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Association between Disease Severity, Risk Factors and Demographic Characteristics with Verbal-Auditory Memory Impairment in Patients with Chronic Kidney Disease

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ABSTRACT

Background: *Cognitive impairment is commonly found in patients with Chronic Kidney Disease (CKD) and might affect several domains. Early identification is important since it is related to health-related quality of life. This study aimed to assess the verbal-auditory memory function and determine its association with disease severity, risk factors, and demographic characteristics.* ***Methods:*** *We studied 50 CKD patients in Haji Adam Malik General Hospital, Medan, Indonesia, and classified the severity into stages 3, 4, and 5 based on the estimated Glomerular Filtration Rate (GFR). The cognitive function was assessed using Rey Auditory Verbal Learning Test (RALVT) to assess verbal-memory auditory function. We collected demographic data and vascular risk factors.* ***Results:*** *Most subjects were males (33 patients; 66%) and at stage 5 (25 patients; 50%). The mean age was 49.76 ± 12.28 years, the mean duration of CKD was 34.10 ± 33.72 months, and the mean GFR was 20.84 ± 20.30 mL/min/1.73 m^2. We found significantly lower scores of RAVLT in patients with more severe CKD. There was also a significant correlation between GFR and each of the RAVLT scores, and no significant correlation between GFR and age or education. There was no significant difference in the scores based on the presence of the vascular risk factors.* ***Conclusion:*** *Memory impairment was associated with more advanced stages in CKD patients, but not related to demographic or vascular risk factors. Early identification of cognitive impairment is important in CKD patients and should be part of a routine examination.*

Keywords: Chronic kidney disease, Cognitive impairment, Memory, RAVLT, Risk factor

Abbreviation: ANOVA: Analysis of Variant, CKD: Chronic Kidney Disease, CRIC: Chronic Renal Insufficiency Cohort, eGFR: estimated Glomerular Filtration Rate, HD: Hemodialysis, MOCA: Montreal Cognitive Assessment, RAVLT: Rey Auditory Verbal Learning Test

INTRODUCTION

Chronic Kidney Disease (CKD) is now considered as one of the major public health problems and one of the top leading causes of death according to the Global Burden of Disease Study 2010 [1]. Its incidence is predicted to rise significantly over the next decade because of the increasing incidence of several vascular risk factors including diabetes and hypertension in the rapidly aging population [2,3]. CKD is defined as kidney damage lasting more than 3 months or with Glomerular Filtration Rate (GFR) <60 mL/min/1.73 m2 [3].

Cognitive impairments are frequently found in CKD patients. Several previous studies have shown that CKD patients have a higher risk of developing cognitive impairments, ranging from Mild Cognitive Impairment (MCI) to dementia. This risk is generally explained by the high prevalence of vascular risk factors, including hypertension, diabetes, as well as subclinical ischemic cerebrovascular lesions [1-7]. Cognitive decline in patients with CKD might also be related to nephrotoxins, oxidative stress, cytokines, hemodynamic changes, and other factors [2,3]. The link between CKD and cognitive impairment can be explained by several factors, including a higher prevalence of cerebrovascular disease and cardiovascular risk factors as well as non-traditional vascular risk factors such as hyperhomocysteinemia, hemostatic abnormalities, and hypercoagulable states, increased oxidative stress and inflammation due to CKD and higher prevalence of nonvascular risk factors such as anemia, hyperparathyroidism, polypharmacy, sleep disorders, and depression. All these factors can potentially affect any cognitive domain, not only limited to executive function that is commonly found in patients with cognitive impairment related to cerebrovascular lesions, such as stroke [1,3,8].

The prevalence of CKD increases as the disease progress from stage 3 to stage 5 showing a possible relationship between disease severity and cognitive impairment [2]. The degree of renal dysfunction appears to be correlated with the degree of cognitive impairment. However, less than 5% of all CKD patients with cognitive impairment have been screened or received a medical diagnosis, and cognitive assessment has not been included as the routine examination in patients with renal disease [3]. This suggests that cognitive impairment in this group of patients is not adequately addressed. Several studies have reported the evaluation of memory function in CKD patients but its association with disease severity and other factors has not been extensively evaluated. This study aimed to assess the verbal-auditory memory function and determine its association with disease severity, vascular risk factors, and demographic characteristics in CKD patients.

