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Clinical, laboratory, and neuroimaging features and management of ischemic brain infarctions associated with uremic syndrome in chronic kidney disease

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Abstract

Research on cerebrovascular stroke and its predictors in chronic kidney disease (CKD) patients is limited compared to cardiovascular studies. In this study, we aimed to investigate the frequency, types, risk factors, and symptoms of ischemic brain infarctions in CKD patients. This observational study involved 155 adults with CKD, with an average age of 55.36 ± 4.28 years; 70 were males and 85 were females. The mean duration of uremia was 6.40 ± 1.36 years. Among the included patients, 71% were receiving hemodialysis. All participants underwent neurological assessment, laboratory testing, carotid duplex ultrasonography, and brain magnetic resonance imaging. The prevalence of silent ischemic brain infarctions was high at 78.7% (n = 122), with a higher occurrence among end-stage kidney disease patients (n = 110) compared to those not on dialysis (p=0.0001). About 19.7% (n = 24) developed focal stroke symptoms, while 63.2% (n = 98) were asymptomatic. Neurological symptoms included dysarthria, hemihypoesthesia, hemianopia, parkinsonism, and choreodystonia. Regression analysis revealed that brain infarctions were linked to severity of CKD (odds ratio [OR] = 6.32, 95% confidence interval [CI] = 3.20–15.45, p=0.0001), hypertension (OR = 8.34, 95% CI = 5.46–16.25, p=0.0001), hypertriglyceridemia (OR = 5.20, 95% CI = 2.45–12.33, p=0.001), hyperuricemia (OR = 3.40, 95% CI = 1.40–6.32, p=0.001), anemia (OR = 2.43, 95% CI = 1.60–5.28, p=0.01), hypoalbuminemia (OR = 3.25, 95% CI = 1.64–8.42, p=0.01), and albuminuria (OR = 2.53, 95% CI = 1.20–5.42, p=0.03). Persistent brain damage led to poor clinical outcomes in stroke patients. In conclusion, CKD patients face an elevated risk of ischemic brain infarctions and stroke, with various vascular and non-vascular risk factors playing a role. Management strategies should focus on correcting metabolic abnormalities, addressing underdiagnosed risk factors, and implementing preventive measures to reduce the risk of recurrent strokes.

Keywords: Chronic kidney disease; Uremia; Ischemic brain infarctions; Cerebrovascular stroke

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1. Introduction

Chronic kidney disease (CKD) and its uremic syndrome are prevalent global health issues, affecting an estimated 13–35% of the population.[1] CKD encompasses various stages of kidney damage, progressing from mild to severe stages, ultimately leading to uremic manifestations, uremic syndrome, and end-stage kidney disease (ESKD). Uremic manifestations, such as clinical, metabolic, and hormonal changes, typically arise when the estimated renal glomerular filtration rate (eGFR) falls below 50% (i.e., between 50 and 60 mL/min; normal eGFR is 100–120 mL/min/1.73 m^2 of body surface area for an adult).[2] The progressive decline in kidney function is associated with systemic complications, including cardiovascular[3] and cerebrovascular[3,4] issues, as well as an increased prevalence of vascular risk factors.[5-8] Common causes of CKD include diabetic nephropathy, nephritis, and hypertensive nephrosclerosis.[9,10] Patients with mild-to-moderate CKD and ESKD have been found to exhibit various types of cerebral vascular lesions and conditions, such as white matter hyperintensities (WMHs),[10-12] silent brain infarctions,[11] cerebral microbleeds,[13] ischemic and hemorrhagic strokes,[12,14] cerebral atherosclerosis,[15] and arteriosclerosis.[16] Studies have also shown an elevated risk of recurrent stroke and declining eGFR levels in patients with acute ischemic stroke.[17] In addition, individuals with CKD have shown poorer stroke outcomes[18] and higher mortality rates compared to the general population (3–5 times higher).[14]

The development of brain infarctions in patients with uremia is influenced by multiple factors, including kidney function deterioration, vascular risk factors, and micro- and macro-angiopathies.[19]

Despite the significance of vascular brain injuries in patients with CKD and comorbid vascular risk factors, research in this area has been limited in various cultural contexts. Understanding the frequency and types of brain vascular lesions in CKD patients and identifying predictors can have important implications for preventive and treatment strategies.

This observational study examined a cohort of patients with uremia secondary to CKD, following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Table A1). The study aimed to investigate (i) the frequencies and types of ischemic brain infarctions, (ii) the prevalence of vascular and non-vascular causes and comorbid conditions, (iii) the independent predictors for ischemic brain infarctions, and (iv) the clinical outcomes and management of patients who developed cerebrovascular strokes due to ischemic brain infarctions during the period of the study. Patients were neurologically evaluated every 3 months throughout the study. Those who experienced a cerebrovascular stroke were monitored for a minimum of 6 months to assess their clinical outcomes.

2. Methodology

2.1. Subjects

This longitudinal observational study focused on a cohort of patients with uremia due to CKD. Over 2 years (2021–2023), 155 adults with CKD were recruited (70 males [45.2%] and 85 females [54.8%]) from the nephrology and dialysis units of the internal medicine departments at Assiut University Hospital and Al-Azhar University Hospital in Assiut, Egypt, both of which are tertiary referral centers. The sample size for estimating the prevalence and associations of silent brain infarction was determined using an online sample size calculator (http://www.openepi.com/SampleSize/), based on an estimated population of 300 CKD patients who met the study criteria and were able to cover the cost of magnetic resonance imaging (MRI). A sample of approximately 165 patients was deemed necessary to estimate a 50% prevalence of silent brain infarctions with a ±5% margin of error at a 95% confidence level. Ten patients were excluded from the final statistical analyses due to loss of follow-up visits, leaving 155 patients in the study. CKD was defined as kidney damage or eGFR <60 mL/min/1.73 m^2 for ≥3 months.[20] Patients were categorized into groups of non-dialysis (stages 1–3) and dialysis or ESKD (stages 4–5) based on eGFR levels. In addition, 30 age- and sex-matched healthy subjects from the general population were included for statistical comparisons. Inclusion criteria encompassed (i) adults of either sex with uremia due to renal disease, (ii) ESKD patients on hemodialysis for at least 6 months, and (iii) patients who developed clinical evidence of cerebrovascular stroke during the study period. Dialysis adequacy was assessed using the urea reduction ratio (URR), with a target URR average of >45% considered adequate. Exclusion criteria comprised (i) pre-renal or pos*t*-renal causes of uremia, (ii) prior history of cerebrovascular stroke (ischemic or hemorrhagic), (iii) progressive cognitive deterioration (dementia), (iv) lack of cooperation, (v) substance abuse, (vi) contraindications to MRI, (vii) kidney transplantation, and (viii) mortality during the study period.

2.2. Assessment procedures

2.2.1. Medical and neurological histories and examinations

Data collected included demographics, residence, socioeconomic status, special habits (e.g., smoking, drug abuse), etiology and duration of CKD, comorbid medical

conditions and treatments, supportive and supplement therapies, and hemodialysis information. Patient hospital records were also reviewed for additional information. Socioeconomic status was assessed using a structured questionnaire (Socio-Economic Scale [SES]), including information on parents' education level, monthly income, crowding index, and sanitation. The total SES score ranges from 0 to 30, with the following categories: high (>25–30), middle (20–25), low (15–<20), and very low (<15).[21]

2.2.2. Ultrasonography of the kidney

Real-time ultrasonography was performed using a GE Logiq 3 Color Doppler system (Probe: 3.5 MHz; ACUSON, Siemens, Korea), equipped with B-mode, color Doppler flow, power Doppler imaging, and pulsed-wave duplex scanning.

2.2.3. Laboratory investigations

Blood urea nitrogen (BUN), creatinine, urinalysis, complete blood count, arterial blood gases, electrolytes, serum levels of total bilirubin, alanine (ALT) and aspartate aminotransferases, prothrombin time and concentration, international normalized ratio, lipogram, uric acid, hemoglobin A1c (HbA1c), and albumin were measured. Proteinuria (g/day) was assessed by 24-h collection. Median BUN and creatinine levels over the past 6 months were calculated. Serum calcium concentration was adjusted for albumin levels.

2.2.4. Electrocardiography and echocardiography

Electrocardiography was performed using 10 electrodes to obtain 12 leads, each providing a distinct view of the heart's electrical activity. Every lead records the potential difference from a specific orientation, thereby offering a comprehensive assessment of cardiac rhythm and conduction patterns.

