



Original Research Article

A study on cognitive status in chronic kidney patients on dialysis

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ABSTRACT

Introduction: Cognitive impairment is common in uremia and diabetes mellitus. Cognitive impairment affects the activities of daily living in most of chronic kidney disease patients. As per literature, cognitive impairment is less common in non-diabetic than diabetic of chronic kidney disease. There is sparse data regarding incidence and pattern of cognitive impairment in chronic kidney disease patients with regard to mode of dialysis either hemodialysis or peritoneal dialysis.

Aim and Objectives: Aim : To estimate the pattern and prevalence of cognitive impairment in chronic kidney patients on dialysis.

Objectives: 1) To compare the pattern of cognitive impairment between hemodialysis and peritoneal dialysis patients.

2) To study the impact of glycemic status on cognitive impairment in chronic kidney disease patients.

Material and Methods: A prospective cross-sectional observational study conducted at MGM hospital/Kakatiya medical college during May 2016 through December 2017 on chronic dialysis patients who fulfilled the inclusion and exclusion criteria. All the cases were subjected to Cognitive assessment by applying ACE- R adapted to Telugu speaking people.

Results: 1) In our study the prevalence of dementia and mild cognitive impairment (MCI) were 47% & 21% respectively.

2) Among 47 dementia patients 31(66%) were diabetic, 25(53%) were undergoing hemodialysis and 22(46%) were undergoing peritoneal dialysis.

3) The pattern of cognitive decline was memory (89%), language (78%), visuospatial (68%), attention (57%), and fluency (57%).

Conclusions: Present study highlighted not only the burden of cognitive decline in the dialysis patients where hemodialysis and presence of diabetic were significantly associated with dementia.

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1. Introduction

Cognitive impairment has been defined as a deficit in at least two aspects of cognitive function.¹ The key areas of cognition are attention, memory, language, visuospatial skills, and frontal/executive functions.^{2,3} When activities of daily living are not affected, cognitive impairment is said to be mild. Dementia, on the other hand, affects activities of daily living and behavior.^{1,4}

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More than 80% of the approximately 3,50,000 hemodialysis patients in the United States have hypertension, about one half have diabetes,⁵ and almost all have elevated homocysteine levels.^{6,7} It is unknown; however, how commonly cognitive impairment occurs in dialysis patients. Dialysis patients are at increased risk of cognitive impairment due to their older age, high prevalence of cardiovascular risk factors stroke, uremia, inflammation and multiple metabolic disturbances. The burden of cognitive impairment will likely grow as the dialysis population ages and the prevalence of diabetes and vascular disease increases; up to 70% of hemodialysis patients aged 55 years

and older are moderately to severely cognitively impaired.² Whether cognitive impairment is as common in peritoneal dialysis patients is unclear. The age and co-morbidity of dialysis patients has increased dramatically. Twenty years ago, almost all patients were younger than 65 years and few had diabetes.⁸

Today, approximately half of new patients are older than 65 years and approximately one third are diabetic.⁵ Therefore, cognitive impairment in chronic kidney disease (CKD) increases the burden on medical and non medical care givers. It may hinder adherence to the complex regimens often prescribed to CKD patients, increase the risk of adverse events, and impair informed decision making.⁹ Moreover, cognitive impairment in CKD is independently associated with an increased mortality and dialysis withdrawal.^{10,11}

2. Material and Methods

A prospective cross-sectional observational study conducted on chronic dialysis patients at KAKATIYA MEDICAL COLLEGE, Warangal from January 2018 to December 2018 on chronic dialysis patients who fulfilled the inclusion and exclusion criteria.

2.1. Inclusion criteria

1. Patients aged above 18 years and who are diagnosed to have CKD with Serum creatinine more than 2 mg/dl.
2. Patients who are the registered for regular dialysis and follow up were included.
3. Patients who are diagnosed to have Type2 Diabetes mellitus as per ADA guidelines 2011.

