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End-Stage Kidney Disease of Unknown Etiology in Southern Iraq: Clinical Characteristics and a Distinct Cardiometabolic Profile Among Patients Receiving Maintenance Hemodialysis

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ABSTRACT

In several hot, agricultural regions a large share of end-stage kidney disease (ESKD) has no identifiable cause, and this form of disease is now regarded as a separate entity, termed chronic kidney disease of uncertain etiology (CKDu). Whether ESKD of unknown etiology in southern Iraq differs clinically from ESKD with a recorded cause has not been examined. This cross-sectional analysis included all 394 adults receiving maintenance hemodialysis in the five units of Thi-Qar Governorate between September 2025 and January 2026. Patients in whom no primary renal diagnosis could be established were compared with patients with a recorded cause for demographic, comorbidity, and dialysis characteristics. Independent correlates of unknown etiology were identified with multivariable binary logistic regression. The etiology of ESKD was unknown in 62 patients (15.7%; 95% CI 12.5–19.7). The two groups were similar in age (52.2 ± 19.8 vs. 53.7 ± 16.6 years), sex, residence, duration of known CKD, dialysis vintage, dialysis frequency, and vascular access. Patients with unknown etiology less often had diabetes mellitus (19.4% vs. 47.9%), hypertension (69.4% vs. 86.4%), and cardiovascular disease (12.9% vs. 32.5%; all $p \leq 0.002$). In multivariable analysis, diabetes (adjusted odds ratio [aOR] 0.34; 95% CI 0.16–0.69), hypertension (aOR 0.42; 0.21–0.82), and cardiovascular disease (aOR 0.41; 0.18–0.93) were independently associated with lower odds of unknown etiology, whereas age, sex, and dialysis vintage were not. About one in six patients on hemodialysis in Thi-Qar has ESKD of unknown cause. These patients are of working age and carry a markedly lower cardiometabolic burden than patients with a recorded cause, a profile that raises the possibility of a CKDu-like pattern, although occupational, environmental, and histopathological data were not available to confirm it. Systematic diagnostic work-up of these patients and studies of environmental and occupational exposures in southern Iraq are warranted.

KEYWORDS

End-stage kidney disease; unknown etiology; CKD of uncertain etiology; hemodialysis; diabetes mellitus; hypertension; Iraq

ARTICLE INFORMATION

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1. Introduction

An estimated 788 million adults worldwide were living with chronic kidney disease (CKD) in 2023, with North Africa and the Middle East showing the highest age-standardized prevalence (18.0%) of any region [1]. CKD now ranks among the main causes of death and disability worldwide [2–4]. Some of these patients eventually reach end-stage kidney disease (ESKD, or kidney failure) [5], which in most low- and middle-income countries is treated with in-center hemodialysis, and access to kidney replacement therapy remains highly unequal worldwide [6–8]. Knowing why patients reach ESKD is the starting point for prevention: diabetic and hypertensive kidney disease call for cardiometabolic risk control in primary care, whereas obstructive, congenital, or toxic causes call for different strategies [6,9].

In every ESKD registry a proportion of patients has no identified primary renal disease. Registries code these patients separately, often as “CKD, cause unknown” [10,11]. In high-income settings this category largely reflects late presentation with small, scarred kidneys in older patients with multiple comorbidities. In contrast, in parts of Central America, Sri Lanka, India, and other hot agricultural regions, a distinct form of CKD has been described in younger, often male, agricultural workers without diabetes or hypertension. This entity, termed CKD of uncertain or unknown etiology (CKDu), has been linked to recurrent heat stress and

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dehydration [12–14], and possibly to agrochemical or water-borne exposures [15,16]; systematic review data associate it mainly with agricultural occupation [17].

Iraqi data suggest that unexplained ESKD is common. A 2023 national survey of 10,721 hemodialysis patients attributed 23.3% of cases to other or unspecified causes [18], and earlier Iraqi series have also described the causes of ESKD, but mostly in single centres or without population-level coverage [19]. Thi-Qar Governorate, in southern Iraq, has about 2.5 million inhabitants [20], an extremely hot and arid climate, and a large rural, agricultural population, conditions that overlap with those of established CKDu hotspots [14,16]. In a governorate-wide survey of maintenance hemodialysis in Thi-Qar, the cause of ESKD was unknown in about one patient in six [21]. Whether these patients form a clinically distinct group, or simply resemble patients with diabetic and hypertensive ESKD who were not fully investigated, is not known.