METHODS

Study Design

This was an observational, cross-sectional study involving 50 CKD patients attending the outpatient clinic in Adam Malik General Hospital Medan Indonesia. Patients were recruited by a non-random consecutive sampling method from August 2018 to February 2019. All participants provided signed informed consent following local institutional review board approval. The estimated Glomerular Filtration Rate (GFR) was recorded within 3 months of neuropsychological testing and was performed at a single central laboratory using the standard method. The eGFR was calculated using the Modification of Diet in renal Disease study equation [9]. The staging of CKD was based on the estimated GFR. Stage 3 CKD was defined as eGFR 30 ml/min/1.73 m2-59 ml/min/1.73 m2, stage 4 CKD was defined as eGFR 15 ml/min/1.73 m2-29 ml/min/1.73 m2 and stage 5 CKD was defined as eGFR <15 ml/min/1.73 m2.

Participants

Patients were considered for enrollment if they were in stage 3 to 5 CKD, were able to communicate in Bahasa Indonesia, and agreed to participate in the study by signing an informed consent form. Patients with unstable conditions, delirium, dementia, and other degenerative neurological diseases, aphasia, stroke, and psychiatric diseases were excluded. The demographic and clinical data including age, sex, duration of CKD, Glomerular Filtration Rate (GFR), stage of CKD, and the presence of risk factors, including hypertension, diabetes mellitus or both, nephrolithiasis, or others were collected.

Cognitive Measurement

The cognitive function was assessed using Rey Auditory Verbal Learning Test (RALVT) to assess verbal-memory auditory function. The RAVLT is one of the most widely used neuropsychological tests of verbal episodic declarative memory [10]. It measures recent memory, verbal learning, susceptibility to (proactive and retroactive) interference, retention of information after a certain period during which other activities are performed, and recognition memory. It is a fast and straightforward test to administer, and its use has been widely recognized by neuropsychological literature. It is sensitive to deficiencies of memory found in many groups of patients, being useful for the diagnosis of memory disturbances [11]. It provides scores for assessing immediate memory, new verbal learning, susceptibility to interference (proactive and retroactive), retention of information after some time, and memory recognition [12].

First, a 15 noun-word list (list A) was read to the participants with a presentation rate of one word per second. After the presentation of the 15 words, patients were requested to recall as many words as possible. This was repeated 5 times, and after each trial recall was recorded (A1-A5).

The five recall trials were summed into one score (sum). After 5 presentations of list A, an interference-list of 15 other nouns (list B) were read to the participants and they were asked to recall as many words as possible. Immediately after the recall of list B, the participants were again asked to recall list A (short recall, A6). Delayed recall of list A was measured 30 min after the immediate recall (long recall, A7) with no other verbal memory tests administered in this interval. Directly after long recall, A7, a recognition trial of 30 words containing the 15 words from list A and 15 distracter items were applied (10 distracter words were semantically or phonetically similar to the target words) [10-12].

Data were analyzed using SPSS. Qualitative data were described using numbers and percentages. Quantitative data were described using mean and SD. ANOVA test was used to determine the differences of each RAVLT score based on disease severity (CKD staging) and the presence of vascular risk factors. Pearson or Spearman correlation test was used to determine the correlation between each of RAVLT scores with GFR, age, and level of education.

Ethics

Ethical clearance was obtained from Faculty of Medicine Universitas Sumatera Utara/Haji Adam Malik General Hospital Ethical Committee number 549/TGL/KEPK FK USU-RSUP HAM/2018.

Statistical Analysis

The demographic data were presented as mean or frequency, as appropriate. The RAVLT scores were expressed as mean ± standard deviation. The statistical differences of cognitive scores based on CKD severity and vascular risk factors were performed using ANOVA. Pearson's correlation analysis was performed to determine between RAVLT scores and GFR, age, and educational level. The results were considered significant at $p<0.05$. Statistical analysis was performed with a computerized program.

RESULTS

There were 50 CKD patients included in this study, consisting of 33 males (66%) and 17 females (34%). The mean age of the patients was 49.76 ± 12.28 years old, the mean duration of CKD was 34.10 ± 33.72 months, and mean GFR was 20.84 ± 20.30 mL/min/1.73 m2. Most of the patients had more than 12 years of education (44 patients; 88%), had a history of hypertension (33 patients; 66%), and were at stage V CKD (25 patients; 50%) (Table 1).

