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Effect of Fibroblast Growth Factor-23 (FGF-23) on Two-Year Mortality Rate in Chronic Kidney Disease Patients With Hemodialysis

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Abstract

Introduction: Chronic kidney disease (CKD) is a global problem with increasing prevalence, poor prognosis, and high costs. Most deaths of CKD patients with hemodialysis (HD) is cardiovascular disorders. One of risk factors related to cardiovascular disorder is Fibroblast Growth Factor-23 (FGF-23). FGF-23 level is associated with increased mortality in CKD patients with HD.

Aim & Objectives: The aim of this study is to show the effect of Fibroblast Growth Factor-23 (FGF-23 on two year mortality rate in chronic kidney disease patients with hemodialysis.

Materials and Method: This retro-prospective mixcohort study with survival analysis obtained data from medical records of CKD patients undergoing HD at the Rasyidah Renal Hospital in the first week of January 2018. Patients were followed up next two years until 31st of December 2019. Kaplan Meier analysis was used to determine the effect of independent variables on dependent variable that was two years mortality, multivariate cox regression analysis to determine the dominant factor and magnitude of the association between independent variable and dependent variable. P-value <0.05 indicates a significant association.

Result: Kaplan Meier curve showed significant effect of FGF-23 level and Diabetes Mellitus on a two-year survival rate of patients (p = 0.01 and p = 0.04). Based on cox regression multivariate analysis, it was found patients with FGF-23 levels> 365ng/ml had a risk of 3.53 (CI95% 1,104-11,337) times more than group of patients with FGF-23 ≤ 365ng/ml while the presence of diabetes mellitus was risk factor on mortality with HR 3.71 (CI 1,279-10,796).

Conclusion: Statistically, FGF-23 level> 365 ng/ml is dominant factor that significantly influences 2-year mortality rate of CKD patients with HD other than Diabetes Mellitus.

Keywords: *Fibroblast Growth Factor, Chronic kidney disease on Hemodialysis, Mortality*.

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Introduction

Chronic kidney disease (CKD) is a global problem with increasing prevalence, poor prognosis, and high costs. Riskesdas 2018 showed that the percentage of CKD in Indonesia was high at 3.8% [1]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) reported a one-year mortality rate of CKD patients with hemodialysis (HD) due to cardiovascular disease in the US was 21.7% while in Europe, 15.6%. Cardiovascular mortality was reported to be ten times higher in HD patients compared to the general population [2]. Data in Indonesia showed that most deaths of CKD patients with HD were cardiovascular disease, which reached 37% and was followed by other causes (36%) [1]. Factors related to cardiovascular risk included traditional risk factors and non-traditional risk factors. Non-traditional risk factors include malnutrition, inflammatory cytokines, oxidative stress, and FGF-23 [3].

FGF-23 is a hormone produced by osteoblasts in regulating mineral metabolism under normal circumstances and CKD. Under normal circumstances FGF-23 increases urinary phosphate excretion by reducing the expression of sodium phosphate co-transporters, NaPi2a and NaPi2c which expressed on the apical surface of the proximal tubular cells of the kidney, and decreases circulating levels of 1,25-dihydroxy vitamin D (1,25D) by reducing expression of the cytochrome P450 (CYP) 1α-hydroxylase enzyme and CYP27B1 which is also expressed in renal proximal tubular cells [4]. A study by Isakova et al. in 2011 found the increase of FGF-23 three times in patients with CKD compared to patients with healthy kidney (145 RU/ml: {96-239 RU/ ml}) [5]. Whereas in CKD patients undergoing HD, there was an increase in FGF-23 levels to 4715 Ru/ml. There was a significant difference in CKD patients undergoing HD compared to CKD without HD (p-value <0.0001) [6].

Increased levels of FGF-23 are associated with increased mortality due to cardiovascular disease in CKD patients with HD directly or indirectly.

Determine the effect of FGF-23 levels on a two-year mortality rate in CKD patients with HD become the aim of the study besides determining the cut-off point of FGF-23 levels as a predictor of two-year mortality rate and other factors associated with two-year mortality of patients with CKD undergoing HD.