This study therefore compared patients with ESKD of unknown etiology with patients whose cause of ESKD was recorded, across demographic, comorbidity, and dialysis-related characteristics, and identified factors independently associated with unknown etiology.

2. Materials and Methods

2.1 Study design, setting, and data source

The study used an analytical cross-sectional design and is reported following the STROBE guidelines [22]. It used data from a governorate-wide survey of all five hemodialysis units of Thi-Qar Governorate, which together provide all maintenance hemodialysis in the governorate. Data were collected between September 2025 and January 2026. The overall etiological spectrum and vascular access patterns of this cohort are reported separately [21]; the present analysis addresses a different question, namely the clinical profile of patients with ESKD of unknown etiology.

2.2 Participants

Total population sampling was used, and all patients undergoing maintenance hemodialysis in the five units over the data-collection period were invited to participate [21]. Patients were eligible if they were 18 years or older, had clinically and biochemically confirmed ESKD, were on regular maintenance hemodialysis in Thi-Qar, and gave informed consent. Patients dialyzing outside the governorate, those receiving dialysis for acute kidney injury, those with incomplete medical records, and those who declined participation were excluded. A total of 394 patients were analyzed.

2.3 Data collection and definitions

Trained medical students, supervised by a nephrologist, collected data in face-to-face interviews during routine dialysis sessions using a structured questionnaire, and every item was cross-checked against hospital records, dialysis cards, and unit registers, as described for the parent survey [21]. Variables included age, sex, residence (urban or rural), duration of known CKD before dialysis, dialysis vintage, number of dialysis sessions per week, comorbidities (diabetes mellitus, hypertension, and cardiovascular disease), and vascular access at dialysis initiation and at the time of study.

The cause of ESKD was taken as the primary renal diagnosis recorded by the treating nephrologist. Patients were classified as having unknown etiology when no primary renal disease could be established from the available clinical, laboratory, and imaging data, and as having known etiology when any primary renal diagnosis had been recorded (diabetic nephropathy, hypertensive nephrosclerosis, chronic glomerulonephritis, obstructive uropathy, congenital anomalies of the kidney and urinary tract, autosomal dominant polycystic kidney disease, or analgesic nephropathy). Diabetes mellitus, hypertension, and cardiovascular disease were recorded as comorbidities from the medical records, independently of the cause assigned to ESKD.

2.4 Statistical analysis

All analyses were run in IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous data are summarized as mean ± standard deviation (SD), and categorical data as counts with percentages. Continuous variables were compared between the two groups with the independent-samples t-test; homogeneity of variance was checked with Levene's test, and Welch's correction was used where this assumption was not met. Associations between categorical variables were tested with Pearson's chi-square test; when expected cell frequencies were too small, Fisher's exact test was used instead (with the Freeman–Halton extension for tables larger than 2 × 2). The Wilson score method was used to obtain 95% confidence intervals (CIs) for the main proportions. In the multivariable binary logistic regression, the outcome was unknown etiology (coded 1 = unknown, 0 = known). Age, sex, diabetes mellitus, hypertension, cardiovascular disease, and dialysis vintage were entered simultaneously; continuous variables were entered as continuous covariates. With 62 outcome events and six covariates, the model had approximately ten events per variable, the conventional minimum [23]. Associations are presented as adjusted odds ratios (aORs) and their 95% CIs. In a second logistic model, sex, residence, and occupation (employed, unemployed, or retired) were entered to examine whether demographic characteristics were associated with unknown etiology. Statistical significance was set at a two-sided $p < 0.05$.

3. Results

3.1 Frequency of unknown etiology

Of the 394 patients, 332 (84.3%) had a recorded cause of ESKD and 62 (15.7%; 95% CI 12.5–19.7) had ESKD of unknown etiology.

