Research Article

Factors Affecting Cognitive Impairment in Chronic Kidney Disease Patients

Muhammad Shahbaz Pervaiz,[1] Muhammad Anees,[2] Irfan Elahi,[3] Noman Butt,[4] Saba Tauqer[5]

[1-5]*Department of Nephrology, Mayo Hospital, Lahore*

Abstract

Background: Cognitive Impairment (CI) is frequently observed in patients with Chronic Kidney Disease (CKD). There are many factors associated with CI in CKD patients in international studies but no study has been done previously in Pakistan on this important issue.

Objective: To determine factors affecting Cognitive Impairment in Chronic Kidney Disease patients.

Methods: This observational study was carried out in Nephrology Department of Mayo Hospital, Lahore (January 2023 to March 2023). All CKD patients, regardless of cause, were included while patients on renal replacement therapy (RRT) were excluded. The Mini-Mental State Examination (MMSE) tool was employed to evaluate cognitive function.

Results: A total of 100 patients were enrolled. The average age of the patients was 50.44±12.58 years, with diabetes mellitus (DM) being the leading cause of CKD in 53(53.0%) patients. CI was identified in 61(61.0%) patients while mild and moderate CI was found in 34 (34%) and 27 (27 %) respectively. Female gender (RR=1.40, 95%CI=1.01-193, p=0.042), low estimated glomerular filtration rate (eGFR) (RR=1.92, 95% CI=1.27-2.91, p=0.002), anemia (RR=1.23, 95% CI=1.01-1.50, p=0.003) and lower educational qualifications (RR= 3.39, 95% CI=1.65-6.94, p=<0.001) were found significant factors of CI. Increasing age was associated with increased CI severity (r=-0.110, p=0.278) while eGFR has positive correlation with CI score (r=0.271,p=0.006) .

Conclusion: CI was frequently prevalent among patients with CKD. Female gender, low eGFR, anemia and low level of education were independent predictors of CI in CKD patients. Advancing age has negative correlation while GFR has positive correlation with CI score.

Received: 22-01-2024 | **Revision:** 25-05-2024 | **Accepted:** 12-08-2024

Corresponding Author | Dr. Muhammad Shahbaz Pervaiz, Senior Registrar, Department of Nephology, Mayo Hospital, Lahore

Email: drshahbazpervaiz@yahoo.com

Keywords | Cognitive impairment, Chronic Kidney disease, Mini Mental State Examination, Anaemia.

Introduction

Cognition refers to the mental process of gaining knowledge and comprehension through thoughts, experiences, and sensory input.[1] It includes a number of advanced intellectual processes and functions, including language, focus, recall, understanding, problem-solving, strategizing, logical thinking, evaluation, sensory interpretation, and grasping concepts. Cognitive impairment (CI) is term used to describe acquired deficit in any of these cognition processes.[1] Chronic Kidney Disease (CKD), defined by gradual and permanent decline in kidneys functions, may be considered as an important potential risk factor for developing CI.[2] The prevalence of CI among CKD patients ranges from 17% to 87%, depending on the stage of the disease.[3,4] The

Production and Hosting by KEMU

https://doi.org/10.21649/akemu.v30i3.5612

2079-7192/

likelihood of CI rises by 11% with each 10 ml/min/ 1.73 m² decrease in Glomerular Filtration Rate (GFR).[5] The cause of CI among CKD patients is multifactorial. The traditional risk factors for development of CI in CKD patients are older age, being female , illiteracy, ethnicity, Diabetes Mellitus (DM), Hypertension (HTN), and Cerebrovascular Diseases (CVD).[6,7,8] Additional risk factors are uremic toxins, anaemia, calcium –phosphate disturbances, endothelial damage, chronic inflammation, exaggerated cytokine release and oxidative stress which play a vital role in cognitive decline.[2,9] Cognitive decline has been associated with non-adherence to medication, poorer somatic & psychosocial well-being, higher morbidity and mortality.[10] There is a lack of local research on CI in CKD patients, highlighting a significant gap in understanding this crucial and often neglected fact of kidney diseases. The study aimed to identify the factors influencing Cognition in patients with CKD.

