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Survival of Patients on Maintenance Hemodialysis Base on Comorbidity of Cardiovascular Disease in Persahabatan Central General Hospital 2015-2019

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Abstract
Chronic kidney disease is the progressive loss of kidney function over months or years. The significant increase in new cases of chronic kidney disease is in line with the increasing number of patients undergoing hemodialysis as kidney replacement therapy in an effort to survive. Comorbid cardiovascular disease is a major risk factor for morbidity and mortality with chronic kidney disease. The study was conducted to determine the survival of hemodialysis patients in the group with comorbid cardiovascular disease and the group without comorbid cardiovascular disease. This study used a retrospective cohort design. The location of this study was conducted at Persahabatan Central Public Hospital, DKI Jakarta, and used secondary data from the hospital information system data from 2015 to 2019. The variables significantly related to the survival of patients undergoing hemodialysis with comorbid cardiovascular disease were age, complications of anemia, diabetes mellitus, and hypertension. The age variable has a p-value of 0.029 with an HR of 1.54 (95% CI OR 1.043-2.262). The anemia variable has a p-value of 0.013 with an HR of 1.60 (95% CI 1.117-2.515). The diabetes mellitus variable has a p-value of 0.000 with HR2.71 (95% CI 1.780-4.11). The hypertension variable has a p-value of 0.004 with HR1.79 (95% CI 1.208-2.646). In conclusion, patients undergoing hemodialysis with comorbid cardiovascular disease have a risk of death of 0.76 times compared to patients undergoing hemodialysis with the comorbid non-cardiovascular disease. This study's internal validity was not good due to selection bias and non-differential misclassification information bias. Thus, the results of this study cannot be generalized.

Keywords: Survival, Hemodialysis, Cardiovascular Disease.

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1. INTRODUCTION

Chronic kidney disease is the progressive loss of kidney function over months or years (World Kidney Day, 2020). Chronic kidney disease initially does not show signs and symptoms but it can progress to kidney failure (World Kidney Day, 2019). The global prevalence of chronic kidney disease in 2017 was 697.5 million cases (95% CI 649.2-752.0 million) (Bikbov, et al., 2020). According to WHO, worldwide chronic kidney disease currently affects 8%-16% of the world's population (Chen, et al., 2019). In 2017, the Southeast Asia region was ranked 3rd in the world with a prevalence of 69.6 million cases of chronic kidney disease (95%CI 64.2-75.1 million). Indonesia has more than 10 million cases of chronic kidney disease, with a total of 27.2 million cases (Bikbov, et al., 2020). Every year, the number of patients with kidney disease is increasing. Based on Riskesdas 2018, the number of sufferers of chronic kidney disease (CKD) in Indonesia rose from 2.0 per mile in 2013 to 3.8 per mile in 2018 (Kementerian Kesehatan Republik Indonesia, 2018).

Chronic kidney disease is divided into 5 stages in which the last stage is the worst stage. At that stage, the kidneys are no longer functioning optimally so they require renal replacement therapy. One of the most common types of kidney replacement therapy performed by patients with chronic kidney disease is 99% hemodialysis in 2018 (Indonesian Renal Registry, 2018). Chronic kidney disease causes at least 2.4 million deaths per year and is now the sixth leading cause of death (World Kidney Day, 2019). According to research conducted by (Bikbov, et al., 2020), the mortality of chronic kidney disease in the world in 2017 was 1.2 million deaths (95% CI 1.2-1.3 million) while Southeast Asia was ranked 3rd in the world with the number of deaths from chronic kidney disease of 134,459 deaths. Indonesia in 2017 amounted to 35,466 deaths (Bikbov, et al., 2020).

Approximately, 91% of patients who started hemodialysis under the age of 70 years were still alive after 12 months of treatment (Prasad, & Jha, 2015). In Indonesia, the survival study of patients with chronic kidney disease (CKD) with HD in general was 67.84 months at the Soetomo Public Hospital (Yulianto, & Basuki, 2017). Based on the calculations that have been performed, it is known that the survival of patients with kidney failure undergoing hemodialysis is 776 days (Habibah, et al., 2018). One-, two- and three-year survival of patients are 82%, 13% and 10%, respectively. Cardiovascular events are the main cause of death in patients (22.72%) (Msaad, et al., 2019). The most common cause of death in hemodialysis patients is cardiovascular (K1) as much as 42% (Indonesian Renal Registry, 2018). The cause of death among hemodialysis patients 2011-2013 is arrhythmia/cardiac arrest of 28%, other cardiovascular diseases of 12.4%. Patients who are female, and have a history of hypertension, diabetes mellitus and the presence of complications of anemia have a lower average survival (Yulianto, & Basuki, 2017). Patients on hemodialysis with hemoglobin levels <10 g/dL had an increased risk of cardiovascular death, 2.24 (95% CI, 1.40–3.59) in patients with hemoglobin levels <9 mg/dL (Kuo, et al., 2018).