3.2 Demographic and clinical characteristics

Patients with unknown and known etiology were of similar age (52.21 ± 19.77 vs. 53.72 ± 16.62 years; p = 0.573) and sex distribution (female 51.6% vs. 49.4%; p = 0.749) (Table 1, Figure 1). A larger proportion of patients with unknown etiology lived in rural areas (33.9% vs. 25.6%), although this difference did not reach statistical significance (p = 0.178). The duration of known CKD before dialysis (38.0 ± 61.4 vs. 32.2 ± 61.7 months; p = 0.499) and dialysis vintage (26.4 ± 29.2 vs. 23.8 ± 26.0 months; p = 0.475) were comparable in the two groups.

Table 1. Demographic and clinical characteristics of patients with known and unknown etiology of end-stage kidney disease (N = 394)

Variable	Known etiology (n = 332)	Unknown etiology (n = 62)	Test statistic	p-value
Age, years, mean ± SD	53.72 ± 16.62	52.21 ± 19.77	t = 0.567	0.573
Sex	Sex	Sex	Sex	Sex
Male	168 (50.6)	30 (48.4)	χ2 = 0.103	0.749
Female	164 (49.4)	32 (51.6)		
Residence	Residence	Residence	Residence	Residence
Rural	85 (25.6)	21 (33.9)	χ2 = 1.816	0.178
Urban	247 (74.4)	41 (66.1)		
Duration of known CKD before dialysis, months, mean ± SD	32.23 ± 61.71	38.00 ± 61.42	t = −0.677	0.499
Dialysis vintage, months, mean ± SD	23.82 ± 25.98	26.44 ± 29.17	t = −0.716	0.475

Values are n (%) unless otherwise stated. p-values for continuous variables are from the independent-samples t-test (with Welch correction for unequal variances) and for categorical variables from Pearson's chi-square test. CKD, chronic kidney disease; SD, standard deviation.

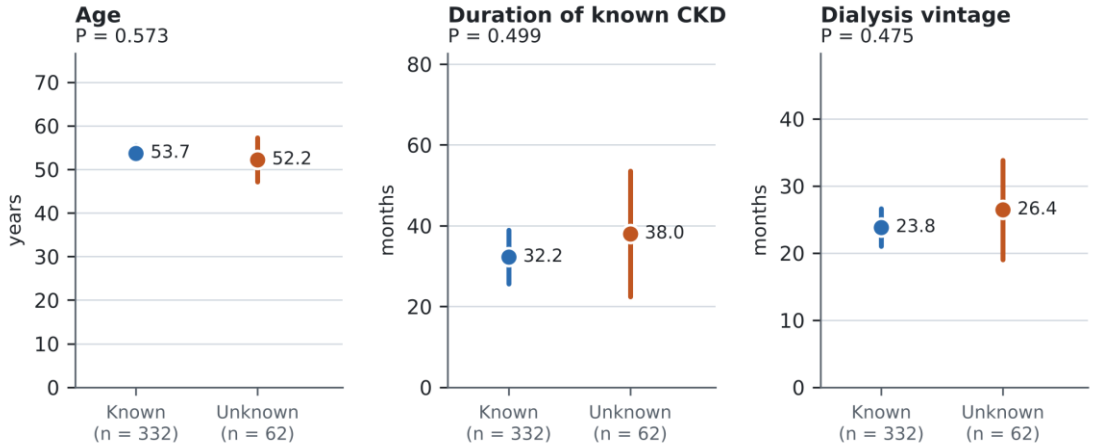


Figure 1. Age, duration of known CKD before dialysis, and dialysis vintage in patients with known (n = 332) and unknown (n = 62) etiology of end-stage kidney disease. Points show group means and vertical lines the 95% confidence intervals of the mean (derived from the mean, SD, and n in Table 1); p-values are from the independent-samples t-test. CKD, chronic kidney disease.

3.3 Comorbidities

The comorbidity profile differed markedly between the groups (Table 2, Figure 2). Diabetes mellitus was present in 19.4% of patients with unknown etiology compared with 47.9% of those with known etiology (χ2 = 17.319; p < 0.001). Hypertension (69.4% vs. 86.4%; p = 0.001) and cardiovascular disease (12.9% vs. 32.5%; p = 0.002) were also less frequent in the unknown-etiology group. Thus, 30.6% of patients with unknown etiology were normotensive and 80.6% were non-diabetic.

