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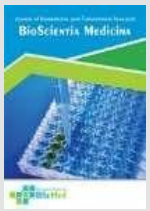

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The Relationship between Serum Cystatin-C Levels and Impaired Cognitive Function in Patients with Chronic Kidney Disease

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A B S T R A C T

Background: Cystatin-C acts as a neuroprotector in the central nervous system at normal levels, but high serum cystatin-C levels are associated with impaired cognitive function. Serum cystatin-C levels increase in impaired renal function, and cognitive impairment are comorbidities that can increase the morbidity and mortality of chronic kidney disease patients. This study aimed to assess the relationship between serum cystatin-C levels and cognitive function in chronic kidney disease patients. **Methods:** This study used a cross-sectional design with 73 samples of non-hemodialysis chronic kidney disease patients. Cognitive function was assessed using the MoCa-Ina. Serum cystatin-C levels of all samples were measured by the ELISA method. Data analysis was carried out using SPSS. **Results:** Impaired cognitive function in CKD patients was found to be 76.7%. The median serum cystatin-C level of CKD patients with impaired cognitive function (n=56) was 1.015 mg/dL, and without cognitive impairment (n=17) was 0.929 mg/dL. There was no significant relationship between serum cystatin-C levels (cut-off point 0.98 mg/dL) and impaired cognitive function (OR : 2.05, 95% CI : 0.680-6.175, p= 0.198). **Conclusion:** There is no relationship between serum cystatin-C levels and cognitive function impairment in non-hemodialysis chronic kidney disease patients.

1. Introduction

Cystatin-C is a low molecular weight cysteine protease inhibitor that is produced by all nucleated cells in the body, freely filtered through the glomerulus, and degraded by the proximal tubules of the kidney.[1] Serum cystatin-C level is a new parameter in determining the condition of kidney function.[2] At normal levels, cystatin-C acts as a neuroprotector in the central nervous system,[3] however, high serum cystatin-C levels are associated with impaired cognitive function.[4,5] Chronic kidney disease (CKD) patients are a population at high risk of experiencing high serum cystatin-C levels. Elevated cystatin-C levels increase the risk of mild cognitive impairment to dementia in CKD patients.[4,6]

Impaired cognitive function is often found in CKD patients and is a key factor in the decline in health-related quality of life in CKD patients.[7] where the decrease in quality of life in patients with CKD is associated with a marker of impaired glomerular filtration rate, namely cystatin.[4] The risk of impaired cognitive function is related to the stage of CKD. The lower the estimated glomerular filtration rate (eGFR), the higher the risk of impaired cognitive function. Even changes in cognitive function are seen in the early stages of CKD.[6,8] Thus, individuals at all stages of CKD have a higher risk of developing dementia and impaired cognitive function compared to the general population.[6,9]

There are several factors that affect cognitive function in CKD patients, which are divided into 2 categories, namely factors risk traditional form of age, education level, quality of sleep, and vascular comorbidities, then factors risk non-traditional forms of inflammation, oxidative damage, anemia, high levels of cystatin-C and high levels of uremic toxins in the body.[10] Serum cystatin-C levels are a new parameter in determining the condition of kidney function, which in previous studies found a decrease in quality of life in CKD patients.[7] associated with cystatin levels related to impaired glomerular filtration rate and low cognitive function scores in the elderly who have increased levels of cystatin-C.[4,6,8]

Cystatin-C can bind to β-amyloid (Aβ) monomers, preventing β-amyloid aggregation and inhibiting the formation of Aβ fibrils. Based on this, it was concluded that cystatin-C has a protective effect on Alzheimer's by preventing the formation of toxic Aβ, so the role of cystatin-C is as a neuroprotector in the process of neurodegeneration.[3] However, very high levels of cystatin-C will facilitate cystatin-C aggregation so that the ability of cystatin-C to bind β-amyloid is reduced, which then increases the formation of β-amyloid fibrils.[5] facilitate co-deposition of amyloid fibrils in blood vessels and brain parenchyma.[11] The end result of this situation can cause a decrease in the cognitive function of the sufferer.

Several studies support the relationship between cystatin-C and impaired cognitive function, which shows that there is a relationship between cystatin-C levels and impaired cognitive function in CKD patients from demographics and comorbidities. Meanwhile, different results were seen in other studies, which concluded that cystatin-C has a protective effect on Alzheimer's by preventing the formation of toxic Aβ, so the role of cystatin-C here is a neuroprotector in the process of neurodegeneration.

