

SURVIVAL COX PROPORTIONAL HAZARD IN CHRONIC KIDNEY DISEASE WITH HEMODIALYSIS AT HAJI GENERAL HOSPITAL, SURABAYA

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ABSTRACT

Background: Patients with chronic kidney disease should have dialysis therapy throughout their life (usually 1-3 times a week) or until they get a new kidney through a kidney transplant surgery to maintain the existing kidney function. A survival analysis was needed to determine the survival time of hemodialysis patients. The purpose of this study was to analyze the survival of hemodialysis patients with cox proportional hazard at Haji General Hospital, Surabaya.

Material and Method: This research was an observational analytic study with retrospective cohort design through CPH survival analysis. This study was conducted at Haji General Hospital, Surabaya, in Mei 2018. Samples were taken as many as 55 new hemodialysis patients, which registered in 2012. The data used was secondary data from 2012 until March 2018.

Result: The median survival estimate for hemodialysis patients was 581 days. In cox regression analysis simultaneously obtained sex ($p=0.057$), marital status ($p=0.016$), employment status ($p=0.164$), comorbidities ($p=0.0001$). In the further analysis of the cox regression partially obtained marital status ($p=0.043$), comorbidities ($p=0.0001$). Cox regression analysis model was obtained " $h(t) = h_0(t) \exp(0.638 \text{ marital status} + 1.531 \text{ comorbidities})$ ".

Conclusion: Cox regression analysis showed marital status and comorbidities had significant effect on survival of hemodialysis patient at RSU Haji Surabaya

Keywords: cox proportional hazard, survival, chronic kidney disease, hemodialysis

1.0 Introduction

Chronic kidney disease was a condition of kidney damage that occurred for 3 months or more. Renal impairment was defined as structural or functional renal abnormalities with or without a decrease in glomerular filtration rate (GFR), which were manifested as pathological or renal impairment, including an imbalance of substance composition in the blood or urine, and the presence of an impaired GFR imaging result with less than 60 mL/min/1.73 m² for more than 3 months and with or without damage (Departemen Kesehatan Republik Indonesia, 2008).

Chronic kidney disease (CKD) was irreversible or it could not become normal again. All we can do is maintain the existing kidney function. One treatment for people with chronic kidney disease was hemodialysis, or better known as "dialysis", which could prevent death but could not cure or restore overall kidney function. CKD should have dialysis therapy throughout its life (usually 1-3 times a week) or to get a new kidney through a kidney transplant surgery (Pusat Data Informasi, 2017).

Based on the 8th Report of Indonesian Renal Registry, the causes sequence of kidney disease in patients who received hemodialysis in 2015 data were: (1) hypertension (44%); (2) diabetes mellitus or diabetic nephropathy (22%); (3) congenital abnormalities or primary glomerulopathy (8%); (4) chronic pyelonephritis or kidney infection (7%); (5) urinary obstruction or nephropathy obstruction (5%); (6) uric acid (1%); (7) lupus disease (1%); (7) polycystic kidney (1%); (8) other causes (8%); and (9) unknown (3%) (Tim Indonesian Renal Registry, 2015).

Data at Haji General Hospital showed that new hemodialysis patients experienced a significant increase from 2010 to 2014, with details as follows: (1) 26 people (2010); (2) 70 people (2011); (3) 103 people (2012); (4) 111 people (2013); (5) 109 people (2014); and (6) 85 people (2015). Based on the data, the biggest etiology was caused by hypertension (52, 27%) and then followed by diabetes mellitus (36, 36%). The data of hemodialysis patient visits reached 8,930 patients by 2014 (Instalasi Hemodialisis, 2015).