Table 2. Comorbidities in patients with known and unknown etiology of end-stage kidney disease (N = 394)

Comorbidity	Known etiology (n = 332)	Unknown etiology (n = 62)	χ2	p-value
Diabetes mellitus	159 (47.9)	12 (19.4)	17.319	< 0.001
Hypertension	287 (86.4)	43 (69.4)	11.217	0.001
Cardiovascular disease	108 (32.5)	8 (12.9)	9.688	0.002

Values are n (%) of patients with the comorbidity; percentages without the comorbidity are the complements. p-values are from Pearson's chi-square test (exact p for diabetes mellitus = 3.2 × 10−5).

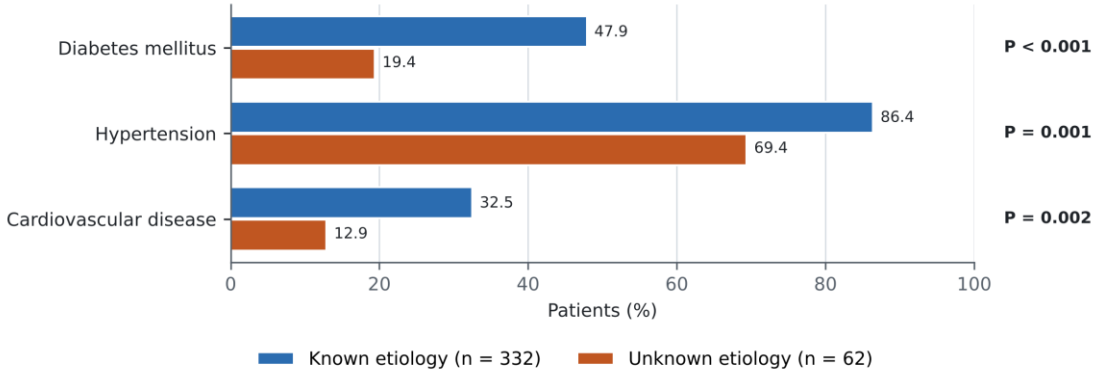


Figure 2. Prevalence of diabetes mellitus, hypertension, and cardiovascular disease in patients with known (n = 332) and unknown (n = 62) etiology of end-stage kidney disease. Bars show the percentage of patients in each group; p-values are from Pearson's chi-square test and significant differences are shown in bold.

3.4 Dialysis-related characteristics

Dialysis prescription and vascular access were similar in the two groups (Table 3, Figure 3). About two-thirds of patients in both groups dialyzed twice weekly (64.5% vs. 66.3%), and fewer than a third received thrice-weekly sessions (p = 0.185). Most patients in both groups had started dialysis through a catheter (87.1% vs. 86.7%; p = 0.940), and current arteriovenous fistula (AVF) use was almost identical (54.8% vs. 53.3%; p = 0.825).

Table 3. Dialysis-related characteristics of patients with known and unknown etiology of end-stage kidney disease (N = 394)

Variable	Known etiology (n = 332)	Unknown etiology (n = 62)	Test statistic	p-value
Dialysis sessions per week	Dialysis sessions per week	Dialysis sessions per week	Dialysis sessions per week	Dialysis sessions per week
Once	17 (5.1)	2 (3.2)	Fisher = 4.70a	0.185
Twice	220 (66.3)	40 (64.5)		
Three times	92 (27.7)	17 (27.4)		
Four times	3 (0.9)	3 (4.8)		
Vascular access at initiation	Vascular access at initiation	Vascular access at initiation	Vascular access at initiation	Vascular access at initiation
Catheter	288 (86.7)	54 (87.1)	$\chi 2$ = 0.006	0.940
AVF	44 (13.3)	8 (12.9)		
Current vascular access	Current vascular access	Current vascular access	Current vascular access	Current vascular access
Catheter	155 (46.7)	28 (45.2)	$\chi 2$ = 0.049	0.825
AVF	177 (53.3)	34 (54.8)		

Values are n (%). aFisher–Freeman–Halton exact test, applied because expected cell frequencies were too low for the chi-square test. AVF, arteriovenous fistula.