Chronic kidney disease is still a major health problem in Indonesia, which is associated with a high mortality rate. Comorbidities are the dominant factors that influence the survival of chronic kidney disease patients undergoing hemodialysis. Through this retrospective cohort study, researchers determined the survival of hemodialysis patients in the group with comorbid cardiovascular disease and the group without comorbid cardiovascular disease at Persahabatan Central Public Hospital,Jakarta in 2015-2019. The benefits of this study are expected to provide information about the description of the survival rate of hemodialysis patients based on

the presence or absence of comorbid cardiovascular disease and provide information about the effect of comorbid cardiovascular disease and other variables on the survival of hemodialysis patients so that the community can make prevention efforts by controlling these factors.

2. RESEARCH METHOD

This study is an observational analytic epidemiological study with a retrospective cohort study. Observations were conducted within a certain period of time from exposure to events (deaths) that had occurred in the past or before the researcher started the study. Data collection was performed using medical record data in the information system from 2015-2019. The population in the study were patients undergoing hemodialysis at Persahabatan Central Public Hospital. The samples were patients from 2015 to 2019 who had met the inclusion criteria. The inclusion criteria were new patients undergoing hemodialysis at the Persahabatan Central Public Hospital. In this study, the sample used was 290 patients who met the inclusion and exclusion criteria. The inclusion criteria in this study were that the patient was a new case of chronic kidney disease diagnosed during January 2015 to November 2019 and only underwent hemodialysis at Persahabatan Central Public Hospital in Jakarta. The exclusion criteria in this study were patients whose medical records were incomplete.

The data obtained was then administered editing, coding, data entry, and data cleaning. This study employed univariate, bivariate, and multivariate analysis with Kaplan meir analysis, log rank and cox regression with 95% confidence level. In this study, the dependent variable was survival, the independent variable was comorbid cardiovascular disease and the covariates were age, sex, hypertension, diabetes mellitus and anemia complications. This article has received ethical approval from the Ethics Commission of the University of Indonesia with ethical no: 356/UN2.F10.D11/PPM.00.02/2021.

3. RESULTS AND DISCUSSION

Table 1. Characteristics of Patients Undergoing Hemodialysis at Persahabatan Central Public Hospital 2015-2019.

Variable	Cardiovascular Disease Comorbid		Not Comorbid Cardiovascular Disease		Total	
	n	%	n	%	n	%
Chronic Kidney Disease Patient Status						
Sensor	68	36,36	119	63,64	187	64,48
Event	42	40,78	61	59,22	103	35,52
Age (average±sd)	55,4±15,3		54,3±11.4			
< 60	53	31,74	114	68,26	167	58,92
≥ 60	57	46,34	66	53,66	123	41,03
Gender						
Male	60	36,14	106	63,86	166	57,24
Female	50	40,32	74	59,68	124	42,76

Anemia						
No	75	36,95	128	63,05	203	70,24
yes	35	40,23	52	59,77	87	29,76
DM						
No	81	36,99	138	63,01	219	75,52
Yes	29	40,85	42	59,15	71	24,48
Hypertension						
No	63	36,42	110	63,58	173	59,66
Yes	47	40,17	70	59,83	117	40,34