Echocardiography was conducted using the standard two-dimensional technique. This imaging modality employs high-frequency sound waves to visualize the heart's structures and assess its function. It allows evaluation of blood flow across the cardiac chambers and valves, as well as visualization of the heart walls, valves, and the major vessels connected to the heart.

2.2.5. Carotid color duplex examination

Intima-media thickness of the carotid arteries (cIMT) was measured using a 5 MHz linear transducer of a color duplex flow imaging system (Acuson 128 XP, Acuson Corporation, United States of America). Increased cIMT was defined as above the 75th percentile for healthy age-matched subjects. Plaque was defined as a protrusion into the vessel lumen of at least 2 mm.[22]

2.2.6. MRI of the brain

MRI (Achieva 1.5T MRI System, Philips, Netherlands) scanning protocol included T1-weighted (T1W), T2-weighted (T2W), fluid-attenuated inversion recovery (FLAIR) sequences, diffusion-weighted images (DWI), and susceptibility-weighted imaging (SWI) to detect microbleeds. Brain lesions were characterized by type, number, side, and site. Ischemic infarction size was classified as large (more than half of a cerebral hemisphere), small (>15 mm in diameter but less than half of a cerebral hemisphere), or lacunar (<15 mm). Patients were interviewed every 3 months for a year to reassess neurological conditions and monitor clinical outcomes for those who developed cerebrovascular strokes during the study period. Patients with cerebrovascular stroke underwent MRI-brain at presentation and after 3 months of follow-up.

2.3. Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences software version 22.0 (SPSS Inc., United States). Data were screened for outliers, skewness, and variance homogeneity before analysis to ensure appropriate statistical tests. Continuous data were presented as mean (standard deviation), while non-continuous data were reported as median and percentiles (25th, 50th, and 75th). Categorical variables were shown as numbers and percentages. Statistical comparisons were performed using the χ^2 test and one-tailed chi-square analysis for categorical variables, unpaired Student's *t*-tests (two-tailed) for continuous variables, and analysis of variance for comparisons involving more than two categories. Correlation analyses were conducted using Spearman's correlation coefficient. Multiple regression analysis was conducted to determine the relationships between silent ischemic brain infarctions (dependent variable) and various demographics, laboratory, and imaging variables (independent variables). Initially, a univariate model was used to identify variables significantly associated with ischemic brain infarctions. The variables showing the strongest relationships in the univariate model were then selected for inclusion in the final stepwise model. A Bonferroni correction was applied during the analysis to reduce errors and false positives. Results were reported as odds ratio (OR) with 95% confidence interval (CI). Statistical significance was set at $p<0.05$.

3. Results

3.1. Demographic and clinical characteristics

Participants with CKD had a mean age of 55.36 ± 4.28 years and a mean duration of uremia of 6.40 ±

1.36 years. The majority lived in rural areas and had low to middle socioeconomic status. None reported a history of smoking since the onset of kidney disease. Forty-five patients (29%) had stage 3 kidney disease, managed through dietary control and supportive therapy, while ESKD was present in 110 patients (71%). Patients with ESKD had been on regular hemodialysis for an average of 8.06 ± 2.53 years, with dialysis sessions ranging from 1 to 3 times/week and lasting 3.5 ± 0.5 h on average. The main causes and comorbid conditions were nephritis (47%), hypertension with or without ischemic heart disease (42.6%), and diabetes (36%) (Table 1). The duration of hypertension at presentation was 8.32 ± 2.52 years, but it was unclear if hypertensive nephrosclerosis was the cause of uremia, as there was no documented evidence. All patients were well-controlled on antihypertensive medications 6 months before the study. The medications used included angiotensin-converting enzyme (ACE) inhibitors (enalapril and lisinopril; n = 42), potassium-sparing diuretics (amiloride and spironolactone; n = 10), as well as beta blockers (carvedilol) and calcium channel blockers (amlodipine; n = 14). The mean duration of diabetes at presentation was 10.35 ± 2.33 years, with 76% (n = 32) of patients having diabetic nephropathy. Diabetes

Table 1. Demographic, clinical, laboratory, and neuroimaging characteristics of the studied patients

Demographic, clinical laboratory, and neuroimaging characteristics	All patients (n=155)	CKD (n=45)	ESKD (n=110)	p-value[a]	p-value[b]
Gender (%)					
Male	70 (45.2)	18 (40)	52 (47.3)	0.324	0.437
Female	85 (54.8)	27 (60)	58 (52.7)		0.386
Residence (%)				0.001*	0.348
Urban	31 (20)	15 (33.3)	16 (14.5)		
Rural	124 (80)	30 (44.7)	94 (85.5)		
Socioeconomic status (%)				0.001*	0.530
Low	93 (60)	20 (44.4)	73 (66.4)		
Middle	62 (40)	25 (55.6)	37 (33.6)		
Age, years (range [mean±SD])	45–65 (55.36±4.28)	45–55 (50.24±3.26)	50–65 (56.63±2.80)	-	0.08
Duration of uremia, years (range [mean±SD])	3–10 (6.40±1.36)	3–5 (4.27±1.40)	5–10 (8.06±2.53)	-	0.001*
Causes and comorbid medical conditions (%)				-	-
Hypertension without or with ischemic heart disease	40 (25.8)	12 (26.7)	28 (25.5)		
Diabetes mellitus	16 (10.3)	6 (13.3)	10 (9)		
Hypertension and diabetes	26 (16.8)	8 (17.8)	18 (16.4)		
Nephritis	73 (47)	19 (42.2)	54 (49)		
Atrial fibrillation	28 (18)	-	28 (25.5)		
CKD	45 (29)	45 (100)	-	-	-
ESKD	110 (71)	-	110 (100)	-	-
Laboratory abnormalities (%)					
Hyponatremia	22 (14)	-	22 (20)	-	0.542
Hypokalemia	30 (19.4)	-	30 (27.3)	-	-
Hypocalcemia	86 (55.5)	16 (35.6)	70 (63.6)	-	0.001*
Hypomagnesemia	45 (29)	8 (17.8)	35 (31.8)	-	0.001*
Hyperphosphatemia	52 (33.5)	-	52 (47.3)	-	-
Anemia	93 (60)	13 (28.9)	80 (72.7)	-	0.001*
Hypoalbuminemia	96 (62)	-	96 (87.3)	-	-
Proteinuria	55 (35.5)	14 (31)	41 (37.3)	-	<0.05*
Hyperparathyroidism	36 (23.2)	-	36 (32.7)	-	-
Hyperuricemia	56 (36)	8 (17.8)	48 (43.6)	-	0.001*

(Cont'd)

Table 1. ***(Continued)***

Demographic, clinical laboratory, and neuroimaging characteristics	All patients (*n*=155)	CKD (*n*=45)	ESKD (*n*=110)	*p*-value[a]	*p*-value[b]
Hypercholesterolemia	53 (34.2)	8 (17.8)	45 (41)	-	0.001*
Dyslipidemia	76 (49)	13 (28.9)	63 (57.3)	-	0.001*
Hyperglycemia	16 (10.3)	-	16 (14.5)		-
Carotid duplex sonography (%)					
Carotid stenosis	73 (47)	12 (26.7)	61 (55.5)	-	0.001*
Atheromatous plaque	43 (28)	-	43 (39)	-	
Neurologic manifestations (%)					
History of uremic encephalopathy	32 (20.6)	-	32 (29)	-	-
Uremic seizures (%)					
Generalized tonic-clonic seizures	15 (9.7)	-	15 (13.6)	-	-
Focal seizures	21 (13.5)	-	21 (19)	-	-
Peripheral neuropathy	42 (27.1)	14 (31)	28 (25.5)	-	0.463
Muscle cramps	86 (55.5)	16 (35.6)	70 (63.6)	-	0.001*
Asterixis	110 (71)	-	110 (100)	-	-
Myoclonic jerking	94 (60.6)	-	94 (85)	-	-
Restless leg syndrome	80 (51.6)	-	80 (72.7)	-	-
Focal neurologic manifestations	24 (15.5)	-	24 (21.8)	-	-
Parkinsonism	6 (3.9)	-	6 (5.5)	-	-
Choreo-dystonia	2 (1.3)	-	2 (1.8)	-	-
Dysarthria	3 (1.9)	-	3 (2.7)	-	-
Hemihypoesthesia	9 (5.8)	-	9 (8.2)	-	-
Visual field defects	4 (2.6)	-	4 (3.6)	-	-

Notes: Data are expressed as *n* (%), unless otherwise indicated. [a]Within group comparisons; [b]Between group comparisons (CKD vs. ESKD); *indicates statistically significant values ($p<0.05$).
Abbreviations: CKD: Chronic kidney disease; ESKD: End-stage kidney disease; SD: Standard deviation.

treatment included insulin (n = 27, 64.3%) and oral anti-hyperglycemic agents (n = 42). The oral medications used in different combinations were as follows: sulfonylureas (glimepiride) in 14 patients (33.3%), biguanides (metformin) in 28 patients (66.7%), dipeptidyl peptidase 4 inhibitors (vildagliptin) in 16 patients (38%), and sodium-glucose cotransporter-2 inhibitors (dapagliflozin) in four patients (9.5%). Of the 42 patients with diabetes, 26 (62%) were well-controlled for at least 6 months before the study, while 16 (38%) were poorly controlled on medications.

