One way to overcome this by using Cox Stratified Regression Without Interaction and Cox Stratified Regression with Interaction. Based on the results of the analysis that meets the proportional hazard assumption is the method of Cox Stratified Regression Without Interaction and obtained the factors that affect the length of survival of CKD patients are age, diastolic blood pressure, respiratory rate, and urea levels. Interpretation of equation model of Cox Stratified Regression Without Interaction obtained result of increase of age patient have chance to die bigger of 1.0208 times, increase of diastolic blood pressure patient has chance to die smaller equal to 1.0571 times, increase of respiration rate patient have chance to die bigger equal to 1.0677 times, and increase of ureum level patient have chance to die bigger of 1.0073 times.

Keywords: *CKD, Cox Proportional Hazard, Stratified Cox*

INTRODUCTION

Chronic kidney disease (CKD) is a condition in which the kidneys are damaged or cannot filter blood as well as healthy kidneys[1]. CKD is a global public health problem with increased prevalence and incidence of CKD, poor prognosis and high costs. The prevalence of CKD increases with the increasing number of elderly population and the incidence of diabetes mellitus and hypertension. About 1 in 10 global populations experience CKD at a particular stage. The result of systematic review and metaanalysis conducted by Hill et al, 2016, get the global prevalence of CKD of 13.4%. According to the 2010 Global Burden of Disease results, CKD was the 27th leading cause of death in the world in 1990 and increased to 18th in 2010. In Indonesia in 2013, 499.800 Indonesians suffered CKD. While in Indonesia, the treatment of kidney disease is the second largest funding ranking of BPJS health after heart disease[2]. Based on the Basic Health Research data of 2013, the prevalence of CKD in Riau Province is 0.1% of the population of patients with kidney disease in Indonesia, including patients undergoing treatment, renal replacement therapy, peritoneal dialysis, and hemodialysis by 2013[3].

Arifin Achmad Hospital is one of the government-owned hospitals in the city of Pekanbaru, Riau. This hospital is used as a referral hospital from government hospitals and puskesmas in Riau Province. In addition the hospital also has hemodialysis service and installation of CAPD (Continuous Ambulatory Peritoneal Dyalisis) for patients with CKD. CKD itself is a disease classified in the list of 10 major outpatient diseases. CKD lies in the

9th sequence after medical observation and evaluation for alleged illness and condition, gastric function disturbance, lower back pain, impact teeth, follow-up examination after fracture treatment, primary essential hypertension, insulin dependent militant militus, and other ear disorders outside.

Departing from the background of the above phenomenon, then selected life test analysis method as a method of analysis to solve the problem. Life test analysis is an analysis of the individuals of one population by focusing on the length of time the individual performs its function well until the individual's healing or death. Live test data usually will follow a certain distribution pattern. Therefore, in this study will be compared some results of life test analysis using Cox regression method.

In addition to looking for factors that influence and the best model of CKD data in RSUD Arifin Achmad Pekanbaru, Riau, there is one assumption that must be met in cox regression method that is proportional hazard assumption. This assumption is useful for examining the independent variables in the model meeting the proportional hazard assumptions or not. If the assumption is fulfilled then the model can be directly interpreted, whereas if the assumption is not met can be done two ways. First issue an independent variable that does not meet the proportional hazard assumption. The two do strata on variables that do not meet the proportional hazard assumption with the Cox Stratified Regression method. Independent variables that previously met proportional hazard assumptions remain included in the model, but not strata in those variables.

METHODOLOGY

The data used in this study is secondary data in the form of medical record data of CKD patients in 2015-2017 at Arifin Achmad Hospital, Pekanbaru, Riau. In this study, the target population was taken namely patients affected by chronic kidney disease from 2015-2017 which amounted to 454 patients. As well as the sample that the authors use in this study as many as 230 patients. The research variables used were survival variable as dependent variable, while the independent variables used were gender variables (X_1), age (X_2), disease history (X_3), systolic blood pressure (X_4), diastolic blood pressure (X_5), respiratory rate (X_6), pain (X_7), pain scale (X_8), diabetes mellitus (X_9), urea (X_{10}), *creatine* (X_{11}), action (X_{12}), dan therapy (X_{13}). The research method used as follows:

a. Cox Proportional Hazard Regression with Paramal Likelihood Parameter Estimation Approach Cox regression is generally more commonly used in the health field, but the growing time of Cox regression can be applied to other fields. In general, the Cox Proportional Hazard equation can be written as follows[5]:

$$h(t, X) = h_0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p)$$

$$= h_0(t)\exp\left(\sum_{i}^{p} \beta_i X_i\right)$$

The method with partial likelihood exact approach is an alternative method of case incident. However, this method has a very intensive computational level but is capable of generating estimated parameters that have a bias close to 0 even if the data of joint events or ties are of a very large size. In general, the partial likelihood exact approach has the following form of equation[6]:

$$L(\beta_{\text{Exact}}) = \prod_{i \in D} \frac{\exp(^2 S_k)}{\sum_{i \in R_{t_i}, d_k} \exp(^2 X_i)}$$

b. Testing Parameters: In regression cox proportional hazard required testing the significance of parameters in order to know whether the independent variable significantly affect the cox equation formed. Testing of significance is done by simultaneous test (overall), partial test, and proportional hazard assumption test[5].

1. Overall Test

Hypothesis : $H_0 : \beta_i = 0$

H_1 : At least there is one $\beta_i \neq 0$ where i = 1, 2, …, p

Level of Significance: $\alpha = 5\% = 0.05$

Statistic Test: $G = -2[\text{In } L_R - \text{In } L_f]$ …(3)

Area of Critism: H_0 is rejected if *p-value* $\leq \alpha$ or $G \geq \chi^2_{\alpha;ab=p}$

2. Partial Test

Hypothesis: $H_0 : \beta_i = 0$

$H_1 : \beta_i \neq 0$ where $i = 1, 2, \ldots, p$

Level of Significance: $\alpha = 5\% = 0.05$

Statistic Test: $Z = \dfrac{\beta_i}{SE(\beta_i)}$ …(4)

Area of Critism: H_0 is rejected *p-value* $\leq \alpha$ or $|Z| \geq Z_{0.05/2}$

3. Proportional Hazard Assumptions Test

   Hypothesis: H_0 : $\rho = 0$ (Proportional hazard assumptions are met)

   H_1 : $\rho \neq 0$ (Proportional hazard assumptions are not met)

   Level of Significance: α = 50% = 0.05

   Statistic Test:*p-value* …(5)

   Area of Critism: H_0 is rejected *p-value* $\leq \alpha$

c. **Selection of the Best Model:** AIC method is a method that can be used to select the best regression model invented by Akaike and Schwarz[7]. How to select several models to choose the best model is based on AIC with the following formula+:

   $$AIC = 2\ln \hat{L} + 2k$$

d. **Cox Stratified Regression:** Cox Stratified Regression is one of the methods used to overcome independent variables that have non proportional hazard assumptions. Cox Stratified model is a modification of the Cox Proportional Hazard model in which the Cox Stratified model divides the hazard function into the strata or stages of the covariate. The covariates divided into these strata are covariates that do not meet the proportional hazard assumptions[5].

   Cox Stratified model without interaction is as follows:

   $$h_g(t, X) = h_{0g}(t)\exp(\beta_1 X_1 + \beta^2 X_2 + \ldots + \beta_p X_p) \quad \ldots(7)$$

   The Stratified Cox model with interaction is as follows:

   $$h_g(t, X) = h_{0g}(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_{pg} X_p) \quad \ldots(8)$$

RESULTS

There are three forms of probability distribution of survival, namely parametric survival function, non-parametric survival function, and semi-parametric survival function. In this parametric survival function there are three methods, namely Regression with Exponential Distribution, Weibull, and Log-Logistics. While in this semi-parametric survival function there is one method, namely Cox Regression. In this study, the data obtained will be comparative analysis using regression method with parametric and semi parametric survival function. Based on calculations using software R, then obtained comparison of analysis using regression method of survival function with the best parameter estimation as follows:

Table 1: Selection of the Best Survival Function Model with AIC Value Comparison

Regression Models	AIC Values
Eksponential Distribution	583.5625
Weibull Distribution	543.1974
Log-Logistic Distribution	537.3215
Cox with Breslow Partial Likelihood Approach Method	392.1115
Cox with Efron Partial Likelihood Approach Method	384.7155
Cox with Exact Partial Likelihood Approach Method	321.0316

Based on Table 1, it's to obtain the best model by looking at the smallest AIC value as a relative measure of the fit goodness of the statistical model. The smallest AIC value is in Cox Regression model with Exact Parameter Estimation. Furthermore, because the value of AIC for regression analysis with parametric survival function and cox regression with Breslow and Efron Partial Likelihood parameter estimation still big enough, then the next step the authors do regression analysis using cox regression method with estimated parameters of Exact Partial Likelihood.