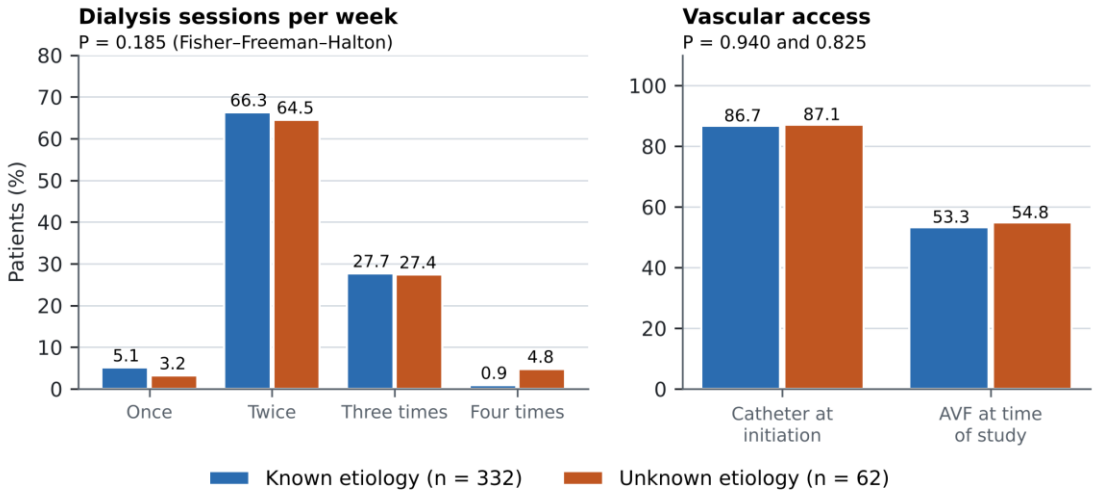


Figure 3. Dialysis-related characteristics in patients with known and unknown etiology of end-stage kidney disease: distribution of dialysis sessions per week (left) and vascular access at initiation and at the time of study (right). Bars show the percentage of patients in each group. AVF, arteriovenous fistula.

3.5 Factors independently associated with unknown etiology

In multivariable logistic regression (Table 4, Figure 4), diabetes mellitus (aOR 0.337; 95% CI 0.164–0.690; p = 0.003), hypertension (aOR 0.416; 0.212–0.818; p = 0.011), and cardiovascular disease (aOR 0.411; 0.181–0.932; p = 0.033) were each independently associated with lower odds of unknown etiology. Age (aOR 1.011 per year; p = 0.220), sex (p = 0.426), and dialysis vintage (aOR 1.001 per month; p = 0.785) were not associated with unknown etiology.

Table 4. Multivariable binary logistic regression of factors associated with unknown etiology of end-stage kidney disease (N = 394)

Variable	aOR [Exp(B)]	95% CI	p-value
Age (per year)	1.011	0.994–1.028	0.220
Sex (male vs. female)a	0.790	0.443–1.411	0.426
Diabetes mellitus (yes vs. no)	0.337	0.164–0.690	0.003
Hypertension (yes vs. no)	0.416	0.212–0.818	0.011
Cardiovascular disease (yes vs. no)	0.411	0.181–0.932	0.033
Dialysis vintage (per month)	1.001	0.991–1.011	0.785

Dependent variable coded 1 = unknown etiology, 0 = known etiology; all covariates were entered simultaneously. aReference category: female. aOR, adjusted odds ratio; CI, confidence interval.