Some patients with hypertension and/or diabetes (n = 35, 22.6%) were prescribed antiplatelet medications. These medications included aspirin (cyclooxygenase inhibitor; n = 28, 22.6%) and/or clopidogrel (adenosine diphosphate receptor inhibitors; n = 14, 9%).

Atrial fibrillation (AF) was reported in 18% of patients with ESKD, which equates to 28 individuals or 25% of the ESKD patient population. Six patients had been diagnosed with AF before starting hemodialysis, while the rest were diagnosed during the study period. All patients were treated with bisoprolol, a selective beta-blocker, but none were prescribed oral anticoagulants.

3.2. Laboratory investigations

Table 2 presents the results of laboratory investigations for the studied groups. Patients showed significantly higher levels of BUN (p=0.0001), creatinine (p=0.0001), HbA1c (p=0.001), uric acid (p=0.0001), total cholesterol (p=0.0001), low-density lipoprotein (LDL)-C (p=0.001), triglycerides (p=0.0001), and phosphate (p=0.001) compared to controls. Conversely, patients had lower levels of calcium (p=0.01), albumin (p=0.05), hemoglobin (p=0.003), and red blood cell count (p=0.02). The frequency of laboratory abnormalities in patients, ranked from highest to lowest (Table 1), was as follows: anemia (60%, n = 93), hypocalcemia (55.5%, n = 86), hyperuricemia (52%, n = 80), hypertriglyceridemia (49%, n = 76), proteinuria (35.5%, n = 55), hypercholesterolemia (34.2%, n = 53), and hypomagnesemia (29%, n = 45).

Table 2. Laboratory results of patients with CKD, ESKD, and control subjects

Laboratory characteristics	All patients (*n*=155)	CKD (*n*=45)	ESKD (*n*=110)	Control subjects (*n*=30)	*p*-value[a]	*p*-value[b]
Sodium level, mmol/L	120.00–147.23 (134.03±3.67)	132.00–145.00 (136.00±2.84)	120.00–147.23 (132.63±3.04)	132.00–183.23 (138.46±2.48)	0.564	0.428
Potassium level, mmol/L	2.00–5.30 (3.03±0.82)	2.50–5.00 (4.32±0.45)	2.00–5.30 (4.52±0.58)	3.50–5.00 (4.20±0.35)	0.363	0.468
Magnesium level, mg/dL	1.06–2.80 (2.30±0.63)	1.20–2.70 (2.32±0.64)	1.06–2.80 (2.36±0.86)	1.50–2.83 (2.00±0.52)	0.368	0.503
Calcium level, mg/dL	5.30–9.80 (6.36±0.58)	7.00–10.00 (7.57±0.55)	5.30–9.80 (7.08±0.33)	8.40–11.00 (9.39±0.46)	0.010*	0.233
Phosphate level, mg/dL	2.73–9.60 (5.68±1.40)	2.80–8.50 (5.68±1.46)	2.73–9.30 (6.35±1.68)	2.50–4.80 (3.25±0.60)	0.001*	0.708
[c]Blood urea nitrogen, mmol/L	6.00–32.00 (14.32±3.45)	7.00–13.00 (10.85±1.82)	6.00–32.00 (18.56±2.46)	2.80–5.80 (3.46±2.46)	0.0001*	0.010*
[c]Creatinine, µmol/L	185.00–698.00 (356.68±65.38)	185.00–340.00 (253.20±67.23)	185.00–1,480.00 (586.31±83.70)	66.00–121.00 (89.27±8.09)	0.0001*	0.0001*
International normalized ratio, %	1.00–1.50 (1.27±0.05)	1.00–1.50 1.37±0.60)	1.00–1.63 (1.37±0.17)	0.8–1.30 (1.01±0.05)	0.688	1.00
AST, µ/L	13.00–75.00 (30.50±5.46)	20.00–60.00 (25.86±6.46)	13.00–75.00 (45.54±4.56)	15.00–45.00 (25.50±4.52)	0.542	0.353
ALT, µ/L	20.00–106.00 (35.50±5.63)	25.00–58.00 (28.42±6.87)	20.00–106.00 (48.36±5.60)	19.00–56.00 (30.60±4.68)	0.458	0.468
Total bilirubin, µmol/L	3.00–18.00 (10.32±3.38)	3.00–15.00 (9.24±3.60)	4.00–18.00 (14.35±3.56)	3.50–15.00 (9.85±3.36)	0.658	0.546
Albumin, g/L	1.53–4.80 (3.50±0.62)	2.80–4.80 (3.24±0.82)	1.30–4.10 (2.32±0.45)	3.00–5.00 (3.90±0.64)	0.050*	0.030*
Red blood cell count, million/mcL	1.80–5.32 (3.45±0.62)	1.80–5.32 (3.25±0.45)	2.26–4.68 (3.15±0.55)	4.23–6.20 (4.60±0.73)	0.020*	0.658
Hemoglobin, mg/dL	6.00–10.00 (7.42±1.45)	6.20–10.00 (8.50±1.33)	6.00–10.00 (7.86±1.33)	10.80–13.20 (12.20±1.46)	0.003*	0.524
Platelet count,/µL	250.00–375.00 (320.74±35.65)	250.00–375.00 (380.600±40.68)	250.00–350.00 (256.95±50.60)	250.00–450.00 (350.56±30.50)	0.543	0.473
Hemoglobin A1c, %	3.40–8.00 (6.85±1.35)	5.50–8.00 (7.35±2.02)	3.40–8.00 (7.80±1.56)	4.00–5.80 (4.80±0.80)	0.001*	0.144
Uric acid, mg/dL	3.50–12.00 (10.58±1.26)	3.50–10.00 (8.46±1.33)	6.00–12.00 (11.58±2.05)	3.50–6.00 (4.32±1.05)	0.0001*	0.01*
Lipid profile, mg/dL						
Total cholesterol	100–550 (370.50±50.30)	100–300 (250.70±30.60)	100–550 (480.50±70.20)	100–200 (120.60±10.05)	0.0001*	0.0001*
LDL-C	150–270 (200.30±70.40)	150–200 (180.60±50.00)	150–270 (220.50±45.60)	80–150 100.40±8.60)	0.001*	0.248
HDL-C	30–60 (45.20±10.20)	30–60 (40.20±10.50)	30–45 (35.50±10.45)	40–60 (50.60±5.30)	0.01*	0.02
Triglycerides	200–800 (450.56±100.55)	200–400 (330.35±45.32)	200–800 (670.30±85.68)	100–230 (150.46±15.43)	0.0001*	0.0001*
Arterial blood gases						
pH	7.30–7.43 (7.35±0.03)	7.30–7.44 (7.35±0.20)	7.30–7.44 (7.35±0.03)	7.35–7.45 (7.38±0.02)	0.534	0.640
PO_2, mmHg	80.00–99.00 (92.30±3.60)	85.00–99.00 (90.65±4.22)	80.00–99.00 (90.53±3.65)	88.00–100.00 (95.00±3.65)	0.468	0.563
PCO_2, mmHg	23.00–42.00 (32.56±3.80)	27.00–39.00 (35.35±3.70)	23.00–42.00 (36.45±3.80)	32.00–42.00 (38.27±2.65)	0.286	0.332
HCO, MEq/L	20.00–24.00 (18.56±2.03)	20.00–26.00 (23.26±1.72)	20.00–24.00 (16.20±2.34)	22.00–26.00 (22.53±1.81)	0.020*	0.001*
Oxygen saturation, %	80–100 (90.30±2.50)	90–100 (95.80±3.60)	80–100 (90.55±2.30)	90–100 (95.63±2.80)	0.568	0.680

Notes: Data are expressed as range and mean±standard deviation, unless otherwise indicated. [a]Comparison between patients and controls; [b]Comparison between CKD and ESKD; [c]Blood urea nitrogen and creatinine levels represent median levels over the preceding 6 months. *indicates statistically significant values ($p<0.05$).