2.2. Exclusion criteria

1. Patients with history of vitamin B12 deficiency.
2. Patients with manifest cerebro-vascular accident and psychiatric disorder.
3. Patients with diagnosed malignancy, visual, auditory impairment, delirium, hepatic disorder and alcohol ingestion or dyselectrolytemia.
4. Patients on drugs known to cause cognitive impairment.
5. Patients with steroid use > 10mg/day, accelerated HTN, and severe anemia (HB < 7 %).

Total number of subjects enrolled in the study (N=135) out of which 35 subjects were excluded (15-previous history of stroke, 8-severe anemia, 7-using medication causing sedation, 5-electrolyte derangements). Remaining 100 cases were divided 50 each into hemodialysis cohort (N=50) and peritoneal dialysis group (N=50), each group has equal number of diabetics and non- diabetics in their groups.

Demographic data including age, sex, and level of education were obtained using the self-administered

questionnaires. Clinical information including dry weight, duration of illness, and clinical features were obtained from their medical records. A general physical examination and detailed neurological examination were carried out in all subjects. Blood samples were taken within two days on assessment of cognitive function.

Cognitive assessment was done by applying ACE-R adapted to Telugu speaking people which was validated to both literate and illiterates with a satisfactory validity and reliability reported in several Telugu speaking populations. ACE-R is a comprehensive and one of the most studied cognitive assessment scoring systems developed in NIMS Hyderabad and used extensively in many Indian languages with fairly similar results when compared to English versions.

ACE-R is the recent modified version which was adapted to Telugu speaking people with sensitivity value of 84% and specificity value of 98% with total score 82 and below used for the diagnosis of dementia; with a sensitivity value of 86, specificity value of 89 for the total score between 83 and 88 for the diagnosis of mild cognitive impairment. Cognitive assessment in peritoneal dialysis cohort was assessed anytime during the hospital stay or at the time of follow up visit whereas in hemodialysis cohort assessed after finishing the dialysis sessions.

2.3. Statistical analysis

Data was analyzed using SPSS version 20. All the continuous variables are expressed as mean \pm SD. Prevalence of cognitive impairment is expressed as percentage. Fischer's Exact t-test was applied to compare nominal data between the groups and p value less than 0.05 will be considered significant. The relation of ACE-III scores with hemodialysis and peritoneal dialysis in both diabetics and non-diabetics were assessed by the Pearson correlation coefficient.

2.4. Regulatory approvals

Written informed consent was obtained from all study participants. The study was approved by the Institutional Ethical Committee of Kakatiya medical college, Warangal. Vide reference No: KIEC/KMC/NCT/NIS/2017 Dated 27/12/2017.

3. Results

The mean age of patients in the present study was 51.9 \pm 14.7 years, 47%, 33% and 19% of them belong to the 40-59, 60-79 and 18-39 years age range group respectively. Among which Males were 71(71%) and 29(29%) were females with male to female ratio of 2.4:1. The literacy rate of the study population was 74%. Out of 100 patients, 74(74%) were literates and 26(26%) were illiterates.

Primary causes of CKD were diabetes (50%), chronic glomerular nephritis (28%), chronic interstitial nephritis (14%), and obstructive nephropathy (8%). The mean duration of CKD, and diabetes mellitus were 5.5 ± 3.2 , 15.9 ± 8.1 years respectively. The median (IQR) duration of hypertension was 5(4-10) years. The mean duration hemodialysis and peritoneal dialysis were 4.4 ± 2.5 and 2 ± 1.3 years respectively. Among the 100 subjects who participated in the study the biochemical parameters are shown in Table 1. Median, interquartile range (IQR) of serum creatinine value is 7.4(5.8-8.9) and blood urea is 78.5(61.8-110).

In our study, prevalence of dementia in the 100 subjects was 47% and prevalence of mild cognitive impairment (MCI) was 21%. Patients with dementia were significantly older than the MCI and no-dementia group ($P < 0.0001$). The mean \pm SD for ACE-R scores was 82.2 ± 9.7 . Number of patients whose ACE-R scores are ≤ 82 , 83-88 and > 88 are 47(47%), 21(21%) and 32(32%) respectively. Among 47 dementia patients 31(66%) were diabetic, 25(53%) were undergoing hemodialysis and 22(46%) were undergoing peritoneal dialysis.

