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Predictors of Cognitive Dysfunction among Patients with Moderate to Severe Chronic Kidney Disease

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Predictors of Cognitive Dysfunction among Patients with Moderate to Severe Chronic Kidney Disease

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Abstract
Cognitive dysfunction including dementia is a common complication of chronic kidney disease (CKD) that has just been recently appreciated. It has negative outcomes in the management of patients with CKD. This study explored the possible biochemical and clinical features of patients with CKD that can predict the occurrence of cognitive impairment in patients with moderate to severe CKD. We evaluate patients with stages 3-5 CKD for the occurrence and predictors of cognitive impairment. Multiple areas of cognitive function were tested in this single-center study using Community Screening Interview for Dementia (CSID) and Trial-Making Test A (TMTA)/Trial-Making Test B (TMTB). Cognitive impairment was correlated with patients' routine biochemical, hematological, and selected clinical parameters. We observed a negative correlation between cognitive impairment and patient's serum calcium ($r = 0.240$; $p = 0.033$) and estimated Glomerular filtration rate (eGFR) ($r = 0.379$; $p = 0.0006$). Therefore, eGFR is an accurate predictor of cognitive dysfunction in patients with moderate to severe CKD. Early evaluation of cognitive function in CKD is indeed advised for optimal outcome in the management of patients with CKD.

Keywords: Community screening interview for dementia; Trial-making test; Cognitive impairment; Chronic kidney disease.

1. INTRODUCTION

Cognitive impairment is frequently reported in CKD, and the degree of impairment could just be mild cognitive decline or frank dementia. Indeed, several studies have reported end-stage renal disease as a predisposing factor for dementia [1, 2]. This high burden is said to be poorly recognized by nephrologists who are the primary physicians caring for patients with CKD [3]. The high burden of cognitive decline in patients with CKD has only been recently recognized [4, 5]. Murray observed that up to 70% of hemodialysis patients aged 55 years and above have moderate to severe cognitive impairment [6]. Khatri *et al.* [7] prospectively studying a cohort of multiethnic stroke-free patients with CKD observed that CKD correlated with cognitive decline even in patients with mildly impaired renal function. Early diagnosis and prompt treatment to retard the progress of cognitive decline in patients with CKD is very important, as poor cognitive function has been associated with a greater risk of death in dialysis patients, poor compliance to treatment, and increased occurrence of cerebrovascular disease and longer hospital stay [3, 8-10]. Apart from being a significant contributor to mortality, it is a key determinant of the quality of life because the patient's decision making and adherence to both pharmacological and nonpharmacological management principles depend on a sound cognitive state [11].

The exact pathophysiological mechanism for cognitive deterioration in patients with CKD is not yet determined [12-14]. Several factors have been associated with the development of cognitive impairment in the setting of CKD including elevated cytokines, serum lipids [11], and clinical factors such as asterixis, hypertension, anemia, nausea, and vomiting. Electrolyte derangement and uremic acidosis are also thought to play an important role. A positive correlation has also been established between cognitive impairment in CKD and serum creatinine, urea, uric acid, and serum calcium levels [15]. Reports have also highlighted the high incidence of cerebral ischemia in the etiopathogenesis of cognitive impairment in CKD, and this is thought to be due to the shared microvascular risk factors between CKD and brain ischemia [16]. Systematic cardiovascular risk factors directly predict poorer executive function [17]. It has been observed that in early stages of chronic renal disease, high levels of albuminuria, a surrogate for systemic vascular disease, is associated with worsening executive function and abnormal magnetic resonance imaging (MRI) findings [18-20].

Other factors implicated in the causation of cognitive decline in CKD includes hyperhomocysteinemia, vitamin B12 deficiency, oxidative stress, immune-inflammatory factors, and endothelial dysfunction [21-23]. Among the clinical symptoms and signs of patients with CKD, anemia has been documented as a risk factor for cognitive decline, and a reversal of anemia in patients with CKD resulted in improvement in cognitive function [24, 25]. Silva *et al.* [26] found that the routine dialysis process had no harmful effect on cognition and memory.

Very few studies in Nigeria and indeed sub-Saharan Africa as a whole have attempted to establish any biochemical and hematological parameters as surrogate markers of neurocognitive dysfunction. Hence, the need for a study to provide tools that can be used in our setting with a limited number of neurologists to predict the existence of cognitive dysfunction in patients with CKD.