Methodology

Patient Selected

A retro-prospective mixcohort study with survival analysis obtained data from the medical records of all CKD patients undergoing hemodialysis at the Rasyida Renal Hospital in the first week of January 2018, with complete medical record data (identity, age, sex, ethnic group, comorbidities, smoking, body mass index, phosphate levels, calcium levels, CaxPh levels, hemoglobin, albumin); aged>18 years as inclusion criteria and are suffering from other diseases such as infections, chronic diseases and malignancies as exclusion criteria. All patient was followed up for the next two years until 31st of December 2019 to determine the patient's condition. The study was set under Declaration of Helsinki ethical principles and health research ethical committee by medical faculty of Universitas Sumatera Utara (No.324/TGL/KEPK FK USU-RSUP HAM/2018).

Data Analysis

The characteristics of each variable were presented in the central measure (mean, median, or proportion) and distribution variation (standard deviation or range). Kaplan Meier analysis was used to determine the effect of FGF-23 levels, age, sex, ethnicity, comorbidities, smoking, body mass index, calcium, phosphate, Ca x Ph value, hemoglobin, and albumin on two years survival rate. Cox regression multivariate analysis was used to determine the dominant factor and the magnitude of the association between the independent variable and the dependent variable. P-value <0.05 indicates a statistically significant association.

Results

Demographic and Clinical Characteristics of Patients

Of the 75 patients who met the inclusion and exclusion criteria, the majority of the sample was male (60.0%) with mean of age was 48.09 ± 12.41 years. The most ethnic group was Toba (41.3%). Laboratory data showed that the median value of FGF-23 was 328 ng/ml (217-950).

Table 1: Demographic and Clinical Characteristics of Regular Hemodialysis Patients.

Characteristics	n = 75
Sex	
Male	45 (60.0%)
Female	30 (40.0%)
Ethnic	
Toba	31 (41.3%)
Karo	16 (24.0%)
Melayu	14 (18.7%)
Java	6 (8.0%)
Mandailing	3 (4.0%)
Tionghoa	3 (4.0%)
Age, Years[a]	48.09 ± 12.41
Long of hemodialysis [m] (*vintage*)	77 (31-250)
BMI (kg/m^2)	23.3 (16.7-42.6)
BMI ≤ 23.3	37 (49.3%)
BMI > 23.3	38 (50.3%)
FGF-23 levels (ng/ml)	328 (217-950)
Calcium level [b] (mg/dl)	9.8 (8.0-10.9)
Phosphate level (mg/dl)	5.479 ± 0.60
Ca x Ph[a] (mg/dl)	53.6 ± 8.6
Albumin (g/dl)	4.0 (2.9-4.9)
Hemoglobin (g/dl)	10.01 ± 1.19
History of Hypertension	
No	19 (25.3%)
Hypertension	56 (74.7%)
History of Diabetes Mellitus	
No	61 (81.3%)
Yes	14 (18.7%)
History of Smoking	
No	51 (68.0%)
Yes	24 (32.0%)
History of Cerebrovascular Disease	
No	66 (88.0%)
Yes	9 (12.0%)
History of Cardiovascular Disease	
No	12 (16.0%)
Yes	63 (84.0%)

Category data: n (%); a: Numeric data: normal distribution: mean ± deviation standard; b: Not normal distributionb: median (minimum - maksimum); m: Months

Survival of Patients with Regular HD

After two years of follow-up, 14 patients (18.7%) died, and 61 patients (81.3%) survived until the study was completed. Based on the *Receiving Operating Characteristics* (ROC) curve, the cut off FGF-23 level was 365 ng/ml, with an Area Under Curve (AUC) area was 72% (p = 0.01), and the sensitivity and specificity values are 71.4% and 65.6%.