Individuals with CKD are at high risk for cognitive decline and dementia, which are associated with reduced quality of life. Changes in cognitive function have been seen in the early stages of CKD. Previous studies found a high incidence of cognitive dysfunction in the late stages, so early detection is needed to assess the occurrence of cognitive decline in CKD sufferers from the start of the disease. The incidence of the decreased cognitive function itself is related to the degree of impaired kidney function in patients with CKD. Serum cystatin-C levels can be a measure in determining kidney function where levels increase in impaired kidney function. In addition, high serum cystatin-C levels are said to be associated with impaired cognitive function.[12] This study aimed to determine the relationship between cystatin-C levels and cognitive function in chronic kidney disease patients.

2. Methods

This study is an analytic observational study with a cross-sectional approach. A total of 73 research subjects participated in this study, and the subjects met the inclusion criteria. The inclusion criteria in this study were patients who at diagnosed with chronic kidney disease*, b* never/not undergoing hemodialysis, and were willing to participate in the study. This research is located at the polyclinic and inpatient renal internal medicine-hypertension Dr. M. Djamil General Hospital, Padang, from September 2022 to February 2023. This research was approved by the medical and health research ethics committee of Dr. M. Djamil General Hospital, Padang, Indonesia (No. 908/UN.16.2/KEP FK/2022).

In all research subjects, observations were made on basic characteristics such as age, gender, education level, hypertension, diabetes mellitus, duration of CKD, and cognitive function, which was assessed using the Montreal Cognitive Assessment Indonesia (MoCA-Ina). Cystatin-C levels were assessed using the ELISA method, according to the instructions in the ELISA kit manual. Data analysis was carried out using SPSS software version 25. Data analysis was performed univariate and bivariate with $p<0.05$.

3. Results

The distribution of the basic characteristics of the sample for this study is shown in Table 1. The mean

age of the sample was 53.14 ± 12.89 years, with the youngest being 21 years old and the oldest being 82 years. There were more male samples (56.2%) than females (43%) in the current study, and 46 samples (63%) had education ≥ 12 years. More than half of the sample (58%) suffer from hypertension, while 29% suffer from diabetes. In the current study, apart from hypertension and DM as risk factors for CKD, other factors were also found that caused patients to experience CKD, such as infection-inflammation of the kidneys and post-renal obstruction such as nephrolithiasis or neoplasms. The average length of suffering from CKD is 6 months, with an average eGFR of 10 ml/minute/1.73 m^2, and as many as 45 people (61.6%) were at stage 5 CKD. Impaired cognitive function was found in 56 samples (76.7%) with a median serum cystatin-C level of 0.998 mg/dL.

There were statistically significant differences in the basic characteristics of impaired cognitive function and without impaired cognitive function, namely age, gender, length of education, diabetes mellitus, and duration of CKD. Meanwhile, there were no statistically significant differences in hypertension, eGFR, and CKD stage with regard to impaired cognitive function.

Table 1. The relationship between the basic characteristics of the research sample and impaired cognitive function.

Variable	**Global cognitive function (Moca-Ina)**		**p**	**OR**	**95% CI**	
	Impaired (n= 56)	**Normal (n= 17)**			**Minimum**	**Maximum**
Age			0,033*	0,937	0,090	0,937
≤ 50 years	23 (65,7%)	12(34,3%)				
> 50 years	33 (86,8%)	5(13,2%)				
Gender, n (%)			0,048*	3,056	0,985	9,481
Male	35 (85,4%)	6 (14,6%)				
Female	21 (56,3%)	11(34,4%)				
Length of education, n(%)			0,002*	13,87	1,720	111,823
< 12 years	26 (96,3%)	1 (3,7%)				
≥ 12 years	30 (65,2%)	16(34,8%)				
Risk factors for CKD hypertension, n(%)			0,496*	0,676	0,219	2,085
With hypertension	31 (73,8%)	11(26,2%)				
No hypertension	25(80,6%)	6(19,4%)				
DM, n(%)			0,017*	8,889	1,096	72,076
With DM	20 (95,2%)	1(4,8%)				
No DM	36 (69,2%)	16 (30,8%)				
Long suffered from CKD (month), median (min-max)	6 (4-36)	5 (4-12)	0,031O			
GFR estimation (1 ml/min/1.73 m^2), median (min-max)	9 (1-69)	14 (2-52)	0,237 O			
CKD stages, n(%)			0,485*			
Stage 1 Stage 2 Stage 3 Stage 4 Stage 5	0 (0%) 3(100%) 5 (62,5%) 12 (70.6%) 36 (80%)	0 (0%) 0 (0%) 3 (37.5%) 5 (29.4%) 9 (20%)				

* Chi-square test
O Mann-Whitney test.

Table 2. Differences in serum cystatin-C levels in non-hemodialysis CKD patients with and without impaired cognitive function.