2. METHODS

This was a prospective case-control single-center study involving patients with moderate to severe CKD. The study excluded patients with a history of stroke, seizure disorder, psychiatric illness, traumatic brain injury, or visual/auditory impairment. Controls were selected from healthy patient's relatives, hospital staff, and medical students without any history suggestive of renal disease. A semistructured questionnaire was used to evaluate consenting patients with eGFR equal to or less than 59 ml/min/1.73 m^2 to obtain their demographic and clinical information. Cognitive function was screened using the CSID, TMTA, and TMTB. These test instruments had been used for assessing cognitive impairment, and satisfactory validity and reliability have been reported [27-30]. A total of 79 patients were selected by convenient sampling method based on order of presentation at the outpatient clinic, renal dialysis unit, or renal ward. In the earlier publication [28] from this research, we reported the prevalence of cognitive impairment based on CSID and both TMTA and TMTB were 51.9, 53.2, and 40%, respectively. Due to the difficulties encountered by our semiliterate patients in completing the TMTB, we discontinued its use when further evaluation was carried out to establish the predictive value of laboratory and clinical parameters on their cognitive performance.

Cognitive function was correlated with patients' serum potassium, bicarbonate, chloride, urea, creatinine, uric acid, phosphate, calcium, and eGFR. Cognitive function was also correlated with their blood pressure and packed cell volume. Blood samples for postdialysis patients were obtained within 48 h after dialysis, while the most recent biochemical and hematological results were used for the nondialyzed patients. An equal number of controls were matched for age, sex, and educational attainment.

The Research and Ethical Committee of the institution where the study was carried out gave ethical approval for this study. The protocol followed was in keeping with the high ethical standards of this committee. All patients and controls gave either informed write or verbal consent after the study was carefully explained to them before they were enrolled in the study.

The CSID was pretested in a sample of the general population and normative cutoff points obtained for each of the cognitive domains. Subjects with scores 2-standard deviation below the cutoff were regarded as being cognitively impaired. The standardized score for TMTA from previous studies [28] was used to determine the patients who had cognitive impairment. Total scores on the two neuropsychological tests were matched with hematological, biochemical, and selected clinical parameters to determine the association between cognitive scores and their laboratory values.

Subjects had their blood pressure measured using a mercury sphygmomanometer after they had rested for about 5 min in a sitting position. The measurement of blood pressure for each patient was rechecked three times and the average calculated. Serum electrolytes including sodium, potassium, bicarbonate, phosphate, and calcium, urea, creatinine, and uric acid were measured using Hitachi® automated machine under standardized conditions. The packed cell volume (PCV) was determined by centrifuging heparinized blood in a microhematocrit tube and the value read with a microhematocrit reader.

Creatinine clearance was estimated using the Cockcroft and Gault formula for predicting glomerular filtration (GFR) [31, 32]. Only patients with stage 3-5 CKD based on the National Kidney Foundation classification of CKD were included in the study [33]. We excluded patients in delirium and frank encephalopathy.

Statistical Package for the Social Sciences (SPSS) was the software package used in analyzing the data generated from this study. Results are presented in proses, tables, and illustrations. Correlation analysis for biochemical factors and CKD was done using both the Pearson correlation for parametric data and Spearman's ranked correlation nonparametric data. The difference in frequencies was analyzed using chi-square test among the categorical variables, while the difference between means was tested using the Student's *t*-test. Significant level was set at *p*-value less than 0.05.

3. RESULTS

3.1. Demographic Characteristics of Subjects

Seventy-nine consenting subjects aged 17-72 years with stages 3-5 CKD and an equal number of controls matched for educational status, age, and sex formed subjects for this study. We had more male patients than females, with a total number of males being 52 (65.8%), and the females were 27 (34.2%). One patient each was aged less than 20 years and more than 70 years respectively. The number of the other patients by their age was 25 (31.6%) 41-50 years; 21 (25.3%) 21-30 years; and 18 (21.4%) 31-40 years. The mean age of patients was 39.7 years (SD = 11.0), while that of the control was 39.0 years (SD = 11.9).

3.2. Mean Blood Pressures, Biochemical Parameters and eGFR of Patients with CKD

The mean systolic and diastolic blood pressures, biochemical parameters, and eGFR are given in Table 1. The mean systolic blood pressure was 145.0 (26.61) mmHg, and the mean diastolic blood pressure was 88.5 (16.77) mmHg. The other mean values of biochemical parameters for the patients with CKD are given in Table 1.

