CHARACTERISTICS OF PATIENTS WITH CHRONIC KIDNEY DISEASE OF UNKNOWN ETIOLOGY

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Abstract

OBJECTIVE

To determine the clinical characteristics of patients with chronic kidney disease of unknown etiology.

METHODOLOGY

This was a descriptive cross-sectional study done at the Hemodialysis Outpatient Department of Indus hospital in Karachi on the unknown etiology of adult CKD patients. The inclusion criteria were chronic kidney disease (CKD) stages I to V and age of the patient being 18 to 70 years, excluding patients with known identifiable causes or acute situations. The data were collected through demographic questionnaires, blood tests, and urine samples (24 hour). The analysis of data was done using SPSS 26, and descriptive statistics were produced to summarise the demographic and clinical variables.

RESULTS

In a sample comprising 267 patients with average age was recorded as 51.6 ± 12.4 years, with a representation of 54.3% being female. A predominant proportion of the cohort was categorized within CKD stage IIIB (38.2%). The average serum creatinine levels were measured at 2.93 ± 1.29 mg/dL, with an estimated Glomerular Filtration Rate (eGFR) of 40.76 ± 13.84 mL/min/1.73 m², proteinuria levels at 356.12 ± 222.14 mg/day, and hemoglobin concentrations at 10.07 ± 1.75 g/dL. No statistically significant differences pertaining to gender or age were identified in the clinical parameters ($p > 0.05$).

CONCLUSION

These findings concluded that the patient with chronic kidney disease of unknown cause, recording high serum creatinine, low eGFR, low level proteinuria, anemia and trends to increase electrolyte imbalances. Such clinical features combining in the absence of classical risk factors underline the unique picture of CKDu and the necessity of regular biochemical tests to facilitate early diagnosis and risk stratification within populations exposed to them

INTRODUCTION

Chronic Kidney Disease of Unknown Etiology (CKDu) is an emerging public health concern, particularly in regions with high prevalence but unclear causative factors [1]. Unlike traditional chronic kidney disease (CKD), which is commonly associated with diabetes and hypertension, CKDu predominantly affects young to middle-aged adults (30–50 years old), particularly agricultural workers in Central America, Sri Lanka, India, and parts of Africa, suggesting a potential link to environmental and occupational exposures [2,3].

In Pakistan, CKD is a growing concern, with an estimated 21.2 million adults (≈19.8% of the population) affected by CKD stages 1–5 [4]. While diabetes and hypertension remain the leading causes, undiagnosed and non-traditional CKD cases, potentially CKDu, are emerging in rural regions [3,4]. The southern Punjab, Sindh, and Balochistan provinces—home to large farming communities—report increased CKD prevalence among agricultural workers, aligning with global CKDu trends. Poor water quality, nephrotoxic agrochemicals, and extreme heat exposure may be significant contributors [5].

The clinical profile of CKDu patients is distinct from other forms of CKD. Affected individuals are often present with elevated serum creatinine levels, with reported mean values ranging from 1.20 ± 0.74 mg/dL and eGFR 49±23 mL/min [6]. Hemoglobin levels are lower in CKDu patients, with a mean hemoglobin concentration of 10.2±1.8 g/dL, indicating mild to moderate anemia. The mean estimated glomerular filtration rate (eGFR) is 33.04±18.01 mL/min/1.73m², reflecting advanced renal impairment characteristic of CKDu [7]. Unlike diabetic nephropathy, proteinuria in CKDu is common, with 49.6% of patients exhibiting proteinuria, indicating renal involvement [8]. Electrolyte imbalances such as hyperkalemia 33.9% and hyponatremia 41.9% are also common findings [9-10]. The pathogenesis of CKDu is not well known, although several theories are put forward. These are chronic dehydration and heat stress as a result of hard work in hot conditions, contact with nephrotoxic substances like heavy metals (arsenic, cadmium, lead), pesticides, and infected drinking water [11]. There is still no clear causative agent even though these risk

factors have been increasingly recognized. Given the silent presence of early-stage CKDu, the majority of patients arrive at late stages, where serum creatinine concentration is as high as 2 mg/dL and at the eGFR already less than 60 mL/min/1.73 m 2 in more than half of patients [12]. Establishing the clinical parameters of chronic kidney disease of unknown etiology (CKDu) is vital to facilitate early diagnosis and monitoring. This research would be attributed to evaluating essential variables of kidney functionality like a serum creatinine level and an estimated glomerular filtration rate (eGFR) together with the variables reflected on the progress of a disease, like proteinuria, hemoglobin rates, and electrolyte disturbances. The analysis of these parameters will assist in recognition of the patterns related to CKDu, which can further be used to stratify the risk, presuppose early intervention, and disease control within patients.