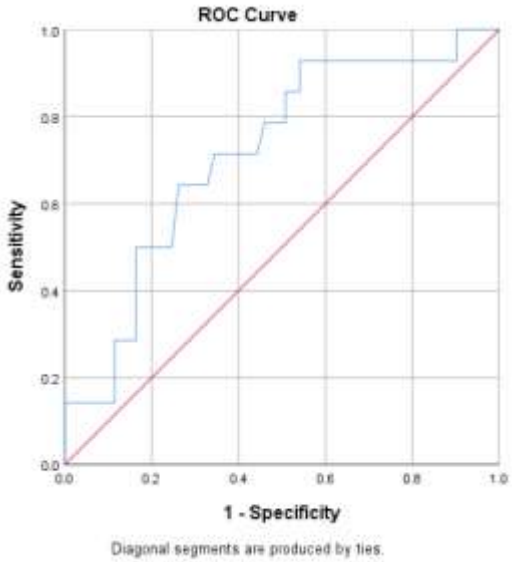

Figure 1: Cut off point of FGF-23 based on Receiving Operating Characteristics (ROC).

Effect of demographic and clinical characteristics on two years survival rate

Statistical test with Kaplan Meier method found a significant effect on FGF-23> 365 ng/ ml levels on the two years survival rate of CKD patients with HD (p = 0.01). The group of patients with FGF-23 levels ≤365 ng/ml had survival for 23 months, whereas survival time in the group of patients with FGF-23 value> 365 ng /ml was 22 months.

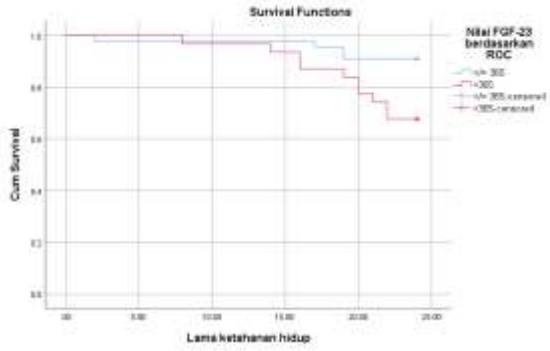

Figure 2: Survival time of regular hemodialysis patients based on FGF-23 Level.

Statistical analysis found a significant effect of diabetes mellitus on the two-year survival rate (p = 0.04). The mean survival time in the diabetes mellitus group was 20.5 months, while the group without diabetes mellitus was 23.2 months.

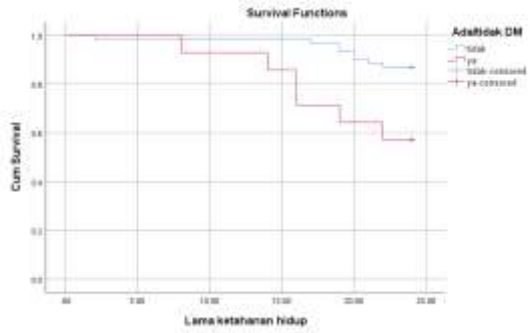

Figure 3: Survival time of regular hemodialysis patients based on Diabetes Mellitus.

There was no statistically significant effect of other minor independent variables on the two-year survival rate in CKD patients with HD with the p-value > 0.05.

After adjusting the variables FGF-23 levels, diabetes mellitus, smoking history, hemoglobin levels, and BMI, it was found that factors influencing two-year mortality were FGF-23 levels and history of DM.

Table 2: The final step of cox regression multivariate analysis

Variable	B	Wald	Sig	Exp (B)	95.0% CI for Exp (B)	
					Lower	Upper
FGF-23 >365 ng/ml	1.264	4.524	.033	3.538	1.104	11.337
Diabetes Mellitus	1.312	5.816	.016	3.715	1.279	10.796

Discussion

The prevalence of men was more than women in this study. This was consistent with the study of Muzasti et al. in 2016 (men vs. women; 64.3% vs. 34.7%) and study by the Indonesian Renal Registry (56% vs. 44%) [1,18]. Iseki et al. explained that women were protected for CKD at reproductive age. Differences in lifestyle, such as smoking and drinking alcohol, were more often in men and became risk factors for CKD [19].

From laboratory tests, the median FGF-23 level in this study was 328 ng/ml. Research by Torres et al. found that increased levels of FGF 23 were 100-10000 times the normal value [9].