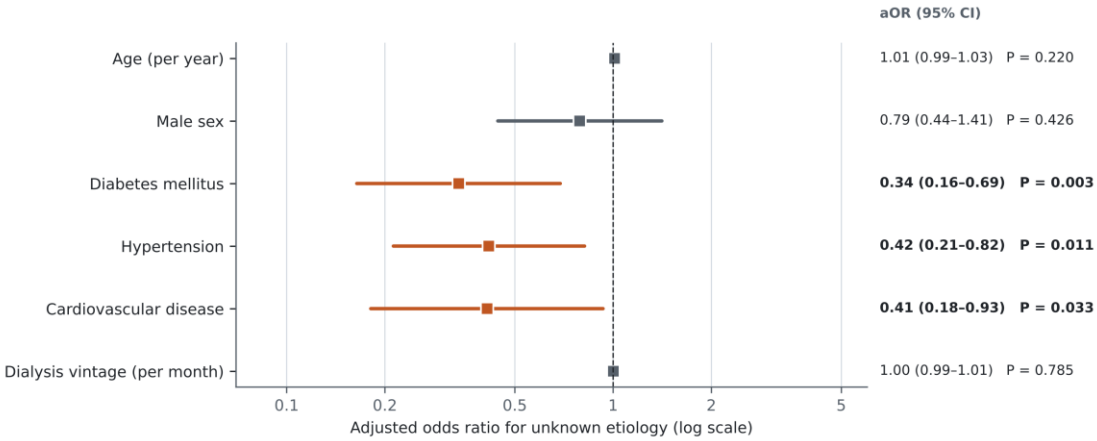


Figure 4. Forest plot of the multivariable binary logistic regression for unknown etiology of end-stage kidney disease. Each square represents an adjusted odds ratio, with horizontal bars showing its 95% confidence interval (log scale); the vertical dashed line denotes no association (odds ratio = 1). Values to the left of the line indicate lower odds of unknown etiology. Significant associations are shown in color and bold. aOR, adjusted odds ratio; CI, confidence interval.

3.6 Demographic predictors of unknown etiology

In a separate logistic regression model including sex, residence, and occupation, none of these variables was a significant predictor of unknown etiology (sex, p = 0.816; residence, p = 0.269; occupation, p = 0.301). The model as a whole did not differ from a model without predictors (omnibus $\chi 2 = 2.679$, df = 3, p = 0.444; Nagelkerke R2 = 0.012).

4. Discussion

In this governorate-wide study, about one hemodialysis patient in six in Thi-Qar had ESKD of unknown etiology. These patients were demographically indistinguishable from patients with a recorded cause; they were of the same working age, had the same sex distribution, had known about their CKD for a similar time, and were treated in the same way. Their comorbidity profile, however, was different: they were less than half as likely to have diabetes or cardiovascular disease, and a third of them were normotensive. Diabetes, hypertension, and cardiovascular disease each remained independently associated with lower odds of unknown etiology after adjustment.

4.1 Interpreting the comorbidity gradient

The lower frequency of diabetes and hypertension among patients with unknown etiology is, in part, an artifact of how etiology was assigned. A nephrologist who sees a patient with long-standing diabetes or hypertension will usually record diabetic nephropathy or hypertensive nephrosclerosis as the cause, particularly in the absence of a kidney biopsy, so patients who carry these diagnoses are less likely to be left in the unknown category. Registry coding systems acknowledge that such clinical attribution is often presumptive [10,24]. This incorporation effect is the main reason why the associations with diabetes and hypertension should not be read as protective effects.

The finding for cardiovascular disease is less easily explained this way. Cardiovascular disease is not a criterion for assigning a renal diagnosis, yet it was 2.5 times less frequent in patients with unknown etiology and retained its independent association once diabetes and hypertension were accounted for. A low burden of atherosclerotic disease in patients who are of the same age as the rest of the cohort suggests that unknown-etiology ESKD in Thi-Qar is not simply undiagnosed diabetic or hypertensive kidney disease. Instead, it points to a group whose kidney disease developed largely outside the classical cardiometabolic pathway.

4.2 Comparison with CKD of uncertain etiology

The profile observed here shares several features with CKDu described in Central America, Sri Lanka, and India, where affected patients are typically of working age, without diabetes or hypertension, and live in hot rural areas with heavy agricultural labor [16,17]. Current pathogenic models of these nephropathies give a central role to heat stress and repeated volume depletion [12,13], and cohort data from sugarcane workers link workload in the heat to kidney injury within a single harvest season [25]. Climate warming is expected to extend the regions at risk [14]. Southern Iraq has some of the highest summer temperatures in the world, and outdoor agricultural and manual work is common in Thi-Qar. The non-significant excess of rural residents in the unknown-etiology group (33.9% vs. 25.6%) is consistent with this hypothesis but could also be a chance finding, and the sample was too small to detect a difference of this magnitude reliably. A model including sex, residence, and occupation likewise identified no significant predictor of unknown etiology (omnibus p = 0.444), although the available occupational categories (employed, unemployed, retired) do not identify agricultural work.

Some features of the classical CKDu phenotype were not observed. Patients with unknown etiology were not younger, and there was no male predominance, whereas most CKDu series report middle-aged men [17]. Occupational and environmental exposures, water sources, and heat exposure were not recorded, so the present data do not allow this hypothesis to be tested. Our findings therefore do not establish that a CKDu-like nephropathy exists in southern Iraq. They do identify a sizeable, phenotypically distinct group in whom this question needs to be asked.