Cox Regression with Exact Partial Likelihood Approach Method: The parameter estimation using the exact partial likelihood approach method is the same parameter estimation method as the approach of the efron parameter used to overcome the common occurrence in small and large size. However, the approach method of the exact parameter is capable of producing better estimation value. It's caused by the resulting error is close to zero compared to other parameter estimation approach methods. The calculation result of cox regression parameter with approach of partial likelihood approach is obtained by the model determined by using backward elimination method. Backward elimination method is a way to get the best model by issuing one by one the largest p-value first. Based on calculations using software R, then obtained the best parameter estimation as follows:

Table 2: Best Parameter Estimation Results Using Cox Regression with Exact Partial Likelihood Approach

Variables	Coefficients	p-value			Decisions
X_2	0.0245	0.0290	<	0.05	Reject H_0
X_5	– 0.0592	3.01×10^{-8}	<		Reject H_0
X_6	0.0679	4.91×10^{-5}	<		Reject H_0
X_{10}	0.0081	7.26×10^{-7}	<		Reject H_0
X12 (Drug Administration and Blood Transfusion)	– 1.6761	5.42×10^{-6}	<		Reject H_0
X12 (Drug Administration, Blood Transfusion and Surgery)	– 1.9646	0.0002	<		Reject H_0

Based on Table 2 it can be seen that the p-value of all variables is less than 0.05, so H_0 rejected. This is because the p-value < level significance. It can be concluded that the cox regression model with parameter estimation using the exact partial likelihood approach is feasible to use. The model formed is as follows:

$$h(t, X) = h_0(t)\exp(0.0245X_2 - 0.0592X_5 + 0.067X_6 + 0.0081X_{10} - 1.6761X_{12\text{ (Drug administration and blood transfusion)}} - 1.9646X_{12\text{ (Drug administration, Blood transfusion and Surgery)}})$$

The next step to find out whether a best equation using cox regression method with exact partial likelihood approach has independent variable which influence significantly to dependent variable, hence need to do testing which include test of overalls, partial test, and proportional hazard assumption test. Based on the results of the analysis of the overall test on the cox regression with exact partial likelihood approach can be concluded with the significance level of 0.05 H_0 rejected, because the p-value < significance level, ie 0 < 0.05, causing one of the parameters contained in regression β_i has a value not equal to 0. Therefore it is necessary to do a partial test to examine one by one regression coefficient β_i.

Based on the partial test results obtained results that the six variables in Table 1 are analyzed significantly to the model. This is because the p-value < level of significance, thus causing the six variables affect the long survival of CKD patients. Further testing of proportional hazard assumptions by using the Schoenfeld Residual correlation value. Schoenfeld's residual value is one of the statistical tests used in this method. Based on calculations using software R, then Schoenfeld residual value obtained as follows:

Table 3: Schoenfeld Residual Correlation Value

Variables	Correlation	p-value			Decisions
X_2	0.0420	0.7087	>	0.05	Failed to Reject H_0
X_5	–0.1086	0.4362	>		Failed to Reject H_0
X_6	0.0043	0.9797	>		Failed to Reject H_0
X_{10}	–0.0274	0.8292	>		Failed to Reject H_0
X12 (Drug Administration and Blood Transfusion)	0.3253	0.0401	<		Reject H_0
X12 (Drug Administration, Blood Transfusion and Surgery)	0.3699	0.0252	<		Reject H_0

It can be seen in Table 3 that not all variables have p-value more than 0.05. Based on the result of assumption test proportional hazard can be concluded with significance level 0.05 H_0 failed to be rejected for variable X_2, X_5, X_6, dan X_{10}, because the *p-value* > level of significance. Then it can be concluded that there is data that supports the value of H_0, so that the four independent variables meet the proportional hazard assumption. While the significance level of 0.05 H_0 is rejected for X_{12} variables with the category of Drug Administration and Blood Transfusion and Drug Administration, Blood Transfusion and Surgery category, because the p-value < level of significance. Then it can be concluded that there is data that supports the value of H_1, thus causing the two independent variables do not meet the proportional hazard assumption. The next step to overcome these problems, the authors tries to issue a variable that does not meet the proportional hazard assumptions and use Cox Stratified Regression.