Statistical analysis that could be used to determine patient survival was survival analysis. Survival analysis was a special statistical analysis used when the case was related to the time and particular event. In survival analysis, we needed a model that could describe survival, such as cox proportional hazard model (CPH) (Kleinbaum and Klein, 2012)

Based on Ardianto's research (2016) on classical CPH modeling and multivariate adaptive regression splines in hemodialysis patient survival, median survival was achieved in Ibnu Sina Hospital, Gresik, for 210 weeks (4.375 years). Research from Yulianto (2016), entitled as "Analysis of the survival of chronic kidney disease patients with hemodialysis in RSUD Dr. Soetomo" showed survival rate of 67.84 months.

The purpose of this study was to determine the cox regression model using CPH on hemodialysis patient survival data at Haji General Hospital, Surabaya.

2.0 Material and Methods

The type of research was observational analytic research with retrospective cohort design. The study was conducted using secondary data of hemodialysis patients. The independent variables were age, gender, marital status, employment status, coexisting illness and comorbidities. The dependent variable is the survival time.

The secondary data was obtained from medical record data of hemodialysis patients, who first experienced hemodialysis in 2012 and observed until March 2018. This research was conducted in hemodialysis unit Haji General Hospital, Surabaya, East Java Province. The samples were all new hemodialysis patients who experienced hemodialysis in 2012, which amounted to 98 patients. There were inclusion criteria, which were complete medical record data from regular hemodialysis patients. From the inclusion criteria, sample of 55 patients hemodialysis were obtained. The analysis in this study was using cox proportional hazard regression.

Cox proportional hazard regression was a statistical technique that used to explore the relationship between patient survival and a number of variables. CPH regression could be used to describe the relationship between survival times as a dependent variable with a number of independent variable (Kuntoro, 2017).

The technique of data analysis was done by descriptive, Kaplan-Meier curve analysis and Log Rank test, proportional hazard assumption test, and then cox regression test for variable that fulfilled proportional hazard assumption (Dahlan, 2012). Data was analyzed using software computer. The result of cox regression test was survival model of hemodialysis patient at Haji General Hospital, Surabaya.

3.0 Study Instruments

Data collection from secondary data in medical record or computer at hemodialysis installation of RSU Haji Surabaya. Data taken include age, gender, marital status, employment status, underlying disease, comorbidities. The complete data is censored with the right sensor, is failure occurs when data is collected, but it is not known when and only the time information of the observation. Data was analyzed using computer software with curve Kaplan-Meier, cox proportional hazard regression.

4.0 Result

4.1 Description of Hemodialysis Patients at Haji General Hospital Surabaya

Descriptive analysis was used to describe the factors characteristics that allegedly affected the survival conditions of hemodialysis patients. Table-1 showed the hemodialysis patients characteristics at Haji General Hospital, Surabaya.

Table-1. Description of Hemodialysis Patients Haji General Hospital, Surabaya

Characteristic	Status		Total
	Censored	Uncensored/ event	
Age			
1. ≤55 years old	11 (29.7%)	26 (70.3%)	37 (100%)
2. >55 years old	1 (5.6%)	17 (94.4%)	18 (100%)
Gender			
1. Male	7 (25.0%)	21 (75.0%)	28 (100%)
2. Female	5 (18.5%)	22 (81.5%)	27 (100%)
Marital Status			
1. Married	6 (21.4%)	22 (78.6%)	28 (100%)
2. Not married	6 (22.2%)	21 (77.8%)	27 (100%)
Employment status			
1. Unemployed	8 (23.5%)	26 (76.5%)	34 (100%)
2. Employed	4 (19.0%)	17 (81.0%)	21 (100%)
Underlying diseases			
1. Systemic lupus erythematosus	0 (0%)	1 (100%)	1 (100%)
2. Diabetes Mellitus	2 (12.5%)	14 (87.5%)	16 (100%)
3. Hypertension	10 (26.3%)	28 (73.7%)	38 (100%)
Comorbidities			
1. Did not have	7 (31.8%)	15 (68.1%)	22 (100%)
2. Have	5 (15.2%)	28 (84.8%)	33 (100%)

According to Table-1, it was known that most hemodialysis patients were elderly (> 55 years old), male, married, unemployed, hypertension etiology, and had comorbidities. Based on age factor, hemodialysis patients who experienced the most events by percentage were elderly (>55 years old). The gender factor that experienced the most event was female. Marital status factors that experienced the most event based on the percentage were patients with married status. Based on the employment status factor, the patient's percentage who experienced the most events were patients who had a job. Based on the underlying diseases factor, patients with the most events were patients with hypertension etiology. In comorbidities factor, patients with multiple events were hemodialysis patients with comorbidities.

