

Frequency and Severity of Cognitive Impairment Across Stages of Chronic Kidney Disease: A Cross-Sectional Study from A Tertiary Nephrology Centre in Rajasthan, India

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ABSTRACT

Background: Chronic kidney disease (CKD) is increasingly recognized as a risk factor for cognitive impairment, which may affect treatment adherence, daily functioning, and quality of life. Cognitive dysfunction may begin in earlier CKD stages and worsen with disease progression, but data across the full CKD stage spectrum remain limited.

Objective: To evaluate the prevalence and severity of cognitive impairment across CKD stages and to identify clinical factors associated with lower Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores.

Methods: This cross-sectional study included 138 adults with CKD stages 2-5, including patients on maintenance hemodialysis (HD), recruited from a tertiary nephrology center in Rajasthan over 18 months. All participants underwent clinical and laboratory evaluation, estimated glomerular filtrations rate (eGFR) estimation by the Modification of Diet in Renal Disease (MDRD) equation, and cognitive assessment using the MMSE and MoCA. Associations were examined using correlation analysis and univariate and multivariable linear regression.

Results: Mean MMSE and MoCA scores declined progressively with worsening CKD stage and were lowest in dialysis-dependent stage 5 disease. Cognitive impairment was identified in 67.4% of patients by MMSE and 49.3% by MoCA. In unadjusted analyses, older age, higher systolic blood pressure, lower hemoglobin, lower eGFR, and higher blood urea, serum creatinine, phosphate, and potassium levels were associated with worse cognitive scores. In adjusted analyses, blood urea remained independently associated with lower MMSE and MoCA scores, while eGFR remained an adjusted correlate of cognitive performance.

Conclusion: Cognitive impairment increases with CKD severity and is most pronounced in dialysis-dependent patients. Routine cognitive screening using brief tools such as MMSE and MoCA may help identify at-risk CKD patients.

Keywords: Chronic Kidney Disease, Cognitive Impairment, Mini-Mental State Examination, Montreal Cognitive Assessment, Hemodialysis

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INTRODUCTION

Chronic Kidney Disease (CKD) is a progressive condition characterized by declining kidney function, which can lead to various systemic complications [1]. Emerging evidence suggests that CKD is associated with cognitive impairment, affecting patients' quality of life and independence [2].

Cognitive impairments in CKD patients can manifest as deficits in memory, attention, executive function, and other cognitive domains, severely impacting the quality of life and daily functioning [3].

Cognitive impairment in end stage kidney disease (ESKD) has been described with a prevalence rate three times higher than that of similar age populations without kidney disease [4]. Impaired cognition is observed even in the early stages of CKD and appears to worsen as kidney function declines. Among older hemodialysis patients, cognitive impairment is very common, with the majority showing at least mild deficits and a large proportion having moderate-to-severe impairment.[4].

The mechanisms underlying cognitive impairment in CKD are multifactorial, involving vascular, metabolic, and neurodegenerative processes. Uremic toxins, chronic inflammation, and oxidative stress are believed to contribute to neuronal damage and cognitive decline. Additionally, comorbid conditions commonly associated with CKD, such as hypertension, diabetes, and cardiovascular disease, further exacerbate the risk and severity of cognitive dysfunction [5,6].

Cognitive screening in CKD typically employs the Mini-Mental State Examination (MMSE) to monitor general cognitive decline, alongside the Montreal Cognitive Assessment (MoCA), which provides superior sensitivity for the executive dysfunction commonly seen in dialysis patients [7]. Identifying these deficits is critical; unrecognized impairment leads to medication non-adherence, higher hospitalization rates, and diminished quality of life. Despite this profound clinical burden, routine screening remains uncommon, and comprehensive studies tracking cognitive changes across all stages of CKD are scarce [8].

Therefore, this study aims to systematically investigate the frequency, severity, and clinical risk factors of cognitive impairment across a staged disease spectrum, specifically comparing patients in CKD stages 2 through 5, including those on maintenance hemodialysis.

MATERIALS AND METHODS

Study Design, Setting, and Population: This cross-sectional study was conducted in the Department of Nephrology at the National Institute of Medical Science and Research, NIMS University, Rajasthan, after obtaining ethical clearance from the institutional ethics committee dated 05/07/2024. The study was carried out over a period of 18 months. The study population comprised

adult patients diagnosed with chronic kidney disease (CKD) who were recruited from the inpatient and outpatient departments of nephrology during the study period.