Methods

This observational, analytical study was carried out at Mayo Hospital Nephrology Department in Lahore during 1st January, 2023 to 31th March, 2023. After getting ethical approval from King Edward Medical University Institutional Review Board (IRB) on 17th December 2022, (IRB No.1063/ RC/ KEMU), Lahore, all patients of CKD with age ≥ 18 years were included in the study. However patients with pregnancy, Liver impairments, hypertensive encephalopathy, history of neurological diseases, psychosis substance abuse and who didn't consented to participate were excluded. After obtaining written informed consent from those who were eligible for inclusion, CI was assessed using Urdu Variant of Mini Mental State Examination (MMSE) scale.[11] This scale consists of questions assessing positioning (10 points), enrollment (3 points), focus, computation (5 points), recollection (3 points), speech, and implementation (9 points). Based on the cognitive status score, patients were categorized as having normal (≥24), mild (19-23), moderate (10-18), or severe (≤ 9) CI. Demographics (patient's age, gender, education, marital and socioeconomic statuses) and Clinical information, including the cause and duration of CKD, was collected using a standardized questionnaire. Blood samples were obtained and analyzed for hematological (hemoglobin) and biochemical markers (renal function tests and serum electrolytes) and urine complete analysis was done. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate the estimated glomerular filtration rate (eGFR). CKD was staged as I (≥ 90), II (60-89), IIIa (45-59), IIIb (30-44), IV (15-29), and V (<15) based on the eGFR in ml/min/1.73m^2.[12] A hemoglobin level below 13 g/dL in males and below 12 g/dL in females was considered indicative of anemia.[13]

The entered data were evaluated by using Med Calc Ver -20.009 and IBM-SPSS Ver-23. While Categorical variables were summarized using frequencies and percentages, continuous variables were presented as mean ± standard deviation. To identify significant predictors of CI, relative risk (RR) with a 95% confidence interval was calculated. Pearson correlation coefficients were used to examine the linear relationship between the CI score and other continuous variables. A p-value less than 0.05 was considered statistically significant.

Results

Initially, 150 participants were recruited, however only 100 patients fulfilled inclusion criteria and enrolled in study. Most participants (71%, n=71) were over 45 years old, with an average age of 50.44 ± 12.58 years. A significant number of patients were male (51%, n=51), not employed (84%, n=84), and had less than a 10th-grade education (78%, n=78).DM was most common cause of CKD in 53(53%) and the mean Haemoglobin level was 10.24±2.26 g/dl.CI was prevalent in 61% (n=61) of the patients, with most cases being mild (34%, n=34) and moderate (27%, n=27).Female gender (RR=1.40, 95%CI=1.01-193, p=0.042), low eGFR (RR=1.92, 95% CI=1.27-2.91, p=0.002), anaemia (RR=1.23, 95% CI=1.01-1.50, p=0.003) and low educational attainment (RR=3.39, 95% CI=1.65-6.94, p<0.001) was found to be a strong predictor of CI (Table-I). Significant positive relationship (r=0.271, p=0.006.) of CI score was found with eGFR (Figure 1 and 2) and negative association (r=-0.110,p=0.278) was found between CI score and age of patients (Figure 3).

Table 1: *Factors Associated with Cognitive Impairment (n=100)*

Sr#	Parameters	Cognitive Status		RR	95% CI	p-value
		Impaired (n=61) %	Normal (n=39) %			
1	Gender					
	1. Male	26 (42.6)	25 (64.1)	1.40	1.01-1.93	0.042
	2. Female	35 (57.4)	14 (35.9)			
2	Education (grades)					
	1. < 10th	55 (90.2)	18 (46.2)	3.39	1.65-6.74	<0.001
	2. ≥ 10th	6 (9.8)	21(53.8)			
3	Marital Status					
	1. Married	52 (85.2)	32 (82.1)	1.10	0.69-1.74	0.685
	2. Unmarried	9 (14.8)	7 (17.9)			
4	eGFR(ml/min)					
	1. ≤ 30	47 (77.0)	22(56.4)	1.92	1.27-2.91	0.002
	2. > 30	14(23.0)	17 (43.6)			
5	Cause of ESRD					
	1. Diabetic	30 (49.2)	23(59.0)	0.85	0.62-1.17	0.337
	2. Non-Diabetic	31 (50.8)	16 (41.0)			
6	Anaemia					
	1. Yes	56 (91.8)	29 (74.4)	1.23	1.01-1.50	0.038
	2. No	5 (8.2)	10 (25.6)			
7	Urinary Proteins					
	1. Yes	49 (80.3)	25 (64.1)	1.43	0.91-2.24	0.11
	2. No	12 (19.7)	14 (35.9)			