4.2 Survival Analysis of Kaplan-Meier Curves and Log-Rank Test

The Kaplan-Meier curve analysis was performed to describe the survival time characteristic, while the Log-Rank test was used to determine whether there was a difference between the survival curves of different factor groups. Graph-1 was the result of Kaplan-Meier curve analysis in general from 55 hemodialysis patients at Haji General Hospital, Surabaya.

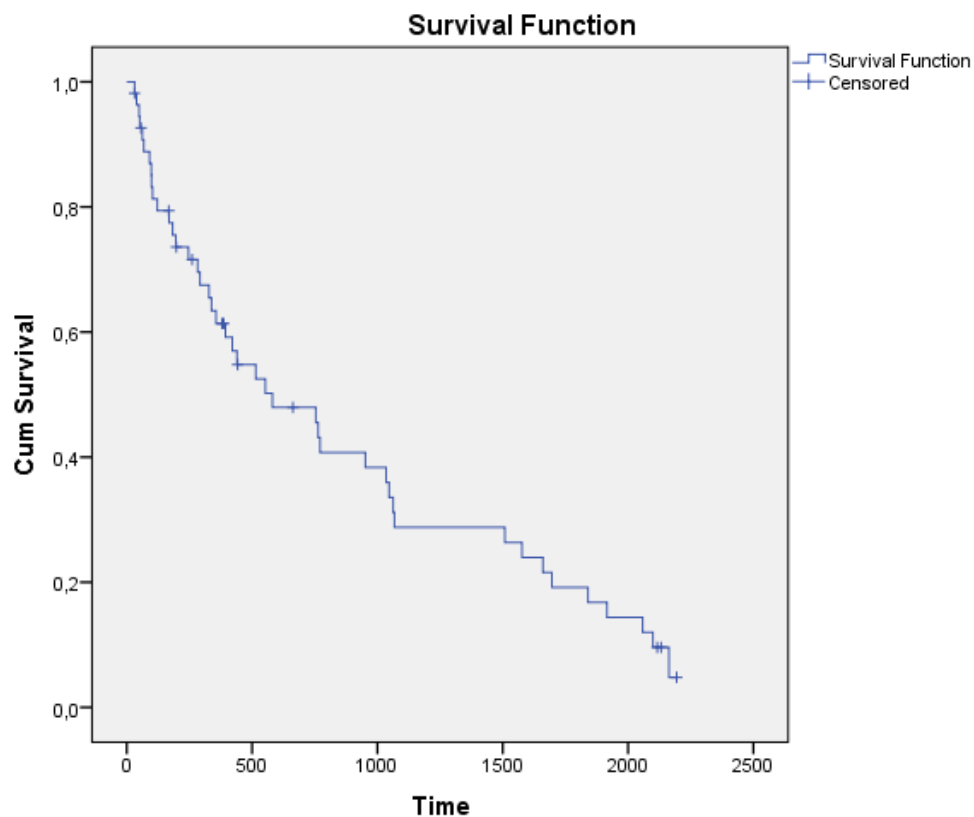


Figure 1. Kaplan-Meier Curve of Hemodialysis Patients

Based on Figure-1, it was known that median survival of hemodialysis patients based on 0.5 line on cum survival was 581 days. It meant, on day 581, hemodialysis patients experienced the event as much as 50%.