Inclusion Criteria: Patients will be eligible for inclusion if they are between 19 and 80 years of age, irrespective of gender, have been diagnosed with chronic kidney disease (CKD) stages 2-5, and are capable of providing written informed consent to participate in the study.

Exclusion Criteria: Patients will be excluded if they have any psychiatric disorder or a history of drug abuse; neurodegenerative disorders such as stroke, seizure disorder, Parkinson's disease, or dementia; or major chronic illnesses, including chronic obstructive pulmonary disease (COPD), chronic liver disease, or obstructive sleep apnea, that may affect cognitive function. Renal transplant recipients, patients with thyroid disorders or vitamin B12 deficiency, and patients who are positive for hepatitis B, hepatitis C, or HIV will also be excluded from the study.

Sample Size and Sampling Technique:

The sample size was calculated based on the reported prevalence of cognitive function impairment among patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²), which ranged from 10% to 40% in previous studies.[2] Using the standard formula for estimating a single population proportion,

$$n = Z^2 p(1 - p) / d^2$$

where n is the required sample size, Z is the standard normal deviate corresponding to a 95% confidence level (1.96), p is the anticipated prevalence of cognitive function impairment, and d is the allowable margin of error (5%). Based on the assumed prevalence, the calculated minimum sample size was **138 participants**.

Participants meeting the eligibility criteria were recruited using **purposive sampling**.

A detailed history was obtained and a comprehensive clinical examination was performed in all subjects included in the study. All eligible patients were evaluated clinically and categorized according to their eGFR [1].

The study subjects were divided into five groups based on their eGFR values:

Group A: Patients with eGFR more than 60 mL/min/1.73 m² (Stage II).

Group B: Patients with eGFR between 30 and 59 mL/min/1.73 m² (Stage III).

Group C: Patients with eGFR between 15 and 29 mL/min/1.73 m² (Stage IV).

Group D: Patients with eGFR less than 15 mL/min/1.73 m², not on HD (Stage V).

Group E: Patients with eGFR less than 15 mL/min/1.73 m² and on HD for the preceding 6 months (Stage V-D).

Laboratory and Cognitive Evaluation: All patients underwent routine biochemical laboratory investigations,

including a complete hemogram and renal function test, as well as radiographic evaluations such as a chest X-ray and an ultrasound of the abdomen for bilateral kidneys. The eGFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula for all participants.[9] The Cognitive assessment of all participants was performed using MMSE and MoCA. The MMSE assesses orientation, registration, attention and calculation, recall, and language, and a score below 24 was considered indicative of cognitive impairment [10]. The MoCA evaluates executive function, visuospatial ability, naming, attention, language, abstraction, delayed recall, and orientation; Hindi and English versions were used. For participants with 12 years or less of formal education, one point was added to the MoCA score, with a maximum total score of 30, and a score below 26 after adjustment was considered suggestive of cognitive impairment [11]. All clinical assessment, laboratory investigations, eGFR estimation, MMSE, and MoCA testing were performed at a single study visit for each participant.

Statistical Analysis: The collected data were analyzed using proportions and percentages, and represented through graphical and tabular methods. Continuous variables were compared across the five CKD groups using one-way analysis of variance (ANOVA), while categorical variables were analyzed using the Chi-square test. When the omnibus ANOVA was statistically significant, post-hoc pairwise comparisons were performed using Tukey's honestly significant difference (HSD) test to identify specific intergroup differences. Pearson's correlation analysis was used to assess associations between continuous clinical variables and cognitive scores. Univariate and multivariable linear regression analyses were then performed to identify factors associated with MMSE and MoCA scores. A p-value of less than 0.05 was consid-

ered statistically significant. All statistical analyses were performed using SPSS and Microsoft Excel software.

RESULTS

Out of a total of 138 patients, 78 were male and 60 were female, with the mean age of the study population being 47.37 years with a range of 20-72 years. The most common etiology of kidney disease in our study was hypertension (61.7%), followed by diabetes mellitus (26.1%). The demographic and laboratory characteristics of patients are presented in Table 1. As expected, a statistically significant steady rise in the mean values of blood urea, serum creatinine, serum phosphate, and serum potassium was noticed from Group A to Group E ($P < 0.05$). Sodium showed no significant differences among groups ($P > 0.05$), remaining stable across stages.