The results of the analysis in Table 1 can be seen, the percentage of events (died) was more in hemodialysis patients without comorbid non-cardiovascular disease (59.22%) compared to comorbid cardiovascular disease patients (40.78%). The mean age of patients in the comorbid cardiovascular disease group was 55.4(±15.3) years while the non-cardiovascular comorbid patients were 54.3(±11.4) years. Age category ≥60 years are more (46.34%) compared to age <60 years in patients undergoing hemodialysis in patients with comorbid cardiovascular disease (31.74%). There are more female patients (40.32%) compared to male ones in hemodialysis patients with comorbid cardiovascular disease (36.14%). Complications of anemia were more in patients undergoing hemodialysis with comorbid cardiovascular disease (40.23%) compared to patients without anemia (36.95%). Diabetes mellitus was more common in patients undergoing hemodialysis with comorbid cardiovascular disease (40.85%) compared to patients undergoing hemodialysis without diabetes mellitus (36.99%). Hypertension was more common in patients undergoing hemodialysis for comorbid cardiovascular disease (40.17%) than patients undergoing comorbid hemodialysis for cardiovascular disease without hypertension (36.42%). It appears that there are differences in characteristics between groups of patients undergoing hemodialysis with comorbid cardiovascular disease and non-comorbid cardiovascular disease. Therefore, it will be controlled in a multivariate analysis.

Table 2. Average Survival of Patients Undergoing Hemodialysis at Friendship Hospital in 2015-2019.

Patients undergoing hemodialysis	***Mean***	***Min-Max***
Cardiovascular Disease Comorbid	32 months	1-78 month
Comorbid Not Cardiovascular Disease	23 months	1-78 month

The results of the analysis in Table 2 can be seen that the average survival of patients undergoing hemodialysis with comorbid cardiovascular disease is longer than patients without comorbid cardiovascular disease. The average survival of patients undergoing hemodialysis with comorbid cardiovascular disease was 32 months, while for non-comorbid cardiovascular disease was 23 months.

Table 3. The relationship between independent variables and covariate variables on the survival of patients undergoing hemodialysis at Persahabatan Central Public Hospitalin 2015-2019 using the Cox Regression Test.

Variable	**HR**	**95%CI**	**P-Value**
Independent			
Cardiovascular Disease Comorbid	0,76	0,513 – 1,134	0,181
Not Cardiovascular Disease	1		
Covariate Variable			
Age			

< 60 years	1,54	1,043 - 2,262	0,029
≥ 60 years	1		
Gender			
Male	0,87	0,587 - 1,276	0,467
Female	1		
Anemia			
Yes	0,68	1,117 - 2,515	0,013
No	1		
Diabetes Mellitus			
Yes	2,71	1,780 - 4.11	0.000
No	1		

The results of the bivariate analysis in table 3 above show that of the 5 variables, which are cardiovascular disease, age, hypertension, comorbid diabetes mellitus and anemia complications. There are 4 variables that have a significant risk for survival of patients undergoing hemodialysis with p <0.05. These variables include age, anemia, diabetes mellitus and hypertension. After selecting the confounding variables on the candidate variables, it was found that there was no change in HR in the independent variables of >10%. Hence, there are no confounding variables that will enter into the final model.