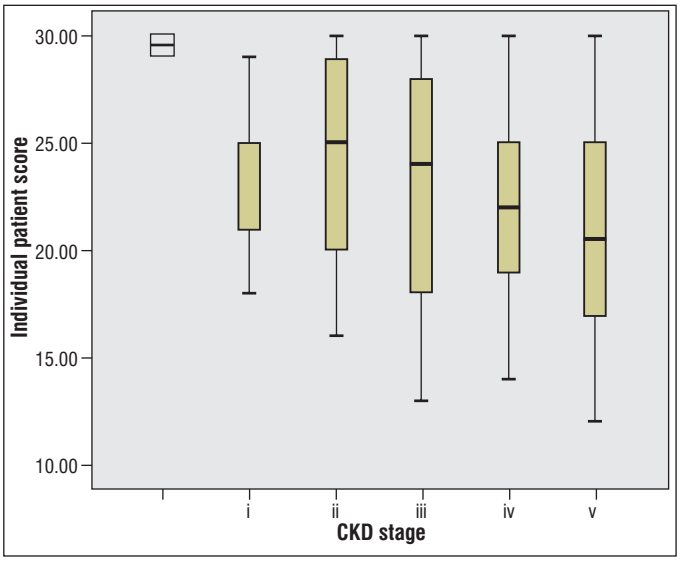

Figure 1: *Box plot demonstrating relationship among CI score and CKD stage.*

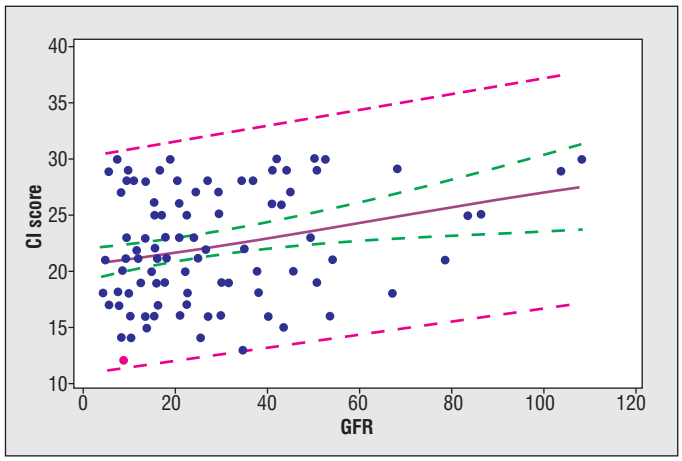

Figure 2: *Scatter plot displaying association among CI score and GFR.*

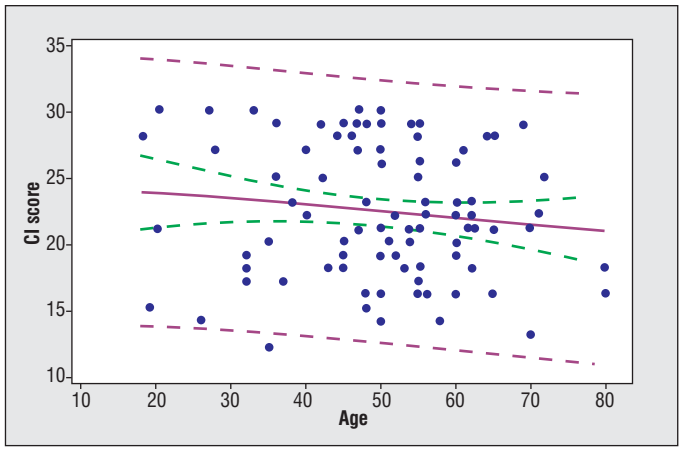

Figure 3: *Scatter plot presenting relationship among CI score and age of patients*

