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A CASE-CONTROL STUDY: COGNITIVE IMPAIRMENT IN CHRONIC KIDNEY DISEASE (CKD)

Internal Medicine

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ABSTRACT

Introduction- Cognitive impairment (CI) is a significant concern in patients with chronic kidney disease (CKD), yet its relationship with CKD severity and associated factors remains underexplored. CKD is a progressive condition characterized by persistent kidney damage or an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² for at least three months. As CKD progresses, it leads to various complications, including cardiovascular disease, metabolic dysfunction, and, notably, cognitive decline, which significantly contributes to morbidity. The global prevalence of CKD continues to rise, and cognitive impairment in these patients is associated with a poorer quality of life, reduced adherence to treatment, and increased morbidity and mortality. This study aims to evaluate cognitive function in CKD patients of Indian descent, investigating its correlation with CKD severity, biochemical markers, and cardiovascular risk factors. Understanding these relationships is crucial for improving early diagnosis and management strategies to mitigate the burden of cognitive dysfunction in CKD. **Materials And Methods-** This case-control study was conducted from September 2023 to March 2024 at Indira Gandhi Government Medical College & Hospital, Nagpur. We recruited 100 CKD patients from the Medicine OPD/IPD, CKD clinic, and Dialysis Center, and matched them with 100 healthy controls based on age, gender, and educational status. Inclusion criteria for CKD patients included an eGFR <60 ml/min/1.73 m² and age between 18 and 75 years. Controls were healthy individuals or their relatives attending the hospital, excluding those with CKD or cognitive-affecting conditions. Cognitive impairment was assessed using the MMSE, with scores categorized as severe (≤9), moderate (10–18), or mild (19–23). eGFR was classified into four groups: stage 3A+3B, stage 4, stage 5 non-dialysis, and stage 5 on hemodialysis. **Results-** The study identified chronic kidney disease (CKD) as an independent and significant risk factor for cognitive impairment. Multivariate analysis revealed that CKD patients had substantially higher odds of cognitive decline, with an odds ratio of 7.87 (95% CI: 4.04–15.36, p < 0.001) indicating a strong association. Cognitive impairment was significantly more prevalent in CKD patients (60%) compared to controls (16%) (p < 0.001). The mean MMSE score for CKD patients was significantly lower (22.0 ± 4.61) compared to controls (27.08 ± 3.29). CKD patients had significantly reduced eGFR (mean 17.9 mL/min/1.74 m²) compared to controls (103 mL/min/1.74 m²) (p < 0.001), with lower eGFR strongly associated with worse cognitive function (p < 0.001). Hypertension (78%) and diabetes mellitus (42%) were the most common comorbidities in CKD patients found to have significant association to cognitive decline. Multivariate linear regression analysis revealed that eGFR, HDL, and total cholesterol are significant predictors of cognitive impairment in CKD patients (p = 0.041 for HDL; p = 0.048 for total cholesterol). These findings suggest that CKD is a significant and independent risk factor for cognitive decline, influenced by both renal and metabolic factors, including hypertension, diabetes, and lipid parameters. **Discussion-** This study underscores chronic kidney disease (CKD) as a significant independent risk factor for cognitive decline, with CKD patients being 7.87 times more likely to experience cognitive impairment compared to controls (OR: 7.87, 95% CI: 4.04–15.36, p < 0.001). A positive correlation between eGFR and MMSE scores further links declining kidney function to worsening cognitive performance. Additionally, higher HDL cholesterol levels were associated with better cognitive outcomes, while higher total cholesterol levels were inversely related to cognitive function. Hypertension and diabetes, common comorbidities in CKD, were also strongly associated with cognitive impairment. These findings suggest that early interventions targeting kidney function i.e. eGFR, lipid profiles, and traditional risk factors could help mitigate cognitive decline in CKD patients.

KEYWORDS

Chronic Kidney Disease, End-stage renal disease, Cognitive Impairment, Low Density Lipoprotein, Montreal Cognitive Assessment

INTRODUCTION-

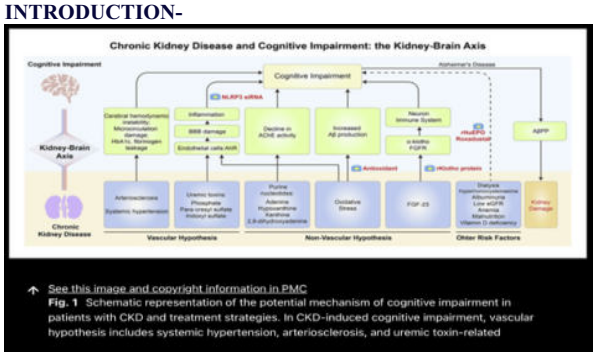

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Fig. 1 Schematic representation of the potential mechanism of cognitive impairment in patients with CKD and treatment strategies. In CKD-induced cognitive impairment, vascular hypothesis includes systemic hypertension, arteriosclerosis, and uremic toxin-related

Image Reference [1]

Chronic kidney disease (CKD) is a progressive multisystem condition defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m², persisting for 3 months or more, regardless of the cause [2]. It affects various organ systems and significantly contributes to morbidity and mortality, often necessitating renal replacement therapy, such as dialysis or transplantation. The global prevalence of CKD was reported to be 13.4% in 2022 [17], with a staggering increase observed each subsequent year. There was also an increase in prevalence from 11.8% between 1988 and 1994 to 14.2% between 2015 and 2016 [19], with India facing an even higher prevalence of 16.7% and a 30% increase over the past decade [15]. CKD-related mortality rates vary from 15% to 30%, depending on the disease stage and comorbidities. The rising incidence of CKD is largely attributed to increasing rates of diabetes

and hypertension [3]. According to Global Burden of Disease (GBD) estimates, CKD is projected to become the fifth leading cause of years of life lost globally by 2040, underscoring the urgent need for effective public health interventions [18].

Disease severity is classified using a five-stage system based on the estimated glomerular filtration rate (eGFR), a calculation of waste cleared by the kidneys per minute [29]

Classification of chronic kidney disease	
Stage 1	Evidence of kidney damage with normal eGFR >90 mL/min/1.73 m2
Stage 2	Evidence of kidney damage with mild reduction of eGFR 60–89 mL/min/1.73 m2
Stage 3	Moderately reduced eGFR 30–59 mL/min/1.73 m2
Stage 4	Severely reduced eGFR 15–29 mL/min/1.73 m2
Stage 5	Renal failure or dialysis eGFR <15 mL/min/1.73 m2

Progression of CKD is associated with a number of serious complications, including increased incidence of cardiovascular disease, hyperlipidemia, anemia and metabolic bone disease. A global systematic review of population-based CKD studies published in 2024 documented an overall prevalence of cognitive impairment (CI) in CKD patients at 40% [16]. This prevalence is higher among individuals of African and Asian descent, as well as those undergoing hemodialysis compared to those not on dialysis. These findings underscore the urgent need for early detection and management to enhance the quality of life for affected individuals.

The most important mechanism contributing to cognitive impairment in patients with CKD is the macrovascular effects of longstanding hypertension causing neuronal damage, as evidenced by multiple studies indicating the extent of brain atrophy [7]. Hypertension in chronic kidney disease (CKD) creates a vicious cycle characterized by sodium retention and increased activity of the renin-angiotensin system and sympathetic nervous system, leading to decreased renal perfusion and nephrosclerosis, which further exacerbates kidney damage and worsens hypertension. Other significant vascular factors include diabetes, aging, and metabolic conditions that inflict further neuronal injury. Metabolic factors contributing to cognitive decline involve oxidative stress, chronic inflammation, anemia, hyperparathyroidism, elevated levels of fibroblast growth factor 23 (FGF23), hypercoagulability, hyperhomocysteinemia, and deficiencies in vitamin D and vitamin B12. Additionally, lower eGFR contributes to retention of neurotoxins, such as nitrogen metabolism byproducts and parathyroid hormone, that exacerbate the cognitive decline [8]. Addressing these factors may help reduce cognitive decline in chronic kidney disease (CKD), though definitive evidence is limited. Specifically, managing blood pressure and reducing albuminuria with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) can lead to modest improvements in cognitive function. While dialysis can improve severe cognitive deficits related to uremia, it doesn't significantly affect more subtle cognitive impairments. In contrast, kidney transplantation often results in enhanced cognitive abilities in recipients, indicating that the benefits of a functioning kidney extend beyond the capabilities of dialysis treatments. This highlights the vital role of healthy kidney function in preserving cognitive health [8, 23].

Cognitive impairment presents as dysfunction in one or more cognitive domains that are typically tested during neuropsychological evaluation. These domains include memory, language, executive functions, attention, and motor functions [30]. Cognitive impairment and dementia commonly occur in chronic kidney disease (CKD), especially in the advanced stages, and despite their high burden, they are often poorly diagnosed. This under-recognition leads to poor adherence to recommended treatments due to dementia, abnormal behavioral symptoms, functional dependence, emotional distress, and decreased quality of life. Even mild cognitive impairment carries a high risk of progression to dementia, with an annual rate of 1.9% [4].

The extent of cognitive decline correlates with renal dysfunction, being more pronounced in dialysis patients due to subclinical vascular insults to the brain [5]. A study by Findlay et al. highlighted this connection by showing decreased cerebral blood flow (measured by mean flow velocity) during hemodialysis. This reduction in blood flow was associated with chronic white matter changes visible on brain MRI, contributing to worsening cognitive function [21]. In these patients, cognitive impairment often manifests as a range of neuropsychiatric issues, including delirium, dementia, anxiety, depression, withdrawal from dialysis, sleep disorders and suicidal tendency [6].

In mild CKD, executive function and attention are primarily affected, while severe CKD leads to more widespread cognitive deficits that involve general cognitive abilities, executive function, and episodic memory [9]. Although the evidence suggests that early hemodialysis improves cognitive abilities, and hemodialysis patients perform better in attention and overall cognitive function than non-dialyzed CKD patients, yet their memory remains inferior to that of the general population and individuals with non-dialysis-dependent CKD [13,4]. This can be implicated to factors like reduced cerebral perfusion, increased cytokine release, and electrolyte fluctuations [5, 16]. Such complications highlight the urgent need for better recognition and management of cognitive health in CKD patients.

Overall, cognitive impairment is a major contributor to morbidity in CKD, leading to lower quality of life and difficulties in medication adherence. With prevalence of CI rates of 30% to 70% among dialysis patients, addressing cognitive deficits is crucial for improving patient outcomes [11, 12].

A neurological examination is crucial for all patients with CKD, utilizing tools such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Our study focuses on assessing the severity of cognitive impairment across different CKD stages in the Indian ethnicity, employing the MMSE. We also aim to evaluate risk factors and explore the association between biochemical parameters—such as serum creatinine, urine albumin, and estimated glomerular filtration rate (eGFR)—and the severity of cognitive decline.

Aims And Objectives:

1. To determine cognitive impairment (as assessed by the Mini-Mental State Examination) in subjects with chronic kidney disease (CKD).
2. To assess the level of cognitive impairment in relation to the severity of CKD, as assessed by eGFR criteria
3. To determine the association of cognitive dysfunction with other cardiovascular risk factors—hypertension, diabetes, and hyperlipidemia—in patients with CKD.

Ethical Considerations-

- Written informed consent was obtained prior to enrolling cases.
- Strict confidentiality of data and subjects was maintained.
- Institutional ethical committee clearance was obtained before commencing the study.