Table-2 was the result of Kaplan-Meier curve analysis and Log-Rank test of hemodialysis patient of Haji General Hospital, Surabaya based on age, gender, marital status, employment status, underlying diseases, and comorbidities.

Table-2. Results of Kaplan-Meier Curve Analysis and Log-Rank Test

Variable	Kaplan-Meier Curve	Log-Rank Test (P-Value)
Age	Not Intersecting	0.046
Gender	Intersecting	0.329
Marital status	Not intersecting	0.078
Employment status	Intersecting	0.468
Underlying diseases	Intersecting	0.838
Comorbidities	Not intersecting	0.0001

Based on the Kaplan-Meier curve and Log-Rank test, it was known that the variables of age, marital status, and comorbidities have significant differences in survival with a 5% confidence level. The median survival of each factor could be seen in Table-3.

Table 3. Median Survival of Hemodialysis Patients by Factor

Variable	Estimation (days)	Median	
		CI 95%	
		Lower	Upper
Age			
≤55 years old	771	44.667	1497.333
>55 years old	440	141.092	738.908
Gender			
Male	581	0.0001	1330.509
Female	440	0.0001	102.140
Marital status			
Married	771	193.312	1348.688
Not Married	283	47.868	518.132
Employment status			
Unemployed	952	617.080	1286.920
Employed	356	249.669	462.331
Coexisting illness			
Systemic lupus erythematosus	515	-	-
Diabetes mellitus	754	417.965	1090.035
Hypertension	440	182.175	697.825
Comorbidities			
Did not have	1.577	722.416	2431.584
Have	328	234.735	421.265

From Table-3, it was known that the highest median survival was on no coexisting factor, i.e. for 1.577 days, meaning that on day 1.577 (4.32 years or 4 years), hemodialysis patients who did not have a comorbid disease experienced the event as much as 50%.

Based the age factor, the probability of experiencing greater events was in hemodialysis patients aged > 55 years. The gender factor with the experiencing probability of the most events was female patients. Patients aged > 55 years and female patients alike had a median survival of 440 days, meaning that on day-to-440 (1.2 years), hemodialysis patients aged > 55 years old and female patients experienced an event of 50%.

In the marital status factor, the lowest median survival was unmarried status of 283 days, meaning that patients with unmarried status on day 283 experienced an event of 50%. The median survival in the lowest employment status factor was 356 days of working patients. On the underlying diseases factor median survival was lowest in patients with a history of hypertension disease of 440 days.

4.3 Testing Proportional Hazard Assumptions

The proportional hazard assumption test was conducted to find out which factors met proportional hazard assumptions. The method was done by two approaches, i.e. log minus log chart and goodness of fit statistical test. The analysis results were shown by Table-4.

Table-4. Log (-Log S (t)) Graph Analysis Results

Variable	log(-log S(t)) Graphic	Proportional Hazard Assumption
Age	Parallel	Met the assumptions
Gender	Parallel	Met the assumptions
Marital status	Parallel	Met the assumptions
Employment status	Parallel	Met the assumptions
Underlying diseases	Not Parallel	Not met the assumptions
Comorbidities	Parallel	Met the assumptions

From Table-4, it was found that there was one variable that did not meet the proportional hazard assumptions, that was underlying diseases variable. Furthermore, goodness of fit statistical test was done to support the descriptive analysis results.

Table-5. Goodness of Fit Test Result

Variable	P-Value	Proportional Hazard Assumption
Age	0.010	Not met the assumptions
Gender	0.893	Met the assumptions
Marital status	0.893	Met the assumptions
Employment status	0.080	Met the assumptions
Underlying diseases	0.0001	Not met the assumptions
Comorbidities	0.138	Met the assumptions

From Table-5, it was found that at the 5% significance level, the variables that met the proportional hazard assumptions were gender, marital status, employment status, and comorbidities.

4.4 Parameter Estimation of Proportional Hazard Model

Based on the variable that met the assumption, cox proportional hazard (CPH) test was conducted simultaneously to find out whether the independent variable used in the model had significant or not significant effect. The results of the simultaneous test were shown by Table-6.