Discussion

The prevalence of CI in our study was comparable with studies conducted in developing countries like India (68.0%),[14] Nigeria (51.9%)[15] and Ethiopia (49.1%).[16] But this was very high as compared with studies conducted in United Kingdom (20%).[17] It is possible that socio-economic factors and the choice of assessment tool for CI could potentially contribute to these results. Developing countries like Pakistan has amalgamation of exclusive risk factors that lead to development of CI such as air pollution, poverty, lack of basic health facilities, illiteracy and gender inequality. Astonishingly 99% of the world population live in areas where air quality does not meet guidelines set by WHO. Emerging studies suggest that pollution is associated with CI.[18] Lahore, the Pakistan second thickly populated city, remains most time of the year at top in air quality index

which lies in the range of unhealthy to hazardous ratio. Illiteracy is another important risk factor causing CI. According to UNICEF, Pakistan currently has the world second highest out of school children with an estimation of 44%, between the age of 5-16 years (22.8 million). Illiterate people are not well versed about the disease and its manifestations ending up with advanced complications. Issues related to hemodialysis are also important in these patients like depression, infrequent social contact, physical inactivity and poor diets. According to study conducted by Anees et al, prevalence of depression was 70% in dialysis patients.[19] Quality of the life of the dialysis patients is very underprivileged, most of the patients are unemployed and socially inactive which aggravates the condition of CI.

CKD is considered as a major causative factor for development of CI.[3] With progression of CKD, the kidney function of filtration and tubular secretion gradually deteriorates which leads to collection of various uremic metabolites in the body. These uremic toxins could potentially traverse the blood-brain barrier and lead to CI. In this study, decrease in eGFR was significant determinant of CI as observed in previous studies.[14,15] In the present study, the patients who had eGFR ≤30ml/min/1.73m^2 developed CI as compared to those who had eGFR > 30ml/min/1.73m^2. It was due to the nephrogenic risk factors playing a prominent role in advanced CKD. The toxic effects of uraemia, endothelial dysfunction, calcium phosphate disturbances and other metabolic disorders due to CKD also affects brain vasculature and cause cognitive dysfunction. The important toxins are phosphate, para cresyl sulphate (PCS), indoxyl sulfate (IS), xanthine, hypoxanthine, 2,8-dihyroxyadenine, fibroblast growth factor 23(FGF 23), hyperhomocystenemia and high level of cytokines found in CKD patients.[20]

CI primarily affects females in the general population. Women may experience a more rapid cognitive decline with age, potentially due to decreased gonadal hormone production, structural brain development, genetics and psychosocial factors. In present study, CI was prevalent among most female CKD patients as observed in previous studies.[15,16] In this patriarchal society, the idea of dutiful wife and devoted mother hinders women's participation in higher education and professional occupations by keeping them busy in domestic work. Lower educational attainment in women, compared to that in men, contributes to lower cognitive functioning at baseline and a higher risk of cognitive decline later in life. The gender inequality also causes increased depression, anxiety among females and predisposes them to develop CI.

Ageing is associated with CI among general population.[21] With increasing age, the brain experiences structural changes, including brain atrophy, reduced hippocampal volume, and thinning of the cerebral cortex, inner capsule, and thalamus, potentially affecting cognitive function.[21] It has been observed in previous studies that cognitive decline is rapid in CKD patients and CI begins to develop at relatively younger age in CKD patients as compared with general population.[15,16] Similar findings were established in this study, where the average age of the patients was relatively young and increasing age was associated with CI. The rapid decline in cognition in CKD patients is further supported by presence of multiple comorbidities, anaemia, bone mineral disease, polypharmacy, depression, inflammation and oxidative stress.

In Pakistan, prevalence of iron deficiency anemia is very high even among general population due to malnutrition.[22] In CKD patients anaemia is further worsened due to anorexia, poor absorption of iron, folic acid and Vitamin B12, chronic inflammation and erythropoietin (EPO) deficiency. Anemia is linked with higher morbidity and mortality among CKD patients and negatively impacts patients' health-associated quality of life.[23] The present study revealed a significant correlation between anemia and CI, with a majority of patients exhibiting low hemoglobin levels. Low concentration of Hb contributes to cerebral hypo perfusion, brain hypoxia and altered brain metabolism thus increasing the risk of cognitive decline. The literature suggests that treating anemia may contribute to a reduction in CI.[23] Majority of CKD patients in Pakistan rely on non-pharmacological and self-treatment due to lack of awareness and financial constrains that creates hurdle in timely management of anaemia and worsens CI.

According to estimates, DM patients have a 1.5 times higher risk of developing CI than do healthy, normal people.[24] DM was considered as significant aggravating factor for development of CI in CKD patients in earlier

studies.[17] It is because of its vascular and neurodegenerative effects through insulin resistance, accumulation of advanced glycation end products, both hyperglycemia and hypoglycemia, dyslipidemia, HTN and inflammation.[2] Although the majority of diabetic patients have CI in our study, but DM was not statistically significant with CI. The small sample size of the present study may have contributed to the observed results.