Comparison of demographic and clinical characteristics of CKD patients among dementia, MCI and non-dementia groups are shown in Table 2. The clinical characteristics are homogeneously distributed among the three groups and the difference was not statistically significant.

Pattern of cognitive impairment among dementia, MCI and non-dementia groups are shown in Figure 1. Among 47 patients with dementia the domain wise impairment in the decreasing order of frequency was as follows, 42(89.3%) had memory function impairment, 37(78.7%) had language function impairment, 32(68%) had visuospatial function impairment, 29(61.7%) had attention deficit and 27(57.4%) had fluency function impairment.

Among the both dialysis groups, the peritoneal dialysis cohort were having lesser duration of CKD and dialysis procedure which was statistically significant when compared to hemodialysis cohort ($P = 0.005$ and < 0.001). The overall ACE-R scores for hemodialysis and peritoneal dialysis cohorts were 82.0 ± 8.8 and 82.3 ± 10.7 respectively ($P = 0.419$). Though there was no significant difference between the mean ACE-R scores among the dialysis groups the incidence of dementia was more in hemodialysis group than peritoneal dialysis group (50% vs 44%). The incidence of dementia and MCI among hemodialysis were 25(50%) and 22(44%) and in peritoneal dialysis group 9(18%) and 12(24%).

Language domain impairment was more in hemodialysis cohort than peritoneal dialysis cohort which was statistically significant ($P = 0.04$), whereas the remaining domains was not statistically significant between two cohorts in relation to mode of dialysis Figure 2.

CKD patients with diabetes had mean ACE-R scores among the three groups of dementia, MCI, non-dementia was 73.5 ± 6.8 , 84.9 ± 1.8 and 90.7 ± 2.8 respectively which was statistically significant ($P < 0.0001$). Out of 47 patients in dementia group 31(66%) were diabetic and 16(34%) were non diabetic, 25(53%) were undergoing hemodialysis and 22(46%) were undergoing peritoneal dialysis, with mean \pm SD ACE-R scores of peritoneal dialysis group (72.8 ± 8) less than the hemodialysis group (74.5 ± 6.8), however which was statistically not significant ($P = 0.79$).

Diabetic status has negative impact on cognitive functions with respect to all demographic characteristics. The incidence of dementia and MCI among diabetic CKD and non-diabetic CKD groups was 31(62%) and 16(32%); 8(16%) and 13(26%) respectively, which was statistically significant ($p < 0.0001$). statistically significant ($p < 0.0001$).

Memory, language and, visuospatial domains were more significantly impaired in diabetic CKD cohort than non-diabetic CKD cohort ($P = 0.0001$, 0.008, 0.02). However, diabetic status does not show statistically significant effect on the attention and fluency domain ($P = 0.61$, 0.06).

Diabetic status has a positive impact on the attention domain in the hemodialysis cohort when compared to non-diabetics ($P = 0.049$). Remaining domains were worse in the diabetic cohort.

In multiple logistic regression analysis, older age ($p < 0.0001$), males ($p < 0.0001$), education ≤ 3 years ($p < 0.0001$), hemodialysis ($p = 0.041$), and diabetes mellitus ($p = 0.003$) were significant and independent predictors of dementia.

On adjusted odd's, hemodialysis and presence of diabetes was associated with a 1.28 and 3.5 fold increased risk of dementia when compared to peritoneal dialysis group (odd's ratio 1, CI (0.57-1.74), $P = 0.568$) and non-diabetic group (odd's ratio 0.613, CI (0.35-1.08), $P < 0.418$).

Table 1: Biochemical parameters of CKD

Biochemical parameter	Median (IQR)
Hemoglobin	10.46(9.8 - 11.5) gm%;
Hb A1c	7.2(6.2 -7.8) %
Serum creatinine	7.4(5.8-8.9) mg%
Serum urea	78.5(61.8-110) mg%
Total proteins	6.4 (5.8 - 7.2) gm%;
Serum albumin	3.7(3.2-4.3) gm%;
serum cholesterol	174(146 -199) mg%
Serum triglycerides	127(92 - 172) mg%
Serum LDL	96(76 - 123) mg%
Serum HDL	40(34 - 45) mg%
Serum calcium	8.7(8.3 - 9.2) mg%
Serum phosphorous	4.3(3.7 -5.0) mg%
Serum PTH	232.5(106-383) pg/ml
Serum vitamin D	36.5(25.8-48) ng/ml.