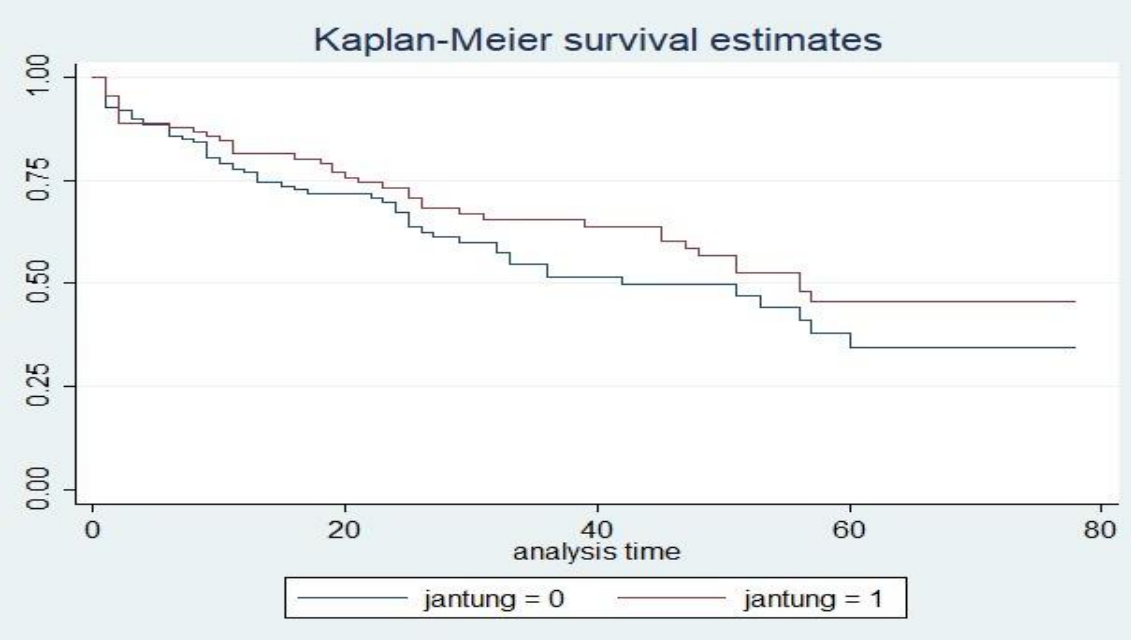

Figure 1. Probability of Survival of Patients Undergoing Hemodialysis Based on Comorbid Cardiovascular Disease at Persahabatan Central Public Hospital 2015-2019.

The curve in Figure1. showed that patients with comorbid cardiovascular disease were more likely to survive than non-cardiovascular comorbid patients. The results of the log rank test with p-value = 0.175 (>0.05) displayed that there was no statistically significant difference in the probability of survival between patients with cardiovascular comorbidities and no cardiovascular comorbidities. To describe the probability of survival of patients undergoing hemodialysis, a survival function with the life table method is used which can be seen in table 4.

Table 4. Life Table of Survival of Patients Undergoing Hemodialysis Based on Comorbid Cardiovascular Disease at Persahabatan Central Public Hospital 2015-2019

Time (month)	Cardiovascular Disease Comorbid (%)	Not Comorbid Cardiovascular Disease (%)
12	81.4	76.8
24	73.3	67.3
36	65.4	51.6
48	56.6	49.8
60	45.7	34.5

Table 4 above shows that the probability of survival of hemodialysis patients is higher with comorbid cardiovascular disease compared to comorbid non-cardiovascular disease. In the first year or 12 months, 81.4% of comorbid cardiovascular disease patients were still alive, while 76.8% of HD patients were not comorbid with cardiovascular disease. Year 5- or 60-months survival of HD patients with comorbid cardiovascular disease is 45% while non-comorbid cardiovascular disease is 34.5%.

Table 5. Final Model of Survival of Patients Undergoing Hemodialysis at Persahabatan Central Public Hospital in 2015-2019 using the Cox Regression Test

Variable	HR	SE	95% CI	P-Value
Cardiovascular Disease	0,76	0,15	0,51-1,13	0,181

Patients undergoing hemodialysis with comorbid cardiovascular disease will have a hazard of 0.76 times for death compared to patients with non-cardiovascular comorbidities.

In this study, the average age of patients with kidney disease undergoing hemodialysis based on comorbid cardiovascular disease was 55.4 years in patients with comorbid cardiovascular disease. The mean age of patients older than the Msaad study (2019), is 44.3 years for comorbid cardiovascular disease patients. The age group of ≥60 years is more than age <60 years. The age of the elderly based on the 2014 Minister of Health is someone who is 60 years old. Various studies regarding the low survival of patients undergoing hemodialysis state that older age is one of the most significant predictors of advanced age (Indonesian Renal Registry, 2018). In chronic kidney disease and some forms of acute renal failure, the GFR falls below the normal value of 125 ml/min. GFR also decreases with age, after the age of 30, the GFR value decreases at a rate of about 1 ml/min (Price, & Wilson, 2005). With increasing age, physiological functions decrease due to the aging process so that non-communicable diseases appear in the elderly (Kementerian Kesehatan Republik Indonesia, 2016). The kidneys cannot regenerate new nephrons so that when there is kidney damage or the aging process, there is a decrease in the number of nephrons. At the age of 40, the number of functioning nephrons decreases by about 10% every 10 years, and at the age of 80 years, only 40% of the nephrons are functioning (Siagian, & Damayanty, 2018).

Female gender was higher than male patients, namely 40.32%. This is in line with research conducted by Msaad, that patients undergoing hemodialysis both with comorbid cardiovascular disease and non-comorbid cardiovascular disease with female sex as much as 54.4%, while patients with male gender 40% (Msaad, et al., 2019). This study is also in line with research conducted by Sikole A which states that women survive more than men (Sikole, et al., 2007). This study is not the same as the research conducted by IRR (Indonesian Renal Registry) in 2016 which explained that there were more males than females.