Cox Regression with Exact Partial Likelihood Estimation Approach Without Action Variable in Overcoming Non Proportional Hazard Assumptions: One of the easiest ways to overcome the non proportional hazard assumption is by removing the independent variable from within the model. In this research, the authors use exact partial likelihood parameter approach. The calculation result of cox regression parameter with exact partial likelihood approach without action variable in overcoming non proportional hazard assumption using software R as below:

Table 4: Best Parameter Estimation Results Using Cox Regression with Exact Partial Likelihood Approach Without Action Variable in Overcoming Non Proportional Assumptions Hazard

Variables	Coefficients	p-value			Decisions
X_2	0.0316	0.0027	<	0.05	Reject H_0
X_5	–0.0532	1.36×10^{-7}	<		Reject H_0
X_6	0.0612	0.0001	<		Reject H_0
X_{10}	0.0076	1.02×10^{-6}	<		Reject H_0

Based on Table 4 it can be seen that the p-value of all variables is less than 0.05, so H_0 is rejected. It because the p-value < level of significance. It can be concluded that the cox regression model with parameter estimation using the exact partial likelihood approach without the action variable is feasible to use. The model formed is as follows:

$$h(t, X) = h_0(t) \exp(0.0316 X_2 - 0.0532 X_5 + 0.0612 X_6 + 0.0076 X_{10})$$

The next step is to find out whether a best equation using cox regression method with exact partial likelihood approach without action variable has independent variable which have significant effect to dependent variable, it is necessary to test which include test of overalls, partial test, and proportional hazard assumption test. Based on the result of the analysis of the overall test on the cox regression with exact partial likelihood approach without the action variable can be concluded with the significance level of 0.05, H_0 rejected, because the p-value < significance level, ie $4.846 \times 10^{-13} < 0.05$, which causes one of the parameters contained in the regression β_i has a value not equal to 0. Therefore it is necessary to do a partial test to examine one by one regression coefficient β_i.

Based on the partial test results obtained the result that the four variables in Table 4 were analyzed significantly to the model. This is because the value of p-value < level of significance, thus causing the four variables affect the long survival of CKD patients. Further testing of proportional hazard assumptions by using the Schoenfeld Residual correlation value. Based on calculations using software R, then Schoenfeld residual value obtained as follows:

Table 5: Schoenfeld Residual Correlation Value

Variables	Correlation	p-value			Decisions
X_2	–0.0809	0.477	>	0.05	Failed to Reject H_0
X_5	–0.1189	0.391	>		Failed to Reject H_0
X_6	0.0011	0.995	>		Failed to Reject H_0
X_{10}	–0.0618	0.605	>		Failed to Reject H_0

It can be seen in Table 5 that all variables have p-value values greater than 0.05. Based on the result of testing proportional hazard assumption can be concluded with significance level 0.05 H_0 failed to be rejected for all variable, because the p-value > level of significance. So it can be concluded that there is data that supports the value of H_0, so that the four independent variables meet the proportional hazard assumption. The next step The authors tries to overcome in another way against the variable that does not meet the proportional hazard assumption, namely using Cox Stratified Regression.

Cox Stratified Regression in Overcoming Non-Proportional Hazard Assumptions: Cox stratified regression is one way to overcome independent variables that do not meet proportional hazard assumptions. Cox Stratified Regression is a modification of the Cox

Regression model by strata on independent variables that do not meet the proportional hazard assumptions. Independent variables that previously met proportional hazard assumptions remain included in the model, but not strata in those variables[4].

Cox Stratified Regression without Interaction: Regression method cox stratified without interaction is a method to overcome the assumption of non proportional hazard that produces the model with the same parameters assumption. Based on calculations using software R, then obtained parameter estimation as follows:

Table 6: Parameter Estimation Results Using Cox Stratified Regression Without Interaction

Variables	Coefficients	p-value			Decisions
X_2	0.0206	0.059	>	0.05	Failed to Reject H_0
X_5	–0.0555	8.43×10^{-8}	<		Reject H_0
X_6	0.0655	5.84×10^{-5}	<		Reject H_0
X_{10}	0.0073	2.90×10^{-6}	<		Reject H_0

Based on Table 6 it can be seen that not all variables have p-value less than 0.05. However, this does not have a significant effect due to stratified cox regression without this interaction only to overcome the problem of unfulfilled proportional hazard assumptions. Then the parameter estimation in Table 6 obtained the model formed is as follows:

$$h_g(t, X) = h_{0g}(t)\exp(0.0206\,X_2 - 0.0555\,X_5 + 0.0655\,X_6 + 0.0073\,X_{10})$$