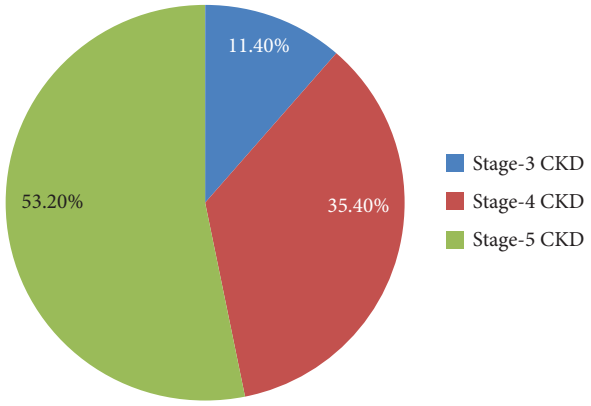
3.3. Percentage Distribution of the Patients with CKD According to the Stage of CKD

Figure 1 is a pie chart showing the distribution of the patients according to their stage of CKD. The greater proportion of the patients, 42 (53.2%), had stage-5 CKD, while 28 (35.4%) and nine (11.4%) were in stage-4 and stage-3 CKD, respectively.

Table 1: Mean blood pressures, biochemical parameters, and eGFR of patients with CKD.

Variables	Mean (SD)
Systolic blood pressure	145.0 (26.61)
Diastolic blood pressure	88.5 (16.77)
Serum sodium	130.1 (20.75)
Serum potassium	4.6 (2.12)
Serum bicarbonate	17.5 (3.63)
Serum chloride	100.5 (12.24)
Serum urea	137.4 (69.07)
Serum creatinine	7.7 (5.93)
eGFR	15.9 (10.31)
Serum uric acid	10.0 (10.70)
Serum phosphate	8.1 (16.93)
Serum calcium	7.6 (1.44)
Packed cell volume	23.1 (5.45)

Figure 1: Percentage distribution of the patients with CKD according to the disease stage of CKD.



3.4. Correlation of CSID Scores in CKD Patients with Biochemical Parameters, Packed Cell Volume and Blood Pressure

Table 2 shows the correlation of cognitive impairment in CKD patients with their biochemical parameters (serum urea, creatinine, sodium, potassium, phosphate, uric acid, and calcium), PCV, and blood pressure. Weak negative correlations were found for urea ($r = -0.192$, $p = 0.091$), creatinine ($r = -0.218$, $p = 0.054$), sodium ($r = -0.032$, $p = 0.778$), and PCV ($= -0.019$, $p = 0.0870$). There was no significant correlation between cognitive impairment and serum potassium ($r = 0.041$, $p = 0.718$), phosphate ($r = 0.027$, $p = 0.810$), uric acid ($r = 0.074$, $p = 0.515$), systolic blood pressure ($r = 0.004$, $p = 0.971$), or diastolic blood pressure ($r = 0.140$, $p = 0.220$). Significant correlation was obtained for serum calcium ($r = 0.240$; $p = 0.033$) and eGFR ($r = 0.379$; $p = 0.0006$).

3.5. Correlation of TMTA Time in CKD Patients with Biochemical Parameters, Packed Cell Volume and Blood Pressure

Correlational analysis of the performance of patients with CKD on TMTA shows that there was no significant correlation between cognitive impairment in the patients with CKD and their serum urea, creatinine, potassium, phosphate, calcium, sodium, uric acid, PCV, eGFR, systolic blood pressure, or diastolic blood pressure. These are shown in Table 3.

3.6. Multivariate Linear Regression Analysis of Accurate Predictors of Cognitive Impairment using CSID

The serum calcium and eGFR were parameters with a strong linear relationship with cognitive impairment after adjusted for confounders using multivariate linear regression technique. The results are presented in Table 4. Serum calcium has no predictive value ($\beta = -0.159$, $p = 0.132$), while eGFR has a strong predictive value ($\beta = 0.378$, $p \leq 0.001$).

Table 2: Correlation of TMTA time of CKD patients with biochemical parameters, packed cell volume and blood pressure.

Variables	Cognitive impairment (n = 79) *Correlation coefficient	p-value
Phosphate	0.027	0.810
Uric acid	0.074	0.515
Calcium	0.240	0.033**
PCV	0.019	0.870
eGFR	0.379	0.0006**
SBP	0.004	0.971
DBP	0.140	0.220

DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; PCV: packed cell volume; SBP: systolic blood pressure.
*Test statistic—Spearman's ranked correlation.
**Significant p-value.