The results of this study indicate that patients who experience anemia while undergoing hemodialysis are higher in patients with comorbid cardiovascular disease

(40.23%) compared to non-cardiovascular comorbidities (36.95%). Anemia is the most common abnormality in patients with decreased kidney function followed by a decrease in hemoglobin or hematocrit. Hence, the routine hematological examination of patients is important whether there is anemia. More than 85% of patients with chronic kidney disease (CKD), particularly in the advanced stages will experience anemia. Mortality of Chronic Kidney Disease (CKD) will be higher if accompanied by anemia (Syam, 2013).

The results of this study indicate that patients with comorbid diabetes mellitus while undergoing hemodialysis are higher in patients with comorbid cardiovascular disease (40.85%) compared to non-cardiovascular comorbidities (36.99%).

In this study, the survival probabilities of 1 year, 2 years, 3 years, 4 years and 5 years of patients undergoing hemodialysis with comorbid cardiovascular disease were 81.4%, 73.3%, 65.4%, 56.6% and 45.7% while non-cardiovascular comorbidities were 76.8%, 67.3%, 51.6%, 49.8% and 34.5%. From these results, it can be seen that the probability of survival of patients undergoing hemodialysis with comorbid cardiovascular disease is higher than that of non-cardiovascular comorbidities. It is in accordance with research conducted by Mardhatillah, which states that the 1-year survival of chronic kidney failure patients undergoing hemodialysis is 82% each (Mardhatillah, 2020).

Furthermore, based on survival time, patients undergoing hemodialysis with comorbid cardiovascular disease have a longer mean time to death, which is 32 months compared to patients with non-cardiovascular comorbidities. The results of this study are lower than the research conducted at Soetomo Public Hospital which states that patients undergoing hemodialysis are generally 67.84 months old (Yulianto, & Basuki, 2017).

The risk of survival of patients undergoing hemodialysis based on comorbid cardiovascular disease in this study was bivariate and multivariate, the HR value was 0.762 (95% CI 0.513 - 1.134). This is not in accordance with a study conducted in Morocco, that cardiovascular disease can increase 2.9 (95% CI 1.33-7.0) times the occurrence of death in hemodialysis patients compared to patients without comorbid cardiovascular disease (Msaad, et al., 2019). The results of this study are also not in line with research in the United States, that cardiovascular disease can increase 1.31 times the occurrence of death in hemodialysis patients compared to patients without comorbid cardiovascular disease after controlling for age, gender, race, age at first kidney failure, and comorbidities that others (Modi, et al., 2019). This is due to the high loss to follow in both groups (comorbid cardiovascular disease group with non-cardiovascular disease).

Although cardiovascular disease is the most common cause of death in chronic kidney disease (CKD) patients undergoing HD, Jager *et al*. in 2009 reached a different conclusion. In her study, chronic kidney disease (CKD) patients who started HD had a higher risk of death than the general population but was not specifically caused by cardiovascular disease (Umami, et al., 2017). Death in patients with chronic kidney disease (CKD) was 39% with cardiovascular disease and 51% were non-cardiovascular. In the general population, 40% of deaths are cardiovascular and 58% are non-cardiovascular diseases (De Jager, et al., 2009).

Retrieval of data from the hospital information system has several advantages, especially efficiency in terms of time, cost and some field resources. However, it also has limitations related to the observed factors because it must be adjusted to the availability of data which then results in limited determination of variables. Lost to

follow-up in this study was 36.2%, because this lost to follow was more than 20%. Therefore, in this study, there is a selection bias that can affect internal validity. This study employed secondary data so that researchers have not been able to control the quality at the data collection stage. Therefore, researchers have not been able to control the possible bias.

4. CONCLUSION

Patients undergoing hemodialysis with comorbid cardiovascular disease have a risk of death of 0.76 times compared to patients undergoing hemodialysis with the comorbid non-cardiovascular disease. However, the results of this study are influenced by selection bias and non-differential misclassification information bias. Thus, the results of this study cannot be generalized. It is hoped that this study can be developed further by examining the survival of patients undergoing hemodialysis with other variables such as comorbid protein-energy malnutrition, hepatitis, and others.

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