The next step to find out whether a best equation using stratified cox regression method without interaction has independent variables that significantly affect the dependent variable, it is necessary to test that includes the test of overalls, partial test, and proportional hazard assumptions test. Based on the results of the overall test analysis on stratified cox regression without interaction can be concluded with the significance level of 0.05 H_0 rejected, because the p-value < significance level, ie $2.867 \times 10^{-12} < 0.05$, causing one of the parameters contained in the regression β_i has a value not equal to 0. Therefore it is necessary to do a partial test to examine one by one regression coefficient β_i.

Based on the result of partial test, it is found that not all variables in Table 6 are analyzed significantly to the model. This is because there are only three variables, namely X_5, X_6, and X_{10} which have the *p-value* < level of significance, thus causing the three variables to affect the long life of CKD patients. While one of variable, that is X_2 has the *p-value* > level of significance, so cause variable X_2 does not have an effect on long life of CKD patient. However, the variable X_2 remains incorporated into the model, due to stratified cox regression without this interaction only to overcome the problem of unfulfilled proportional hazard assumptions. Further testing of proportional hazard assumptions by using the Schoenfeld Residual correlation value. Based on calculations using software R, then Schoenfeld residual value obtained as follows:

Table 7: Schoenfeld Residual Correlation Value

Variables	Correlation	p-value			Decisions
X_2	0.0076	0.948	>	0.05	Failed to Reject H_0
X_5	–0.1187	0.405	>		Failed to Reject H_0
X_6	0.0425	0.808	>		Failed to Reject H_0
X_{10}	–0.0480	0.731	>		Failed to Reject H_0

It can be seen in Table 7 that all variables have p-value values greater than . Based on the result of testing proportional hazard assumption can be concluded with significance level failed to be rejected for all variable, because the *p-value* > level of significance. So it can be concluded that there is data that supports the value of , so that the four independent variables meet the proportional hazard assumption.

Cox Stratified Regression with Interaction: Cox stratified regression method with interaction is a method to overcome non proportional hazard assumption which produce model with different parameter assumption for each strata. Based on calculations using software R, then obtained parameter estimation as below:

Table 8: Parameter Estimation Results Using Cox Stratified Regression with Interaction

Variables	Coefficient	p-value			**Decisions**
X2	0.0239	0.0890	>	0.05	Failed to Reject H_0
X5	–0.0570	0.0003	<		Reject H_0
X6	0.0914	0.0055	<		Reject H_0
X10	0.0089	0.0001	<		Reject H_0
X2 × X12 (Drug Administration and Blood Transfusion)	–0.0193	0.4278	>		Failed to Reject H_0
X2 × X12 (Drug Administration, Blood Transfusion and Surgery)	0.2028	0.1016	>		Failed to Reject H_0
X5 × X12 (Drug Administration and Blood Transfusion)	0.0058	0.8011	>		Failed to Reject H_0
X5 × X12 (Drug Administration, Blood Transfusion and Surgery)	–0.0548	0.2145	>		Failed to Reject H_0
X6 × X12 (Drug Administration and Blood Transfusion)	–0.0641	0.1926	>		Failed to Reject H_0
X6 × X12 (Drug Administration, Blood Transfusion and Surgery)	0.4112	0.0721	>		Failed to Reject H_0
X10 × X12 (Drug Administration and Blood Transfusion)	–0.0036	0.3060	>		Failed to Reject H_0
X10 × X12 (Drug Administration, Blood Transfusion and Surgery)	0.0170	0.2212	>		Failed to Reject H_0

