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Cognitive Disorders in Patients with Chronic Kidney Disease

Mujeeb Ur Rehman, Shahneela Tabassum, Mohsin Qayyum, Muhammad Irfan, Syed Onaiz Anwar, Areesh Akbar

ABSTRACT

Objective: To asses and identify prevalence and severity of cognitive disorders through cognitive screening test in patients with Chronic Kidney Disease (CKD).

Study Design and Setting: This observational cross-sectional study was conducted in Nephrology Department at PNS Shifa hospital Karachi from February 01, 2025 to July 31, 2025.

Methodology: Total of 201 patients who either visited OPD or came in dialysis center were included in study. All adult patients with CKD, aged above 18 years, either gender, with or without comorbids were enrolled after informed consent both verbal and written. A set questionnaire was used for data collection, subsequently was analyzed by using SPSS version 25.

Results: Cognitive impairment (CI) has been found in 122 (60.69%) patients suffering from CKD while 79 (30.3%) were devoid of such presentation. Significant point of note among cognitively impaired persons was that greater proportion had mild form of disease, i-e: 79 (64.75%) otherwise 28 (22.9%) patients had revealed moderate form and 8 (6.5%) patients had severe form of cognitive disorder. It was also evident that moderate and severe form of CI were more pronounced in patients who were on maintenance hemodialysis.

Conclusion: CKD patients particularly those who are on maintenance hemodialysis are prone to suffer from cognitive disorders, an overlooked complication. It is necessary to make physicians/ Nephrologists aware of this complication so that all patients with CKD maybe screened for CI and early application of required therapy be initiated to curb further deterioration.

Key Words: Chronic Kidney Disease: Cognitive disorders: Cognitive Screening Test.

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INTRODUCTION

With a high global incidence and prevalence, chronic kidney disease (CKD) is a serious public health issue that can have costly treatments and poor results due to significant multi-systemic consequences. Kidney Disease: Improving Global Outcomes (KDIGO) defines CKD as abnormalities of the kidney's structure or function that have been present for more than three months and have an impact on health. The diagnosis is made based on the following criteria: Reduced GFR (60 mL/min/1.73 m2) or indications of renal injury (albuminuria, tubular problems, aberrant urine sediment, structural aberrations identified by histology or imaging techniques or history of kidney transplantation). The development of CKD consequences is mostly dependent on decreased GFR and increasing albuminuria. For this reason, the disease is categorized into five stages based on GFR, with risk levels being further sub-categorized depending on albuminuria levels.[1] Estimated GFR (eGFR) based stages of CKD are: (1) Stage 1 CKD: Mild kidney damage, eGFR 90 or higher, (2) Stage 2 CKD: Mild loss of kidney function, eGFR 60-89, (3) Stage 3a & 3b CKD: Mild to severe loss of kidney function, eGFR 30-59, (4) Stage 4 CKD: Severe loss of kidney function, eGFR 15-

29, (5) Stage 5 CKD: Kidney failure or close to failure, eGFR less than 15. CKD stages correlate with all-cause mortality, cardiovascular mortality, anemia, and bone mineral disorders.[2] Among other complications of CKD, cognitive impairment (CI) is more common as people age. One more thing of prime note here is that CI is also common in renal transplant patients which is an underappreciated yet clinically significant issue. It is currently not common practice to screen for CI following kidney transplantation.[3] Furthermore, early in CKD, CI can emerge even before GFR drops to <60 mL/min/1.73 m2.[4,] There are certain drugs that are used in CKD patients such as antidepressants, anticholinergics, opiates and benzodiazepines have been found to be associated with development of cognitive disorders.[5] Established prevalence of CI in CKD ranges from 10% to 40%.[6]