Several explanations for ESKD of unknown etiology in this cohort remain possible, and they are not mutually exclusive. In many patients, an identifiable primary disease may have been obscured by advanced CKD with irreversible renal scarring at presentation, when earlier investigations were unavailable and kidney biopsy was no longer informative. Others may have had undiagnosed chronic glomerulonephritis, chronic tubulointerstitial nephritis, or unrecognized congenital or hereditary kidney disease, none of which can be excluded without urinalysis, imaging, family history, and histology. Environmental or occupational nephrotoxicity and heat-stress-associated kidney disease are further possibilities given the climate and labor patterns of the region, and other, as yet unidentified, causes may also contribute. The present data cannot distinguish between these explanations.

4.3 Diagnostic gaps and late presentation

The absence of differences in CKD duration, dialysis frequency, and vascular access suggests that unknown etiology does not simply reflect worse access to care for one subgroup. Rather, the whole cohort presented late; in the governorate-wide survey, many patients had known about their CKD for only a short time before dialysis and almost nine in ten started through a catheter [21]. When patients present with advanced disease and small kidneys, biopsy is rarely possible and the original disease cannot be identified. Patients with CKD who are referred late to nephrology have poorer outcomes [26], and in this setting it also removes the opportunity to establish the cause. Earlier detection of CKD in primary care, as recommended by KDIGO [6], would therefore serve both treatment and diagnosis. For patients still in the earlier stages of CKD without diabetes or hypertension, a structured

diagnostic protocol, including urinalysis, tubular markers, imaging, and, when feasible, kidney biopsy, could clarify whether a tubulointerstitial pattern typical of CKDu is present [16].

4.4 Strengths and limitations

A key strength of this study is its coverage of the entire maintenance hemodialysis population of the governorate, with interview data verified against medical records, which avoids the selection bias of single-center series. The groups were compared across a broad set of demographic, clinical, and dialysis characteristics, and the multivariable model met the conventional minimum of ten events per variable [23].

Several limitations must be considered. First, etiology was based on clinical attribution with very limited access to biopsy, so misclassification between the hypertensive, diabetic, and unknown categories is likely, and the associations with diabetes and hypertension are partly a consequence of how etiology was assigned. Second, the cross-sectional design captures prevalent patients on dialysis and under-represents those who died before or soon after starting dialysis. Third, occupation-specific exposures, heat exposure, water sources, use of nephrotoxic agents, family history, urinalysis, and kidney size were not collected, so the CKDu hypothesis could not be tested directly. Fourth, residence and occupation were examined only in a separate demographic model rather than in the main model, and some residual confounding may remain. Finally, the number of patients with unknown etiology was modest, which limited power for secondary comparisons.

4.5 Implications

Three practical implications follow. First, "unknown etiology" should be treated as a category to be investigated rather than accepted, and patients reaching ESKD without diabetes or hypertension should be prioritized for diagnostic work-up. Second, CKD screening in Thi-Qar should not be restricted to people with diabetes or hypertension, because these risk-based strategies will miss a large proportion of patients who eventually need dialysis. Third, prospective studies in southern Iraq should collect data on occupation, heat and water exposure, and agrochemical use, together with urinary and histological markers, to determine whether a CKDu-type nephropathy contributes to the local burden of ESKD.

5. Conclusion

ESKD of unknown etiology accounts for about one in six patients on maintenance hemodialysis in Thi-Qar Governorate. These patients are of working age and are treated in the same way as other dialysis patients, but they carry a substantially lower burden of diabetes, hypertension, and cardiovascular disease. The observed clinical profile raises the possibility of a CKDu-like pattern; however, the absence of occupational, environmental, and histopathological data prevents classification of these patients as having CKDu. Systematic investigation of these patients and of environmental and occupational exposures in southern Iraq is needed.

5.1 Declarations

Ethical approval: The study was approved by the Ethics Committee of the College of Medicine, University of Thi-Qar, and administrative permission was obtained from the Thi-Qar Health Directorate.

Informed consent: Informed consent was obtained from all participants.

Data availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author contributions: A.L.K. Al-Abdullah: conceptualization, methodology, investigation, formal analysis, writing – original draft, and writing – review & editing. The author read and approved the final manuscript.

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