METHODOLOGY

The descriptive cross-sectional study was undertaken at the Hemodialysis Outpatient Department of Nephrology, Indus hospital in Karachi Pakistan, after getting an institutional ethical approval. Chronic kidney disease was operationally delineated as a sustained estimated glomerular filtration rate (eGFR) for a duration exceeding three months, computed utilizing the Cockcroft–Gault equation and classified in accordance with established categories (stage 1: >90; stage 2: 60–90; stage 3A: 45–59). The designation of unknown etiology was attributed when patients presented without any prior history or demonstrable clinical, laboratory, or imaging evidence indicative of diabetes mellitus, hypertension, glomerulonephritis, autoimmune renal disorders, congenital or hereditary anomalies, obstructive uropathy, nephrotoxic exposures, or other discernible causes.

The sample size was calculated using the WHO sample size calculator, based on a previously reported frequency of proteinuria (49.6%)[8], with a margin of error (d) of 6% and a 95% confidence level (CI). The estimated sample size was calculated to be n=267. Using non-probability consecutive sampling, adult patients (aged 18–70 years) of either sex, with CKD stages I–V of unknown etiology and disease duration

exceeding three months, were enrolled; those with acute or rapidly progressive renal failure, structural kidney disease, documented diabetes or hypertension, prior nephrotoxic exposure, or who declined consent were excluded. After obtaining written informed consent, the principal investigator collected demographic data (age, gender, residential, educational and employment status and body mass index. Venous blood samples were drawn for serum creatinine (mg/dL), hemoglobin (g/dL), sodium and potassium (mmol/L) assays, processed in the institutional diagnostic laboratory under standardized protocols. Proteinuria was quantified by 24-hour urinary protein excretion and categorized as minimal (<150 mg/day), mild (150–500 mg/day) or severe (>500 mg/day). Data will be entered and analyzed using SPSS v26. Demographic and clinical variables were computed using descriptive statistics computed using means, SD, and frequencies. The statistical significance would be determined at the p-value ≤ 0.05 using the independent sample t- test.

RESULTS

A total of 267 individuals were incorporated into the research endeavor. The average age of the participants was 51.60 ± 12.40 years, with a 95% confidence interval (CI) extending from 50.10 to 53.09 years. The mean body mass index (BMI) was calculated to be 21.80 ± 5.60 kg/m² (95% CI: 21.13–22.48), and the average duration of chronic kidney disease (CKD) was determined to be 32.09 ± 15.76 months (95% CI: 30.19–33.99). Among the participants, 122 (45.7%) were identified as male and 145 (54.3%) as female. A majority of the patients hailed from urban locales (n=171, 64.0%), whereas 96 (36.0%) resided in rural settings. In terms of educational attainment, 112 (41.9%) were classified as illiterate and 155 (58.1%) as literate. With respect to employment status, 173 (64.8%) were gainfully employed, while 94 (35.2%) were categorized as unemployed. The predominant marital status among the participants was married (n=182, 68.2%), followed by single individuals (n=47, 17.6%), those who were widowed (n=22, 8.2%), and divorced individuals (n=16, 6.0%). An analysis of CKD staging indicated that the majority of patients were classified in Stage IIIB (n=102, 38.2%), followed by Stage IIIA (n=85, 31.8%), Stage IV (n=50, 18.7%),

Stage II (n=21, 7.9%), and Stage V (n=9, 3.4%) (TABLE I).

Table II delineates the comparative analysis of clinical characteristics between male and female participants (n=267). The average serum creatinine concentration was recorded at 2.92 ± 1.20 mg/dL for males and 2.94 ± 1.38 mg/dL for females, with no statistically significant difference identified (p = 0.884). The estimated glomerular filtration rate (eGFR) exhibited a marginal elevation in males (41.92 ± 14.76 mL/min/1.73 m²) relative to females (39.74 ± 12.88 mL/min/1.73 m²), although this disparity did not attain statistical significance (p = 0.198). Proteinuria levels were also found to be elevated in males (372.34 ± 226.22 mg/day) in comparison to females (340.52 ± 218.54 mg/day), yet this difference was not statistically significant (p = 0.245). Hemoglobin concentrations were lower in males (9.90 ± 1.73 g/dL) than in females (10.22 ± 1.77 g/dL), with a p-value of 0.137. Serum sodium concentrations were found to be comparable between males (132.98 ± 6.21 mmol/L) and females (132.33 ± 6.30 mmol/L) (p=0.392). In a similar vein, serum potassium concentrations did not reveal any significant differences between males (5.19 ± 1.06 mmol/L) and females (5.02 ± 1.02 mmol/L) (p=0.199).