Neurocognitive disorders (NCD) were classified predominantly as acquired and progressive cognitive problems in the most recent edition of the Diagnostic and Statistical Manual of Mental problems.[7] One of the following six cognitive domains complex attention, executive function, language, learning and memory, perceptual motor and social cognition can be compromised by degradation. While a person with serious NCD (which includes dementia) has CI severe enough to limit social and/or occupational functioning, a person with moderate NCD (corresponding to the state typically labeled "mild CI") remains functionally independent.[8] After deliberation on correlation of CKD with CI, a systematic review and meta-analysis was carried out and it has been found that CKD possesses strong standing as an independent risk factor for development of CI.[9] It is probable that the pathophysiology is complex, combining aspects of neurodegenerative and vascular diseases. The risk factors and susceptibilities for CI seem to cluster in patients with CKD. These include renal-specific factors (uraemia, inflammation, intradialytic "cerebral stunning"), cardiometabolic risk factors (hypertension, diabetes, obesity, stroke), neuropsychiatric comorbidities (depression, sleep disorders), and lower cognitive reserve (aging, lower educational and occupational attainment).[10] CKD is a very debilitating condition for patients who ultimately ends up in a catastrophe and disastrous situations especially for those who are on maintenance hemodialysis. Such patients suffer multiple aspects of mental health problems, among whom cognitive impairment has significant importance in terms of stability of memory and other relevant parameters because these play vital role in maintaining quality of life of these patients. Unfavorable results, as well as monetary and social expenses, such as caregiver stress, are other stress factors for both patient and family that are linked to CI. Individuals with CKD who are receiving renal replacement therapy (RRT) may find cognitive screening beneficial. When CI is detected in CKD patients, it can be used to evaluate adherence to a CKD risk reduction strategy, find dementia reasons that may be reversible, adjust medication, educate the patient and caregiver and offer the right kind of support. Our study is aimed at ascertaining occurrence of CI and identifying its severity in correlation with duration and stages of CKD.

METHODOLOGY

This observational cross-sectional study was conducted in the department of Nephrology in PNS Shifa hospital at Karachi from 01 February 2025 to 31 July 2025. The Hospital Ethical Review Committee permission was obtained (IERC No. ERC/2024/Neph/121 dated 06-11-2024). The sample size was calculated by using WHO sample size calculator (Confidence level [CI]= 95%, expected precision rate 6%) with 25% reported prevalence (Prevalence ranges from 10% to 40%).[6] Non-probability sampling technique was used and 201 subjects were included and evaluated in this study.

Inclusion Criteria: All adult patients with CKD of age above 18 years, either gender, with or without comorbids and consent enrolled were included in study.

Exclusion Criteria: Individuals with any neurological or psychiatric disorder, difficulty in communication, unwilling to participate were excluded from study.

All subjects who met the eligibility requirements were enrolled after providing both written and verbal informed permission. A demographic information, clinical history and physical examination were carried out. CI was assessed by using MoCA (Montreal Cognitive Assessment) test that has significant sensitivity and specificity as compared to other bed-side test like MMSE. In a recently published study, Drew et al[11] compared the predictive ability of MMSE, 3MSE, MoCA, Trail Making Test (TMT) Part B, Mini-Cog Test and the Digit Symbol Substitution Test performance for identifying severe CI among patients with HD. The MoCA had the highest overall predictive ability for severe CI (AUC 0.81). The score of 21/30 patients had a sensitivity of 86% and specificity of 55% for severe impairment, with a negative predictive value of 91%. The principal investigator recorded proforma that is set according to inclusion criteria. All subjects were clinically evaluated by Neurologist and Nephrologist.

All statistical analysis was performed by using Statistical Packages for Social Science (SPSS) version 25. Frequencies and percentages were computed for nominal variables like gender, CI and CKD and its stages and mean/ standard deviation for quantitative variables like age, duration of CKD etc. Effect modifiers like age, gender and duration of CKD were addressed through stratification. Various Variables were assessed in correlation with severity of CI.

RESULTS

Analysis of data revealed astonishing results in comparison to international data results. Substantial proportion of CKD patients were found as sufferers from cognitive disorders but marked number of patients had mild form of disease. The mean age of patients was 52.32