Table 2: clinical & demographic characters of CKD among three cognitive states.

	Dementia (n=47)	MCI (n=21)	Non dementia (n=32)	P-value
Age*	55.9 ± 14	55.3 ± 12.3	43.5 ± 14.1	<0.0001
Age range#				
18-39 years	5(10.6%)	1(4.7%)	13(40.6%)	0.003
40-59 years	21(44.7%)	11(52.4%)	15(46.9%)	0.19
60-79 years	20(42.6%)	9(42.9%)	4(12.5%)	0.002
≥ 80 years	1(2.1%)	0	0	–
Gender#				
Male	32(68.1%)	15(71.4%)	24(75%)	0.047
Female	15(31.9%)	6(28.6%)	8(25%)	0.09
Literacy#				
Literates	31(66.1%)	13(61.9%)	30(93.8%)	0.02
Illiterates	16(33.9%)	8(38.1%)	2(6.2%)	0.003
Level of education#				
≤3 years	14(45.1%)	3(23%)	1(3.3%)	<0.0001
4-12 years	9(29%)	3(23%)	10(33.3%)	0.14
Graduation	8(25.8%)	7(53.8%)	13(43.3%)	0.33
Post-graduation	0	0	6(20%)	–
Total educated	31	13	30	
CKD	5.3 ± 2.9	4.6 ± 2.6	6.1 ± 3.9	0.38
HTN	6.8 ± 1.5	7.6 ± 5.3	7.1 ± 4.2	0.88
DM	16.5 ± 8.6	13.8 ± 6	15.1 ± 8.1	0.67
Hemodialysis	4.3 ± 2.2	4.1 ± 2.5	4.8 ± 3.2	0.75
Peritoneal dialysis	1.82 ± 0.6	2.1 ± 1.1	2.25 ± 1.3	0.94
Serum creatinine#	7 ± 2.3	8.2 ± 2.3	7.9 ± 2.4	0.08
Blood urea#	85.6 ± 12.	7.95 ± 22.8	99 ± 28.6	0.42
ACE-R scores				
Over all*	73.7 ± 6.8	85.2 ± 1.8	92.6 ± 2.8	<0.0001
Diabetes status#				
Present	73.5 ± 6.8(31)	84.9 ± 1.8(8)	90.7 ± 2.8(11)	<0.0001
Absent	74.0 ± 6.5(16)	85.4 ± 2(13)	93.5 ± 2.7(21)	0.58
Mode of dialysis#				
Hemodialysis	74.5 ± 6.8(25)	84.8 ± 2(9)	91.9 ± 2.3(16)	0.46
Peritoneal dialysis	72.8 ± 8(22)	85.6 ± 1.7(12)	93.3 ± 3.2(16)	0.47

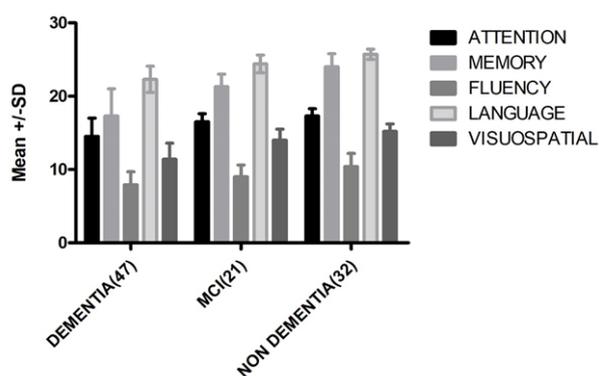


Fig. 1: Pattern of cognitive impairment

4. Discussion

The burden of cognitive impairment will likely grow as the dialysis population ages and the prevalence of diabetes

and vascular disease increases. Up to 70% of hemodialysis patients ages 55 years and older have moderate to severe cognitive impairment, yet it is largely undiagnosed. Dialysis patients are at increased risk of cognitive impairment due to their older age, high prevalence of cardiovascular risk factors,^{2,12,13} stroke,¹⁴ uremia, inflammation,¹⁵ and multiple metabolic disturbances.¹⁶