MATERIALS AND METHODS:

Study Setting –

Cases were recruited from the Medicine OPD/IPD, CKD clinic, and Dialysis Center of Indira Gandhi Government Medical College & Hospital, Nagpur, who met all eligibility criteria. Controls were recruited from healthy subjects and the healthy relatives/friends of patients attending the OPD/IPD of the hospital, who also met all eligibility criteria. The present study was conducted from September 2023 to March 2024.

Study Design–

We conducted a hospital-based case-control study to compare the level of cognitive impairment in cases of CKD versus age- and gender-matched healthy controls (without CKD) who have other comorbidities.

Selection Of Cases -

This is a case-control study conducted on 100 adult patients with diagnosed chronic kidney disease (CKD) coming for regular follow-up at the Medicine OPD/IPD and Dialysis Center. Patients aged between 18 and 75 years with at least a primary level of education were included in the study. Patients with pre-existing psychiatric illnesses, pregnancy, chronic liver disease, malignancy, any intracranial space-occupying lesions, cerebral vascular disease, neurodegenerative disorders, B12 deficiency, hypothyroidism, evidence of meningitis or encephalitis, chronic infectious and inflammatory diseases such as chronic glomerulonephritis, amyloidosis, and obstructive uropathy were excluded.

All participants gave their informed consent. These 100 cases were

matched 1:1 with 100 controls based on age, gender, and educational status. Therefore, the total sample size is 200. Cases are diagnosed patients with CKD, while controls are patients without CKD but having one or more comorbidities.

Baseline information including patient demographics, vascular risk factors, medication history, related lab data was collected. A detailed history of patient was taken and clinical examination was performed for all subjects included in the study. All patients underwent routine biochemical laboratory investigations, including a complete hemogram, chest X-ray, ultrasound of the abdomen for bilateral kidneys, and a non-contrast computerized tomography scan of the head to exclude organic causes of cognitive dysfunction. Estimated GFR was obtained using the CKD-EPI Formula, 2021, for all participants.

The patients were divided into four groups according to their eGFR to compare the levels of cognitive impairment among them. They are:

- **Group A:** Patients with eGFR between 30 and 59 ml/min/1.73 m² (stage 3A + 3B)
- **Group B:** Patients with eGFR between 15 and 29 ml/min/1.73 m² (stage 4)
- **Group C:** Patients with eGFR <15 ml/min/1.73 m² not on hemodialysis (stage 5)
- **Group D:** Patients with eGFR <15 ml/min/1.73 m² on hemodialysis for the last 6 months (stage 5-D)

The cognitive status of each patient was assessed using the MMSE test, which is a 30-point questionnaire with a maximum score of 30. It is a widely used, well-validated screening tool for cognitive impairment. It tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The cut-off score used for detecting cognitive dysfunction on the MMSE is 24. Any score of 24 or more (out of 30) indicates normal cognition. Scores below this can indicate severe (≤9 points), moderate (10–18 points), or mild (19–23 points) cognitive impairment.

Selection Of Controls –
Controls will be age and sex matched volunteers from hospital staff and unrelated attendants of patients. Healthy controls will be recruited based on history, examination, investigations like creatinine and MMSE. Finally, cases and controls will be analyzed.

Approximate Sample Size – 100

Inclusion Criteria For Cases –
1. All cases of diagnosed CKD with estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.74 m², persisting for at least 3 months.
2. Age >18 years and <75 years.
3. Those who are willing to give consent.

Exclusion Criteria For Cases –
1. History of psychiatric disorder.
2. Cases of CKD admitted with other medical emergencies.
3. Any other causes that affect cognition such as
- stroke
- Alzheimer's disease.
- Intracranial space occupying lesions.
- Evidence of meningitis or encephalitis
- Alcoholism
- Vitamin b12 deficiency
- Hypothyroidism
- Parkinson's disease
- Chronic liver disease (encephalopathy)
- Malignancy

4. Those who are not willing to give consent

Inclusion Criteria For Controls –
1. Healthy visitors or relatives of patients
2. Age >18 years and <75 years of age.
3. Those willing to give informed consent.

Exclusion Criteria For Controls-
1. Any evidence of CKD
2. Age <18 years and >75 years
3. Not willing to give informed consent
4. History of psychiatric disorder.
5. Any other causes that affect cognition such as-
- stroke
- Alzheimer's disease.
- Intracranial space occupying lesion.
- Evidence of meningitis or encephalitis
- Alcoholism
- Vitamin b12 deficiency.
- Hypothyroidism
- Parkinson's disease.
- Chronic liver disease (encephalopathy)
- Malignancy

6. Those who are not willing to give consent

Definitions:

1. Hypertension-
Hypertension was defined as systolic BP ≥130 or diastolic BP ≥90 mmHg or receiving medication for treatment of hypertension [25].

2. Type 2 Diabetes Mellitus-
Type 2 DM diagnoses is made by the WHO criteria-
- Past history of DM and/or blood glucose records suggestive of DM.
- Patients on oral hypoglycemic drugs and/or insulin
- Fasting Blood Glucose ≥126 mg/dl, a 2h post 75 gm glucose load glucose of ≥200 mg/dL and/or HbA1c ≥ 6.5%. [26]

3. Chronic Kidney Disease (CKD)-
Chronic kidney disease (CKD) is a state of progressive, long standing (more than 3 months), irreversible worsening of renal function and decline in estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m², regardless of the cause. [27].

eGFR calculation by CKD-EPI 2021 formula-
The CKD-EPI 2021 equation is:
$eGFR = 142 \times \min(\text{standardized Scr/K},1)^{\alpha} * \max(\text{standardized Scr/K},1)^{-1.200} * 0.9938^{\text{ageinyears}} * 1.012$ [if female] where:
- Scr = serum creatinine in mg/dL
- K = 0.7 (females) or 0.9 (males)
- α = -0.241 (females) or -0.302 (males)
- min (standardized Scr/K,1) = the minimum of Scr/K or 1
- max (standardized Scr/K,1) = the maximum of Scr/K or 1

4. Cognitive Assessment–
The term "cognition" is derived from Latin and originates from the Greek verb "gignosko," meaning to recognize, perceive, and know. [28] Cognition refers to the mental processes involved in acquiring knowledge and understanding through thought, experience, and sensory input. It encompasses various intellectual functions and processes, including attention, knowledge formation, memory (including working memory), judgment and evaluation, reasoning and problem-solving, as well as language comprehension and production.

Global Screening Measures For Assessing Cognitive Impairment Include:

1. Mini-Mental State Examination (MMSE)
The Mini-Mental State Examination (MMSE) is the most widely used brief global cognitive screening tool among Indian clinicians in outpatient settings and at the bedside. The MMSE is a pencil-and-paper test with a maximum score of 30, where lower scores indicate severe cognitive impairment. A cutoff score of 24 is commonly used to detect cognitive dysfunction. It assesses for five components that include orientation (time and place), registration, attention and calculation, recall (memory), and language and visuospatial skills. While the MMSE provides a standardized index of cognitive dysfunction severity, it has demonstrated low sensitivity and specificity, particularly in cases of mild or early disease, which may lead to an overestimation of cognitive impairment.

2. Hindi Mental State Examination (HMSE)
The Hindi Mental State Examination (HMSE) is a translation and adaptation of the MMSE designed for screening the Hindi-speaking illiterate rural elderly population. Like the MMSE, the maximum score achievable is 30 if all items are answered correctly. This tool is freely available for use.

3. Montreal Cognitive Assessment (MoCA)
The Montreal Cognitive Assessment (MoCA) is a brief, easily administered global cognitive screening tool that is increasingly

popular due to its availability in multiple languages, including various Indian languages such as Bengali, Kannada, Malayalam, Marathi, Tamil, Telugu, Hindi, and Urdu. The MoCA has been validated for use in Malayalam-speaking patients with Parkinson's disease. It has a maximum score of 30 and includes provisions for scoring adjustments based on low education levels, visual impairments, and physical disabilities. The MoCA demonstrates good test-retest reliability for repeated assessments, with a cutoff score of 26 distinguishing normal subjects from those with mild cognitive impairment.

4. Multi-Domain Cognitive Screening Test (MDCST)

The Multi-Domain Cognitive Screening Test (MDCST) is a sensitive and easy-to-administer tool developed for the early detection of mild cognitive impairment (MCI). It exhibits strong psychometric properties and is suitable for demographic studies. The MDCST has been validated for use in populations acclimatized to altitudes above 4300 meters.

Additional Cognitive Assessment Tools Include:

- Blessed Information-Memory Concentration (BIMC)
- Blessed Orientation-Memory Concentration (BOMC)
- Short Test of Mental Status (STMS)
- Short Blessed Test (SBT)
- Memory Impairment Screen (MIS)
- Saint Louis University Mental Status (SLUMS)

These various instruments collectively enhance our ability to assess cognitive function across diverse populations and clinical settings.

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

5. Dyslipidemia

Dyslipidemia is elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein cholesterol (HDL-C) level that contributes to the development of atherosclerosis.

According to ADA classification:

- Elevated triglyceride- serum triglyceride concentrations >150 mg/dl.
- Reduced HDL-C levels - serum HDL concentration <40 mg/dl in females and <50 mg/dl in males.
- Elevated LDL-C levels- serum LDL concentration >100 mg/dl [24]

Review of Literature: Cognitive Impairment in chronic kidney disease (CKD)

1. Introduction To Chronic Kidney Disease

Chronic Kidney Disease (CKD) is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications on health. The kidneys play a crucial role in maintaining overall health by filtering waste products from the blood, regulating blood pressure, producing hormones, and maintaining electrolyte balance [60]. The criteria for CKD include:

A) Markers Of Kidney Damage (One Or More)

- Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol])
- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

b). Decreased eGFR

- eGFR <60 mL/min/1.73 m^2 (eGFR categories G3a–G5)

CKD is a global public health problem, affecting 8-16% of the population worldwide. It is associated with increased all-cause and cardiovascular mortality, kidney failure, and acute kidney injury [48]. CKD is typically diagnosed based on the presence of kidney damage (usually detected as albumin in the urine) or decreased kidney function (measured by glomerular filtration rate, GFR) for three or more months. The disease is classified into five stages based on the level of kidney function.

2. 5 Stages Of CKD

To accurately stage chronic kidney disease (CKD), it is crucial to estimate the glomerular filtration rate (GFR) rather than relying solely on serum creatinine levels. Many laboratories now provide an estimated GFR (eGFR), calculated using standard equations. However, these formulas are only valid when the patient is in a steady state, meaning their serum creatinine levels remain stable over several days. Recent discussions have raised concerns about the use of race as a factor in these calculations, pushing for more individualized methods that avoid the potential harms of racial categorizations [61].