+ 13.46 with commonly affected age group of 55 and 58 years followed by 47 and 38 years of age. Moderate and severe form of CI were found significantly affecting patients with age 55 years and above. As far as gender distribution is concerned, study was conducted upon 115 males and 86 females. Males are slightly more affected by cognitive disorder as compared to females. Evaluation of educational status of patients revealed significant number of patients having secondary and higher education. More patients who have had CKD for less than five years have made a substantial contribution to the research. Out of 201 patients, 104 were on maintenance hemodialysis while 97 were not on hemodialysis. Among non-hemodialysis patients, stage IV CKD was found more prevalent. Comorbids alongside CKD, either as cause or a consequence, Hypertension (HTN) was found as a more common contributory agent followed by hypertension and diabetes mellitus (HTN + DM) together. Diabetes Mellitus (DM) alone along with CKD has also major share but isolated CKD with no obvious cause was more evident (Table I). Patients with CKD had their CI evaluated using the Montreal Cognitive Assessment (MoCA) tool, which classified the disease's severity as mild, moderate and severe. It was discovered that the mild type was very prevalent in CKD patients, followed by the moderate and severe forms (Figure I). When patients were asked about quality of life lived by them, more than 50% patients expressed it as good followed by those with fair and very good. The good thing that came into notice during research was that 98% patients have their family support in background which is extremely necessary for such debilitating patients, even for their mental stability to go along such a catastrophic disease. CKD stage-wise correlation with severity of cognitive disorder in the light of MoCA scoring was critically analyzed among non-hemodialysis and hemodialysis patients that surfaced significant relationship between severity of cognition and each stage of CKD (Table II)

DISCUSSION

Among other complications of CKD, CI remained an overlooked complication in respective patients that likely and ultimately lead to memory issues in CKD patients in long run and leaves patient with a miserable life. It has been revealed in a study that elderly CKD patients with cardiovascular disease (CVD) risk factors are soft targets to develop marked CI.[12] Various studies have been conducted

Table - 1: Cognitive Impairment (CI) Impact in correlation with Demographic Variables in CKD patients

Variable	Total Number n=201 (%)	CI Impact n=122 (%)
Gender distribution		
Males	115 (57.2%)	67 (54.9%)
Females	86 (42.7%)	55 (45.1%)
Education Level		
No Education	37 (18.4%)	35 (28.6%)
Primary Education	28 (13.9%)	20 (16.3%)
Secondary Education	78 (38.8%)	47 (38.5%)
Higher Secondary	58 (28.8%)	20 (16.3%)
Comorbids		
CKD + HTN	85 (42.2%)	47 (38.5%)
CKD + HTN + DM	56 (27.8%)	31 (25.4%)
CKD	29 (14.4%)	26 (21.3%)
CKD + DM	23 (11.5%)	16 (13.1%)
Miscellaneous	8 (3.9%)	2 (1.6%)

Figure 1:Category-wise Prevalence of Cognitive Impairment (CI)

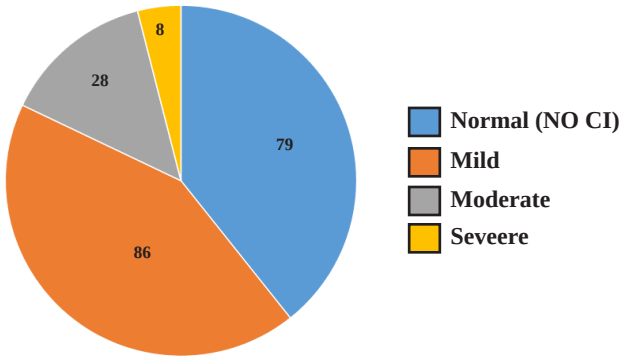

Table 2: CKD stage-wise correlation with severity of Cognitive Impairment (CI)

Parameter			MoCA Score				Total (n=201)
			Normal (>26)	Mild (18-26)	Moderate (10-17)	Severe (<10)	
CKD Stages	Non-Hemodialysis Patients	C1	2	2	0	0	4
		C2	2	0	0	0	2
		C3a	5	9	0	0	14
		C3b	7	3	0	0	10
		C4	25	19	9	2	55
		C5	2	6	4	0	12
	Hemodialysis Patients	C5D	36	47	15	6	104
	Total		79	86	28	8	201