Table-6. Concentration of Cox Regression Test Value

Variable	β	Standard error	P-Value
Gender	0.621	0.326	0.057
Marital status	0.853	0.353	0.016
Employment status	0.511	0.367	0.164
Comorbidities	1.668	0.386	0.0001
Likelihood ratio			0.0001

Based on Table-6, obtained p-value likelihood ratio of $0.0001 < \alpha = 5\%$, which meant there was at least one independent variable that affected the model. The Cox proportional hazard model obtained in the parameter estimation results was " $h(t) = h_0(t) \exp (0.621 \text{ gender} + 0.853 \text{ marital status} + 0.511 \text{ employment status} + 1.668 \text{ comorbidities})$ ".

Subsequently, a partial test was performed. Partial test was done by independent variable test which was significant at regression test simultaneously, that was variable of marital status and comorbidities.

4.5 Estimated Parameter of the Best Cox Proportional Hazard (CPH) Model

Partial test was done to get the best model parameter estimation from significant independent variable. The result of the partial cox regression analysis was shown in Table-7.

Table-7. Estimated Parameter of Best Cox Model

Variable	β	Standard error	P-Value	Exp (B)
Marital status	0.638	0.316	0.043	1.892
Comorbidities	1.531	0.370	0.0001	4.622

Based on Table-7, the best cox proportional hazard model was obtained as follows: “ $h(t) = h_0(t) \exp(0.638 \text{ Marital status} + 1.531 \text{ comorbidities})$ ”. Based on the value of exp (B), it was known that the marital status variable had a hazard ratio of 1.892, meaning that unmarried patients had the risk of experiencing event 1.892 times than married patients. The comorbidities variable had a hazard ratio value of 4.622, meaning that hemodialysis patients who had comorbidities had a risk of dying 4.622 times than patients who did not have comorbidities.

5.0 Discussion

The survival analysis was performed to determine the outcome of the variables that affected an event beginning to the end of the event, in example: recorded in days, weeks, months, or years. There were several methods for survival analysis, which were cox proportional hazard (CPH) regression. The use of CPH regression must satisfy the assumption of so-called proportional hazard assumptions, in which the time used always had the same or constant value.

The results showed that the estimation of CPH model parameters were gender, marital status, employment status, and comorbidities. Based on Table-3, male patients had greater survival than female. This was in line with Mailani’s research that said female hemodialysis patients tend to have a lower quality of life than male (Mailani, 2015).

Unmarried hemodialysis patients had lower survival than married patients. This was in line with Kusuma's research which says that patients with marital status would gain more moral and spiritual support than their spouses, due to their quality of life, especially their psychological condition (Kusuma, 2011). The marital status of patients who were divorced or who did not have a spouse tend to have low social health scores and were prone to depression (Mailani, 2015).

In Table-3, unemployed patients had significantly lower survival than working patients. Working allowed a person to get tired and tired quickly, which affected the quality of health. At work, there was a burden of work that makes physical and psychological conditions decrease. This was in line with Mailani's research which said that job status affected the hemodialysis patient’s quality of life (Mailani, 2015).

Hemodialysis patients with comorbidities had a worse quality of life compared with patients with no comorbidities. This was in line with Yulianto's research that presence of hypertension and diabetes mellitus alike affected the survival of hemodialysis patients (Yulianto, 2016).

6.0 Conclusion

The results of cox regression analysis showed marital status and comorbidities variables had significant effect on survival of chronic kidney disease patients with hemodialysis at RSU Haji Surabaya.

7.0 Recommendation

The suggestion that can be considered in subsequent research was further research by developing an expansion model of cox regression analysis on variables non proportional hazard assumptions.

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Declaration

Author(s) declare that all works are original and this manuscript has not been published in any other journals. There was no financial support of any organization for this work.

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