Based on Table 8 it can be seen that not all variables have the p-value less than 0.05. This does not, however, have a significant effect due to stratified cox regression with this interaction only to overcome the problem of unfulfilled proportional hazard assumptions. Then the parameter estimation in Table 8 obtained model which formed is as follows:

$$
\begin{aligned}
h_g(t, \mathrm{X}) = h_{0g}(t)\exp[&0.0239\,\mathrm{X}_2 - 0.0570\,\mathrm{X}_5 + 0.0914\,\mathrm{X}_6 + 0.0089\,\mathrm{X}_{10} \\
&- 0.0193\,(\mathrm{X}_2 \times \mathrm{X}_{12\ \text{(Drug Administration and Blood Transfusion)}}) \\
&+ 0.2028\,(\mathrm{X}_2 \times \mathrm{X}_{12\ \text{(Drug Administration,Blood Transfusion and Surgery)}}) \\
&+ 0.0058\,(\mathrm{X}_5 \times \mathrm{X}_{12\ \text{(Drug Administration and Blood Transfusion)}}) \\
&- 0.0548\,(\mathrm{X}_5 \times \mathrm{X}_{12\ \text{(Drug Administration,Blood Transfusion and Surgery)}}) \\
&- 0.0641\,(\mathrm{X}_6 \times \mathrm{X}_{12\ \text{(Drug Administration and Blood Transfusion)}}) \\
&+ 0.4112\,(\mathrm{X}_6 \times \mathrm{X}_{12\ \text{(Drug Administration,Blood Transfusion and Surgery)}}) \\
&- 0.0036\,(\mathrm{X}_{10} \times \mathrm{X}_{12\ \text{(Drug Administration and Blood Transfusion)}}) \\
&+ 0.0170\,(\mathrm{X}_{10} \times \mathrm{X}_{12\ \text{(Drug Administration,Blood Transfusion and Surgery)}})]
\end{aligned}
$$

The next step is to find out whether a best equation using cox stratified regression method with interaction has independent variable that significantly influence dependent variable, it is necessary to do testing which include test of overalls, partial test, and proportional hazard assumption test. Based on the results of the overall test analysis on stratified cox regression with interaction can be concluded with a significance level of 0.05 H_0 rejected, because the p-value < significance level, ie $1.225 \times 10^{-10} < 0.05$, which causes one of the parameters contained in the regression β_i has a value not equal to 0. Therefore it is necessary to do a partial test to examine one by one regression coefficient β_i.

Based on the partial test results obtained the results that not all variables in Table 8 analyzed significant to the model. This is because there are only three variables, namely X_5, X_6, and X_{10} which have the *p-value* < level of significance, thus causing the three variables to affect the long life of CKD patients. While the rest have the *p-value* > level of significance, thus causing these variables do not affect the long survival of CKD patients. However, the non-influencing variables are still incorporated into the model, due to stratified cox regression with this interaction only to overcome the problem of non-fulfillment of proportional hazard assumptions. Further testing of proportional hazard assumptions by using the Schoenfeld Residual correlation value. Based on calculations using software R, then Schoenfeld residual value obtained as follows:

Table 9: Schoenfeld Residual Correlation Value

Variables	Correlation	p-value			Decisions
X2	0.0192	0.874	>	0.05	Failed to Reject H_0
X5	–0.0341	0.800	>		Failed to Reject H_0
X6	–0.5090	0.719	>		Failed to Reject H_0
X10	0.0605	0.677	>		Failed to Reject H_0
X2 × X12 (Drug Administration and Blood Transfusion)	–0.0700	0.536	>		Failed to Reject H_0
X2 × X12 (Drug Administration, Blood Transfusion and Surgery)	0.1138	0.490	>		Failed to Reject H_0
X5 × X12 (Drug Administration and Blood Transfusion)	0.0107	0.943	>		Failed to Reject H_0
X5 × X12 (Drug Administration, Blood Transfusion and Surgery)	–0.1593	0.408	>		Failed to Reject H_0
X6 × X12 (Drug Administration and Blood Transfusion)	0.1944	0.249	>		Failed to Reject H_0
X6 × X12 (Drug Administration, Blood Transfusion and Surgery)	0.1392	0.530	>		Failed to Reject H_0
X10 × X12 (Drug Administration and Blood Transfusion)	–0.0799	0.575	>		Failed to Reject H_0
X10 × X12 (Drug Administration, Blood Transfusion and Surgery)	0.1103	0.607	>		Failed to Reject H_0

It can be seen in Table 9 that all variables have p-value values greater than 0.05. Based on the result of testing proportional hazard assumption can be concluded with significance level 0.05 H_0 failed to be rejected for all variable, because the *p-value* > level of significance. So it can be concluded that there is data that supports the value of H_0, so that the four independent variables meet the proportional hazard assumption.