Abbreviations: ALT: Alanine transaminase; AST: Aspartate transaminase; CKD: Chronic kidney disease; ESKD: End-stage kidney disease; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

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Compared with patients with CKD who were not on dialysis, those with ESKD receiving hemodialysis exhibited higher levels of BUN (p=0.0001), creatinine (p=0.0001), uric acid (p=0.01), total cholesterol (p=0.0001), and triglycerides (p=0.0001), and lower levels of high-density lipoprotein (HDL)-C (p=0.02) and bicarbonate (p=0.02). Patients with ESKD also had higher frequencies of hypocalcemia (p=0.001), hypomagnesemia (p=0.001), anemia (p=0.001), proteinuria (p=0.05), hyperuricemia (p=0.001), hypercholesterolemia (p=0.001), and hypertriglyceridemia (p=0.001). Hyperphosphatemia, hypoalbuminemia, and hyperglycemia were only observed in patients with ESKD.

Upon reviewing the medical treatment at presentation, it was found that only 22 (14.2%) patients with hyperlipidemia received statin therapy, specifically atorvastatin, fluvastatin, lovastatin, rosuvastatin, or simvastatin, which are lipid-lowering drugs in the class of hydroxymethylglutaryl-CoA reductase inhibitors.

3.3. Intima-media thickness of the carotid arteries

The median cIMT value in healthy subjects was 1.2 mm, with the 25th, 50th, and 75th percentiles at 0.88 mm, 1.2 mm, and 1.8 mm, respectively. An abnormal cIMT was defined as >1.8 mm. Thickened cIMT, indicative of carotid atherosclerosis, was observed in 47% (n = 73) of the subjects. Atheroma plaques were present in 39% (n = 38) of the subjects (Tables 1 and 3).

3.4. MRI findings

Table 4 and Figure 1 present the MRI findings of the patients under study. The results indicate brain infarctions were the most common finding (78.7%), followed by WMHs (63.2%). Microbleeds were observed in a small number of patients with ESKD (11.6%, n = 18). Bilateral calcification of the basal ganglia was reported in 15.5% (n = 24) of cases. WMHs were characterized by small periventricular and subcortical hyperintense lesions in T2WI and FLAIR, and hypointense in T1WI views of MRI. Microbleeds were identified as focal areas of signal loss in brain parenchyma measuring ≤10 mm on susceptibility-weighted MRI. Lacunar brain infarctions were more prevalent in patients (60.6%, n = 94) than small brain infarctions (15.5%, n = 24; p=0.0001). Bilateral infarctions (45.2%, n = 70) were more common than unilateral ones (33.6%, n = 52; p=0.01). Brain infarctions were located in either the cerebral hemispheres (55.5%, n = 86) or the basal ganglia (23.2%, n = 36). In 58% of patients (n = 90), brain infarctions appeared hypointense in T1WI and apparent diffusion coefficient and hyperintense in DWI, T2WI, and FLAIR, indicating acute/subacute ischemic foci. Encephalomalacia was observed in 32 patients (20.6%) (iso-signal to cerebrospinal fluid; hypointense in DWI and hyperintense in T2WI and FLAIR), suggesting old infarctions. In the absence of clinical stroke symptoms, these lesions may be attributed to silent brain infarcts.

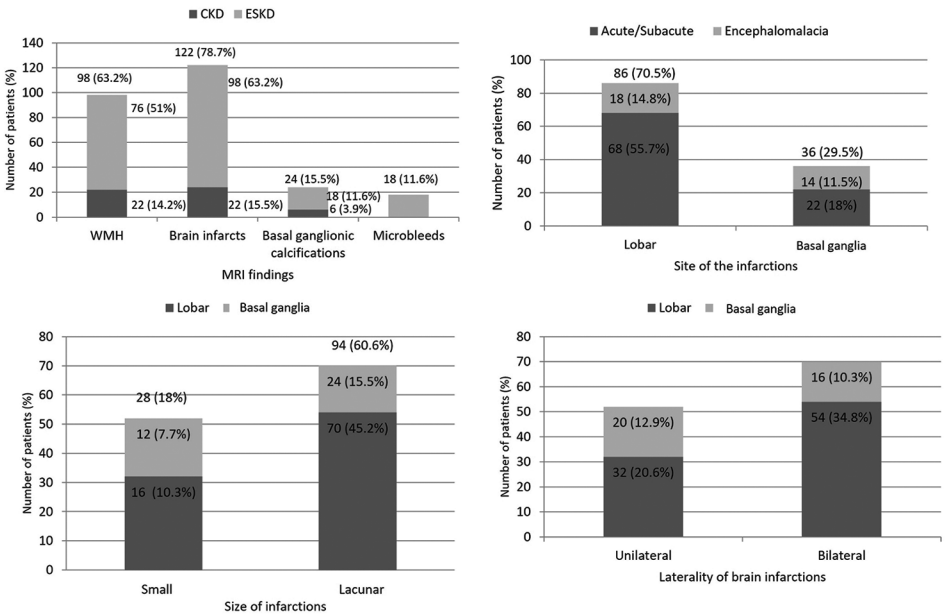

Figure 1. Neuroimaging findings in patients with CKD and ESKD

Abbreviations: CKD: Chronic kidney disease; ESKD: End-stage kidney disease; MRI: Magnetic resonance imaging; WMHs: White matter hyperintensities.

Table 3. Demographic, clinical, laboratory, and neuroimaging characteristics of patients with and without ischemic brain infarctions

Characteristics	All patients (*n*=155) (%)	With brain infarcts (*n*=122, 78.7%)	Without brain infarcts (*n*=33, 21.3%)	*p*-value
Male	70 (45.2)	42 (34.4)	28 (84.8)	0.001*
Female	85 (54.8)	80 (65.6)	5 (15.2)	0.001*
Age, years (range [mean±SD])	45–65 (55.36±4.28)	52–65 (60.52±2.30)	45–65 (52.46±3.60)	0.01*
Duration of uremia, years (range [mean±SD])	3–10 (6.40±1.36)	3–10 (8.23±1.50)	3–7 (5.46±1.82)	0.001*
Causes and comorbid medical conditions				
Hypertension without or with ischemic heart disease	40 (25.8)	30 (24.6)	10 (30.3)	0.126
Diabetes mellitus	16 (10.3)	12 (9.8)	4 (12)	0.543
Hypertension and diabetes	26 (16.8)	20 (16.4)	6 (18.2)	0.01*
Nephritis	73 (47)	60 (49.2)	13 (39.4)	0.236
Atrial fibrillations	24 (15.5)	16 (13)	8 (24.2)	0.126
History of uremic encephalopathy	32 (20.6)	32 (26.2)	0	-
Type of seizures				
Generalized tonic-clonic seizures	15 (9.7)	15 (12.3)	0	-
Focal seizures	21 (13.5)	21 (17.2)	0	-
Focal neurologic manifestations	24 (15.5)	24 (19.7)		
Parkinsonism	6 (3.9)	6 (4.9)	-	-
Left putamen and globus pallidus externa	5 (3.2)	5 (4.1)	-	-
Left caudate and lentiform nuclei	1 (0.7)	1 (0.8)	-	-
Choreo-dystonia	2 (1.3)	2 (1.6)	-	-
Right caudate nucleus	2 (1.3)	2 (1.6)	-	-
Dysarthria	3 (1.9)	3 (2.5)	-	-
Right insular infarction	3 (1.9)	3 (3.5)	-	-
Hemihyposthesia	9 (5.8)	9 (7.4)	-	-
Parietal lobe infarction	9 (5.8)	9 (7.4)	-	-
Visual field defects (occipital lobe infarction)	4 (2.6)	4 (3.3)	-	-
Hyponatremia	22 (14)	22 (18)	0	-
Hypokalemia	30 (19.4)	30 (24.6)	0	-
Hypocalcemia	86 (55.5)	78 (63.9)	8 (24.2)	0.0001*
Hypomagnesaemia	45 (29)	45 (36.9)	-	-
Hyperphosphatemia	52 (33.5)	42 (34.4)	6 (18.2)	0.01*
Anemia	93 (60)	81 (66.4)	12 (36.4)	0.0001*
Hypoalbuminemia	96 (62)	88 (72)	8 (24.2)	0.0001*
Proteinuria	55 (35.5)	49 (40.2)	6 (18.2)	0.0001*
Hyperparathyroidism	36 (23.2)	36 (29.5)	0	-
Hyperuricemia	56 (36)	51 (41.8)	5 (15.2)	0.0001*
Hypercholesterolemia	53 (34.2)	48 (39.4)	5 (15.2)	0.001*
Dyslipidemia	76 (49)	65 (53.3)	11 (33.3)	0.001*
Hyperglycemia	16 (10.3)	16 (14.5)	-	-
Carotid stenosis	73 (47)	58 (45.9)	15 (45.5)	0.546
Atheromatous plaque	43 (28)	32 (26.2)	11 (33.3)	0.328
WMHs	98 (63.2)	76 (62.3)	22 (66.7)	0.658