The concept of mild cognitive impairment, which describes cognitive impairment beyond that of normal ageing but in contrast to dementia, does not interfere notably with activities of daily life,¹⁷ permits timely identification of patients at high risk of developing dementia and implies the potential of a larger therapeutic window for modifiable risk factors.¹⁸

Previous studies reported that the prevalence of moderate to severe cognitive impairment is more than double in hemodialysis patients compared with the general population. Whether cognitive impairment is as common

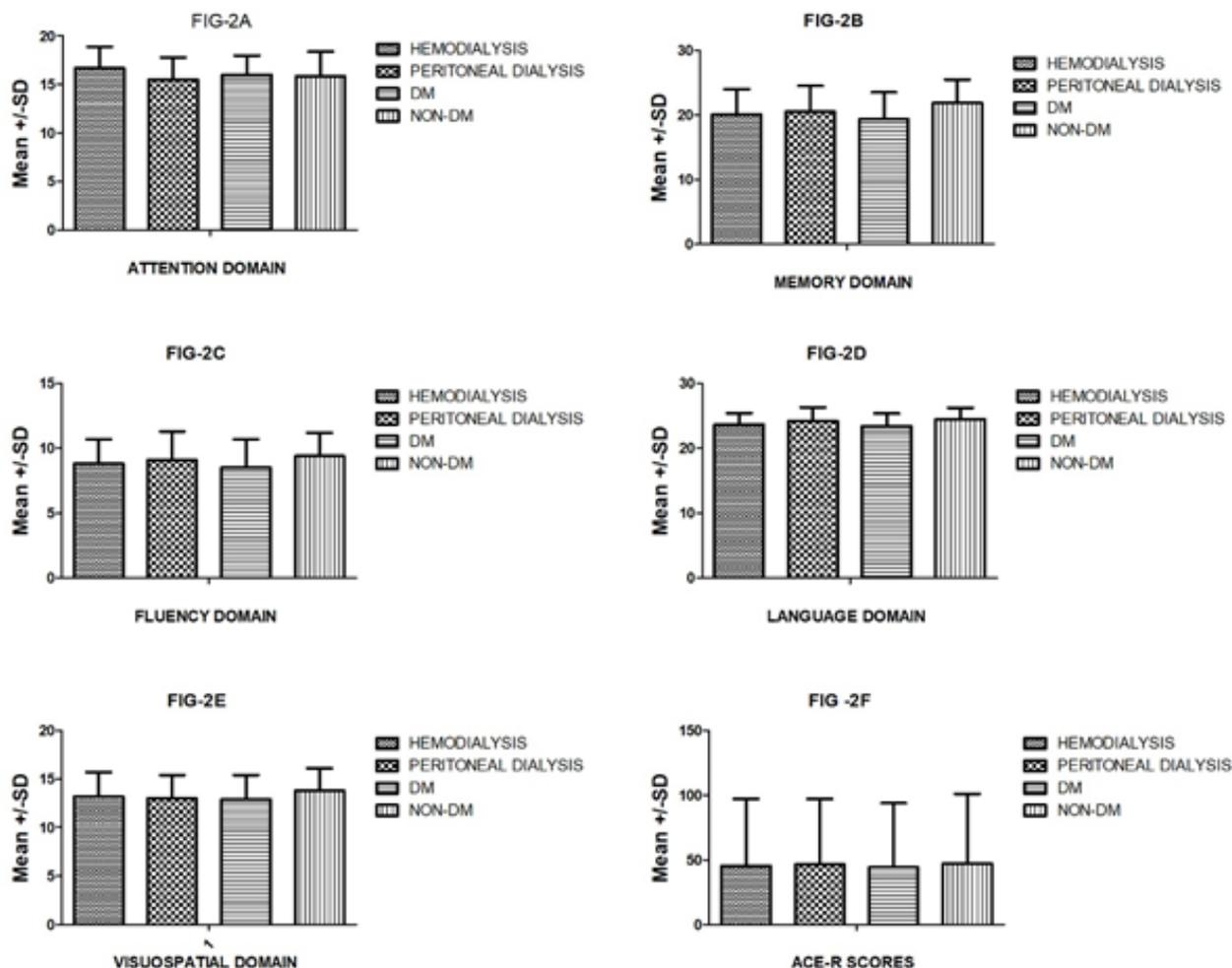


Fig. 2: Cognitive Domains and ACE-R scores among Groups

in peritoneal dialysis patients is unclear.¹⁹

Most of the previous studies were community based using the more conservative tools like MMSE and MOCA. As, MMSE test will not correctly identify the impairment of executive functions and attention, may not be comprehensive. Hence, we used ACE-R, a global cognitive assessment tool which was validated to Telugu language and previously used for assessment of post stroke dementia at various centres.²⁰ Further cognitive assessment by using the ACE-R is much more comprehensive and global.

Both the hemodialysis and peritoneal dialysis CKD patients have almost same risk factors for vascular dementia like diabetes, hypertension, dyslipidemia and old age. However, it is not reported whether the mode of chronic dialysis has any significant effect of the cognitive impairment when the other confounding factors were adjusted. With this background to fill this information gap the present study was conducted to estimate the burden of cognitive impairment in our tertiary care center in south

India.

Our results were comparable with previous studies^{19–23} except mean age was slightly lower when compared to western studies and level of education. This confirms facts that, the mean age of chronic kidney disease was a decade earlier and the level of education is less among some Asian countries like India, which was probably attributable to increased prevalence of traditional risk factors and poor socioeconomic conditions.

4.1. Risk factors

Our risk factors were comparable with the published studies as the majority has the traditional risk factors like hypertension, diabetes and cardiovascular disease in the decreasing order. However, alcoholism was more prevalent in the present study which can be attributable to the lack of awareness of complications and illiteracy as compared to the western countries.