CKD is classified based on cause, eGFR category, and albuminuria category (CGA classification).

eGFR Categories:

- G1: Normal or high (≥90 mL/min/1.73 m^2)
- G2: Mildly decreased (60-89 mL/min/1.73 m^2)
- G3a: Mildly to moderately decreased (45-59 mL/min/1.73 m^2)
- G3b: Moderately to severely decreased (30-44 mL/min/1.73 m^2)
- G4: Severely decreased (15-29 mL/min/1.73 m^2)
- G5: Kidney failure (<15 mL/min/1.73 m^2)

Albuminuria Categories:

- A1: Normal to mildly increased (<30 mg/g)
- A2: Moderately increased (30-300 mg/g)
- A3: Severely increased (>300 mg/g)

The average GFR reaches around 120 mL/min/1.73 m² during the third decade of life and typically declines by about 1 mL/min/1.73 m² per year. By age 70, the average GFR is approximately 70 mL/min/1.73 m², though there is significant variability among individuals. Although a decline in GFR is part of aging, this reduction in kidney function can lead to complications associated with CKD, including the need for medication dosage adjustments. On average, women have lower GFR values compared to men, which is particularly notable in elderly women. For instance, a woman in her eighties with a serum creatinine level in the normal range may still have a GFR below 50 mL/min/1.73 m². Even a slight elevation in serum creatinine in older adults can indicate a significant reduction in GFR [62].

Monitoring albuminuria is also important in assessing nephron damage and therapeutic responses in CKD, particularly in chronic glomerular diseases. The traditional 24-hour urine collection has been replaced by the urinary albumin-to-creatinine ratio (UACR), measured from a single or several first-morning urine samples. A persistent UACR greater than 2.5 mg/mmol in men or 3.5 mg/mmol in women, even with normal dipstick test results, can be an early marker of kidney disease or systemic microvascular damage [65].

The Kidney Failure Risk (KFR) equation is designed to predict progression to stage 5 CKD, or dialysis-dependent kidney failure [66].

CKD in its early stages (1 and 2) is often asymptomatic, and diagnosis is commonly made through routine lab tests conducted for other reasons. In the absence of specific risk factors, population-wide screening is not recommended. However, as CKD progresses to stages 3 and 4, both clinical and lab-related complications become more evident, affecting nearly all organ systems. Common issues include anemia with fatigue, decreased appetite leading to malnutrition, and imbalances in calcium, phosphorus, and hormones like calcitriol, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23). Abnormalities in sodium, potassium, water, and acid-base balance are also frequent.

Many patients, especially older adults, [67] may have eGFR values consistent with stage 2 or 3 CKD but may not experience further

deterioration of kidney function. In such cases, regular monitoring is recommended, and if the kidney function remains stable without associated proteinuria, ongoing care by a primary physician may suffice. However, if a patient's GFR declines, albuminuria develops, or hypertension remains uncontrolled, referral to a nephrologist is warranted. If CKD progresses to stage 5 (GFR <15 mL/min), patients typically experience significant impairments in daily life, well-being, nutrition, and electrolyte balance, ultimately leading to uremia.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (mL/min/1.73 m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

3. The Global Burden Of CKD

The disease burden of CKD remains substantial and continues to grow globally. From 1990 to 2019, global incident cases of CKD have more than doubled and DALYs have almost doubled, and surpassed 40 million years. CKD due to diabetes mellitus type 2 and hypertension contributed nearly 2/3 of DALYs in 2019 of known causes, and had witnessed the highest growth in age-standardized DALY rate. Etiology-specific prevention strategies should be placed as a high priority on the goal of precise control of CKD [63].

Chronic Kidney Disease represents a significant global health burden, affecting millions of people worldwide. The prevalence of CKD has been increasing steadily over the past decades, driven by factors such as population aging, the rising incidence of diabetes and hypertension, and improved survival from cardiovascular diseases [55].

According to the Global Burden of Disease Study 2017, CKD affected approximately 697.5 million people worldwide, with a global prevalence of 9.1% [50]. This prevalence varies significantly across regions and countries, ranging from 7% to 12% in the general population [57]. In 2017, CKD was the 12th leading cause of death globally, accounting for 1.2 million deaths [50].

The impact of CKD extends beyond mortality, significantly affecting quality of life and healthcare costs. In many countries, CKD and its complications acount for a substantial proportion of healthcare expenditures. For instance, in the United States, Medicare spending for beneficiaries with CKD exceeded $120 billion in 2017, representing 22.3% of total Medicare fee-for-service spending [58].

Furthermore, the global burden of CKD is unevenly distributed, with low- and middle-income countries (LMICs) facing disproportionate challenges. These countries often lack resources for early detection and management of CKD, leading to higher rates of progression to end-stage renal disease and increased mortality [59].

4. Etiology and Epidemiology of CKD

Based on population data, it's estimated that at least 6% of adults in the United States have chronic kidney disease (CKD) at stages 1 and 2. An additional 4.5% of the population is believed to have CKD at stages 3 and 4 [64]. The contribution of each cause varies by geographic region. In North America and Europe, diabetic nephropathy, most commonly linked to type 2 diabetes, is the leading cause [68]. Many patients with newly diagnosed CKD also present with hypertension. When there is no clear sign of a primary glomerular or tubulointerstitial disease, CKD is often attributed to hypertension. However, it is now recognized that some of these cases may involve a subclinical primary glomerulopathy, such as focal segmental or global glomerulosclerosis [69]. In other cases, the progression of nephrosclerosis and hypertension may be related to a broader systemic vascular disease affecting other organs like the heart and brain. This combination is particularly common in older adults, where chronic kidney ischemia may be an underdiagnosed cause of CKD.

5. Pathophysiology And Biochemistry Of Uremia

Although doctors measure serum urea and creatinine levels to assess kidney function, the buildup of these substances alone does not explain the symptoms of uremia seen in advanced chronic kidney disease (CKD). When the glomerular filtration rate (GFR) drops, many different toxins accumulate in the body, contributing to the uremic syndrome. These toxins can be water-soluble, fat-soluble, protein-bound, and can carry positive or negative charges [70].

Therefore, while urea and creatinine levels are easy to measure, they provide an incomplete picture of the toxins that remain in the body. Monitoring these levels in patients with kidney problems oversimplifies the complexities of uremia [71]. The uremic syndrome isn't just about the kidneys failing to excrete waste; it also affects many other metabolic and hormonal functions typically handled by the kidneys. This can lead to issues like anemia, malnutrition, and problems with how the body processes carbohydrates, fats, and proteins.

Additionally, levels of several hormones in the blood—such as parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), insulin, glucagon, vitamin D, sex hormones, and prolactin—are altered due to CKD. This happens because the kidneys are less able to excrete these hormones, break them down, or regulate them properly [72].

Moreover, CKD is linked to increased inflammation in the body. This is indicated by higher levels of C-reactive protein and other markers of inflammation, while levels of certain proteins like albumin and fetuin, which usually decrease during inflammation, are lower in CKD patients. This inflammation contributes to a syndrome known as malnutrition-inflammation-atherosclerosis/calcification, which can worsen vascular disease and overall health problems in people with advanced kidney disease [73].

Clinical And Laboratory Manifestations Of CKD And Uremia-

Uremia affects nearly every organ system in the body. While chronic dialysis can help manage many of the complications of uremia, it doesn't completely eliminate all issues related to kidney function loss [68].

6. Fluid, Electrolyte, and Acid-Base Disorders in CKD

a) **Sodium And Water Balance:** Healthy kidneys maintain sodium and water balance, but kidney disease can disrupt this, leading to sodium retention and increased fluid volume. This can cause high blood pressure and further kidney damage. Patients may not usually experience low sodium levels (hyponatremia), but if they do, limiting water intake can help. For those with fluid overload, dietary salt restriction is recommended, and stronger diuretics like loop diuretics may be necessary. If diuretics don't work, it may be time to consider starting dialysis. Some CKD patients may also struggle to hold onto sodium and water, which can lead to dehydration and worsen kidney function.

B) **Potassium Balance:** In CKD, potassium excretion may not decrease in line with kidney function due to other factors, such as increased potassium removal through the gastrointestinal tract. However, conditions like high potassium diets, blood cell breakdown, and certain medications can lead to high potassium levels (hyperkalemia). Medications such as RAS inhibitors and potassium-sparing diuretics can further complicate this. Some kidney conditions may lead to more significant potassium retention even with minor declines in kidney function. Low potassium levels (hypokalemia) are rare and usually occur due to low dietary intake or excessive use of diuretics [74, 75].

C) **Metabolic Acidosis:** Metabolic acidosis is common in CKD. While patients can still acidify urine, they produce less ammonia, making it difficult to excrete enough acid from their diets. This condition often worsens as kidney function declines, leading to the buildup of organic acids in the blood. Most patients experience mild acidosis, which can usually be managed with sodium bicarbonate. Even mild metabolic acidosis can increase protein breakdown and contribute to CKD progression [76].

- **Treatment Of Fluid, Electrolyte, And Acid-base Disorders**

Fluid, Electrolyte, and Acid-Base Disorders Dietary salt restriction

and the use of loop diuretics, occasionally in combination with metolazone, may be needed to maintain euvolemia. Water restriction is indicated only if there is hyponatremia. Hyperkalemia often responds to dietary restriction of potassium, the use of kaliuretic diuretics, and both avoidance of potassium supplements (including occult sources, such as dietary salt substitutes) and dose reduction or avoidance of potassium-retaining medications (especially RAS inhibitors). Kaliuretic diuretics promote urinary potassium excretion, whereas potassium-binding resins, such as calcium resonium, sodium polystyrene, or patiromer, can promote potassium loss through the GI tract and may reduce the incidence of hyperkalemia. Intractable hyperkalemia is an indication (although uncommon) to consider institution of dialysis in a CKD patient. The renal tubular acidosis and subsequent anion-gap metabolic acidosis in progressive CKD will respond to alkali supplementation, typically with sodium bicarbonate. Recent studies suggest that this replacement should be considered when the serum bicarbonate concentration falls below 20–23 mmol/L to avoid the protein catabolic state seen with even mild degrees of metabolic acidosis and to slow the progression of CKD. The sodium load in sodium bicarbonate supplementation needs to be taken into account, when ECFV expansion is present.

7. Disorders Of Calcium And Phosphate Metabolism

Secondary hyperparathyroidism, a major cause of high-turnover bone disease, arises from phosphate retention due to declining GFR. Phosphate retention stimulates increased PTH and FGF-23 production, causing abnormal mineral metabolism and reduced calcitriol levels, leading to hyperparathyroidism and hypocalcemia. This process starts when GFR drops below 60 mL/min, though phosphate retention and FGF-23 elevation can occur earlier. High FGF-23 levels are linked to left ventricular hypertrophy and increased mortality in CKD patients [78].

Hyperparathyroidism increases bone turnover, leading to osteitis fibrosa cystica, with bone pain, fragility, and brown tumors. High PTH levels are also linked to muscle weakness and cardiac fibrosis. Patients with advanced CKD are prone to fractures due to bone disease, while osteomalacia results from a lack of mineralized bone matrix due to reduced 1,25(OH)2 D3. Disorders of calcium and phosphate metabolism in CKD primarily affect the skeleton and vascular system, with occasional soft tissue involvement. Bone disease can be classified into high bone turnover (linked to high PTH levels, such as osteitis fibrosa cystica), osteomalacia (due to low vitamin D activity), and low bone turnover (adynamic bone disease with low or normal PTH) [79].

Hyperphosphatemia is strongly associated with cardiovascular mortality in CKD, partly due to vascular calcification. Studies show CKD patients have significant coronary artery and heart valve calcification, which is linked to age, hyperphosphatemia, and low bone turnover. Additionally, hyperphosphatemia can induce changes in vascular cells, leading to calcification and ossification [77].