Two-year mortality rate reached 18.7% (14 people). This mortality rate was lower than in the study by Sibarani et al. in 2017, which was 36.6% [10]. Based on research data from USRDS, the highest mortality was in the first year after HD initiation, the lowest was in the second year, and mortality will increase again after 2- 5 years, and after five years, mortality will be higher than the first year [11]. This could be caused by easier access to HD units and improved quality of health services. The progress of HD facilities

and techniques was developing rapidly in Indonesia. Based on IRR 2019, there were 832 HD units in Indonesia. However, the fatality rate of HD patients in Indonesia remained high due to differences in demographic characteristics, referral patterns, and HD practice patterns [12]. The study by Yan et al. in comparing the mortality rates for 23 months in each CKD patient with racial and ethnic HD in 50 states in the United States found that each ethnicity and race had different mortality rates in each state. This was influenced by other factors, such as the availability of insurance for HD and the available health infrastructure [13].

Based on cox regression multivariate analysis, this study found a significant effect between FGF-23 levels> 365 ng / ml on two-year mortality in patients with CKD with HD. The group of patients with FGF-23 levels> 365 ng / ml had a risk of 3.54 times (CI95%: 1.10-11.34, p = 0.03) experiencing mortality within two years compared to the group of patients who had FGF-23 levels ≤ 365ng/ml. Gutierrez et al. proved that an increase in FGF-23 levels was associated with an increased risk of death of patients with CKD with HD (p <0.001) [14]. This was consistent with the study by Isakova et al. in CKD patients with HD who found that groups of patients with high levels of FGF 23 had the risk of death 1.7 times higher than the group of patients with normal FGF-23 levels (74 Ru/ml) [15]. Increased cardiovascular mortality 1.92 times at FGF-23 levels> 36, and this risk would decrease to 1.87 times and 1.77 times after the variable confounding phosphate and calcium were removed [14].

A study by Robert et al. explained the effect of FGF-23 on mortality in CKD patients with HD caused by direct and indirect mechanisms [15]. FGF-23 directly affected cardiac remodeling and resulted in left ventricular hypertrophy and affected vascular function [14]. FGF-23 would also directly increase intracellular calcification in cardiac myocyte cells and increased cardiac contractility [16]. Changes in phosphate mineral metabolism, calcium, parathyroid hormone (PTH) and vitamin D were indirect mechanisms for increasing the risk of cardiovascular mortality by FGF-23. FGF-23 increased the release of calcium from the bones, thereby increasing serum calcium levels, which in turn trigger blood vessel calcification, which results in increased death from cardiovascular disorders [17].

Likewise, diabetes mellitus also increased 2 year mortality with HR 3.71 (CI95%: 1.28-10.80, p = 0.02). The study of Schroijen et al. found that the risk of 6-month mortality of CKD patients on dialysis differed significantly between patients with diabetes mellitus and without diabetes mellitus with HR 1.7 (CI 1.3-2.2) [18]. Likewise, a study by Hortemo et al. followed up patients for 3.6 years [19]. The effect of diabetes mellitus on mortality was caused by a decrease in the quality of mental and physical health in diabetes mellitus patients compared to non-diabetes Mellitus patients, besides diabetes mellitus patients also had a higher risk of mortality due to cardiovascular disease compared to non-diabetes Mellitus patients [18,19].

Conclusion

Statistically, FGF-23 level> 365 ng /ml is the dominant factor that significantly influences the 2-year mortality of CKD patients with HD other than Diabetes Mellitus. Further research is needed to prove the mechanism of influence.

Limitation

In this study, the cause of mortality in CKD patients with regular HD was not determined with certainty. Possible causes could be cardiovascular disease or other diseases. The presence of hypertension also was not known with certainty, whether it was the cause or the result of CKD. Besides, this study also did not assess the use of drugs that were routinely consumed, which could affect two-year mortality in CKD patients with regular HD.

Conflict of Interest Statement

This research was held by the author cost and there were no relevant conflict of interest in this research.