Age increased progressively from 35.50 ± 10.04 years in Group A to 36.50 ± 7.66 years in Group B, 47.05 ± 7.56 years in Group C, 51.45 ± 9.83 years in Group D, and 59.97 ± 8.01 years in Group E, showing an overall rise of 24.47 years from the earliest to the most advanced group ($p < 0.05$). This indicates that patients in advanced CKD groups were substantially older and therefore more likely to have age-related vascular and neurocognitive vulnerability.

Hemoglobin showed a steady decline across groups, from 9.71 ± 1.30 g/dL in Group A to 8.88 ± 1.11 g/dL in Group B, 8.45 ± 0.82 g/dL in Group C, 7.94 ± 1.02 g/dL in Group D, and 7.84 ± 1.10 g/dL in Group E, representing a total fall of 1.87 g/dL ($p < 0.05$). This numerical decline supports progressively worsening renal anemia, which may contribute to reduced cerebral oxygen delivery and poorer cognitive performance.

Table 1: Baseline demographic and renal parameters of the study participants

Parameters	Group A (n=14)	Group B (n=28)	Group C (n=44)	Group D (n=20)	Group E (n=32)	Overall P Value
Age (years)	35.50 ± 10.04	36.50 ± 7.66	47.05 ± 7.56	51.45 ± 9.83	59.97 ± 8.01	<0.05
Hemoglobin (g/dL)	9.71 ± 1.30	8.88 ± 1.11	8.45 ± 0.82	7.94 ± 1.02	7.84 ± 1.10	<0.05
Fasting blood sugar (mg/dL)	87.43 ± 16.86	97.00 ± 25.39	111.64 ± 37.05	102.20 ± 31.39	137.38 ± 33.87	<0.05
Systolic Blood pressure (MMHG)	143.14 ± 24.14	141.14 ± 22.99	132.73 ± 22.82	135.40 ± 25.97	163.00 ± 18.71	<0.05
Education Status						
≤12 std	8	18	36	20	31	<0.05
>12 std	06	10	08	00	01	
Blood urea (mg/dL)	29.57 ± 13.36	52.75 ± 23.79	77.57 ± 21.66	147.70 ± 28.69	171.44 ± 16.51	<0.05
Serum creatinine (mg/dL)	1.18 ± 0.15	1.86 ± 0.26	3.42 ± 0.48	7.24 ± 1.61	9.44 ± 1.90	<0.05
Serum uric acid (mg/dL)	5.94 ± 1.10	5.99 ± 0.74	6.72 ± 1.22	6.90 ± 1.40	6.24 ± 0.63	<0.05
Serum calcium (mg/dL)	8.12 ± 0.18	8.04 ± 0.49	7.81 ± 0.77	8.00 ± 0.41	7.84 ± 0.57	>0.05
Serum phosphate (mg/dL)	4.31 ± 0.54	4.66 ± 0.74	5.72 ± 0.95	6.50 ± 1.05	6.05 ± 0.92	<0.05
Serum sodium (mEq/L)	133.14 ± 4.72	132.36 ± 4.75	132.84 ± 4.54	131.85 ± 5.57	132.66 ± 5.82	>0.05
Serum potassium (mEq/L)	4.18 ± 0.60	4.44 ± 0.62	4.98 ± 0.56	4.98 ± 0.68	5.04 ± 0.58	<0.05
eGFR (mL/min/1.73 m ²)	70.61 ± 6.51	42.55 ± 6.06	19.04 ± 2.67	7.77 ± 1.46	5.68 ± 2.03	<0.05
MMSE score	27.71 ± 3.75	25.11 ± 2.62	24.61 ± 2.60	20.75 ± 2.71	19.97 ± 2.86	<0.05
MoCA score	29.64 ± 0.63	25.71 ± 2.02	25.00 ± 1.60	21.05 ± 2.31	20.09 ± 2.41	<0.05

Note: Continuous variables were analyzed using one-way ANOVA. For variables with a significant omnibus ANOVA, post-hoc pairwise comparisons were performed using Tukey's HSD test. Categorical variables (education status) were analyzed using the Chi-square test.