- **Treatment of Calcium and Phosphate Metabolism**

Optimal management of secondary hyperparathyroidism and osteitis fibrosa involves prevention, focusing on controlling plasma phosphate levels in CKD patients. A low-phosphate diet and phosphate-binding agents, like calcium acetate or carbonate, are essential, but calcium binders can cause hypercalcemia, especially in low bone turnover cases. Non-calcium binders like sevelamer and lanthanum reduce this risk. Calcitriol and analogs (e.g., paricalcitol) suppress PTH but may induce hypercalcemia. Calcimimetics like cinacalcet target parathyroid sensitivity to calcium, lowering PTH and calcium levels [80].

8. Cardiovascular Abnormalities

Cardiovascular disease is the leading cause of morbidity and mortality in patients at every stage of CKD. The incremental risk of cardiovascular disease in those with CKD compared to the age- and sex-matched general population ranges from 10- to 200-fold, depending on the stage of CKD. As a result, most patients with CKD succumb to cardiovascular disease before ever reaching stage 5 CKD. Between 30 and 45% of those patients who do reach stage 5 CKD have advanced significant cardiovascular complications. Thus, the focus of patient care in earlier CKD stages should be directed to prevention of cardiovascular complications.

A) Vascular Disease In CKD:

The higher prevalence of vascular disease in chronic kidney disease (CKD) patients is attributed to both traditional and CKD-specific risk factors. Classic factors like high blood pressure, diabetes, excess fluid, and cholesterol issues combine with CKD-related factors such as anemia, high phosphate levels, and systemic inflammation. Inflammation accelerates vascular blockages, and low fetuin levels can hasten vascular calcification, especially in cases of hyperphosphatemia [81]. Issues like left ventricular hypertrophy and microvascular disease can worsen heart problems, while dialysis-related drops in blood pressure can further stress the heart. Interestingly, cardiovascular deaths in dialysis patients are more often linked to heart failure and sudden death rather than heart attacks. Studies point to arrhythmias, such as asystole and bradyarrhythmias, as the primary cause of sudden cardiac death. Elevated cardiac troponin levels, common in CKD patients without acute ischemia, complicate heart attack diagnosis, requiring serial measurements to track trends. Consistently high troponin levels are independent predictors of adverse cardiovascular events [82].

B) Heart Failure In CKD:

Heart failure in CKD stems from a combination of factors including myocardial ischemia, left ventricular hypertrophy, diastolic dysfunction, and cardiomyopathy, which, together with salt and water retention, often lead to fluid buildup in the lungs (pulmonary edema). A unique form of “low-pressure” pulmonary edema can also occur, especially in advanced CKD, presenting with shortness of breath and a "bat wing" pattern of fluid on chest X-rays, even without excess body fluid. This results from increased capillary permeability caused by uremia and typically improves with dialysis [83].

Additional CKD-related factors like anemia and sleep apnea contribute to the risk of heart failure. Hypertension and left ventricular hypertrophy, common complications in CKD, arise early and correlate with adverse outcomes, including faster kidney function decline [84]. Left ventricular hypertrophy and dilated cardiomyopathy are strong predictors of cardiovascular morbidity and mortality in CKD, largely due to prolonged hypertension and fluid overload. Other factors, such as anemia and the creation of arteriovenous fistulas for dialysis, can lead to high-output heart failure. Surprisingly, low blood pressure in dialysis patients often signals poor heart function and a worse prognosis compared to high blood pressure, a phenomenon referred to as "reverse causation."

In the late stages of CKD, factors such as low blood pressure, reduced body mass index, and low cholesterol may indicate a state of malnutrition and inflammation, which is associated with poor outcomes. In contrast, traditional cardiovascular risk factors like hypertension and hyperlipidemia may suggest a better prognosis. Blood pressure can sometimes be controlled with sodium restriction, diuretics, and dialysis, but some patients remain hypertensive due to imbalances in regulatory mechanisms.

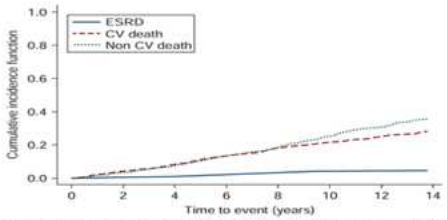


FIGURE 311-6 The cumulative incidence of end-stage renal disease (ESRD), cardiovascular (CV) death, and non-CV death during follow-up in cohort of 1268 participants with an estimated glomerular filtration rate (eGFR). *(Reproduced with permission from LS Dalrymple et al: Chronic kidney disease and the risk of end-stage renal disease versus death. J Gen Int Med 26:379, 2010.)*

Management Of Hypertension In CKD

The primary aim of hypertension treatment in CKD is to prevent cardiovascular disease and stroke. While its role in slowing CKD progression remains uncertain, the benefits for heart and brain health are clear. For CKD patients, especially those with diabetes or significant proteinuria, blood pressure should be reduced to <130/80 mmHg. First-line treatment includes salt restriction, followed by antihypertensives like ACE inhibitors or ARBs, which may reduce kidney function decline. Hyperkalemia and acute kidney injury risks require careful monitoring and adjustments to treatment [85,86].

Management Of Cardiovascular Disease In CKD

Treating both traditional and nontraditional risk factors in CKD patients is crucial, though many therapies have limited evidence in advanced CKD. Hypertension, dyslipidemia, and diabetes drive cardiovascular risk, particularly in dialysis patients. SGLT2 inhibitors (gliflozins) have shown promise in reducing cardiovascular events in

diabetic CKD and are being studied in non-diabetic patients. Pericardial disease, common in underdialyzed patients, necessitates urgent dialysis, often without heparin, to avoid hemorrhage in pericardial effusions [87].

9. Hematologic Abnormalities In CKD

a) Anemia

In chronic kidney disease (CKD), anemia, typically normocytic and normochromic, becomes evident as early as stage 3 and is almost universal by stage 4 [109]. The primary cause is reduced production of erythropoietin (EPO) due to kidney dysfunction. This anemia leads to several adverse effects, such as decreased oxygen delivery to tissues, increased cardiac output, and ventricular changes like dilation and hypertrophy. Clinically, patients experience fatigue, reduced exercise capacity, angina, heart failure, and cognitive impairments, among other issues. In children, anemia may also contribute to growth retardation [110]. While studies show that anemia and resistance to erythropoiesis-stimulating agents (ESAs) correlate with poor outcomes in CKD, it's unclear whether the low hematocrit itself or inflammation causing anemia and ESA resistance is the main contributor [111].

- **Anemia Treatment**

The introduction of recombinant human ESA has been a significant advancement for managing anemia in CKD patients, reducing the need for frequent blood transfusions, which carry risks like infections and iron overload. Adequate iron stores are crucial for the effectiveness of ESA treatment, and iron supplementation, often IV for dialysis patients, is commonly required. However, IV iron therapy may increase susceptibility to bacterial infections, and its long-term effects are still being studied [112]. Besides iron, other substrates like vitamin B12 and folate must be maintained for red cell production. In cases where anemia is resistant to ESA treatment despite sufficient iron levels, other factors such as inflammation, inadequate dialysis, or underlying conditions may be involved [113]. A new class of drugs, prolyl-hydroxylase inhibitors, may offer additional treatment options by increasing endogenous EPO production and iron absorption [114]. Though these agents are promising, randomized trials have shown no cardiovascular benefits from ESA therapy in CKD, and it may increase the risk of stroke, thromboembolism, or renal decline in some cases. Current practice recommends targeting hemoglobin levels between 100–115 g/L.

B) Abnormal Hemostasis

Patients with advanced CKD often experience prolonged bleeding times, impaired platelet function, and increased bleeding tendencies, including from surgical sites or the gastrointestinal tract. Paradoxically, these patients are also more susceptible to thromboembolism, particularly if they have nephrotic-range proteinuria, which can lead to a thrombophilic state due to hypoalbuminemia and loss of anticoagulant factors [115].

- **Hemostasis Treatment**

Abnormal bleeding in CKD can be temporarily managed with desmopressin (DDAVP), cryoprecipitate, IV estrogens, or blood transfusions. Effective dialysis often corrects prolonged bleeding times. Anticoagulation decisions in CKD require careful consideration due to the coexistence of bleeding and thrombosis risks [116]. For instance, warfarin use for atrial fibrillation should be individualized as CKD patients are at higher risk of bleeding complications. Certain anticoagulants, such as low-molecular-weight heparin, may require dose adjustments, with regular monitoring of factor Xa activity where feasible. In hospitalized patients, unfractionated heparin is often preferred for its titratable nature in managing anticoagulation.

10. Neuromuscular Abnormalities In CKD

Chronic kidney disease (CKD) can lead to a range of neuromuscular complications, affecting the central nervous system (CNS), peripheral nerves, autonomic function, and muscle structure [117]. These issues often begin to emerge subtly during stage 3 CKD. Early CNS symptoms include mild cognitive impairments, such as memory lapses, difficulty concentrating, and sleep disturbances. As CKD progresses, neuromuscular irritability, including hiccups, muscle cramps, and twitching, may develop. In severe, untreated kidney failure, more serious neurological symptoms such as asterixis, myoclonus, seizures, and even coma may occur.

Peripheral neuropathy tends to appear clinically during stage 4 CKD, though earlier electrophysiological and histological evidence may be detectable. This type of neuropathy typically affects sensory nerves before motor nerves, lower limbs more than upper, and distal areas more than proximal. Restless leg syndrome is a common manifestation, causing discomfort in the legs and feet that is relieved by movement. Peripheral neuropathy without another underlying cause, such as diabetes or iron deficiency, is often a sign that renal replacement therapy should be initiated. While dialysis can resolve many of these symptoms, subtle abnormalities may persist [118].

11. Gastrointestinal and Nutritional Abnormalities in CKD

Patients with CKD often experience gastrointestinal (GI) complications, including uremic fetor, a urine-like odor on the breath caused by the breakdown of urea into ammonia in saliva. This is often associated with a metallic taste (dysgeusia). CKD patients are at increased risk for gastritis, peptic ulcers, and mucosal ulcerations throughout the GI tract, which can cause abdominal pain, nausea, vomiting, and GI bleeding. Constipation is also common and may be exacerbated by the use of calcium and iron supplements [104].

The accumulation of uremic toxins contributes to anorexia, nausea, and vomiting. While restricting protein intake can help reduce nausea and vomiting, it also increases the risk of malnutrition and should be done under the guidance of a registered dietitian specializing in CKD management. Weight loss and protein-energy malnutrition are prevalent in advanced CKD, often signaling the need for renal replacement therapy [88]. Additionally, metabolic acidosis and inflammatory cytokine activation can accelerate protein breakdown. Nutritional assessments should include dietary history, subjective global assessment, body weight adjusted for fluid retention, and urinary protein nitrogen appearance. Dual-energy X-ray absorptiometry (DEXA) and bioimpedance analysis are widely used to distinguish between lean body mass and fluid weight.

12. Diagnosing Chronic Kidney Disease (CKD) and Identifying Its Underlying Causes

Distinguishing chronic kidney disease (CKD) from acute or subacute renal failure is crucial, as the latter conditions may be reversible with targeted treatment [89]. Previous serum creatinine measurements are valuable for this differentiation - normal historical values suggest acute dysfunction, while previously elevated levels indicate a chronic process. However, acute complications can still occur in chronic cases, such as volume depletion, infections, or nephrotoxin exposure.