Proteinuria is hallmark of clinical manifestation of CKD and is considered as important marker of micro vascular disease in CKD patients. It was assumed in literature that proteinuria was linked to a decline in cognitive function among patients with CKD.[2] It seemed to be interceded by aggravating risk factors such as HTN, DM, exaggerated inflammatory response, oxidative stress and metabolic disturbances.[2] However, proteinuria was not associated with CI in this study as supported by another study[25]. Barzilay JI et al found that albuminuria in patients with type 2 DM at initial presentation and its continuous presence during follow-up were not significantly related with an escalation in abnormal white matter hyper intensity volume or changes in brain volume and supported our finding.[25]

Beside the various significant factors found in the study, even though there are certain limitations of our findings as it was a single centre, small sample size and cross sectional study.

Conclusion

CI was found very prevalent in patients with CKD. Female gender, low eGFR, anemia and low level of education were independent predictors of CI in CKD patients. Advancing age has negative correlation while GFR has positive correlation with CI score.

Ethical Approval: Ethical approval was granted by the IRB of the King Edward Medical University, Lahore, Pakistan vide Letter No. 1063/ RC/ KEMU/ 2022.

Conflict of Interest: The authors declare no conflict of interest.

Funding Source: None

Authors' Contribution

MSP: Conception and design of the study, drafting of the manuscript, analysis, and interpretation of data,

MA: Drafting of the manuscript, revising the manuscript critically for important intellectual content

IE: Acquisition, analysis, and interpretation of data.

NB: Acquisition of data, drafting of the manuscript

ST: Acquisition of data

References

1. Morley JE. An Overview of Cognitive Impairment. Clin Geriatr Med. 2018;34(4):505-513. doi: 10. 1016/ j.cger.2018.06.003.
2. Xie Z, Tong S, Chu X, Feng T, Geng M. Chronic Kidney Disease and Cognitive Impairment: The Kidney-Brain Axis. Kidney Dis (Basel). 2022;8(4):275-285. doi: 10.1159/000524475.
3. Hobson P, Lewis A, Nair H, Wong S, Kumwenda M. How common are neurocognitive disorders in patients with chronic kidney disease and diabetes? Results from a cross-sectional study in a community cohort of patients in North Wales, UK. BMJ Open. 2018; 8(12): e023520. doi: 10.1136/bmjopen-2018-023520.
4. Lu R, Xu C, Li Y, Yu L, Shao X, Xie K,et al. The Incidence Prognosis and Risk Factors of Cognitive Impairment in Maintenance Haemodialysis Patients. Blood Purif. 2019;47(1-3):101-108. doi: 10.1159/ 000493524.
5. Kurella Tamura M, Wadley V, Yaffe K, McClure LA, Howard G, Go R, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis.2008;52(2):227-34.doi: 10.1053/j. ajkd.2008.05.004.
6. Drew DA, Weiner DE, Sarnak MJ. Cognitive Impairment in CKD: Pathophysiology, Management, and Prevention. Am J Kidney Dis.2019;74(6):782-790.doi: 10.1053/ j.ajkd.2019.05.017.
7. Bronass UG, Puzantian H, Hannan M. Cognitive Impairment in Chronic Kidney Disease: Vascular Milieu and the Potential Therapeutic Role of Exercise. Biomed Res Int. 2017;27(2):63-69. Doi: 10.1155/2017/2726369.
8. Gela YY, Getu AA, Adane A, Ayal BM, Akalu Y, Ambelu A, et al. Cognitive Impairment and Associated Factors Among Chronic Kidney Disease Patients: A Comparative Cross-Sectional Study. Neuropsychiatr Dis Treat. 2021;17(1):1483-1492. doi: 10.2147/NDT.S304543.
9. Lin YT, Wu PH, Liang SS, Mubanga M, Yang YH, Hsu YL,et al. Protein-bound uremic toxins are associated with cognitive function among patients undergoing maintenance hemodialysis. Sci Rep. 2019; 9(1): 20388. doi: 10.1038/s41598-019-57004-7.