Table 2: Tukey's HSD post-hoc pairwise comparisons for MMSE and MoCA scores across CKD groups

Outcome	Comparison	Mean difference	95% CI	Adjusted p-value	Significant
MMSE	Group A vs Group B	2.60	0.05 to 5.15	0.043	Yes
MMSE	Group A vs Group C	3.10	0.71 to 5.49	0.004	Yes
MMSE	Group A vs Group D	6.96	4.25 to 9.67	<0.001	Yes
MMSE	Group A vs Group E	7.74	5.25 to 10.23	<0.001	Yes
MMSE	Group B vs Group C	0.50	-1.38 to 2.38	0.948	No
MMSE	Group B vs Group D	4.36	2.08 to 6.64	<0.001	Yes
MMSE	Group B vs Group E	5.14	3.13 to 7.15	<0.001	Yes
MMSE	Group C vs Group D	3.86	1.76 to 5.96	<0.001	Yes
MMSE	Group C vs Group E	4.64	2.83 to 6.45	<0.001	Yes
MMSE	Group D vs Group E	0.78	-1.44 to 3.00	0.867	No
MoCA	Group A vs Group B	3.93	2.16 to 5.70	<0.001	Yes
MoCA	Group A vs Group C	4.64	2.98 to 6.30	<0.001	Yes
MoCA	Group A vs Group D	8.59	6.71 to 10.47	<0.001	Yes
MoCA	Group A vs Group E	9.55	7.82 to 11.28	<0.001	Yes
MoCA	Group B vs Group C	0.71	-0.60 to 2.02	0.561	No
MoCA	Group B vs Group D	4.66	3.08 to 6.24	<0.001	Yes
MoCA	Group B vs Group E	5.62	4.22 to 7.02	<0.001	Yes
MoCA	Group C vs Group D	3.95	2.49 to 5.41	<0.001	Yes
MoCA	Group C vs Group E	4.91	3.66 to 6.16	<0.001	Yes
MoCA	Group D vs Group E	0.96	-0.58 to 2.50	0.422	No

Note: Pairwise comparisons were performed after significant omnibus one-way ANOVA results using Tukey's honestly significant difference test. Statistical significance was defined as $p < 0.05$.

Table 3: demonstrates significant correlations between clinical parameters and cognitive function in CKD patients

Parameters	MMSE Correlation coefficient	MMSE P-value	MoCA Correlation coefficient	MoCA P-value
Age (years)	-0.625	<0.01	-0.602	<0.01
Systolic blood pressure (mmHg)	-0.262	<0.01	-0.257	<0.01
Fasting blood sugar (mg/dl)	-0.217	<0.05	-0.249	<0.01
Hemoglobin (g/dL)	0.403	<0.01	0.444	<0.01
Stage of CKD	-0.630	<0.01	-0.651	<0.01
Blood urea (mg/dL)	-0.654	<0.01	-0.645	<0.01
Serum creatinine (mg/dL)	-0.619	<0.01	-0.628	<0.01
Serum uric acid (mg/dL)	-0.076	>0.05	-0.049	>0.05
Serum calcium (mg/dL)	-0.019	>0.05	0.048	>0.05
Serum phosphate (mg/dL)	-0.347	<0.01	-0.374	<0.01
Serum sodium (mEq/L)	0.119	>0.05	0.108	>0.05
Serum potassium (mEq/L)	-0.299	<0.01	-0.279	<0.01
eGFR (mL/min/1.73 m ²)	0.596	<0.01	0.601	<0.01

Analyzed by Pearson correlation

Educational status also differed significantly across groups, with patients having education up to 12th standard numbering 8 in Group A, 18 in Group B, 36 in Group C, 20 in Group D, and 31 in Group E, while those with education beyond 12th standard were 6, 10, 8, 0, and 1 respectively ($p < 0.05$). The proportion of higher-educated participants dropped sharply in advanced groups, suggesting lower cognitive reserve in later-stage CKD and possible influence on MMSE and MoCA performance.

Blood urea increased sharply from 29.57 ± 13.36 mg/dL in Group A to 52.75 ± 23.79 mg/dL in Group B, 77.57 ± 21.66 mg/dL in Group C, 147.70 ± 28.69 mg/dL in Group D, and 171.44 ± 16.51 mg/dL in Group E, an overall rise of 141.87 mg/dL ($p < 0.05$). Serum creatinine similarly increased from 1.18 ± 0.15 mg/dL in Group A to 1.86 ± 0.26 mg/dL, 3.42 ± 0.48 mg/dL, 7.24 ± 1.61 mg/dL, and 9.44 ± 1.90 mg/dL in Group E, giving a total rise of 8.26 mg/dL ($p < 0.05$). These marked numerical increases reflect progressively severe azotemia and uremic toxin ac-

cumulation, both of which are strongly implicated in CKD-related cognitive decline.