A kidney biopsy may be performed in early CKD (stages 1-3) but isn't always necessary. For instance, in long-standing type 1 diabetes with retinopathy and nephrotic-range proteinuria, diabetic nephropathy can be diagnosed clinically [90]. However, atypical findings like hematuria or absence of retinopathy may warrant a biopsy. In advanced CKD with scarred kidneys, biopsy carries significant risks with limited diagnostic value. Modern genetic testing, including chromosomal microarray and whole exome sequencing, is becoming increasingly important in identifying underlying causes of CKD [91].

13. Recent Advances And Treatment Strategies In CKD

Recent therapeutic advances in CKD include SGLT2 inhibitors (gliflozins) for diabetic kidney disease [92] and targeted genomic therapies for conditions like ADPKD, with promising developments for APOL1-mediated kidney disease [93]. Early intervention is crucial, ideally before GFR decline becomes evident [94].

Regular GFR monitoring is essential, with any accelerated decline warranting investigation for reversible causes such as volume depletion, uncontrolled hypertension, infections, urinary obstruction, nephrotoxic exposures (NSAIDs, contrast media), or disease flares [95].

To slow CKD progression, managing intraglomerular hypertension and proteinuria is vital. ACE inhibitors and ARBs effectively reduce proteinuria and slow progression in both diabetic and non-diabetic CKD [96]. While combination ACE-I/ARB therapy shows greater proteinuria reduction, it's generally avoided due to increased AKI and cardiac event risks [97].

Treatment Approach Varies By Disease Type:

- **For conditions with significant proteinuria (diabetic nephropathy, glomerular diseases):** ACE inhibitors/ARBs are preferred [98]
- **For diseases with minimal initial proteinuria (ADPKD,**

tubulointerstitial diseases): other antihypertensives may be suitable

14. Medication Dose Adjustment in CKD

Although the loading dose of most drugs is not affected by CKD because renal elimination is not used in the calculation, the maintenance doses of many drugs will need to be adjusted. For those agents in which >70% excretion is by a nonrenal route, such as hepatic elimination, dose adjustment may not be needed. Some drugs that should be avoided include metformin, meperidine, and oral antihyperglycemics that are eliminated by the kidney. NSAIDs should be avoided because of the risk of further worsening of kidney function. Many antibiotics, antihypertensives, and antiarrhythmics may require a reduction in dosage or change in the dose interval. Several online Web-based databases for dose adjustment of medications according to stage of CKD or estimated GFR are available (e.g., http:// www.globalrph.com/index_renal.htm). Nephrotoxic radiocontrast agents and gadolinium should be avoided or used according to strict guidelines when medically necessary, as discussed above.

15. Global Health Implications Of CKD

The global healthcare landscape is witnessing a significant epidemiological transition. While many infectious diseases have shown declining trends or have been successfully eradicated, there is an alarming surge in metabolic and vascular diseases across developing nations [100]. This shift presents a particularly concerning scenario in the context of chronic kidney disease, as it represents a growing burden on healthcare systems that are often already resource-constrained [101].

The rising prevalence of diabetes mellitus in developing countries serves as a critical driver of this epidemic. This increase appears to be intricately linked to modernization and lifestyle changes, characterized by shifting dietary patterns favoring processed foods, diminished physical activity in increasingly urbanized populations, and consequent weight gain [102]. As these lifestyle changes become more entrenched, healthcare systems face the inevitable challenge of managing a proportionate surge in associated vascular and renal complications [103].

This evolving healthcare crisis necessitates immediate attention from global health agencies. There is an urgent need to develop and implement comprehensive strategies encompassing early detection through improved screening of high-risk populations, establishment of preventive protocols, and development of culturally appropriate treatment plans [103]. Furthermore, healthcare systems in these nations must begin addressing the complex logistics and financial implications of providing adequate renal replacement therapies to an expanding patient population [105].

A particularly concerning aspect of this global health challenge is the emergence of endemic nephropathies in developing countries. These conditions disproportionately affect young male agricultural workers, representing a significant threat to both public health and economic productivity [106]. The full extent of morbidity and mortality associated with these nephropathies is only beginning to be understood. Current research suggests a complex interplay of potential causative factors, including:

- Population-specific genetic risk factors
- Exposure to endemic nephrotoxins
- Agricultural pesticide exposure
- Widespread NSAID use
- Chronic volume depletion due to working conditions [107, 108]

16. Domains of Cognitive Impairment in CKD

- Chronic kidney disease (CKD) is commonly associated with neuro-cognitive impairments, which can affect multiple cognitive domains, including:
- **Orientation And Attention:** This domain is particularly affected by CKD.
- **Language:** This domain is particularly affected by CKD.
- **Executive Functions:** This domain is affected in mild CKD, and more globally in severe CKD.
- **Concept Formation And Reasoning:** This domain is affected by CKD.
- **Memory:** This domain is affected by CKD. [56]

Cognitive impairment can appear early in the course of CKD, and the severity of the impairment can vary from mild to severe. In severe CKD, cognitive impairment can be more global and more severe, possibly because individuals are older by the time they reach this stage.

- **CKD can lead to cognitive impairment for a number of reasons, including:**

a) Cerebral small vessel disease
b) White matter integrity impairment
c) Cardiovascular and hemodynamic deviances, that damage both the kidneys and the brain simultaneously.
d) Hypertension, that is common in CKD patients and may play a role in the association between kidney function and white matter integrity.

- **Other Factors Contributing To Cognitive Impairment In Ckd Include:**

a) FGF23/Alpha Klotho Axis: FGF23, produced in bones, may directly affect hippocampal neurons and impair memory and learning function.
b) Cerebral microbleeds: These are common in patients treated with hemodialysis and may signify increased risk for larger intra-cranial hemorrhage.

A widely used screening tool for cognitive impairment is the MMSE, a 30-point questionnaire that tests five areas of cognitive function.

Patients with impaired cognitive function may struggle with adhering to treatment regimens and making informed decisions about their care, which can negatively impact their health outcomes.

RESULTS:

Descriptive analysis:

Table 1: Distribution Of Study Participants According To Age Group:

Age group (in years)	Cases		Controls	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
20-30	7	7.00	7	7.00
30-40	14	14.00	14	14.00
40-50	21	21.00	21	21.00
50-60	26	26.00	26	26.00
>60	32	32.00	32	32.00
Total	100	100.00	100	100.00

From the above table it is evident that both case and control groups are similar with respect to age distribution of study participants and the maximum number of study participants being in the age group of 40-60 years which amount to 47%. The geriatric population amounts to 32%.

The Summary Statistics For Both Cases And Controls Is As Follows:

Summary statistics for age (in years)	Cases (n=100)	Controls (n=100)
Mean	54.0	52.5
Median		53.5
IQR		
Standard deviation	13.1	13.5
Minimum	23	21
Maximum	74	75
Range	51	54

The normal distribution of the data is checked with Shapiro wilk test and both cases and controls are not normally distributed with respect to age. (p value = <0.05)

Table 2: Distribution Of Study Participants According To Gender:

Gender	Cases		Controls	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Male	60	60.00	60	60.00
Female	40	40.00	40	40.00
Total	100	100.00	100	100.00

From the above table it is evident that majority of study subjects of CKD were males (60%) as compared to females (40%). Both cases and controls are comparable with respect to gender distribution.

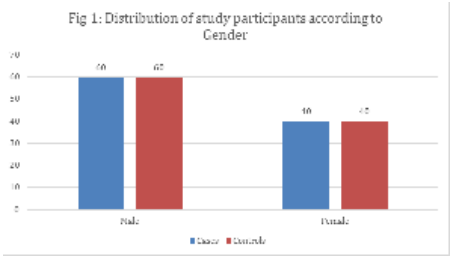
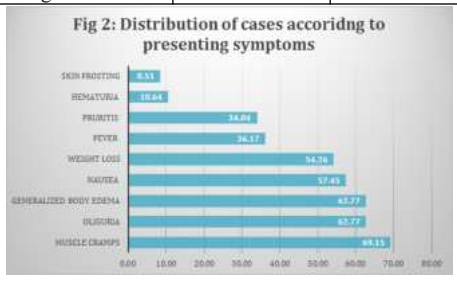


Table 3: Distribution Of Cases According To Presenting Symptoms:

Presenting Symptoms	Number (n=94)	Percentage (%)
Muscle cramps	65	69.15
Oliguria	59	62.77
Generalized body edema	59	62.77
Nausea	54	57.45
Weight loss	51	54.26
Fever	34	36.17
Pruritis	32	34.04
Hematuria	10	10.64
Skin frosting	8	8.51



From the above table it is evident that muscle cramps were the major presenting symptom in most of the cases which amounts to 69.15%, followed by decreased urine output (59%) and anasarca (59%), the lowest being skin frosting which amounts to 8.51%. It can also be seen that only cases had the presenting symptoms and as controls are patients without CKD, they do not have any of the above-mentioned presenting symptoms

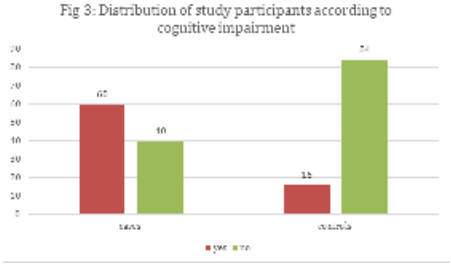


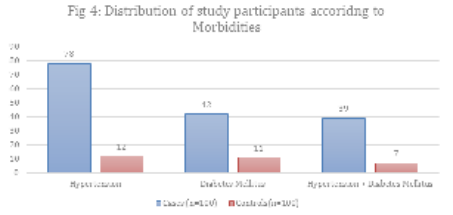
Table 4: Association Between The Cognitive Impairment And Chronic Kidney Disease In Study Participants:

Group of participants	Cognitive impairment		OR	95% CI	X^2 Df P value
	Yes	No			
Cases	60(78.95)	40(32.25)	7.78	4.04-15.54	41.09 1 <0.0000 Significant
Controls	16(21.05)	84(67.75)			
Total	76(100.00)	124(100.00)			

From the above table it is evident that the Odds of occurrence of cognitive impairment is 7.78 times more in patients with CKD in comparison with patients without CKD and it is statistically significant (p value <0.0000)

Table 5: Distribution Of Study Participants According To Presence Of Morbidities:

Gender	Cases (n=100)		Controls(n=100)		P value
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	<0.000
Hypertension	78	78.00	12	12.00	
Diabetes Mellitus	42	42.00	11	11.00	
Hypertension + Diabetes Mellitus	39	39.00	7	7.00	



From the above table it is evident that Hypertension and Diabetes Mellitus are the most common co-morbidities present in cases. It has been found their prevalence is significantly more in cases of CKD as compared to controls without CKD. Hypertension is the major co-morbidity which is present in 78% of cases and 12% of controls, and Diabetes is observed in 42% of cases and 11% controls, both showing statistically significant associations with CKD (<0.000) using chi-square test.

Table 6: Distribution Of Study Participants According To Anemia Status:

Status of anemia	Cases (n=100)		Controls(n=100)		P value
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	
Anemic	94	94.00	61	61.00	<0.000
Not anemic	6	6.00	39	39.00	
Total	100	100.00	100	100.00	

From the above table it is evident that, anemia is the presenting clinical feature which is more prevalent in cases (94%) as compared to controls (61%) with p-value <0.000 which is highly significant.