Variable	Global cognitive function (MoCa-Ina)	
	Impaired (n= 56)	**Normal (n= 17)**
Serum cystatin-C levels (ng/mL) median (min-max)	1,015 (0,008-3,398)	0,929 (0,048 – 1,517)

In Table 2, it can be seen that the mean serum cystatin-C value in the group with impaired cognitive function was 1.015 mg/dL, with a minimum value of 0.008 mg/dL and a maximum value of 3.398 mg/dL. The mean serum cystatin-C levels in the group without impaired cognitive function was 0.929 mg/dL with a minimum value of 0.048 mg/dL and a maximum value of 1.517 mg/dL. The table also shows that the serum cystatin-C levels in the group with impaired cognitive function were slightly higher than in the group without impaired cognitive function. Provisions regarding the normal value of cystatin C in the CKD patient population still vary. Therefore, this study calculated the cut-off point (COP) using the receiver operating characteristic (ROC) curve so that the area under the curve (AUC) was obtained, which can be used to determine the optimal COP for serum cystatin C levels associated with impaired cognitive function in CKD patients. The results of the ROC curve analysis showed that the optimal COP of serum cystatin C levels between groups with and without impaired cognitive function was 0.98 mg/dL. The AUC value obtained from the ROC method was 0.59 (95% confidence index, 0.445 – 0.725, p = 0.293), 58.9% sensitivity, and 58.8% specificity.

Based on the optimal COP value obtained using the ROC curve, in this study, there were 33 people (45.2%) with serum cystatin-C levels below the cut-off point and 40 people (54.8%) with serum cystatin-C levels equal to or above the cut-off point. The results of the bivariate analysis and the estimation of the risk of developing cognitive function disorders are shown in Table 3. In the group with cognitive function disorders, there were 33 people (82.5%) who had cystatin C serum levels equal to or above the cut-off point, while in the group without cognitive function disorders, there were 7 people (17.5%) who had serum cystatin-C levels equal to or above the cut-off point. Chi-square test results showed a significant difference in levels of cystatin-C serum between groups with and without impaired cognitive function (p = 0.198), as well as odds ratio (OR) greater than 2,050, 95% CI, 0.680–6.175.

Table 3. The relationship between serum cystatin-C levels and cognitive dysfunction in CKD patients.

Variable	Cognitive function (Moca-Ina)		P value	OR (95% CI)
	Impaired (n= 56)	**Normal (n= 17)**		
Serum cystatin-C levels			0.198*	2,050 (0,680-6.175)
≥ cut-off point	33 (82,5%)	7 (17,5%)		
< cut-off point	23 (69,7%)	10 (30,3%)		

* Chi-square test.

4. Discussion

The results of this study differ from studies in which patients with higher cystatin-C levels had worse cognitive performance than patients with medium and low levels of cystatin-C. The different results obtained in the current study were due to differences in the ratio of CKD stages in the sample studied, which in the current study were dominated by end-stage CKD sufferers (stage 4: 23.3%, stage 5: 61.6%) so that rate value cystatin-C higher serum compared to other studies, where samples in these other studies had eGFR values or amount samples at each stage of CKD

were almost evenly distributed at each level so that it affects the difference in sample coverage that suffers from impaired cognitive function with those who are normal.[13-16]

This difference is also influenced by the absence of screening for markers of inflammation, malignancy, or the use of glucocorticoids in patients, which for a number of reasons, can cause a significant increase in cystatin-C levels in the blood. In addition to glomerular filtration rate, cystatin-C levels are affected by inflammation, adiposity, thyroid disease, malignancy, and glucocorticoids. Influence cystatin-C levels decrease in value as a measure of renal excretory performance but are not affected by muscle mass or diet and are less associated with age, gender, and race than creatinine.[17,18]

Another study found that serum cystatin-C levels were negatively associated with cognitive function as assessed by MoCA, higher serum cystatin-C levels were weakly associated with worse cognitive performance, concluding that patients with higher cystatin-C levels experienced increased cognitive function. Possible severe cognitive impairment. The findings on the association of serum cystatin C with cognitive impairment are inconsistent; there are studies that do not show an association between cystatin-C and cognitive function, but other studies found a significant correlation between serum cystatin-C levels and cognitive function. The differences in study results are due to differences in the study population, study design, outcome definitions, or the methods used to measure cystatin-C. In general, blood cystatin c levels cannot fully measure true levels. Inside the blood, this is because most of the cystatin-C has experienced aggregation within a certain period of time, and special tests are needed to measure the level of aggregated cystatin-C.[19]

There are some limitations in this study, such as the absence of data regarding cognitive function before the patient had CKD. The current study also did not examine several factors that may be associated with an impaired cognitive function, such as quality of control of hypertension, quality of control of metabolic diseases, markers of oxidative stress, inflammatory markers, other uremic toxins, and examination of other factors that can also affect serum cystatin c levels. as well as the uneven distribution of samples based on eGFR values or at each stage of CKD.[20]

5. Conclusion

There is no significant relationship between serum cystatin-C levels and the incidence of cognitive dysfunction in CKD patients.

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