4.2. Primary cause of CKD

In the present study, most common cause of CKD was diabetes 50% and chronic glomerulonephritis 28% which were comparable to the previously published study by Daniel et al²¹ where diabetes 35.5% and chronic glomerulonephritis 19% were the most common cause of CKD.

4.3. Biochemical parameters

Comparison of biochemical parameters with other published studies suggest that most of the biochemical parameters were on par with the other published studies except for the elevated mean creatinine value, which indicates that the severity of CKD is more in the present study.

4.4. Burden of cognitive decline

Comparison of burden of cognitive decline with other published studies particularly Daniel et al,²¹ in 200 individuals out of which 125 belong to cardiovascular CVD and 75 belong to no CVD groups, found that the individuals with CVD performed 0.50 standard deviation worse ($P=0.001$) on tests assessing processing speed/executive function. This indicates the fact that individuals with history of previous cardiovascular diseases are more prone for vascular dementia where the early involvement of executive function impairment is seen.

Liang Feng et al,²² found that, there was a significant difference between the base line and follow up MMSE and instrumental activities of daily living (IADL) scores of pre dialysis CKD groups when compared to non -CKD control group. This indicates that CKD with the background of traditional risk factors has significant influence on the cognitive decline.

Pankaj et al,²³ assessed the event related potentials (ERP) among pre dialysis groups and compared with age matched controls, concluded that latencies of the evoked potentials were directly proportional to the stage of CKD and it was statistically significant, however they did not correlate these findings with clinical cognitive scoring.

The incidence of dementia among 100 participants in the current study was 47% which was slightly more than the previously published study by Paramjit Kalirao et al,¹⁹ where the incidence of severe cognitive impairment is 37% in hemodialysis patients and 31% in peritoneal dialysis patients.

This difference can be attributable to the fact that most of the patients in the Asian countries, like in the present study were having lesser duration of education, more incidence of traditional risk factors and more duration of CKD when compared to the developed countries of western world.