Selection and Interpretation of the Best Cox Regression Model: To get the best model can be done comparison of AIC value of each regression model that formed. The AIC value is a relative measure of the fit goodness of the statistical model. Based on calculations using software R, then obtained comparison of analysis using cox regression method as follows:

Table 10: Selection of the Best Model of Cox Regression with AIC Value Comparison

Cox Regression Models	AIC Value
Exact Partial Likelihood Approach Method $h(t, X) = h_0(t)\exp(0.0245\, X_2 - 0.0592\, X_5 + 0.0679\, X_6 + 0.0081\, X_{10} - 1.6761\, X_{12\ (\text{Drug Administration and Blood Transfusion})} - 1.9646\, X_{12\ (\text{Drug Administration,Blood Transfusion and Surgery})})$	321.0316
Exact Partial Likelihood Approach Method (without variable Action) $h(t, X) = h_0(t)\exp(0.0316\, X_2 - 0.0532\, X_5 + 0.0612\, X_6 + 0.0076\, X_{10})$	342.4729
Stratified Without Interaction $h_g(t, X) = h_{0g}(t)\exp(0.0206\, X_2 - 0.0555\, X_5 + 0.0655\, X_6 + 0.0073\, X_{10})$	262.8794
Stratified With Interaction $h_g(t, X) = h_{0g}(t)\exp[0.0239\, X_2 - 0.0570\, X_5 + 0.0914\, X_6 + 0.0089\, X_{10} - 0.0193\,(X_2 \times X_{12\ (\text{Drug Administration and Blood Transfusion})}) + 0.2028\,(X_2 \times X_{12\ (\text{Drug Administration,Blood Transfusion and Surgery})}) + 0.0058\,(X_5 \times X_{12\ (\text{Drug Administration and Blood Transfusion})}) - 0.0548\,(X_5 \times X_{12\ (\text{Drug Administration,Blood Transfusion and Surgery})}) - 0.0641\,(X_6 \times X_{12(\text{Drug Administration and Blood Transfusion})}) + 0.4112\,(X_6 \times X_{12\ (\text{Drug Administration,Blood Transfusion and Surgery})}) - 0.0036\,(X_{10} \times X_{12\ (\text{Drug Administration and Blood Transfusion})}) + 0.0170\,(X_{10} \times X_{12\ (\text{Drug Administration,Blood Transfusion and Surgery})})]$	266.6776

Based on Table 10 to get the best model by looking at the smallest AIC value, that is equal to on Cox Stratified Without Interaction Regression model. The best model that is formed is as follows:

Table 11: Estimated Cox Stratified Regression Parameters without Interaction

Variables	Coefficients	Exp (Coefficients)
X_2	0.0206	1.0208
X_5	–0.0555	0.9460
X_6	0.0655	1.0677
X_{10}	0.0073	1.0073

h_g $(t, \mathrm{X}) = h_{0g}$ (t) exp $(0.0206\ \mathrm{X}_2 - 0.0555\ \mathrm{X}_5 + 0.0655\ \mathrm{X}_6 + 0.0073\ \mathrm{X}_{10}$

The above model can be interpreted as follows:

1. At Variable Age has a positive influence. The value of this variable hazard ratio states that with every age, the patient has a greater chance of dying by times.
2. In Diastolic Blood Pressure Variables have a negative effect. The hazard ratio value of this variable states that every increase in diastolic blood pressure, then the patient has a smaller chance of dying by $\frac{1}{0.9460} = 1.0571$ times.
3. In the respiratory rate variable has a positive effect. The value of this variable hazard ratio states that each increase in the respiratory rate, then the patient has a greater chance of dying by 1.0677 times.
4. In the Ureum Content Variables have a positive effect. The value of the hazard ratio of this variable states that every increase in urea level, then the patient has a greater chance of dying by 1.0073 times.

CONCLUSIONS

The best regression model equation is Cox Stratified Regression without Interaction formed is as follows:

$$h_g\ (t, \mathrm{X}) = h_{0g}\ (t) \exp\ (0.0206\ \mathrm{X}_2 - 0.0555\ \mathrm{X}_5 + 0.0655\ \mathrm{X}_6 + 0.0073\ \mathrm{X}_{10})$$

Based on the above equation, the factors that influence the duration of survival of patients with chronic kidney disease are age, diastolic blood pressure, respiratory rate, and urea level. Interpretation of the above model equation is obtained as the result of increasing the age of the patient has a chance to die larger by times, the increase in diastolic blood pressure of the patient has a chance to die smaller by times, increased respiration rate of patients have a greater chance to die by times, and increased urea levels of patients have a greater chance of dying by times.

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