References

1. Indonesia Renal Registry. 10th Report Of Indonesian Renal Registry 2017. Indonesia Renal Regist. 2018
2. Weiner DE, Tighiouart H, Amin MG, et al. Chronic Kidney Disease as a Risk Factor for Cardiovascular Disease and All-Cause Mortality : A Pooled Analysis of Community-Based Studies. J Am Soc Nephrol. 2004;15:1307–15.
3. World Heart Federation . Risk factors of Cardiovascular Disorder . World Heart Federation. 2017.
4. Fructuoso AIS, Maestro ML, Pérez-Flores I, Valero R, Rafael S. Serum level of fibroblast growth factor 23 in maintenance renal transplant patients. Nephrol Dial Transpl. 2012;27:4227–35.
5. Isakova T, Xie H, Yang W, Xie D. Fibroblast Growth Factor 23 and Risks of Mortality and End-Stage Renal Disease in Patients with Chronic Kidney Disease Tamara. JAMA. 2011;305(23):2432–9.
6. Imanishi Yasuo, Inaba Masaaki, Nakatsuka Kiyoshi, Nagasue Kyoko, Okuno Senji YA. FGF-23 in patients with end-stage renal disease on hemodialysis. Kidney Int. 2004;65:1943–6.
7. Muzasti R, Lubis H. Association of phase angle on bioelectrical impedance analysis and dialysis frequency with the survival of chronic hemodialysis patients Association of phase angle on bioelectrical impedance analysis and dialysis frequency with the survival of chronic hemodialysis. IOP Conf Ser Earth Environ Sci. 2018;3–9.
8. Iseki K. Gender differences in chronic kidney disease. Kidney Int [Internet]. 2008;74(4):415–7.
9. Torres PU, Friedlander G, Silve C, Prie D. Bone mass does not correlate with the serum fibroblast growth factor 23 in hemodialysis patients. Int Soc Nephrol. 2008;102–7.
10. Sibarani H, Muzasti RA, Lubis HR. Association between neutrophil-to-lymphocyte ratio and survival rate patient hemodialysis in Adam Malik general hospital in 2016 Association

between neutrophil-to-lymphocyte ratio and survival rate patient hemodialysis in Adam Malik general hospital in 2018. IOP Conf Ser Earth Environ Sci. 2018;125.
11. The United States Renal Data System. Annual Data Report. Am J Kidney Dis. 2017;69.
12. Indonesian Renal Registry. 11th Report Of Indonesian Renal Registry 2018. Indonesia Renal Regist. 2019
13. Yan, G. Article Racial and Ethnic Variations in Mortality Rates for Patients Undergoing Maintenance Dialysis Treated in US Territories Compared with the US 50 States. CJN. 2020.
14. Arnold J, Carlsson AC, Sundstrom J, Ingelsson E, Larsson A, Lind L, et al. Serum FGF23 and Risk of Cardiovascular Events concerning Mineral Metabolism and Cardiovascular Pathology. Clin J Am Soc Nephrol. 2013;8(5):781–6.
15. Robert S, Alexander S, Gunnar HH, Vincent B. FGF23 in Cardiovascular Disease : Innocent Bystander or Active Mediator ? Front Endocrinol (Lausanne). 2018;9(June).
16. Touchberry CD, Green TM, Tchikrizov V, Mannix JE, Mao TF, Carney BW, et al. FGF23 is a novel regulator of intracellular calcium and cardiac contractility in addition to cardiac hypertrophy. Am J Physiol Endocrinol Metab. 2013;304:863–73.
17. Silver J, Rodriguez M, Slatopolsky E. Translational Nephrology FGF23 and PTH — double agents at the heart of CKD. Nephrol Dial Transpl. 2012;27(March):1715–20.
18. Schroijen MA, Dekkers OM, Grootendorst DC, et al. Survival in dialysis patients is not different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. BMC Nephrology .2011;
19. Hortemo TB, Lippe N Von Der, Ribu L, Rustøen T, Leivestad T. Health-related quality of life and all-cause mortality in patients with diabetes on dialysis. BMC Nephrology. 2012;