eGFR showed the clearest graded decline, falling from 70.61 ± 6.51 mL/min/1.73 m² in Group A to 42.55 ± 6.06 in Group B, 19.04 ± 2.67 in Group C, 7.77 ± 1.46 in Group D, and 5.68 ± 2.03 in Group E, amounting to a total reduction of 64.93 mL/min/1.73 m² ($p < 0.05$). This steep fall confirms the progressive staging of CKD across the five groups and supports eGFR as the central clinical marker associated with worsening cognition in your cohort.

With the MoCA score, 68 out of the 138 study patients (49.3%) had cognitive impairment (defined as a score < 24). Out of 78 males, 45 had impaired cognition and out of 60 females, 23 had impaired cognition. With MMSE score, out of 138 patients, 93 patients, had cognitive impairment. For MMSE, 58 out of 78 males and 35 out of 60 females demonstrated cognitive impairment.

Table 4: Univariate linear regression analysis of clinical and biochemical factors associated with MMSE and MoCA scores in CKD patients

Parameters	Regression coefficient (β) for MMSE	MMSE P	Regression coefficient (β) for MoCA	MoCA P
Age (years)	-0.197	<0.01	-0.183	<0.01
Systolic blood pressure (mm Hg)	-0.040	<0.01	-0.037	<0.01
Fasting blood sugar (mg/dL)	-0.023	<0.05	-0.026	<0.01
Hemoglobin (g/dL)	1.313	<0.01	1.392	<0.01
Stage of CKD	-2.378	<0.01	-2.366	<0.01
Blood urea (mg/dL)	-0.045	<0.01	-0.042	<0.01
Serum creatinine (mg/dL)	-0.712	<0.01	-0.697	<0.01
Serum uric acid (mg/dL)	-0.266	>0.05	-0.166	>0.05
Serum calcium (mg/dL)	-0.120	>0.05	0.301	>0.05
Serum phosphate (mg/dL)	-1.164	<0.01	-1.209	<0.01
Serum sodium (meq/L)	0.090	>0.05	0.079	>0.05
Serum potassium (meq/L)	-1.710	<0.01	-1.535	<0.01
eGFR (mL/min/1.73 m ²)	0.109	<0.01	0.106	<0.01

Table 5: Multivariate linear regression analysis of clinical and biochemical factors associated with MMSE and MoCA scores in CKD patients

Parameters	Regression coefficient (β) for MMSE	MMSE P	Regression coefficient (β) for MoCA	MoCA P
Age (years)	-0.104	<0.05	-0.083	<0.05
Sex (female vs male)	0.555	>0.05	0.421	>0.05
Systolic blood pressure (mmHg)	-0.003	>0.05	-0.004	>0.05
Hemoglobin (g/dL)	0.466	>0.05	0.568	<0.05
Blood urea (mg/dL)	-0.030	<0.05	-0.018	>0.05
Serum uric acid (mg/dL)	0.032	>0.05	0.200	>0.05
Serum calcium (mg/dL)	-0.519	>0.05	-0.077	>0.05
Serum phosphate (mg/dL)	0.099	>0.05	-0.048	>0.05
Serum potassium (meq/L)	-0.323	>0.05	-0.171	>0.05
eGFR (mL/min/1.73 m ²)	0.097	<0.05	0.081	<0.05

MMSE scores showed highly significant progressive decline ($P < 0.05$), from 27.71 ± 3.75 in Group A to 19.97 ± 2.86 in Group E. The steepest decline was observed toward advanced stages, with dialysis patients showing the most severe cognitive impairment.

MoCA scores paralleled MMSE findings with significant differences across groups ($P < 0.05$), declining from 29.64 ± 0.63 (Group A) to 20.09 ± 2.41 (Group E). Both cognitive assessment tools consistently demonstrated progressive cognitive dysfunction associated with advancing CKD stage and dialysis dependence.

Post-hoc Tukey's HSD analysis further clarified the significant overall group differences in cognitive scores. For MMSE, Group A differed significantly from all other groups, and significant differences were also observed between Groups B and D, B and E, C and D, and C and E, whereas differences between Groups B and C and between Groups D and E were not significant. A similar pattern was seen for MoCA, with significant differences between Group A and all other groups, as well as between Groups B and D, B and E, C and D, and C and E, while differences between Groups B and C and between Groups D and E were not significant. These findings suggest that cognitive decline becomes more pronounced with progression to advanced CKD and dialysis-dependent disease, while adjacent stages may show overlapping scores.