4.5. Cognitive impairment and mode of dialysis

Very few studies were published which analyzed the effect of mode of dialysis on cognitive impairment Our study showed higher incidence of dementia in hemodialysis dialysis cohort compared to peritoneal dialysis cohort, with an odds of 1.28 for dementia in hemodialysis patients when compared to peritoneal dialysis patients. However, it may be attributed to the significant longer duration of CKD in the hemodialysis (6.34 ± 2.8 years) when compared to the peritoneal dialysis cohort (4.7 ± 2.6 years), ($P=0.005$) and significant longer duration of dialysis in hemodialysis cohort (4.4 ± 2.6 years) when compared to peritoneal dialysis cohort (2.0 ± 1.3), ($P<0.001$).

Except for the language domain which is affected more in hemodialysis patients ($P=0.04$), there was no difference in the pattern of impairment based on the mode of dialysis.

Similar to our study, Paramjit Kalirao et al,¹⁹ showed that moderate to severe cognitive impairment was more common in hemodialysis patients than in peritoneal dialysis patients (36.1% moderate and 37.3% severe cognitive impairment in hemodialysis patients; 35.3% moderate and 31.4 severe cognitive impairment in peritoneal dialysis patients), although the peritoneal dialysis cohort was on average 11 years younger than the hemodialysis cohort. In the same study the odds of cognitive impairment in hemodialysis was 3.16 compared to peritoneal dialysis which was 2.58.

Another study by Tilki HE et al,²⁴ showed that the MMSE score was higher in continuous ambulatory peritoneal dialysis patients compared with hemodialysis patients.

4.6. Cognitive impairment and diabetes

Similar to our study where the odds ratio (OR) for dementia in diabetic cohort was 2.13 (95% CI, 1.17-3.85), USRDS (united states renal data system) data showed an OR of 1.8 (95% CI, 1.14-2.79) for dementia in diabetic cohort. This indicates the fact that individuals with history of previous cardiovascular diseases and diabetes mellitus are more prone for vascular dementia.

In a review by Caa JJ et al and Englund et al, it was hypothesized that disruption of the blood-brain barrier due to microvascular disease may play an analogous role, with damaged vascular endothelial tight junctions causing leakage of protein, potentially contributing to white matter disease and pre-amyloid oligomers^{25,26} in brain similar to proteinuria in chronic renal failure.

4.7. Pattern of cognitive impairment

The cognitive impairment with the background of chronic renal failure most often secondary to the microvascular injury unlike the neurodegeneration pattern because of amyloid protein accumulation in the Alzheimer's disease

(AD).

Usually, the cognitive domains affected early in CKD patients are attention and fluency, depicting the vascular etiology as the major pathogenic cause. However, in our cohort of CKD patients around 30% had memory impairment which denotes the co-existence of degenerative pathology in these patients probably Alzheimer's.

Similar to our findings, Paramjit Kalirao et al,¹⁹ found that, compared with hemodialysis patients, more peritoneal dialysis patients had moderate to severe memory impairment (58% vs 51%), but fewer had impaired executive function (33% vs 50%).

4.8. Factors associated with cognitive impairment

In a study by Paramjit Kalirao et al,¹⁹ the odds of dementia for PD cohort was 2.58 (odd's ratio 2.58, CI (1.02-6.537), and HD was 3.16 (odd's ratio 3.16, CI (1.91-5.24).

In a study by Liang Feng et al⁸⁵, 14% increment in odds of cognitive decline per 10 mL/min/1.73 m² decrease in eGFR (odds ratio = 1.94, 95% confidence interval = 1.23 – 3.05; P = .004 for CKD vs non-CKD). Very few previously published studies have analyzed the odds for dementia apart from our study.

5. Limitations

1. To depict to role of CKD in cognitive decline the same cohort should have been followed with serial cognitive assessments from CKD stage I to ESRD instead single point assessment was done in this study.
2. There were no neuro imaging correlation to the dementia along with ACE-R scores and stroke can go unrecognized sometimes and incidentally detected on the imaging which might have contributed to vascular dementia.

6. Conclusions

1. Present study highlighted the burden of cognitive decline in the dialysis patients where hemodialysis and presence of diabetes were significantly associated with dementia.
2. In addition, memory and language domains were also affected along with fluency, attention and visuospatial domains which depict the role of mixed type of vascular cognitive impairment.

7. Conflict of Interest

None

8. Source of Funding

None

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