Notes: Data are expressed as *n* (%), unless otherwise indicated.*indicates statistically significant values ($p<0.05$).
Abbreviations: CKD: Chronic kidney disease; ESKD: End-stage kidney disease; SD: Standard deviation; WMHs: White matter hyperintensities.

Table 4. Neuroimaging findings in patients with CKD and ESKD

Neuroimaging findings	All patients (*n*=155) (%)	CKD (*n*=45) (%)	ESKD (*n*=110) (%)	*p*-value
WMHs	98 (63.2)	22 (14.2)	76 (49)	0.001*
Ischemic brain infarctions	122 (78.7)	24 (15.5)	98 (63.2)	0.0001*
Cerebral brain infarctions (lobar)	86 (70.5)	18 (11.6)	68 (43.9)	0.001*
Onset				
Acute/subacute infarctions	68 (55.5)	-	68 (43.9)	
Encephalomalacia	18 (11.6)	-	18 (11.6)	
Size				
Small infarctions	16 (10.3)	-	16 (10.3)	
Lacunar infarctions	70 (45.2)	18 (11.6)	52 (33.5)	<0.05*
Laterality				
Unilateral	32 (20.6)	5 (3.2)	27 (17.4)	
Bilateral	54 (34.8)	13 (8.4)	39 (25.2)	
Basal ganglionic ischemic infarctions	36 (23.2)	6 (3.9)	30 (19.4)	0.01*
Onset				
Acute/subacute infarctions	22 (14.2)	-	22 (14.2)	
Encephalomalacia	14 (9)	-	14 (9)	
Size				
Small infarctions	12 (7.7)	-	12 (7.7)	
Lacunar infarctions	24 (15.5)	6 (3.9)	18 (11.6)	<0.05*
Laterality				
Unilateral	20 (12.9)		20 (12.9)	
Bilateral	16 (10.3)	6 (3.9)	10 (6.5)	
Bilateral basal ganglionic calcification (lentiform nuclei)	24 (15.5)	6 (3.9)	18 (11.6)	<0.05*
Microbleeds	18 (11.6)		18 (11.6)	

Notes: Data are expressed as *n* (%), unless otherwise indicated. *$p<0.05$ is considered statistically significant. *P* values indicate comparisons between patients on dialysis and patients not on hemodialysis.
Abbreviations: CKD: Chronic kidney disease; ESKD: End-stage kidney disease; WMHs: White matter hyperintensities.

3.5. Clinical manifestations of the studied group

3.5.1. Uremic symptoms

Patients with kidney disease reported symptoms such as tiredness, itching, loss of appetite, nausea, vomiting, breathlessness, ankle edema, and reduced urine output.

3.5.2. Neurological manifestations

Neurological symptoms reported in patients included asterixis (negative myoclonus; 71%), myoclonic jerking (positive myoclonus; 60.6%, *n* = 94), muscle cramps (55.5%, *n* = 86), restless leg syndrome (RLS; 51.6%, *n* = 80), uremic seizures (23.2%, *n* = 36), peripheral neuropathy (27%, *n* = 42), and uremic encephalopathy (20.6%, *n* = 32). Asterixis, myoclonic jerks, RLS, seizures, and encephalopathy were only observed in patients with ESKD. Muscle cramps were common in patients with hypocalcemia, while myoclonic jerks were frequent in patients with uremic encephalopathy. Myoclonic jerking was characterized by brief, irregular, involuntary movements involving various body parts. RLS was described as unpleasant leg sensations with an urge to move the leg, often accompanied by sensory disturbances and periodic leg movements. Peripheral neuropathy, seen in diabetic patients, presented as numbness, burning sensation, and hypoesthesia. It manifested as a stocking distribution of numbness, burning sensation, and hypoesthesia on pin-prick examination. Uremic seizures were either generalized tonic-clonic seizures (*n* =15, 9.7%) or focal seizures (sensorimotor; *n* = 21, 13.5%). Patients with seizures had hypocalcemia, a history of uremic encephalopathy (44.4%; *n* = 16), bilateral basal ganglia calcifications (33.3%; *n* =12), WMHs (100%, *n* = 36), and lacunar brain infarctions (100%, *n* =36). None of the seizure patients were taking antiepileptic medications during the study period.

During the study period, 19.7% (*n* = 24) of patients among 122 with ischemic brain infarctions developed cerebrovascular strokes. The manifestations of stroke

varied depending on the location of the brain infarction (Table 1). Dysarthria and somatosensory deficits were observed in 9.8% of patients (n = 12) with small cerebral ischemic infarctions in the insula and parietal/parieto-temporal brain regions, respectively. Visual field defects and homonymous hemianopia were reported in 2.6% of patients (n = 4) with ischemic infarction in the occipital lobes (Table 1 and Figure 2A). The patients with neurologic deficits were aged between 55 and 65 years and experienced strokes 12–24 months after the onset of uremia. They had chronic hypertension and diabetes. Extrapyramidal movement disorders were observed in 5.2% of patients (n = 8) with ischemic infarctions in the basal ganglia, with six exhibiting parkinsonism and two showing choreo-dystonia. Patients with parkinsonism, characterized by unilateral rest tremors, were aged between 55 and 60 years and developed symptoms 10–24 months after the onset of uremia. They also had diabetic nephropathy. Lesions were found in the putamen, globus pallidus externa, caudate, and lentiform nuclei (Figure 2B). Patients with choreo-dystonic involuntary movements (unilateral) were aged 58 and 62 years and developed symptoms 12–16 months after the onset of uremia, both with a history of chronic hypertension and diabetes. Chorea was characterized by abrupt, irregular, arrhythmic, continuous, and rapid involuntary movements, while dystonia involved sustained, patterned, and repetitive muscle contractions leading to twisting movements or abnormal postures, with lesions in the caudate nucleus. The laboratory profiles of patients with cerebrovascular stroke did not significantly differ from those of other patients with ESKD. All patients with cerebrovascular stroke exhibited WMHs and bilateral lacunar ischemic infarctions.