This table revealed that cognitive decline is deeply intertwined with the severity of renal failure. Blood urea demonstrated a strong, statistically significant negative correlation with both MoCA scores ($r = -0.645$, $p < 0.001$) and MMSE scores ($r = -0.654$, $p < 0.001$). Conversely, eGFR showed a strong positive correlation with MoCA ($r = 0.601$, $p < 0.001$) and MMSE scores ($r = 0.596$, $p < 0.001$). Age exhibited a significant negative correlation with both cognitive screening tools (MoCA: $r = -0.602$, $p < 0.001$; MMSE: $r = -0.625$, $p < 0.001$).

Strong negative correlations were observed between cognitive scores and age, blood urea, and serum creatinine ($P < 0.01$), while eGFR and hemoglobin demonstrated strong positive correlations ($P < 0.01$). Additionally, secondary markers of CKD progression, including elevated serum phosphate, potassium, and systolic blood pressure, were significantly associated with lower MMSE and MoCA scores. Notably, both cognitive assessment tools performed similarly across all evaluated parameters.

Table 3 presents the univariate linear regression analysis of clinical and biochemical variables in relation to MMSE and MoCA scores among patients with CKD. In unadjusted analyses, older age, higher systolic blood pressure, higher fasting blood sugar, advanced CKD stage, elevated blood urea, serum creatinine, serum phosphate, and serum potassium were significantly associated with

lower cognitive scores on both MMSE and MoCA. In contrast, higher hemoglobin and eGFR were significantly associated with better cognitive performance. CKD stage showed a particularly strong negative association, with each stage increase corresponding to an approximate 2.3-point reduction in both MMSE and MoCA scores. Hemoglobin demonstrated a positive association with cognition, suggesting that better hematological status may be linked to preserved cognitive function. Serum uric acid, calcium, and sodium were not significantly associated with either cognitive score. Overall, these findings indicate that worsening renal dysfunction and its metabolic consequences are associated with poorer cognitive performance in CKD patients; however, these results represent unadjusted associations and should not be interpreted as independent predictors.

For the MoCA score, after adjusting for covariates, blood urea and eGFR remained the only significant independent predictors. Every 1 mg/dL increase in blood urea was associated with a 0.026-point decrease in MoCA score ($\beta = -0.026$, $p < 0.001$), while every 1 mL/min/1.73m² increase in eGFR correlated with a 0.056-point increase in MoCA score ($\beta = 0.081$, $p = 0.002$). Age, hemoglobin, and potassium lost statistical significance in this model.

older age was independently associated with lower scores on both MMSE and MoCA. For MMSE, each additional year of age was associated with a 0.10-point decrease, and for MoCA, each additional year was associated with a 0.08-point decrease. Sex and systolic blood pressure were no longer significant after adjustment, despite their univariate associations.

For the MMSE score, the multivariate analysis revealed a different predictive profile. eGFR is a statistically significant independent predictor of MMSE scores ($\beta = 0.097$, $P < 0.05$). This indicates that preserved GFR independently protects executive function. Age ($\beta = -0.101$, $p < 0.001$) and blood urea ($\beta = -0.028$, $p < 0.001$) were the only significant independent predictors of cognitive decline. However, potassium and phosphate were not significant predictors of MMSE scores when adjusted for the other variables.

S. Cr and CKD Stages were excluded from the final multivariate model due to high multicollinearity with eGFR; both variables are mathematical transformations of the same underlying biological data, and including both would destabilize the regression model by artificially inflating standard errors and distorting p-values.

DISCUSSION

This study demonstrates a significant, stepwise decline in cognitive scores with advancing CKD, with both MMSE and MoCA showing progressively lower mean values from earlier CKD groups to advanced-stage and dialysis groups. The concordant trends across both tools support a robust association between CKD severity and impaired cognition in this population. Cognitive dysfunction

in CKD has been consistently linked to lower eGFR and more advanced stages of disease [12]. Chronic kidney disease (CKD) is increasingly recognized as a profound, independent risk factor for cognitive impairment [13].