Table 3: Correlation of TMTA time of CKD patients with biochemical parameters, packed cell volume and blood pressure.

Variables	Cognitive impairment (n = 79) *Correlation coefficient	p-value
Urea	0.164	0.149
Creatinine	0.134	0.237
Sodium	−0.023	0.884
Potassium	0.078	0.492
Phosphate	0.038	0.743
Uric acid	−0.084	0.465
Calcium	0.108	0.346
PCV	−0.017	0.885
eGFR	−0.201	0.076
SBP	−0.046	0.686
DBP	−0.047	0.680

DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; PCV: packed cell volume; SBP: systolic blood pressure.
*Test statistics—Spearman's ranked correlation.

Table 4: Multivariate linear regression analysis of accurate predictors of cognitive impairment using CSID.

Variable	Regression coefficient (β)	95% CI for β	p-value
Serum calcium	−0.159	0.1-0.350	<0.132
eGFR	0.378	−1.560-0.208	<0.001**

**Significant p-value.

4. DISCUSSION

4.1. Predictors of Cognitive Impairment in Patients with CKD

Previous studies had documented conflicting correlations between serum electrolytes, urea, creatinine, blood pressure, eGFR, and PCV with cognitive function in patients with CKD. These parameters are particularly helpful in determining the cognitive status of patients with CKD, where tools for detail assessment or trained personnel are not available. In this study, cognitive performances using TMTA did not demonstrate any statistically significant correlations between any of the above-mentioned variables with cognitive function in selected patients with CKD. But the CSID demonstrated a weak positive correlation between serum creatinine and cognitive impairment (r = 0.218; p = 0.054). There was a statistically significant positive correlation between cognitive impairment with serum calcium (r = 0.240; p = 0.033) and eGFR (r = 0.379; p = 0.0006). These findings are similar

to that documented by Ogunrin *et al*. [34]. They had documented a negative correlation between creatinine and cognitive parameters such as auditory time and visual reaction. Additionally, after multiple logistic analyses, they noted negative correlation between cognitive performance with creatinine, urea, and hypertension. Kurella *et al.* [35] found no association between global cognitive function or executive function and clinical factors such as PCV, serum calcium, albumin, cholesterol, parathyroid hormone, and aluminum. Murray *et al.* [36] on bivariate analysis observed that hemoglobin levels less than 11.0 g/dl was associated with cognitive impairment. This relationship between hemoglobin/PCV and cognitive function in CKD could not be reproduced in this study. As this is probably a common practice in this setting, most of the patients had blood transfusion before they were evaluated.

In keeping with the findings of this study, several studies have documented a significant correlation between renal function determined by eGFR or serum creatinine with cognitive function. In this study, we observed that as eGFR decreased, cognitive impairment increases. Among the 60 consecutive renal patients studied by Ogunrin *et al.* [15], creatinine level was observed as the most potent factor affecting the memory performances of subjects. Slinin *et al.* [37] in a study of community-dwelling men found an independent association between low eGFR and poorer cognitive performances on TMTB and Modified Minimental State Examination (3MS), and these findings also noted by Kurella *et al.* [35]. After a multivariate logistic regression analysis of accurate predictors of cognitive impairment using CSID, we noted a weak predictive value for serum calcium compared to that of eGFR, which is in keeping with findings from these studies.

5. CONCLUSION

Estimated glomerular filtration rate and the stages of CKD are the best predictors of cognitive impairment in patients with CKD.

5.1. Limitations of the Study

The inclusion of both predialyzed and dialyzed patients among the cases did not allow for a comparative study of the benefit of dialysis on cognitive function. Time constraints did not allow for a prospective study that would have followed the progression of cognitive deficit in patients with CKD as renal function decline and possible benefits of renal transplant in Nigerian Africans. Assessment of patients after dialysis, blood transfusion, and other treatment measures were initiated would have influenced the findings of this study. The estimation of eGFR from serum creatinine rather than being measured directly may give unduly high or low values in certain patients including the obese ones [38].

Author Contributions

Conceptualization of the study, literature search/review, data collection, and manuscript preparation: U.E. Williams. Conceptualization of study, review of initial draft and manuscript preparation: S.K. Oparah. Conceptualization of the study, data analysis, manuscript preparation and preparation of final manuscript: A. Soter.

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Conflict of Interest

The authors have no conflict of interest to declare.

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