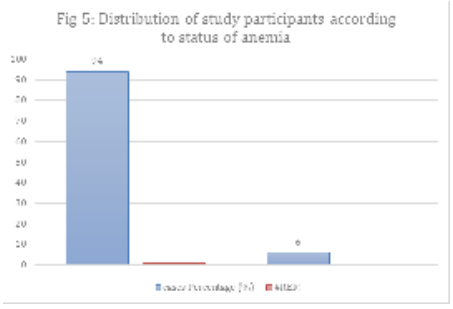


Table 7: Distribution Of Study Participants According To Serum Creatinine Level:

Serum creatinine level	Cases (n=100)		Controls (n=100)	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Decreased	0	0.00	43	43.00
Normal	0	0.00	57	57.00
Elevated	100	100.00	0	0.00
Total	100	100.00	100	100.00

From the above table it is evident that all cases being CKD patients have elevated serum creatinine levels while most of the controls (57%) have normal serum creatinine levels. It is also notable that none of the controls have elevated serum creatinine levels.

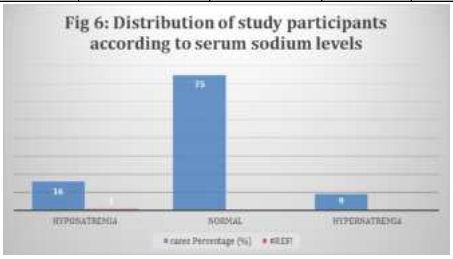
Summary Statistics For Serum Creatinine Levels Are As Follows:

Summary statistics for serum creatinine (in mg/dl)	Cases (n=100)	Controls (n=100)
Mean	4.57	0.70
Median	3.70	0.80
Standard deviation	2.98	0.31
IQR	3.75	0.60
Minimum	1.30	0.20
Maximum	14.0	1.40
Range	12.7	1.20

Table 8: Distribution Of Study Participants According To Serum Sodium Levels:

Serum sodium levels	Cases (n=100)		Controls (n=100)	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Hyponatremia	16	16.00	6	6.00

Normal	75	75.00	94	94.00
Hypernatremia	9	9.00	0	0.00
Total	100	100.00	100	100.00



From the above table it is evident that majority of cases (75%) and controls (94%) have normal serum sodium levels while the proportion of hypernatremia and hyponatremia is more is cases as compared with the controls.

Table 9: Distribution Of Study Participants According To Serum Potassium Levels:

Serum potassium levels	Cases (n=100)		Controls (n=100)	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Hypokalemia	21	21.00	0	0.00
Normal	63	63.00	100	100.00
Hyperkalemia	16	16.00	0	0.00
Total	100	100.00	100	100.00

Summary Statistics For Serum Potassium Levels:

Summary statistics for serum potassium (in mg/dl)	Cases (n=100)	Controls (n=100)
Mean	4.41	4.36
Median	4.30	4.30
Standard deviation	0.98	0.56
IQR	1.38	1.10
Minimum	2.10	3.50
Maximum	6.39	5.20
Range	4.29	1.70

From the above table it is evident that the proportion of hyperkalemia in cases is 16% while all the controls have normal serum potassium levels.

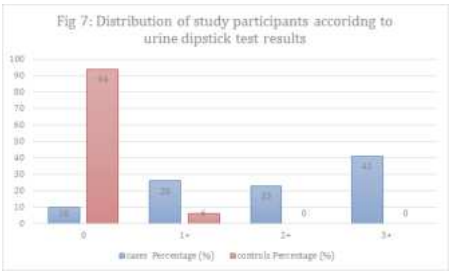
Table 10: Distribution Of Study Participants According To Lipid Profile Parameters:

Lipid profile parameters		Cases (n=100)		Controls (n=100)	
		Number (n)	Percentage (%)	Number (n)	Percentage (%)
HDL	Optimal (up to 60 mg/dl)	42	42.00	84	84.00
	Not optimal (<60 mg/dl)	58	58.00	16	16.00
LDL	Optimal (<100 mg/dl)	92	92.00	100	100.00
	Not optimal (>=100 mg/dl)	8	8.00	0	0.00
Total cholesterol	Optimal (<200 mg/dl)	90	90.00	100	100.00
	Not optimal (>=200 mg/dl)	10	10.00	0	0.00
Triglycerides	Optimal (<150 mg/dl)	69	69.00	100	100.00
	Not optimal (>=150 mg/dl)	31	31.00	0	0.00

From the above table it is evident that the lipid parameters are normal in control group while most case group participants (58%) have deranged HDL levels and serum triglyceride levels (31%). Also, minimal number of participants in case group have deranged LDL and total cholesterol levels.

Table 11: Distribution Of Study Participants According To Urine Dipstick Test Results:

Urine dipstick test results	Cases (n=100)		Controls(n=100)	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
0	10	10.00	94	94.00
1+	26	26.00	6	6.00
2+	23	23.00	0	0.00
3+	41	41.00	0	0.00
Total	100	100.00	100	100.00

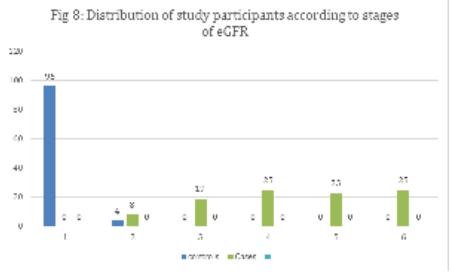


From the above table it is evident that majority of cases (41%) have 3+ urinary excretion of albumin while most of the controls (94%) have normal dipstick results.

Table 12: Distribution of study participants according to staging of eGFR:

Staging of eGFR	Cases (n=100)		Controls (n=100)	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Normal	0	0.00	96	96.00
Stage 3A	8	8.00	4	4.00
Stage 3B	19	19.00	0	0.00
Stage 4	25	25.00	0	0.00
Stage 5 off dialysis	23	23.00	0	0.00
Stage 5 on dialysis	25	25.00	0	0.00

From the above table it is evident that there is even distribution of patients in categories, and majority of cases (47%) are in the stage of Kidney failure while majority of controls (96%) have normal eGFR.



Summary statistics for the eGFR levels is as follows:

Summary statistics for eGFR (In ml/min/1.74 m2)	Cases (n=100)	Controls (n=100)
Mean	20.8	106
Median	16.1	107
Standard deviation	14.3	27.5
IQR	21.1	36.3
Minimum	2.67	55.4
Maximum	58.1	178
Range	55.5	122

Table 13: Distribution of study participants as per level of cognitive impairment according to MMSE scores:

Level of Cognitive impairment	Cases (n=100)		Controls (n=100)	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
No impairment	40	40.00	84	84.00
Mild	34	34.00	11	11.00
Moderate	25	25.00	5	5.00
Severe	1	1.00	0	0.00

From the above table it is evident that the proportion of cognitive impaired individuals in cases is 60% while the proportion of cognitive impaired individuals in controls is 16%.

Summary statistics for the MMSE scores for cases is as follows:

Summary statistics for MMSE scores	Cases (n=100)
Mean	22.0
Median	22.0
Standard deviation	4.61
IQR	7.25
Minimum	9
Maximum	30
Range	21

Table 14: Comparison of eGFR levels in patients with cognitive impairment in both the study groups:

Patients with cognitive impairment	eGFR (in ml/min/1.74 m2) Mean±SD	t statistic	Mean difference	Df	P value*
Cases	17.9±11.1	-20.6	-85.1	74	<0.001 Significant
Controls	103±24				

*** Independent sample t test**

From the above table it is evident that there is significant difference in mean eGFR values in patients with cognitive impairment in the group of study participants.

Table 15: Comparison Of Serum Potassium Levels In Patients With Cognitive Impairment In Both The Study Groups:

Patients with cognitive impairment	Serum potassium Mean±SD	t statistic	Mean difference	Df	P value*
Cases	4.42±1.03	-0.58		74	0.55 Not significant
Controls	4.58±0.61				

*** Independent sample t test**

From the above table it is evident that there is no significant difference in mean serum potassium values in patients of cognitive impairment in both the study groups

Table 16: Association Between Hyperkalemia And Cognitive Impairment In Study Participants:

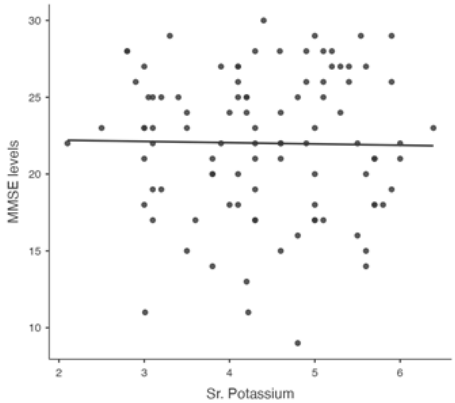
Hyperkalemia (K >5.0 mg/dl)	Cognitive impairment		OR	95% CI	P value *
	Cases	Controls			
yes	16(26.67)	6(37.50)	0.61	0.18-2.07	0.578 Not significant
No	44(73.33)	10(62.50)			
Total	60(100.00)	16(100.00)			

*** Fischer Exact Test**

From the above table it is evident that patients with hyperkalemia are having 0.61 times lesser chance of occurrence of cognitive impairment than patients who don't have hyperkalemia and it is not statistically significant. This means that there is no significant association between hyperkalemia and cognitive impairment in both the group of study participants.

Table 17: Correlation between MMSE scores and Serum potassium levels in patients with CKD:

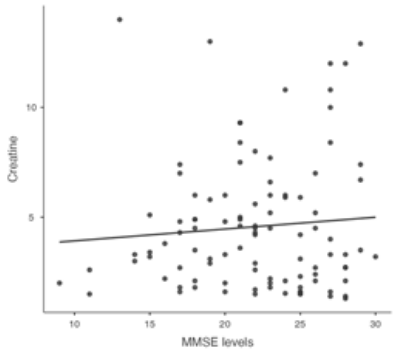
Pearson correlation coefficient	-0.018
Df	98
P value	0.861



From the above table it is evident that there is a mild negative correlation between Serum potassium levels and MMSE scores in patients with CKD and it is not statistically significant.

Table 18: Correlation between serum creatinine levels and MMSE scores in patients with CKD:

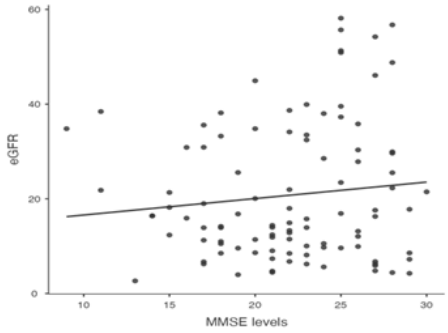
Pearson correlation coefficient	0.083
Df	98
P value	0.410



From the above table it is evident that there is a slight positive correlation between the serum creatinine levels and MMSE scores in patients with CKD but it is not statistically significant.

Table 19: Correlation between eGFR and MMSE scores in patients with cognitive impairment:

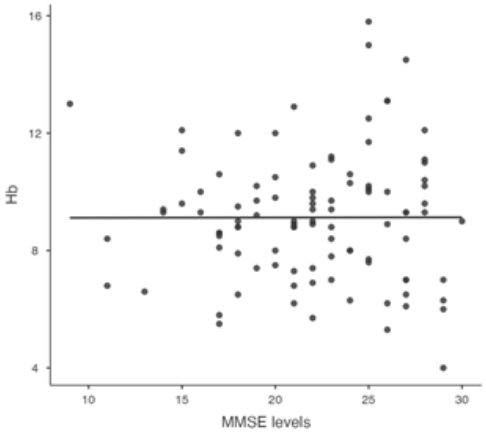
Pearson correlation coefficient	0.112
Df	98
P value	0.226



From the above table it is evident that there is a slight. positive correlation between the MMSE scores and eGFR values in patients with CKD but it is not statistically significant.