10. Guo Y, Tian R, Ye P, Li X, Li G, Lu F, et al. Cognitive Domain Impairment and All-Cause Mortality in Older Patients Undergoing Hemodialysis. Front Endocrinol (Lausanne). 2022 ;13(1):828-862. doi: 10.3389/ fendo. 2022.828162.
11. Awan S, Shahbaz N, Akhta S W, Ahmad A, Iqba S, Ahmed S,et al. Validation Study of the Mini Mental State Examination in Urdu Language for Pakistani Population. The Open Neurology Journal.2015; 9(1): 53-58.
12. Stevens PE, Levin A.Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158(11):825-30. doi: 10.7326/0003-4819-158-11-201306040-00007. PMID: 23732715.
13. Locatelli F, Nissenson AR, Barrett BJ, Walker RG, Wheeler DC, Eckardt KU, et al. Clinical practice guidelines for anemia in chronic kidney disease: problems and solutions. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2008;74(10):1237-40. doi: 10.1038/ki.2008.299. Epub 2008 Jul 2. PMID: 18596731.
14. Aggarwal HK, Jain D, Bhavikatti A. Cognitive Dysfunction in Patients with Chronic Kidney Disease. Saudi J Kidney Dis Transpl. 2020;31(4):796-804. doi: 10.4103/ 1319-2442.292313.
15. Williams UE, Owolabi MO, Ogunniyi A, Ezunu EO. Prevalence and pattern of neurocognitive impairment in Nigerians with Chronic Kidney Disease. ISRN Neurol. 2013;2013:1–6.doi: 10.1155/2013/374890
16. Gela YY, Getu AA, Adane A, Ayal BM, Akalu Y, Ambelu A, et al. Cognitive Impairment and Associated Factors Among Chronic Kidney Disease Patients: A Comparative Cross-Sectional Study. Neuropsychiatr Dis Treat. 2021;17(1):1483-1492.doi: 10.2147/NDT.S304543.
17. Khatri M, Ryan CM, Gao X, de Boer IH, Braffett BH, Molitch M,et al. CKD Associates with Cognitive Decline in Middle-Aged and Older Adults with Long-Standing Type 1 Diabetes. Kidney360. 2023; 4(8): 1058-1071. doi: 10.34067/KID.0000000000000178.
18. Chandra M, Rai CB, Kumari N, Sandhu VK, Chandra K, Krishna M,et al. Air Pollution and Cognitive Impairment across the Life Course in Humans: A Systematic Review with Specific Focus on Income Level of Study Area. Int J Environ Res Public Health. 2022;19(3):1405. doi: 10.3390/ijerph19031405.
19. Anees M, Barki H, Masood M, Mumtaz A, Kausar T. Depression in hemodialysis patients. Pak J Med Sci. 2008;24(4):560-5.
20. Six I, Flissi N, Lenglet G, Louvet L, Kamel S, Gallet M, et al.Uremic Toxins and Vascular Dysfunction. Toxins (Basel). 2020;12(6):404. doi: 10.3390/toxins12060404
21. Handing EP, Jiao Y, Aichele S. Age-Related Trajectories of General Fluid Cognition and Functional Decline in the Health and Retirement Study: A Bivariate Latent Growth Analysis. J Intell. 2023;11(4):65. doi: 10.3390/ jintelligence11040065.
22. Hammad M, Fardoos S, Arif R, Khan AZ, Rasheed A. Factors Related to Anemia Prevalence Among Women of Childbearing Age in the Period of Global Pandemic. Cureus. 2023;15(5):e38491. doi: 10.7759/cureus. 38491.
23. Kurella Tamura M, Vittinghoff E, Yang J, Go AS, Seliger SL, Kusek JW,et al. Anemia and risk for cognitive decline in Chronic Kidney Disease. BMC Nephrol. 2016; 17(1):13. doi: 10.1186/s12882-016-0226-6.
24. Varghese SM, Joy N, John AM, George G, Chandy GM, Benjamin AI. Sweet Memories or Not? A Comparative Study on Cognitive Impairment in Diabetes Mellitus. Front Public Health.2022;10(1):822062.doi:10. 3389/ fpubh.2022.822062.
25. Barzilay JI, Morgan TM, Murray AM, Bryan RN, Williamson JD, Schnall A,et al. Brain MRI Volume Findings in Diabetic Adults With Albuminuria: The ACCORD-MIND Study. J Gerontol A Biol Sci Med Sci. 2016;71(6):803-10.doi: 10.1093/ gerona/glv187.