3.6. Comparative statistical analyses of demographic, clinical, and laboratory variables between patients with and without brain infarctions

Patients with ESKD had a higher incidence of cerebral (p=0.001) and basal ganglionic (p=0.01) infarctions compared to those not on dialysis. Brain infarctions were more common in females (p=0.0001), older individuals (p=0.0001), longer duration of kidney disease (p=0.001), those with both hypertension and diabetes (p=0.0001), hypocalcemia (p=0.0001), hyperphosphatemia (p=0.01), anemia (p=0.0001), hypoalbuminemia (p=0.01), hypercholesterolemia (p=0.001), dyslipidemia (p=0.001), and hyperuricemia (p=0.0001) (Table 3). No specific laboratory abnormalities or MRI findings distinguished patients with myoclonic jerks or RLS from other patients

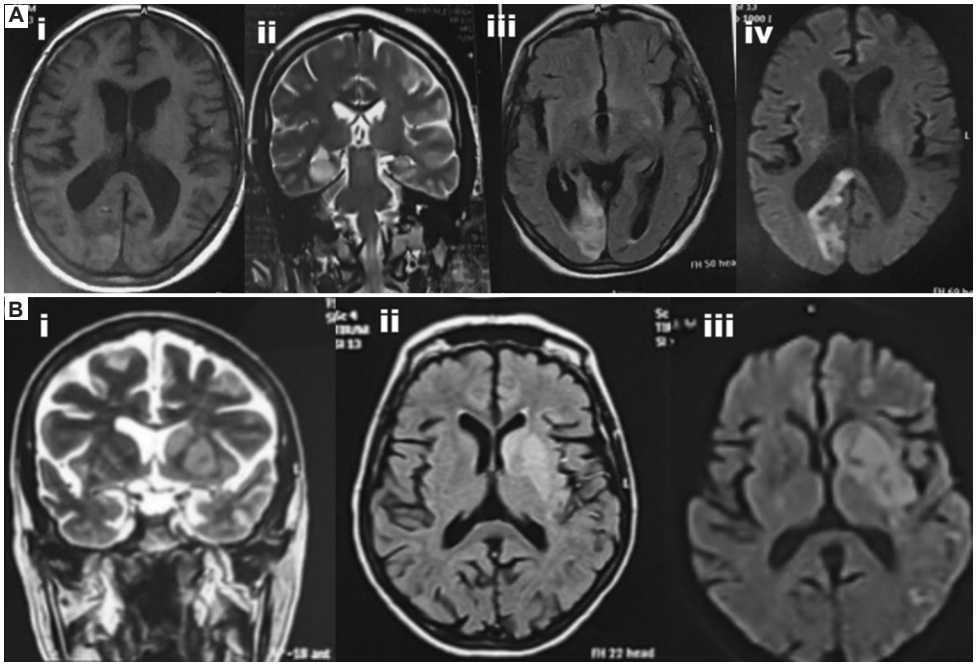

Figure 2. Magnetic resonance imaging (MRI) of patients with uremia and cerebrovascular stroke. (A) MRI-brain axial and coronal views) of a 62-year-old man. He had hypertension for 10 years and uremia at the age of 55 years. He developed a visual field defect. He had a lesion in the right occipital lobe. The lesion is hypointense in (i) T1WI and hyperintense in (ii) TWI, (iii) FLAIR, and (iv) DWI (i.e., ischemic lesion). (B) MRI-brain (coronal and axial views) of a 60-year-old male (age at presentation). He had diabetes for 8 years, developed uremia at the age of 55 years, and is on regular hemodialysis. He developed right-sided rest tremors and rigidity (parkinsonism) during the period of the study. He had MRI lesions in the left caudate and lentiform nuclei. Lesions are hypointense in TWI and hyperintense in (i) T2WI, (ii) FLAIR, and (iii) DWI (i.e., ischemic lesions).
Abbreviations: DWI: Diffusion-weighted imaging; FLAIR: Fluid-attenuated inversion recovery; T1WI: T1-weighted imaging; T2WI: T2-weighted imaging.

with ESKD. In addition, there were no significant differences in the prevalence of abnormal cIMT between those with and without ischemic brain infarctions.

3.7. Correlation analyses

The correlation analysis between variables showed significant correlations between hypertension and hyperglycemia, hypercholesterolemia (p=0.001), hypertriglyceridemia (p=0.001), hyperuricemia (p=0.001), and cIMT (p=0.001). Hyperuricemia was significantly correlated with hypercholesterolemia (p=0.001), hypertriglyceridemia (p=0.001), and cIMT (p=0.001). Hypertriglyceridemia significantly correlated with hypercholesterolemia (p=0.001) and cIMT (p=0.001). Hypoalbuminemia and proteinuria were significantly correlated (p=0.001).

3.8. Multiple regression analysis

A multiple regression analysis revealed that the presence of brain infarcts, compared to those without brain infarctions, was independently associated with the severity of kidney disease (OR = 6.32, 95% CI = 3.20–15.45, p=0.0001) after adjusting for age and sex, hypertension (OR = 8.34, 95% CI = 5.46–16.25, p=0.0001), hypertriglyceridemia (OR = 5.20, 95% CI = 2.45–12.33, p=0.001), hyperuricemia (OR = 3.40, 95% CI = 1.40–6.32, p=0.001), anemia (OR = 2.43, 95% CI = 1.60–5.28, p=0.01), hypoalbuminemia (OR = 3.25, 95% CI = 1.64–8.42, p=0.01), and albuminuria (OR = 2.53, 95% CI = 1.20–5.42, p=0.03). Notably, the presence of diabetes, hypercholesterolemia, hyperphosphatemia, thickened cIMT, WMHs, type of antihypertensive drugs, oral hypoglycemic medications, and the use of statins or antiplatelet medications did not show significant odds ratios (95% CI) in the presence of ischemic brain infarctions.

3.9. Management of patients with silent brain infarctions and cerebrovascular stroke

The treatment approach included optimizing renal replacement therapy, correcting associated metabolic derangements, using antiplatelets (aspirin and/or clopidogrel), and addressing comorbid medical conditions (such as hyperlipidemia, hyperuricemia, anemia, hypocalcemia, and hyperglycemia). Statins were prescribed for hyperlipidemia and allopurinol for hyperuricemia. Oral anticoagulants were not part of the management. Supportive or symptomatic treatments were also provided, such as L-DOPA/carbidopa for parkinsonism, tetrabenazine for chorea, dopamine agonists and gabapentin for RLS, and carbamazepine for seizures.

3.10. Clinical outcome of patients with cerebrovascular stroke

A follow-up of patients who developed a stroke was conducted for over 6 months, which showed persistent neurological manifestations. Antiplatelet and statins were continued to prevent recurrent ischemic strokes.

4. Discussion

This cohort study was conducted on a group of patients with uremia due to CKD over 2 years to estimate the prevalence of silent brain infarctions and the development of cerebrovascular stroke in these patients, along with the associated vascular and non-vascular risk factors and the manifestations and clinical outcomes of cerebrovascular strokes.

In this study, silent brain infarctions were the most common findings in CKD patients, with lacunar (60.7%) and small (18%) brain infarctions being predominant, indicating occlusion of small brain vessels. Ischemic brain infarctions were more frequent in the cerebral hemisphere compared to the basal ganglia (70.5% versus 14.2% or 5:1). Studies have shown a link between reduced eGFR due to CKD and subclinical cerebral brain infarctions and small vessel disease.[11,18,23-26] However, most studies reported lower frequencies (around 50%) of ischemic brain infarctions in patients with CKD. This could be explained by the fact that approximately 70% of the included patients in this study had ESKD. In this study, WMHs were present in 63.2% of patients, with no significant difference in frequency between patients with and without ischemic infarctions.[27] WMHs were not independently associated with silent brain infarctions. They are non-specific findings and can be present in various conditions as hypertension, diabetes, multiple sclerosis, and pyridoxine deficiency.[28,29] WMHs have also been known as leukoaraiosis. The pathogenesis of WMHs is different from silent ischemic brain infarctions. They are characterized by neuronal loss, demyelination, and gliosis.[28] While lacunar ischemic brain infarctions represent a neuropathological change involving hyalinosis of the small end-perforating arterioles in the white matter of the brain.[30] Therefore, many researchers considered ischemic brain infarctions and not WMHs as the better marker for lacunar stroke in brain MRI images. In contrast, some studies have linked CKD with WMHs, albuminuria, and decreased eGFR.[31] This study found that ESKD was linked to ischemic brain infarctions regardless of other risk factors. Previous studies have shown that kidney dysfunction at various stages is independently associated with a higher risk of cerebrovascular disease, separate from traditional risk factors.[32]

In this study, hypertension was found in 42.6% of patients with CKD, of whom 41% had brain infarctions. Previous studies have reported hypertension in 67–92% of patients with CKD.[6] It is unclear in this study if hypertensive nephrosclerosis was the cause of uremia. Hypertension

commonly affects the small perforating arteries in various regions of the body, including the kidney and brain,[33] causing lipohyalinosis of subcortical penetrating arteries and the accumulation of proteins in the arteriolar subendothelial space (hyalinosis), which often extends into the media.[12,17] This is known as arteriosclerosis, a characteristic feature of lacunar brain stroke. Hypertensive nephrosclerosis is characterized by subintimal hyalinosis, medial vascular smooth muscle cells replaced by connective tissue, and glomerular and tubular atrophy with interstitial fibrosis.[34] In addition, hypertension accelerates the progression of systemic and cerebral atherosclerosis.[35] In this study, patients were well-controlled on different groups of antihypertensive medications, including ACE inhibitors (63.6%), potassium-sparing diuretics (15.2%), and beta blockers and calcium channel blockers (21%). There were no significant differences in the frequency of ischemic brain infarctions based on the type of antihypertensive medication used.