Table 20: Correlation between hemoglobin and MMSE scores in patients with CKD:

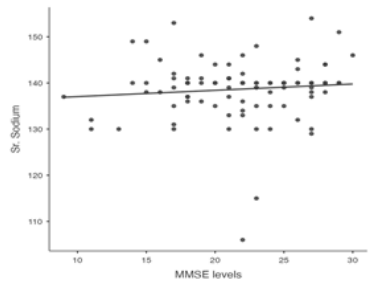
Pearson correlation coefficient	0.002
Df	98
P value	0.987



From the above table it is found that there is very minimal positive correlation between hemoglobin values and MMSE scores in patients with CKD but it is not statistically significant.

Table 21: Correlation between serum sodium values and MMSE scores in patients with CKD:

Pearson correlation coefficient	0.099
Df	98
P value	0.326



From the above table it is evident that the correlation between serum sodium levels and MMSE scores in patients with CKD is not statistically significant.

Table 22: Correlation between serum lipid parameters and MMSE scores in patients with CKD:

Lipid profile parameters V/S MMSE Scores	Parameters	Value
HDL	Pearson correlation coefficient	0.205
	Df	98
	P value	0.041(significant)
LDL	Pearson correlation coefficient	-0.137
	Df	98
	P value	0.174
Total cholesterol	Pearson correlation coefficient	-0.198
	Df	98
	P value	0.048 (significant)
Triglycerides	Pearson correlation coefficient	-0.061
	Df	98
	P value	0.550

From the above table it is evident that there is a statistically significant correlation between MMSE scores and levels of HDL and total cholesterol in patients with CKD. The MMSE scores increases when the serum HDL levels are high while the MMSE scores increases when there is lesser total cholesterol level.

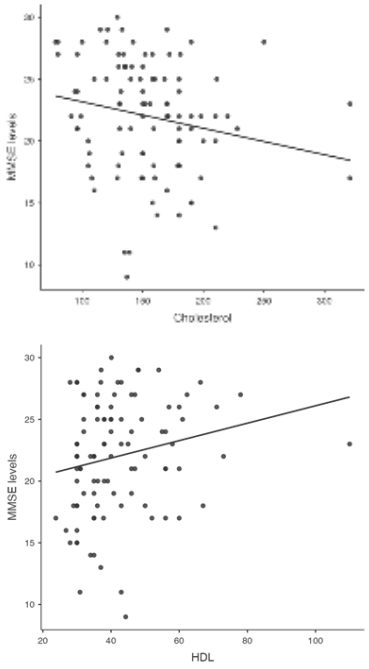


Table 23: Multiple Linear Regression (MLR) analysis for the predictors of cognitive impairment in the group of study participants:

Model Coefficients - cognitive impairment status					
			95% Confidence Interval		
Predictor	Estimate	SE	Lower	Upper	t	p
Intercept	0.56893	0.22970	0.11592	1.02195	2.477	0.014
egfr	-0.00367	6.60e-4	-0.00498	-0.00237	-5.562	< .001
HDL	-0.00940	0.00265	-0.01462	-0.00419	-3.554	< .001
cholesterol	0.00229	8.29e-4	6.58e-4	0.00393	2.767	0.006

The variables which were significant in univariate analysis were taken for the multivariate linear regression analysis.

The adjusted R^2 for the overall regression model is 0.259, which means 25.9% of variation in results will be explained by the presence of the below mentioned 4 variables in the model.

From the above table it is evident that, for every 1 unit increase in MMSE scores the eGFR levels decreases by 0.00367 units and it is statistically highly significant. for every one unit increase in MMSE scores the HDL levels decrease by 0.00940 units, and it is also statistically significant. At last, for every one unit increase in MMSE scores the total cholesterol level increases by 0.00229 units and it is statistically significant.

Thus eGFR, HDL and serum total cholesterol can be considered as significant predictors for the cognitive impairment in both the group of study participants.

Table 24: Comparison of mean MMSE scores in study participants:

Study participants	MMSE Scores Mean±SD	t statistic	Mean difference	Df	P value*
Cases	22.01±4.6	8.94	5.07	198	<0.001 Significant
Controls	27.08±3.29				

***Independent sample t test**

From the above table it is evident that the MMSE scores are comparatively low in case group than the control group and it is statistically significant indicating that the level of cognitive impairment is more in case group than the control groups.

Table 25: Comparison of severity of cognitive impairment and level of eGFR among cases:

MMSE Levels	Stage 3(A+B)	Stage 4	Stage 5(On & Off dialysis)	Total
Mild	7	6	21	34
Moderate	6	7	12	25
Severe	1	0	0	1
Total	14	13	33	60

From the above table it is evident that 60% of study participants have cognitive impairment.

Majority of participants having mild and moderate cognitive impairment, have stage 5 renal failure.

Model	Deviance	AIC	R2mcf
1	234.170	238.170	0.155

Model Coefficients – sr no

						95% Confidence interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-1.322	0.281	-4.698	<0.001	0.267	0.154	0.463
mmse coded: 1-0	2.064	0.341	6.057	<0.001	7.875	4.039	15.355

Note. Estimates represent the log odds of "sr no = 2" vs. "sr no = 1"

The multivariate analysis revealed that chronic kidney disease (CKD) is a significant risk factor for cognitive decline, with an odds ratio of 7.87 (95% CI: 4.04–15.36, p < 0.001), indicating patients with CKD have markedly higher odds of cognitive impairment compared to those without.

Statistical Analysis:

- Data is collected through a questionnaire, cleaned and entered in MS excel and analysis is done through Jamovi software version 2.3.28.
- Quantitative data is expressed as Mean and Standard deviation after checking for Normality through Shapiro-Wilk test. If not

normally distributed then it is expressed as Median and Inter Quartile range (IQR).
- Qualitative data is expressed as Frequency and Percentage. Chi square and Fischer exact test is used for finding the association between the qualitative variables.
- Pearson's correlation test is used for finding the correlation between two quantitative variables.
- Multiple Linear regression analysis is used for finding the factors contributing to cognitive impairment.
- P value less than 0.05 is considered as statistically significant.

DISCUSSION:

Chronic kidney disease (CKD) represents a global health crisis, affecting approximately 10% of the world's population [50]. WHO identified CKD as the 10th leading cause of morbidity and mortality in 2020, with its prevalence and mortality rising significantly. The gravity of CKD extends beyond its direct impact on renal function, encompassing a wide array of under-recognized systemic complications such as cognitive impairment, which significantly impact patient outcomes and quality of living [51, 52, 53]. Notably, individuals with CKD have been found to have a 65% higher risk of developing cognitive impairment compared to those with normal kidney function, even after adjusting for traditional vascular risk factors [54].

This striking trend of rising prevalence raises concerns of CKD as an emerging independent risk factor for cognitive decline among affected patients. While traditional risk factors such as hypertension (HTN) and diabetes mellitus (DM) have been extensively studied, the onset of kidney damage results in the retention of uremic toxic compounds like indoxyl sulfate and p-cresyl sulfate which further exacerbate cognitive impairment. Notably, this relationship can be also evidenced by the fact that renal transplantation has been shown to improve cognitive function in patients with severe kidney impairment, highlighting a direct link between kidney health and cognitive outcomes. Similar to how CKD itself is a risk factor for cognitive decline, increase in various biochemical markers can serve as predictors of kidney damage, guiding management strategies. Early detection of cognitive impairment is crucial, as it is often reversible initially; thus, understanding these associations is vital for preventing progression to irreversible cognitive decline and poorer prognoses.

Moreover, the burden of kidney disease is highest among the historically disadvantaged population, having limited access and means to healthcare, and hence we conducted a case control study assessing cognitive impairment in patients with chronic kidney disease at IGGMCH, Nagpur. This research also explores the association between various risk factors and cognitive impairment, with a specific focus on the severity of cognitive decline in different stages, while comparing the finding with similar studies in the existing literature.

In our study, the participants were equally distributed, revealing that majority of the participants in both cases and controls were aged between 40-60 years, with mean age being around 54 years in both groups. This distribution is consistent with other studies indicating that cognitive impairment in CKD predominantly affects older adults [8,9]. For instance, a study conducted in India by Aggarwal et al. (2020) reported a mean age of 50.34 years, closely aligning with our findings [35]. Additionally, a cross-sectional study by Gela et al. (2021) in Ethiopia found a median age of 57.5 years for both CKD patients and healthy controls, further supporting the age distribution observed in our research.

Moreover, it is noteworthy that age-standardized mortality rates have increased by 41.5% between 1990 and 2017 [49]. This trend, coupled with the aging global population, suggests a substantial rise in the burden of CKD-associated cognitive dysfunction in the coming decades [20].

Several factors contribute to the potential danger of cognitive impairment in CKD:

1. The high prevalence of hypertension (78%) among cases in our study aligns with the established understanding that hypertension is the most prevalent risk factor in chronic kidney disease (CKD). According to Ku et al. (2019), the prevalence of hypertension among CKD patients ranges from 60% to 90%, depending on the disease stage [40]. Furthermore, Liu et al. (2023) highlighted a concerning trend, reporting an incidence rate of HTN-related CKD of 19.45% and a mortality rate of 5.88 per 100 K population in 2019 [41], both of which are on the rise annually.

2. The presence of diabetes (42%) among our cases corresponds with findings by Liao et al. (2023), who identified diabetes as a major contributor to both the severity and mortality in CKD patients. Their study revealed a mortality rate of 29.3% among diabetic patients with CKD compared to controls, highlighting diabetes as a more critical factor for mortality in CKD patients compared to hypertension.

3.The lipid profile analysis revealed significant associations between HDL and total cholesterol levels and the degree of cognitive impairment. Higher HDL levels were linked to improved cognition (p value 0.041), supporting findings from Rysz et al. [34], which suggest that HDL may play a neuroprotective role through its anti-inflammatory and antioxidative properties. Conversely, elevated total cholesterol was associated with decreased cognitive function ($p = 0.048$), consistent with the results of Pang K et al. study [44] and several other studies. However, some research offers a different perspective. For instance, the study by Cheng Y et al. reported an inverse U-shaped relationship between total cholesterol level and cognitive scores, indicating that both low and high cholesterol levels were associated with poorer cognitive performance [43].

Cognitive decline in CKD can impair a patient's ability to adhere to complex medication regimens and dietary restrictions, potentially accelerating disease progression and increasing the risk of complications [22,14]. This can severely impact their overall quality of life, contributing to the already substantial psychosocial burden of CKD [10,12].

Our study also found that muscle cramps and weakness were the most common symptoms, observed in 69.15% of patients, with a higher incidence in those on dialysis. This was followed by oliguria, generalized body edema, nausea, and weight loss. This finding aligns with Caravaca et al., who reported that 38% of patients with CKD experienced chronic musculoskeletal symptoms due to uremia and associated comorbidities [38].

Additionally, 94% of the patients in our study were found to have mild to moderate anemia, consistent with findings from numerous studies. A recent cross-sectional study by Filagot Bishaw et al. (2024) reported an overall prevalence of anemia among patients with stages 3 to 5 chronic kidney disease (CKD) at 85.33% [39]. Anemia can lead to reduced blood flow and impaired kidney function, which may further exacerbate kidney deterioration and contribute to cognitive impairment.