Table 1 Characteristics data of the subjects

Characteristics	Frequency (N=50)	Percentage (%)
Gender		
Male	33	66
Female	17	34
Age (years), Mean ± SD	49.76 ± 12.28	-
Educational Level		
Junior high school	6	12
Senior high school	27	54
University	17	34
Risk Factors		
Hypertension	24	48
Nephrolithiasis	11	22
Hypertension and Diabetes Mellitus	9	18
Nephrolithiasis and Diabetes Mellitus	3	6
Diabetes Mellitus	2	4
Glomerulonephritis	1	2
Stage of CKD		
Stage III	11	22
Stage IV	14	28
Stage V	25	50
Duration of CKD, months, mean ± SD	34.10 ± 33.72	-
GFR, mean ± SD	20.84 ± 20.30	-
RAVLT Scores, mean ± SD, range		

A1	4.16 ± 2.17 (1-8)	
A2	5.08 ± 1.65 (2-8)	
A3	6.5 ± 1.32 (3-9)	
A4	7.28 ± 1.83 (2-11)	
A5	7.76 ± 1.94 (4-13)	
A6	5.54 ± 2.08 (2-11)	
A7	4.38 ± 1.65 (2-8)	
B	4.34 ± 1.89 (1-9)	
Recog A	11.34 ± 3.12 (6-15)	
Recog B	8.5 ± 3.43 (1-14)	
Sum	30.86 ± 7.29 (14-48)	

There were significant differences in each of the RAVLT scores based on the severity of CKD. Lower scores of RAVLT were found in patients with more severe CKD (Table 2).

Table 2 Differences of RAVLT scores based on the severity of CKD; ANOVA

RAVLT Scores, Mean ± SD	CKD Stage III	CKD Stage IV	CKD Stage V	p-value
A1	6.27 ± 2.19	4.5 ± 1.99	3.04 ± 1.42	<0.001
A2	6.55 ± 1.63	5.57 ± 1.45	4.16 ± 1.14	<0.001
A3	7.55 ± 1.03	6.21 ± 1.42	6.20 ± 1.19	0.01
A4	8.55 ± 1.57	7.00 ± 2.11	6.88 ± 1.56	0.03
A5	9.18 ± 1.72	8.07 ± 2.20	6.96 ± 1.48	0.003
A6	6.73 ± 2.41	6.14 ± 2.28	4.68 ± 1.40	0.008
A7	5.45 ± 1.86	4.86 ± 1.83	3.64 ± 1.03	0.003
B	6.00 ± 2.40	4.50 ± 1.87	3.52 ± 1.05	0.001
Recog A	14.18 ± 0.98	13.93 ± 1.43	8.64 ± 1.80	<0.001
Recog B	12.36 ± 0.81	10.36 ± 3.05	5.76 ± 1.42	<0.001
Sum	38.09 ± 6.18	31.36 ± 8.21	27.4 ± 4.41	<0.001

There was also a significant correlation between GFR and each of the RAVLT scores, and no significant correlation between GFR and age or education, except for A6 and Recognition A that were significantly correlated with the level of education (Table 3).

Table 3 Correlation between RAVLT scores and GFR, age and education; Pearson correlation test

RAVLT Scores	GFR		Age		Educational Level	
	r-value	p-value	r-value	p-value	r-value	p-value
A1	0.597	<0.001	-0.001	0.95	0.218	0.128
A2	0.496	<0.001	-0.006	0.56	0.213	0.138
A3	0.33	0.019	-0.061	0.67	0.184	0.202
A4	0.339	0.016	-0.176	0.22	0.072	0.62
A5	0.376	0.007	-0.213	0.13	0.14	0.332
A6	0.417	0.003	-0.274	0.05	0.449	0.001

A7	0.452	0.001	-0.118	0.41	0.377	0.007
B	0.562	0.001	0.107	0.46	0.175	0.224
Recog A	0.615	<0.001	0.072	0.62	0.306	0.031
Recog B	0.648	<0.001	-0.101	0.48	0.204	0.155
Sum	0.526	<0.001	-0.113	0.43	0.186	0.196

To assess the potential contribution of vascular risk factors to cognitive impairment, we analyzed the differences of each RAVLT score based on the presence of vascular risk factors and found no significant differences in the scores (Table 4).