In this study, diabetes was found in 27% of patients, among whom 26% were diagnosed with diabetic nephropathy before developing uremia. This same group of patients also had brain infarctions. Previous studies have shown a significant association between CKD, silent brain infarctions, cardiovascular disease, metabolic syndrome, and diabetes.[7] The pathological features of diabetic CKD include glomerular hypertrophy, thickened glomerular basement membrane, and vascular hyalinosis.[36] It is also known that insulin resistance plays a crucial role in developing and progressing systemic and cerebral atherosclerosis and arteriosclerosis. Diabetes is often accompanied by hyperlipidemia,[37] a risk factor for atherosclerosis. The majority of patients had been on insulin and oral hypoglycemic medications (e.g., sulfonylureas, biguanides [metformin], dipeptidyl peptidase 4 inhibitors, and sodium-glucose cotransporter-2 inhibitors) for at least 6 months before being included in the study, while 38% of them had poorly controlled diabetes.

In addition, in this study, 73 patients (47%) with both hypertension and diabetes had carotid stenosis, and 28% of them had atheroma. Carotid atherosclerosis was not found to be independently associated with ischemic brain infarctions, but its potential contribution to ischemic brain infarctions and cerebrovascular stroke in patients with uremia cannot be ruled out. Studies have shown an increase in cIMT and increased stiffness of carotid arteries in patients with CKD.[15] In addition, there is a higher risk of frequent rupture of atheromatous lesions in patients with CKD, independent of traditional cardiovascular risk factors.[38]

In this study, a small percentage of participants had AF (18%). However, AF was not a predictor of ischemic brain infarctions. There was also no observed association between AF and hypertension. It remains unclear if ESKD was the underlying cause of AF in this patient group. Previous research has shown that the prevalence of AF in ESKD patients was 11.6%, with an overall incidence of 2.7/100 patient-years.[5] Patients with AF were prescribed bisoprolol, a selective beta-blocker, but none were given oral anticoagulants to prevent thrombotic/embolic events associated with AF.

Over half of the patients with ischemic brain infarctions had hypertriglyceridemia (dyslipidemia) with or without hypercholesterolemia. Hypertriglyceridemia was significantly linked to hypertension, hyperglycemia, hyperuricemia, hypercholesterolemia, and low HDL cholesterol levels. In addition, hyperlipidemia was independently linked to ischemic brain infarctions regardless of other risk factors. Studies indicated that excess cholesterol in the blood can lead to plaque formation, which can narrow or block blood vessels, causing ruptures and thromboembolic brain infarctions.[37]

It has been noted that dyslipidemia in patients with CKD, especially ESKD, may be atherogenic or uremic. Atherogenic dyslipidemia, common in insulin-resistant patients, is characterized by high total cholesterol, LDL cholesterol, and triglyceride levels, and low HDL cholesterol levels. Uremic dyslipidemia, on the other hand, is characterized by nearly normal LDL and HDL cholesterol levels but high triglyceride levels.[8] Studies indicated that progressive proteinuria in CKD can disrupt lipoprotein transport, leading to elevated triglycerides, very LDL, and LDL cholesterol levels, and reduced HDL cholesterol levels. Furthermore, progressive proteinuria in CKD can upregulate hydroxymethylglutaryl-CoA reductase, causing hypercholesterolemia and increased LDL synthesis. Uremia can also alter the structure and function of HDL, and the loss of lecithin-cholesterol acyltransferase in urine can result in low HDL levels and impaired maturation of HDL-3 to cholesterol-rich HDL-2.[38,39] Only 14.2% of patients with hyperlipidemia in the study received statin treatment, indicating that hyperlipidemia/dyslipidemia was often overlooked and undertreated in kidney disease patients. We also found that statins were not associated with a reduced risk of ischemic brain infarctions.

In this study, approximately 42% of patients with ischemic brain infarctions were found to have hyperuricemia. Hyperuricemia was significantly associated with hypertension, hyperglycemia, and hyperlipidemia. In addition, hyperuricemia was independently linked to ischemic brain infarctions regardless of other risk factors. It is known that uric acid is a major antioxidant in human blood, with two-thirds normally excreted in the

urine.[40-42] CKD impairs uric acid excretion, especially in the presence of insulin resistance and increased renal vascular resistance. In the atherosclerotic environment of CKD, uric acid's antioxidant properties can paradoxically become prooxidant (an antioxidant–prooxidant urate redox shuttle),[41,42] leading to increased reactive oxygen species, arterial endothelial damage, oxidation of lipoproteins in atherosclerotic plaques, and the development of renal fibrosis and glomerulosclerosis. During the study period, hyperuricemia was diagnosed in all patients, none of whom had received treatment for the condition before being included. This suggests that hyperuricemia may have been overlooked in patients with CKD.

Anemia was present in 60% of patients, while ischemic brain infarctions were found in 66% of patients with ESKD. Anemia was identified as an independent variable associated with the presence of ischemic brain infarction. Studies have shown that CKD and anemia elevate the risk of stroke, with individuals without anemia showing a slight, non-significant increase in stroke risk.[43] It is important to note that the correction of anemia in CKD patients should adhere to the Kidney Disease Outcomes Quality Initiative guidelines, aiming to raise hemoglobin levels to between 11 and 12 g/dL. Large randomized clinical trials have demonstrated that treating anemia with erythropoietin-stimulating agents in hemodialysis patients can heighten the risk of stroke.[44]

In this study, the prevalence of hypoalbuminemia was significantly higher in patients with ischemic brain infarctions (74% vs. 24%). In addition, albuminuria was substantially more common in patients with ischemic brain infarctions (40% vs. 18%, p=0.001). Hypoalbuminemia showed a significant correlation with proteinuria. Both hypoalbuminemia and albuminuria were independently linked to ischemic brain infarctions. Kidney damage often leads to progressive proteinuria, resulting in hypoalbuminemia. Research has shown a higher risk of cerebrovascular stroke in patients with kidney disease and macroalbuminuria compared to those with microalbuminuria.[45] Proteinuria is strongly associated with hypertension and other cardiovascular risk factors.[46] Albuminuria not only indicates localized renal damage but also serves as a biomarker for generalized endothelial dysfunction, increasing the risk of vascular events such as ischemic brain infarctions and stroke. Low serum albumin levels may indicate factors that influence the atherosclerotic process, platelet function, blood viscosity, free fatty acid transport, and antioxidant levels.[47]

In this study, approximately 20% of individuals with ischemic infarctions developed cerebrovascular stroke during the period of the study. Patients with cerebrovascular stroke accounted for approximately 22% of those with ESKD. No specific laboratory or MRI findings distinguished this subgroup of patients from the rest with ESKD. Studies have shown that individuals with ESRD have a significantly higher incidence of stroke, 8–10 times greater than the general population, with rates ranging from 10 to 33/1,000 patients/year.[48] The prevalence of stroke was 17% among dialysis patients compared to 10% among non-dialysis CKD patients and 4% in the general population.[49,50] Previous research has indicated an inverse linear relationship between eGFR and the risk of stroke (ischemic or hemorrhagic), with the risk of stroke increasing by 7% for every 10 mL/min/1.73 m^2 decrease in eGFR[12] and by 10%/25 mg/mmol increase in the albumin-to-creatinine ratio independent of eGFR.[18] Focal neurologic stroke manifestations included dysarthria, hemihypoesthesia, and visual field defects. Eight out of 36 patients with basal ganglionic brain infarctions (22%) experienced an acute onset of extrapyramidal movement disorders, including parkinsonism (n = 6) and chorea-dystonia (n = 2). Reviewing the literature revealed case reports of extrapyramidal movement disorders in uremic patients, including parkinsonism,[10,51-53] chorea,[10,54,55] and dystonia.[10,56] In a previous study,[10] we examined 70 adults (mean age: 45.87 ± 3.36 years) with uremia due to CKD with a duration of uremia of 5.5 ± 1.5 years. Basal ganglia lesions were found in 21.4% of the patients, with 8.6% developing extrapyramidal movement disorders after ~10 months from the onset of uremia. These disorders were attributed to basal ganglia edema and ischemic infarctions.