Table III delineates the comparative analysis of clinical characteristics across two distinct age cohorts (18–50 years and >50 years) among the participants in the study (n=267). The mean serum creatinine concentration was marginally lower in the younger cohort (2.84 ± 1.33 mg/dL) in contrast to the elder cohort (3.02 ± 1.26 mg/dL); however, this discrepancy did not achieve statistical significance (p=0.278). Likewise, the estimated Glomerular Filtration Rate (eGFR) was recorded at 40.17 ± 13.31 mL/min/1.73 m² for the younger cohort, compared to 41.31 ± 14.28 mL/min/1.73 m² for the older cohort, with no statistically significant difference noted (p=0.501). The levels of proteinuria were nearly indistinguishable between the two age groups (354.66 ± 215.84 mg/day versus 355.45 ± 229.30 mg/day; p=0.977). Hemoglobin concentrations were also found to be comparable, with a mean of 10.02 ± 1.82 g/dL in the 18–50 age group and 10.12 ± 1.69 g/dL in participants aged over 50 years (p=0.647). The mean serum sodium and potassium concentrations exhibited no significant variations between the two

cohorts, with sodium levels at 132.34 ± 5.87 mmol/L versus 132.91 ± 6.62 mmol/L (p=0.459), and potassium levels at 5.19 ± 1.11 mmol/L versus 5.01 ± 0.95 mmol/L (p=0.148). In summary, none of the clinical parameters demonstrated statistically significant differences between the two age groups.

Table I: Demographic and Clinical Characteristics of Study Participants (n=267)		
Mean± Standard Deviation		**95% Confidence Interval**
Age in years = **51.60 ± 12.40**		50.10⁓53.09
Body Mass Index in kg/m^2 = **21.80 ± 5.60**		21.13⁓22.48
Duration of CKD in months = **32.09 ± 15.76**		30.19⁓33.99
n (%)		
Gender	Male	122 (45.7)
	Female	145 (54.3)
Residential Status	Urban	171 (64.0)
	Rural	96 (36.0)
Educational Status	Illiterate	112 (41.9)
	Literate	155 (58.1)
Employment Status	Employed	173 (64.8)
	Unemployed	94 (35.2)
Marital Status	Single	47 (17.6)
	Married	182 (68.2)
	Divorced	16 (6.0)
	Widowed	22 (8.2)
CKD Stage	Stage II	21 (7.9)
	Stage IIIA	85 (31.8)
	Stage IIIB	102 (38.2)
	Stage IV	50 (18.7)
	Stage V	9 (3.4)

Table II: Comparison of Clinical Characteristics with Gender (n=267)			
Clinical Characteristics	**Gender**		**P-Value**
	Male	**Female**	
Serum Creatinine in **mg/dL**	2.92 ± 1.20	2.94 ± 1.38	0.884
eGFR in **mL/min/1.73 m²**	41.92 ± 14.76	39.74 ± 12.88	0.198
Proteinuria in **mg/day**	372.34 ± 226.22	340.52 ± 218.54	0.245
Hemoglobin in **g/dL**	9.90 ± 1.73	10.22 ± 1.77	0.137
Sodium in **mmol/L**	132.98 ± 6.21	132.33 ± 6.30	0.392
Potassium in **mmol/L**	5.19 ± 1.06	5.02 ± 1.02	0.199

Table III: Comparison of Clinical Characteristics with Age Group (n=267)			
Clinical Characteristics	**Age Group**		**P-Value**
	18⁓50	**>50**	
Serum Creatinine in **mg/dL**	2.84 ± 1.33	3.02 ± 1.26	0.278
eGFR in **mL/min/1.73 m²**	40.17 ± 13.31	41.31 ± 14.28	0.501
Proteinuria in **mg/day**	354.66 ± 215.84	355.45 ± 229.30	0.977

Hemoglobin in g/dL	10.02 ± 1.82	10.12 ± 1.69	0.647
Sodium in mmol/L	132.34 ± 5.87	132.91 ± 6.62	0.459
Potassium in mmol/L	5.19 ± 1.11	5.01 ± 0.95	0.148