Moreover, unlike our study, which found cognitive impairment even in patients with mild and moderate CKD (stages 3a and 3b), a large cohort study of older adults in 2020 found that only severe CKD (stage 4) was associated with cognitive impairment at baseline and with cognitive decline over time. There was no significant link between mild to moderate CKD and cognitive dysfunction in that study. The difference in findings may be because kidney-related risk factors become more prominent in advanced CKD. In earlier stages, cognitive impairment could be more closely related to vascular damage, as conditions like hypertension can cause small vessel disease in the brain [37].

Our study revealed a statistically significant difference in mean estimated glomerular filtration rate (eGFR) values among both groups. Specifically, we found that patients with cognitive impairment had a mean eGFR of 20.8 mL/min/1.73m², which was significantly lower than the mean eGFR of 106 mL/min/1.73m² in patients without cognitive impairment ($p < 0.001$). Cases also had 7.78 times higher odds of cognitive decline than controls.

Our findings are consistent with, but also extend previous research in this area. For instance, Szerlip et al. reported that an eGFR under 45 mL/min per 1.73 m² increased the odds of mild cognitive impairment (OR = 2.4) across multiple cognitive domains, particularly in men [31]. Our study not only confirms this association but also demonstrates its persistence across a broader range of eGFR values and in a more diverse patient population.

Similarly, Li et al. found that low eGFR is linked to cognitive dysfunction in older adults, especially those with stages 3–5 chronic kidney disease (CKD) [32]. While their study focused on executive

function and memory deficits, our research utilized a comprehensive cognitive assessment battery, allowing us to identify impairments across a wider spectrum of cognitive domains.

Interestingly, our results diverge from those reported by Martens et al., who found no relationship between eGFR and cognitive performance in a population aged 40 to 75 years [33]. This discrepancy might be explained by differences in study populations, cognitive assessment tools, or the range of eGFR values examined, and also deviates from most established researches till date.

Our study found no statistically significant correlation between serum potassium levels and cognitive function, as measured by MMSE scores. This suggests that neither hypokalemia nor hyperkalemia are directly linked to cognitive impairment. While potassium imbalances are common in chronic kidney disease (CKD), their impact on cognitive function may be limited or affected by other factors. There is a scarcity of studies supporting this finding, indicating a need for further research to clarify the relationship between potassium levels and cognitive performance in CKD patients.

The multivariate analysis revealed a significant association between chronic kidney disease (CKD) and cognitive impairment, with CKD patients having 7.87 times higher odds of cognitive impairment compared to non-CKD patients (odds ratio: 7.87; 95% CI: 4.04–15.36, $p < 0.001$), indicating that CKD is an independent risk factor for cognitive dysfunction. This finding is consistent with several studies, including Zijlstra et al. [37], Zhang, QL. Et al. [45], [27] which demonstrate which demonstrate that cognitive impairment becomes increasingly prevalent and severe as kidney function declines, particularly in the later stages of CKD. Notably, the 2012 meta-analysis by Etgen et al., which included 54,779 participants from cross-sectional and longitudinal studies, further confirmed CKD as an independent risk factor for cognitive impairment, reinforcing the need for early screening and intervention in this population [54].

Thus, our study established a statistically significant relationship between eGFR, HDL, total cholesterol, and MMSE scores. Targeting these factors may help slow cognitive decline in CKD patients, making it essential to control them alongside traditional risk factors like hypertension and diabetes. In contrast, electrolytes such as sodium, potassium, and serum triglycerides were not linked to cognitive impairment.

The clinical implications of our findings are significant for future practice, as they suggest that CKD should be regarded as an independent risk factor for cognitive decline. Early assessment and management may help mitigate its progression. However, further research is necessary to explore how effectively managing these biochemical markers can influence or slow cognitive impairment in both the early and late stages of kidney failure.

Strengths

One of the key strengths of our study lies in the classification of CKD patients based on estimated glomerular filtration rates (eGFR), a well-established and reliable indicator of kidney function. Using the standardized method provided a robust framework for comparing cognitive impairment across different levels of kidney function, enhancing the validity of our findings. By using eGFR, we ensured that our assessment of CKD severity was objective and consistent, which is crucial for analyzing its association with cognitive outcomes.

Another significant strength of our study was the meticulous use of exclusion criteria to minimize confounding variables. We excluded CKD patients with other medical conditions, such as stroke, space-occupying lesions, meningitis, encephalitis, alcoholism, vitamin B12 deficiency, and hypothyroidism, all of which are known to independently affect cognitive function. This rigorous approach helped isolate the impact of CKD on cognitive impairment, ensuring that other neurological or metabolic conditions did not skew the results. The exclusion of these conditions provided a clearer picture of the relationship between CKD and cognitive function, further strengthening the reliability of our conclusions.

Additionally, the retrospective design of the study allowed us to review the medical records, ensuring the accuracy of patient history and clinical assessments. We also conducted real-time data collection, which enhanced the integrity of our findings. Moreover, the inclusion of a control group enabled a direct comparison, enhancing the strength of our findings regarding the cognitive decline observed in CKD patients. These methodological strengths contribute to the robustness of our study and underscore the reliability of our conclusions.

Limitations

1. The case-control design limits our ability to establish causality between CKD and cognitive impairment.
2. Our sample was limited to a specific ethnic population, potentially limiting generalizability.
3. The cognitive assessment tools used may not have covered all domains of cognitive performance.
4. Potential confounding factors, such as depression and physical activity, were not included in the analysis.
5. Lack of longitudinal follow-up to evaluate how changes in biochemical parameters may influence the progression of cognitive impairment severity over time. Hence, longitudinal studies would be necessary to better understand the temporal progression of cognitive decline in CKD.
6. Confounding HTN and DM independently can help tell how much CI is caused individually by HTN, DM, and HLD.
7. Albuminuria or proteinuria has recently been proposed as a complementary risk factor of cognitive decline, which our study couldn't explore.

CONCLUSION

1. Increased Odds of Cognitive Impairment: Chronic kidney disease (CKD) significantly increases the odds of cognitive impairment by 7.87 compared to non-CKD patients, positioning CKD as an independent risk factor for cognitive dysfunction.
2. Severity of Impairment: The level of cognitive impairment is more pronounced in the advanced stages of CKD, as assessed by estimated glomerular filtration rate (eGFR) criteria.
3. Predictors of Cognitive Decline: eGFR, HDL, total cholesterol, and comorbidities such as hypertension (HTN) and diabetes mellitus (DM) are significantly associated to cognitive decline in CKD patients. These findings underscore the multifactorial nature of cognitive impairment in CKD, where both renal dysfunction and metabolic abnormalities contribute to cognitive deterioration.

Implications:

Multivariate analysis revealed that CKD was a strong independent risk factor for cognitive impairment, with an odds ratio of 7.87 (95% CI: 4.04–15.36) and a p value of < 0.001.

1. Importance of Cognitive Screening: Given the substantial burden of cognitive dysfunction in CKD patients, particularly in advanced stages, it is crucial to incorporate routine cognitive screening into CKD management.
2. Intervention Strategies: Targeting modifiable risk factors, such as lipid metabolism and kidney function, may offer promising strategies to mitigate cognitive decline in this vulnerable population.

In summary, our case-control study provides compelling evidence for the association between CKD and cognitive impairment, with key implications for clinical practice and future research. Identifying specific biochemical markers, along with monitoring comorbidities such as hypertension and diabetes, offers potential targets for early intervention. A comprehensive, multidisciplinary approach that addresses both vascular (HTN, DM) and non-vascular factors will be essential in developing effective strategies to preserve cognitive function in CKD patients.

CASE RECORD FORM

Name : .....

Age in years : .....

Gender : ☐ Male ☐ Female

Registration no. .....

Date of screening : .....

Address:- _____

_____

Occupation : _____

Inclusion criteria for cases -

1. Age >18years and <75 years - Yes - ☐ No - ☐

2. Consent given - Yes - ☐ No - ☐

Exclusion criteria for cases –

1. History of Psychiatric Disorder - Yes - ☐ No - ☐
2. Stroke - Yes - ☐ No - ☐
3. Alzheimer's Disease - Yes - ☐ No - ☐
4. Intracranial space occupying lesion - Yes - ☐ No - ☐
5. Evidence of meningitis or encephalitis – Yes - ☐ No - ☐
6. Alcoholism - Yes - ☐ No - ☐
7. Vitamin B12 deficiency- Yes - ☐ No - ☐
8. Hypothyroidism - Yes - ☐ No - ☐
9. Parkinson's disease - Yes - ☐ No - ☐
10. Chronic liver disease (encephalopathy) - Yes - ☐ No - ☐
11. Malignancy - Yes - ☐ No - ☐

Mini-Mental State Examination (MMSE)

Patient's Name:_____ Date:_____

Instructions: Ask the questions in the order listed.
Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials:_____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79,72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Symptoms:

1. Oliguria- Yes ☐ No ☐
2. Hematuria- Yes ☐ No ☐
3. Swelling over body/ Puffiness of face/pedal edema Yes ☐ No ☐
4. Nausea/Vomiting Yes ☐ No ☐
5. Fever Yes ☐ No ☐
6. Pruritis Yes ☐ No ☐
7. Muscle Cramps Yes ☐ No ☐
8. Malaise/Weight loss Yes ☐ No ☐
9. Skin frosting Yes ☐ No ☐
10. Flapping tremors Yes ☐ No ☐

Past history

- Hypertensive ☐ YES ☐ NO

If yes duration in years - _____
Treatment receiving - _____

- Diabetes mellitus ☐ YES ☐ NO

If yes duration in years - _____
Treatment receiving - _____

Personal History

Smoking ☐ YES ☐ NO
Alcohol ☐ YES ☐ NO

General Examination

Pallor _____
Icterus _____
Temperature _____
Pulse _____
Blood pressure _____
Respiratory rate _____
Edema _____

OTHERS
Xanthoma _____
Xanthelasma _____
Arcus Senilus _____

Systemic Examination :-

CVS _____
RS _____
P/A _____
CNS _____

Investigations :-

(1)CBC: Hb_____
(2)Blood sugar:

- Fasting _____
- post prandial _____

(3)KFT:

- Serum Creatinine _____
- Serum sodium_____
- Serum potassium_____
- Blood Urea

(4) Urine albumin- nil ☐ 1+ ☐ 2+ ☐ 3+ ☐
(5) eGFR-_____
(6) Lipid Profile- _____

INFORMED CONSENT FORM

I, Mr,Mrs,Miss _____, age_____ years am exercising my free will/choice without any pressure/ lure of incentive in any form, hereby give my consent to be included as a case in the study entitles " Assessment of Cognitive Impairment in Patients With Chronic Kidney Disease".

I have been informed to my satisfaction by investigator about the purpose of the study and advantages of this study to me and the society. I agree to co-operate fully with the investigator/supervising Doctor and I hereby record my permission to use the data for this study for publication or academic presentations. No compensation and incentives will be available to me for participating in this study.

Signature of patient_____

Name of patient_____

Date_____

The volunteer was explicitly explained all the contents of this consent form and then signed before me.

Signature of Investigator_____

Name_____

Date_____

Mobile No. of Investigator_____

Contact No. and Name of IEC_____

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