Table 4 Differences of RAVLT scores based on the presence of vascular risk factors; ANOVA

RAVLT Scores, Mean ± SD	Hypertension (24)	Diabetes Mellitus (5)	Hypertension and DM (9)	No risk factor (12)	p-value
A1	3.75 ± 2.23	6.00 ± 1.22	4.33 ± 2.69	4.08 ± 1.67	0.212
A2	4.75 ± 1.77	6.20 ± 0.83	5.44 ± 2.07	5.00 ± 1.20	0.299
A3	6.38 ± 1.31	6.60 ± 1.14	6.67 ± 2.07	6.58 ± 0.99	0.938
A4	7.08 ± 1.84	7.00 ± 1.58	7.33 ± 2.64	7.75 ± 1.21	0.766
A5	8.04 ± 2.11	8.00 ± 1.00	7.00 ± 2.29	7.67 ± 1.61	0.589
A6	5.63 ± 2.37	5.60 ± 1.94	5.33 ± 1.50	5.50 ± 2.11	0.988
A7	4.29 ± 1.73	5.80 ± 1.09	3.67 ± 1.73	4.50 ± 1.38	0.136
B	3.79 ± 1.86	5.20 ± 1.30	5.11 ± 2.42	4.50 ± 1.50	0.202
Recog A	11.21 ± 3.28	14.00 ± 1.00	12.11 ± 2.52	7.33 ± 3.05	0.078
Recog B	8.21 ± 3.85	10.20 ± 2.05	9.89 ± 2.84	7.33 ± 3.05	0.237
Sum	30.17 ± 7.52	33.80 ± 4.91	30.78 ± 10.35	31.08 ± 5.16	0.801

DISCUSSION

This study included 50 CKD patients with 66% male patients, mean age was 49.76 ± 12.28 years, mean duration of CKD was 34.10 ± 33.72 months, and mean eGFR was 20.84 ± 20.30 mL/min/1.73 m2. The mean age of our patients was similar to the study from a previous study that reported the mean age of their subjects was 47.13 ± 14.28 years [5]. This demographic finding is slightly different from the CRIC (Chronic Renal Insufficiency Cohort) study, which found the mean age of the sample was 57.7 ± 11.0 years and the mean eGFR was 45.0 ± 16.9 mL/min/1.73 m2 [4]. Another study also found higher mean age which was 54.68 ± 15.19 years [6]. This difference might be caused by the fact that we included patients with various CKD causes, such as glomerulonephritis that is more commonly found in younger patients. The lower eGFR in our study can be explained by the fact that most of the patients (50%) were in stage 5, hence had lower eGFR.

Cognitive impairment commonly occurs in CKD patients especially in advanced stages [1-3]. Our study found a significant association between disease severity, as measured by the eGFR, and cognitive function. Each of the RAVLT scores was significantly lower in the more severe stage of CKD. Several previous studies have suggested a link between CKD and cognitive impairment. A previous study comparing cognitive function between 30 CKD patients with 30 HD patients and 30 controls found that the mean executive function, attention, memory, and total MOCA scores were significantly lower in HD and CKD patients in comparison with the control group [5]. One study found 76.76% of CKD patients had lower-than-expected cognitive scores, suggesting the presence of cognitive impairment [6]. A study in 3034 participants with CKD with cognitive function assessment with the Modified Mini-Mental State Exam (3MS) at baseline and then 2 and 4 years after baseline found that more advanced stages of CKD were associated with an increased risk for cognitive impairment with Odds Ratio (OR) 1.32 (95% CI 1.03 to 1.69) and OR 2.43 (95% CI

1.38 to 4.29) for eGFR 45 to 59 ml/min per 1.73 m2 and <45 ml/min per 1.73 m2, respectively, adjusted for case-mix, baseline 3MS scores, and other potential confounders [13].

Our study did not find a significant association between cognitive function and demographic factors, such as age and educational levels that could affect cognition. This was also stated in a previous study that found an association between CKD and increased risk for cognitive impairment in the elderly that cannot be fully explained by other well-established risk factors including age and level of education. Our finding is different from one study that found that individuals with CKD who were older and had less education presented greater cognitive impairment [6].