DISCUSSION

In this descriptive cross-sectional study, the clinical characteristics of patients diagnosed with chronic kidney disease of unknown etiology (CKDu) were analyzed, offering critical insight into the manifestation of this underrecognized condition within the Pakistani population. The average patient age was approximately 51 years, with the majority presenting at stages IIIA and IIIB of chronic kidney disease (CKD). These findings reflect a trend of delayed diagnosis, similar to patterns reported in endemic regions such as Central America, Sri Lanka, and South India, where CKDu often remains asymptomatic until moderate to advanced stages [1–3,6,7]. Unlike global studies that typically report a male predominance, especially among agricultural workers [1,2], this study observed a slight female predominance. This deviation may be attributed to sociocultural healthcare-seeking behaviors or regional demographic patterns and warrants further investigation.

The majority of patients exhibited elevated serum creatinine and reduced estimated glomerular filtration rate (eGFR), averaging below 45 mL/min/1.73 m², indicating significant renal impairment. These biochemical parameters closely align with previously documented profiles of CKDu in endemic populations [6,7,12]. Proteinuria, although typically non-nephrotic in CKDu, was present in nearly half of the participants, a feature consistent with findings from Uddanam, India and Sri Lanka [8,13]. The observed hemoglobin levels (~10 g/dL) suggest mild to moderate anemia, which is frequently reported among CKDu patients and reflects chronic kidney dysfunction absent of the classical diabetic or hypertensive causes [7,12]. Electrolyte disturbances such as hyponatremia and hyperkalemia were common but did not significantly vary by gender or age. These findings suggest a dominant tubulointerstitial involvement, as supported by studies describing impaired tubular sodium and potassium handling in CKDu [9,10,14].

Emerging literature from the past decade continues to reinforce the hypothesis that CKDu is multifactorial in origin, with significant environmental and occupational determinants. Priyadarshani et al. (2024) emphasized the role of contaminated water sources and agrochemical exposure in renal injury mechanisms linked to CKDu [13]. Similar concerns were echoed in a multi-country review by Vlahos et al., who stressed the importance of clean water access and environmental regulation in CKDu prevention [14]. Occupational hazards such as heat stress, dehydration, and pesticide handling are increasingly implicated in CKDu's pathogenesis, as highlighted by Byrne-Hamilton et al. [15]. Additionally, environmental nephrotoxins, including heavy metals and glyphosate, have been identified as potential contributors, with documented renal histological damage in endemic communities [16].

Broader global analyses, such as the one by Stanifer et al., have acknowledged the rising burden of CKD, including CKDu, in low- and middle-income countries, where underdiagnosis and limited environmental monitoring hinder effective disease control [17]. In the Pakistani context, Imtiaz and Alam have reported increasing cases of CKD without known etiology, often presenting with small, echogenic kidneys and lacking conventional risk factors, further confirming the relevance of CKDu in local nephrology practice [18].

This study's strengths include a well-defined operational criterion for CKDu, use of standardized laboratory protocols, and a relatively large and diverse patient sample from a high-volume tertiary center. Nevertheless, certain limitations must be acknowledged. The single-center design and non-probability sampling may limit generalizability. The absence of renal imaging and biopsy restricts the ability to rule out subclinical or hereditary renal pathologies. Most notably, environmental, occupational, and lifestyle data were not collected, precluding a more comprehensive understanding of potential etiological exposures. These limitations highlight the need for future multi-center and

longitudinal studies that incorporate environmental toxicology, geospatial mapping, and genetic profiling to fully elucidate CKDu's multifaceted origins.

This study contributes to the growing body of evidence that CKDu is a significant and under-recognized condition in Pakistan. The clinical profile observed mirrors global patterns—late-stage presentation, mild proteinuria, anemia, and electrolyte imbalance—consistent with tubulointerstitial injury rather than glomerular pathology. These findings underscore the need for integrated strategies focused on early detection, environmental monitoring, and public health interventions to prevent disease progression and improve outcomes in affected communities.

CONCLUSION

These findings concluded that the patient with chronic kidney disease of unknown cause, recording high serum creatinine, low eGFR, low level proteinuria, anemia and trends to increase electrolyte imbalances. Such clinical features combining in the absence of classical risk factors underline the unique picture of CKDu and the necessity of regular biochemical tests to facilitate early diagnosis and risk stratification within populations exposed to them.

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