to surface prevalence of CI in different stages of CKD. Some researchers conducted such kind of study on non-hemodialysis patients, on the other hand some have carried out same work on hemodialysis patients. Our study has included patients of both ends to ascertain occurrence as well as severity of CI in CKD patients. World-wide, different results have been highlighted regarding prevalence of CI in CKD patients ranging from 10% to 40%.[6] Our study has achieved results somewhat higher than this reported prevalence so a critical analysis of literature is required for comparison. Pepin M et al[13] analyzed 3033 patients with CKD stage 3-5 using MMSE tool to ascertain CI and found that 393 (13%) patients had MMSE score of <24. Furthermore, when compared to individuals with an MMSE score of 24 or higher, those with a score below 24 had significantly greater levels of parathyroid hormone, lower levels of hemoglobin, albumin and eGFR and were more likely to be prone to cardiovascular (CV) risk factors and CV comorbidities. Both before and after controlling for age, sex, education level, cardiovascular risk factors, cardiovascular disease, and depression, the eGFR was positively correlated with the MMSE score. For every 10 mL/min/1.73 m2 increase in eGFR, the MMSE score increased by 0.24 (0.15–0.33: P <.001) and 0.14 (0.04–0.23: P =.006). In multivariate analysis, age, female sex, lower educational attainment, diabetes, obesity, cerebrovascular illness, atrial fibrillation, and CES-D-10 score were additional risk variables that were substantially linked to a lower MMSE score. In a cross-sectional study, 433 patients with CKD stage 3-5 were assessed for depression, cognitive and nutritional disorders through Beck Depression Inventory (BDI), the Mini Mental State Examination (MMSE) and the Mini Nutritional Assessment (MNA), respectively. Results for all three parameters revealed (1) the frequency of malnutrition was 50.1%, depression was 40.9%, and CI was 20.3%. (2) patients without CI are more likely to experience depression than those with normal nutritional status or CI: patients with stage 3–5 are at risk of malnutrition or undernutrition.[14] Pépin M et al[15] carried out a study in vice versa manner and advised that renal functions must be assessed in patients having CI as the disorder is 3 to 4 times more common in CKD especially in patients with End Stage Kidney Disease (ESKD).

S et al[16] conducted study on 101 patients with CKD with respect to assessment of prevalence and severity of CI and its relationship with blood cystatin C levels. Of the 28 patients with CKD in stages C1–C4, 18 (64.2%) had mild CI and 10 (35.7%) had moderate CI: scores that corresponded to dementia were not obtained. Nine (30.0%) of the 30 patients undergoing hemodialysis (C5) had mild CI, 18 (60.0%) had moderate CI and 2 (6.6%) had dementia symptoms. Of the 43 patients who received a kidney transplant, 3 (7.0%) had no CI, 33 (76.6%) had mild CI, and 7 (16.2%) had moderate CI. A control cohort study conducted in North Wales UK for assessment of CI that comprised of 92 CKD patients and 143 age and gender matched controls. Assessment was done at baseline and at 36 months by using neurophysiological assessment and Diagnostic and Statistical Manual of Mental Disorders V.5 (DSM-5). The DSM-5 criteria and follow-up neuropsychological evaluation of the cognitively normal patients and controls showed that 20/143 (13.9%) of the control group and 25/92 (27%) of the CKD developed an NCD. After controlling for age and sex, the CKD cohort's risk of developing an NCD was double that of the controls. Incidence rates for an NCD were 10.5 in the CKD cohort and 5.1 in the control group. There was no correlation seen between cognitive function and CKD stage.[17] Recently, a cohort study was conducted by Huang Z et al[18] that analyzed 4261 CKD patients to assess relationship between kidney function and CI. CKD severity was standardized with eGFR and urine protein creatinine ratio (UPCR) while using the modified mini-mental status assessment (3MS), Buschke Selective Reminding test, Trail Making Test A (TMTA) and Trail Making Test B (TMTB), global cognition and the domains of verbal memory, attention/processing speed and executive function were evaluated over an extended period of time respectively. Very significant comparative results were yielded and it was found that patients with stage C4/C5 CKD (eGFR<30) were 36% more likely to experience CI than those with stage C2 CKD (eGFR=60-89). Moreover, upon comparison of patients with UPCR >500 mg/g to patients with UPCR <150 mg/g, 26% had increased risk of CI. Furthermore, declining eGFR was significantly related to impairment in global cognition while there was strong relationship between increasing UPCR and impairment in executive function and attention.