The cause of cognitive impairment in CKD is multifactorial, including vascular, degenerative, toxins, and others. The vascular hypothesis is the most widely accepted in explaining the association between CKD and CI. The brain and the kidneys have many common anatomic and vasoregulatory features; they are low resistance end organs exposed to high-volume blood flow and thus are susceptible to vascular damage. Additionally, the prevalence of traditional vascular risk factors, such as arterial hypertension, is higher in patients with CKD than in the general population. This might explain the association between CKD and cerebrovascular disease because the latter plays the largest role in the pathogenesis of cognitive impairment in CKD patients [1-3,13,14]. The meta-analysis also showed that the incidence of cognitive impairment in CKD patients with hypertension or diabetes was higher compared with CKD alone (CKD with hypertension vs. CKD alone, OR=1.33, 95% CI: 1.26 to 1.53; CKD with diabetes vs. CKD alone, OR=1.39, 95% CI, 1.16 to 1.53) [3].

Although the prevalence of hypertension and diabetes mellitus in our study was high (66% and 28% respectively), we did not find significant differences in cognitive function based on the presence of these vascular risk factors. This was in line with the finding from a study in 3034 participants that CKD is associated with an increased risk for cognitive impairment in the elderly that was independent of hypertension, diabetes mellitus, heart failure, and lipid profile [12].

Our finding suggests that cognitive impairment in CKD patients might not be fully explained by the presence or directly influence by vascular or demographic risk factors and support the hypothesis that the cognitive impairment might be directly related to the toxic and metabolic effect of kidney damage [1,8,13,14].

The contribution of cerebral vascular lesions to cognitive impairment in CKD patients is also supported by the pattern of cognitive disorders; the prominent impairment of executive functions and psychomotor speed. However, the results of a neuropathologic study indicate that patients with small-vessel cerebrovascular disease present broader cognitive impairment, which can also include memory deficits [1,3,14]. In a study of 24 CKD and 27 HD patients, MCI occurred in 76% of the group and HD patients showed a higher prevalence of MCI compared to CKD patients (89% vs. 63%) with a preponderance (>70%) of cases across both groups classified as non-amnestic MCI [15].

We used RAVLT to assess cognitive function in our study to assess mainly memory function and found lower scores in a more advanced stage of CKD showing greater memory impairment. This was in line with one study in 80 HD patients that also demonstrated that end-stage HD patients who were under HD for a long time had significantly lower scores in the memory and attention tests [7].

Jones, et al. conducted a study to assess memory impairment in End-Stage Renal Disease (ESRD) patients in 2 experiments in which the stimulus words were presented visually and auditory. Participants were tested on conceptual or perceptual memory tasks, with retrieval being either explicit or implicit. Compared with healthy controls, ESRD patients were impaired when the memory required conceptual but not when it required perceptual processing, regardless of whether the retrieval was explicit or implicit. They concluded that the type of processing required by the task (conceptual vs. perceptual) was more important than the type of retrieval (explicit vs. implicit) in memory failures in ESRD patients, perhaps because temporal brain regions are more susceptible to the effects of the illness than are posterior regions [16].

The memory impairment in our study still needed to be elaborated in further study, to determine the factors affecting the progression and other related factors, especially with a cohort prospective study. Sacre, et al. studied 4,128 individuals to determine whether kidney damage (indicated by albuminuria) or kidney dysfunction predict future (12-year) cognitive function independently of their shared risk factors and found that albuminuria predicted worse memory function at 12 years follow-up, whereas its effect on processing speed was driven largely by differences in cardiovascular risk [17]. In a well-defined cohort in 120 CKD patients receiving state-of-the-art therapy, cognitive performance did not decrease over 2 years. Their data emphasize the aspect of risk factor control, suggesting that dedicated medical care might prevent cognitive decline in CKD patients [18].

Findings from our study suggest the importance of assessment of cognitive function in CKD patients irrespective of their hemodialysis status. Early detection of cognitive impairment in this group of patients is important because it becomes one modifiable factor that could contribute to the quality of life.

CONCLUSION

The severity of kidney damage as reflected by eGFR is associated with verbal-auditory memory function, independent of other vascular risk factors and demographic characteristics.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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