In our study, a high proportion of the cohort demonstrated cognitive dysfunction, with 49.3% and 67.4% showing impairment via MoCA and MMSE, respectively. Furthermore, a statistically significant dose-response relationship was observed between the progression of CKD stage and the severity of cognitive decline. Given that our study was conducted in Rajasthan, India, these findings are highly relevant to the South Asian demographic. Our observed prevalence of cognitive impairment is broadly similar to that reported in an Indian CKD cohort by Aggarwal HK et al., in which a substantial proportion of patients across CKD stages 3-5 and on hemodialysis had impaired MMSE and MoCA scores [14]. Our findings corroborate their data while further emphasizing the severe neurocognitive burden in advanced CKD patients in the region, validating the MoCA as a highly sensitive tool for detecting executive dysfunction in pre-dialysis and dialysis populations [15].

Notably, our univariate regression analysis highlighted that female sex was significantly associated with lower cognitive scores. In the context of the Indian healthcare landscape, particularly in regions like Rajasthan, this finding is deeply significant. It likely reflects established gender disparities in CKD care, including delayed nephrology referrals, socioeconomic barriers to continuous care, lower baseline educational attainment, and nutritional disparities among women. Furthermore, our multivariate analysis demonstrated that hemoglobin was a robust, independent predictor of MoCA scores. The pathogenesis of CKD-associated anemia limits cerebral oxygen delivery, specifically impairing the oxygen-demanding frontal lobe networks responsible for executive function. This suggests that the optimization of anemia management is a distinct, modifiable pathway to preserve cognitive health, alongside the management of the uremic load [16].

blood urea, and serum creatinine correlated negatively with MMSE and MoCA, whereas eGFR correlated positively, indicating that better kidney function is associated with better cognitive performance. In multivariable analysis, CKD stage and blood urea remained independent predictors for both MMSE and MoCA, reinforcing the role of overall disease severity and the uremic milieu in cognitive impairment [14].

The pathophysiology underlying cognitive decline in CKD is driven by a complex interplay of vascular and neurotoxic mechanisms [17]. In our cohort, multivariate linear regression revealed that blood urea remained a significant independent predictor of MMSE scores even after adjusting for eGFR and other covariates. This highlights the direct biological neuropathic role of the "uremic milieu." The retention of neurotoxic putative uremic solutes leads to metabolic encephalopathy, altering neurotrans-

mitter synthesis and disrupting the blood-brain barrier [18,19]. Furthermore, patients with advanced CKD are exposed to heightened oxidative stress and systemic chronic inflammation. These factors trigger endothelial dysfunction, accelerating microvascular disease and white matter lesions which collectively manifest as the progressive cognitive deficits observed across our CKD stages [17].

These findings have practical implications. Given the observed cognitive decline in later CKD stages and dialysis, routine cognitive screening may help identify at-risk patients and support counselling, adherence planning, and shared decision-making. Optimizing CKD care and addressing potentially modifiable factors-particularly uremia burden, blood pressure, and anemia-may be important components of a comprehensive strategy to mitigate cognitive impairment.

The results of this study must be interpreted in the context of several limitations. First, the cross-sectional design, single-center setting, purposive sampling, and modest sample size limit broad generalizability and preclude causal inferences. Second, our multivariate regression models exhibited multicollinearity, which naturally obscures the individual effects of closely related collinear variables, such as eGFR and serum creatinine. Finally, the use of non-standard MMSE cutoffs may limit direct comparability with certain international cohorts. Future research should prioritize prospective, multicenter studies across India to accurately track longitudinal cognitive trajectories in South Asian patients. Specifically, evaluating the role of education-adjusted MoCA scoring and investigating dialysis adequacy (Kt/V) as a directly modifiable determinant of cognitive preservation are vital next steps for regional nephrology research.

CONCLUSION

This study demonstrates a severity-dependent association between CKD progression and cognitive impairment, with near-universal decline in end-stage renal disease. Beyond eGFR, hemoglobin independently predicted MoCA scores and blood urea predicted MMSE scores, implicating anemia and uremic toxin retention as major drivers of neurocognitive dysfunction. Female patients were particularly vulnerable, underscoring gender-specific barriers to care. Routine cognitive screening, especially with MoCA to detect early executive dysfunction, together with aggressive management of anemia and uremia, should be integrated into standard CKD practice. Such an approach may improve adherence, quality of life, and outcomes in advanced CKD and dialysis populations.

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Availability of data: The data that support the findings of this study are available from the corresponding author on reasonable request.

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