The results of this study highlight the bidirectional causal relationship between vascular brain diseases and CKD and uremic syndrome. It has been indicated that the uremic environment also significantly contributes to and exacerbates systemic and cerebral vascular damage, arteriosclerosis, atherosclerosis, and calcification. This environment includes uremic toxins, anemia, chronic inflammation, endothelial dysfunction, cerebral hypoperfusion, impaired autoregulation, increased cytokine release, oxidative stress, reduced nitric oxide availability, hyperhomocysteinemia, dyslipidemia, platelet dysfunction, increased aggregation, and elevated levels of hemostatic factors.[3,4]

In this study, the treatment of acute cerebrovascular stroke in CKD involved several approaches optimizing renal replacement therapy (such as more frequent and adequate dialysis), correcting associated metabolic imbalances, addressing the underlying cause of CKD and its comorbidities, using antiplatelets to prevent recurrent strokes, and providing supportive or symptomatic care (e.g., levodopa therapy for parkinsonism, anti-dopaminergic

drugs for chorea). ACE2 inhibitors or blockers are the preferred treatment for hypertension in patients with CKD. These medications reduce the risk of cardiovascular and cerebrovascular events and slow the progression of CKD.[57,58] Studies have demonstrated the effectiveness of sodium-dependent glucose transporter inhibitors in managing diabetes, diabetic nephropathy, cardiac disease, stroke, and kidney disease.[59] Statins have been proven effective in treating hyperlipidemia in CKD patients.[60] Allopurinol is the primary treatment of hyperuricemia in CKD patients, although febuxostat has emerged as an alternative to allopurinol.[61]

We and others agree on the use of antiplatelets (aspirin or clopidogrel) in the treatment of patients with silent ischemic brain infarction and for preventive purposes. However, the management of silent infarctions remains a topic of debate. It has been recommended that the use of antiplatelets for preventing ischemic stroke in patients with CKD should adhere to the clinical guidelines of the Kidney Disease Outcomes Quality Initiative. There is evidence that supports the effectiveness of antiplatelets in preventing stroke in non-dialysis CKD patients.[62] Furthermore, prior research has suggested that patients with CKD, including those with ESKD, can be treated for acute stroke similarly to the general population,[63] including the use of thrombolysis (e.g., tissue plasminogen activator) and endovascular thrombectomy.[64] However, these studies have also noted a higher risk of intracerebral hemorrhage with tissue plasminogen activator in CKD patients compared to the general population.[65]

We did not prescribe anticoagulants to prevent stroke in patients with AF and CKD due to the controversial nature of their use in this population. Studies have shown that warfarin, a commonly used anticoagulant, may increase the risk of bleeding in CKD patients on dialysis without significantly reducing the risk of stroke compared to no anticoagulation. Warfarin works by affecting vitamin K-dependent clotting factors and anticoagulant proteins.[66] Some studies suggest that apixaban, a newer anticoagulant that selectively inhibits factor Xa, may be a safer and more effective option for these patients. Authors have recommended switching from warfarin to apixaban in this population.[67] It is essential to closely monitor the international normalized ratio when using anticoagulants in patients with ESKD to adjust the dosage and prevent bleeding.

In this study, patients with a history of cerebrovascular stroke more than 6 months prior were followed up, and it was found that they still had persistent neurological symptoms. The clinical poor outcomes observed may be due to the combination of uremia and underlying microvascular diseases such as hypertension and diabetes in predisposed patients. Previous studies have shown different outcomes, with 20% experiencing complete improvement, 50% showing improvement with remaining deficits, and 30% with no improvement.[51,52]

5. Study limitations

The study primarily included patients with ESKD undergoing dialysis, potentially underestimating the frequency and progression of ischemic brain infarctions in early stages of kidney disease. This has been explained by the fact that patients were recruited from tertiary referral hospitals, where severe cases are commonly referred for dialysis and complications management, while ESKD patients are often treated in private clinics. The restrictive inclusion/exclusion criteria (e.g., exclusion of patients with previous ischemic or hemorrhagic strokes, but many CKD patients have mixed pathologies) may limit generalizability. In addition, the study only focused on the clinical outcomes of patients who experienced cerebrovascular stroke due to ischemic brain infarctions during the follow-up period. We did not assess the functional outcome of patients with CKD who developed stroke. Future studies should examine the functional outcomes and quality of life of CKD patients who develop cerebrovascular stroke, considering different neurological complications of CKD, such as cognitive impairment. The temporal relationship between brain infarction development and hemodialysis initiation was not established. Previous reports suggest a higher stroke risk within the first 30 days of starting hemodialysis due to rapid intravascular volume changes. Recurrent seizures were observed in 23% of patients, often coinciding with renal function decline and a history of uremic encephalopathy. While all patients had ischemic brain infarctions, the direct link between infarctions and seizures was not definitive. Uremic toxins and metabolic disturbances are potential contributors to uremic seizures. Antiseizure medications recommended for CKD patients undergoing hemodialysis are those primarily metabolized by the liver (e.g., carbamazepine, phenytoin, and valproate), with potential dose adjustments needed due to dialysis clearance. Monitoring free drug levels is crucial in CKD patients with hypoalbuminemia to prevent drug toxicity.[68,69]

6. Conclusion

There is limited and conflicting data in the literature on the types, prevalence, treatment, and prevention of cerebral infarctions caused by uremic syndrome in CKD due to the diverse range of causes and comorbidities in the a*t*-risk population. This study systematically examined a cohort of patients at various stages of kidney failure to

investigate the occurrence of ischemic brain infarctions and cerebrovascular strokes. The findings revealed a high incidence of silent cerebral infarctions in CKD patients, affecting over two-thirds of individuals, with small bilateral lacunar infarctions being the most common type. Approximately 22% of patients with silent ischemic infarctions developed cerebrovascular strokes. Risk factors for ischemic infarctions in CKD included advanced renal dysfunction, hypertension, diabetes, hyperlipidemia, hyperuricemia, anemia, hypoalbuminemia, and albuminuria. Recommendations were provided for managing these patients and preventing recurrent strokes, emphasizing the importance of addressing all vascular risk factors and implementing preventive measures. The study also highlighted the underdiagnosis and undertreatment of hyperlipidemia and hyperuricemia in this patient population. Patients with cerebrovascular stroke in ESKD often have a poor prognosis due to ongoing neuronal damage from uremic brain injury and underlying microvascular disease.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Formal analysis: All authors
Investigation: All authors
Methodology: All authors
Writing–original draft: Sherifa A. Hamed
Writing–review & editing: All authors

Ethics approval and consent to participate

The study protocol was conducted in accordance with the Ethical Standards of the National Research Committee of the Faculty of Medicine of Assiut (ID: AUFM_SH_0135/2021) and Al-Azhar University Hospital, Assiut, Egypt, which is comparable to the ethical standards of the Helsinki Declaration and its later amendments. Informed consent to participate in the study was obtained from patients or their relatives.

Consent for publication

Written informed consent was obtained from all participants to publish their data.

Availability of data

Data will be made available through the corresponding authors upon reasonable request.

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Appendix

Table A1. Strengthening the reporting of observational studies in epidemiology (STROBE) statement

Parameter	Item no	Recommendation	Page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State-specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of the study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up case–control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls cross-sectional study—Give the eligibility criteria, and the sources and methods of the selection of participants	4
		(b) Cohort study—For matched studies, give the matching criteria and the number of exposed and unexposed case–control study—For matched studies, give the matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe the comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	6
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed case–control study—If applicable, explain how matching of cases and controls was addressed cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	6
		(e) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	7–11
		(b) Give reasons for non-participation at each stage	-
		(c) Consider the use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate the number of participants with missing data for each variable of interest	-
		(c) Cohort study—Summarize follow-up time (e.g., average and total amount)	-
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	7–11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-

(Cont'd)

Table A1. ***(Continued)***

Parameter	Item no	Recommendation	Page #
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7–11
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarize key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, considering sources of potential bias or imprecision. Discuss both the direction and the magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12–18
Generalizability	21	Discuss the generalizability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

Notes: An explanation and elaboration article discusses each checklist item, gives methodological background, and provides published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the websites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org. *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.