Alexander Z et al[19] worked on multiple domains of CI, especially cognition function and sex differences in cognition in adults with CKD. The study included 105 individuals with CKD stage C3b and C4 (eGFR= 15-44 ml/min/1.73 m^2). Cognitive and motor functions like memory, dexterity, attention and executive function were assessed by using National Institutes of Health Toolbox Cognition Battery. In comparison to the reference population from the National Institutes of Health Toolbox, participants' average scores on all cognitive domain tests and the dexterity test were below the 50th percentile. They were also below the 50th percentile in terms of total cognition. Fluid cognition scores were considerably poorer in those with stage C4 CKD than in those with stage C3b CKD. Compared to male participants, female CKD patients showed higher average crystallized cognition scores and significantly outperformed male participants on the episodic memory and dexterity tests (dominant and nondominant pegboard tests). Zhang J et al[20] carried out a systematic review and meta-analysis of 50 studies searched from the Web of Science, Embase and PubMed. 29,289 CKD patients were analyzed with respect

to CI. Overall, 40% of people had CI. CKD patients from Africa had a comparatively higher pooled prevalence of CI (58%), followed by those from Asia (44%) and America (37%). The most prevalent symptoms seemed to be executive dysfunction and attention problems. Compared to individuals without dialysis (32%) and those who had received a kidney transplant (26%), the prevalence of CI was higher in patients receiving hemodialysis (53%) and peritoneal dialysis (39%). Furthermore, CKD patients may be more susceptible to CI if they are older, have diabetes or hypertension. In another systematic review and meta-analysis, Berger I et al[21] analyzed 44 studies involving 51,575 participants with CKD. In this study, various aspects of CI were assessed and it was found that CKD patients fared worse than the control group in terms of language, concept formulation and reasoning, executive function, memory and orientation and attention while In contrast, perception, motor praxis and construction were unaffected. Another evidenced review study suggested that the risk of CI is higher in patients with CKD. Recent published research data have demonstrated that CKD is linked to cognitive function (e.g. incident cognitive episodes), notwithstanding some disagreements. While attention and executive function problems are common in CKD patients, it is important to remember that other cognitive abilities, like memory, might remain intact. Vascular injury, hereditary variables, the buildup of uremic toxins, disruption of the blood–brain barrier, malfunction of the lymphatic system and alterations in the gut–brain axis are some of the main processes that have been recently described. When it comes to interpreting biomarkers of CI and, particularly, Alzheimer disease hallmarks, kidney function is increasingly thought to be a game changer.[22] El Belbessi AS et al conducted study in Egyptian population, included 30 patients with CKD without hemodialysis (group I), 30 patients who were undergoing hemodialysis (group II) and 30 sex and age matched controls (group III). The study assessed various parameters of cognitive impairment like executive function, attention and memory. It was found that executive function was more deteriorated in group II as compared to group I and furthermore same was more lower in groups I and II as compared to group III. Mean attention score was much lower in gropus I and II in comparison to group III while memory score was found extremely at lower side in group I and II when compared to group III. Overall, it was evident that MoCA score was markedly affected by deranged renal functions.[23] Another study was conducted in CKD patients in which neurological, psychological and cognitive disorders were assessed in terms of contribution to the morbidity, mortality and poor quality of life of these patients. Renal function, inflammatory and mineral metabolism indicators, electroencephalogram (EEG), psychological (MMPI-2, Sat P) and cognitive assessments (neuropsychological tests, NPZ5) were among the clinical, laboratory and instrumental investigations performed. All assessed parameters were found markedly deranged in CKD patients in correlation with declining renal functions. Moreover, cognitive tests (NPZ5) revealed significant difference among CKD patients and health controls.[24] As far as study limitations are concerned, our study has limitation of being a single center study so for further addition of results, further research work may be carried out at various centers of country or even it can be conducted as multi-center in one or multiple cities.

CONCLUSION

It is noteworthy that CI in CKD patients has not been given clinical importance in terms of assessment and subsequent management that leads patients to land in disastrous and miserable life and concerns are more grave when patients develop dementia. It is therefore of extreme importance that physicians/ Nephrologists must be aware of this complication and make it necessary to ascertain it alongside other complications so that this might be addressed well in time and further preventive strategies may be adopted to curb its deterioration in best interest of patient health.

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Shahneela Tabassum Conception/ Study design, Acquisition of data, Manuscript drafting, Given final approval of version to be published
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