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A Newly Recognized Endemic Region of CKD of Undetermined Etiology (CKDu) in South India—"Tondaimandalam Nephropathy"

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Introduction: Chronic kidney disease (CKD) is being increasingly recognized as a public health problem in India. The entity of CKD of undetermined etiology (CKDu) is increasingly being reported globally. Here we describe the burden of CKDu in a heretofore undescribed population in South India.

Methods: We prospectively enrolled all patients with CKD referred to the nephrology department in an observational registry. We analyzed their sociodemographic and clinical features over 4 years. The diagnosis of CKD and its etiology was determined using predefined criteria. Geolocalization of CKD patients was performed. Subsequently, CKD screening was conducted in a village located in an area of CKDu clustering.

Results: A total of 2424 patients were analyzed; the median age was 52 years and 75.3% were male. Seventy-five percent had advanced CKD. CKDu was the most common (51.7%) etiologic category. This is the highest proportion of CKDu reported among all published CKD studies to date from India. The clinical and demographic profile of this patient population match that of CKDu patients reported from Sri Lanka and Central America, where CKDu is endemic. A clustering of cases of CKDu was noted in specific districts using a geographic information system software. Screening of 447 people in an outreach program at a village located in an area identified to have clustering of CKDu showed a CKD prevalence of 19%.

Conclusion: We report a previously unrecognized endemic area of CKDu among the underprivileged population engaged in agricultural labor in coastal southeastern India in the states of Tamil Nadu and Puducherry (Tondaimandalam) in India.

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KEYWORDS: chronic interstitial nephritis; chronic kidney disease; CKDu; India; public health

Chronic kidney disease is an increasingly common cause of morbidity and mortality across the world.[1] Although diabetes mellitus and hypertension account for much of the CKD burden in most countries, there are regions where a surprisingly high incidence of CKD that remains unexplained has been reported.[2] These CKD clusters, often referred to as CKD of undetermined etiology or chronic interstitial nephritis in agricultural communities, appears to predominantly affect underprivileged populations engaged in farm labor in tropical climates in places such as Sri Lanka and several Central and South American countries such as Ecuador, Nicaragua, El Salvador, Guatemala and Panama.[3] More recently, kidney disease clusters similar to these countries has also been reported from parts of India, especially from the coastal districts of the state of Andhra Pradesh.[4] As a tertiary care medical center, many patients with CKD exhibiting characteristics of CKDu seek treatment at our center located in South

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Table 1. Association of sociodemographic factors with CKD

Characteristics	CKDu, *n* (%) (*n* = 1254)	CKD from other causes, *n* (%) (*n* = 1170)	Total, *n* (%) (*N* = 2424)	Statistical significance (*P* value)
Age, yr, median	52	52	52 (18–87)	
Gender				
Female	325 (25.9)	275 (23.5)	600 (24.8)	0.17
Male	929 (74.1)	895 (76.5)	1824 (75.2)	
Education				
No formal education	684 (54.7)	543 (46.8)	1227 (50.9)	0.001
Primary school	256 (20.5)	245 (21.1)	501 (20.8)	
Secondary school	237 (18.9)	273 (23.5)	510 (21.2)	
Graduate	64 (5.1)	83 (7.2)	147 (6.1)	
Postgraduate	10 (0.8)	16 (1.4)	26 (1.1)	
Total	1251	1160	2411	
Income				
<5000	802 (64.1)	773 (66.3)	1575 (65.2)	0.04
5000–20,000	431 (34.5)	363 (31.1)	794 (32.9)	
>20,000	18 (1.4)	30 (2.6)	48 (2)	
Total	1251	1166	2417	
Occupation				
Agriculture	403 (59.4)	350 (48.2)	753 (53.6)	<0.001
Homemaker	65 (9.6)	75 (10.3)	140 (10)	
Professional	44 (6.5)	82 (11.3)	126 (9)	
Student	7 (1)	12 (1.7)	19 (1.4)	
Other jobs	56 (8.2)	82 (11.3)	138 (9.8)	
Not working	104 (15.3)	125 (17.2)	229 (16.3)	
Total	679	726	1405	

CKD, chronic kidney disease; CKDu, CKD of undetermined etiology.

India and we attempted to define their clinical characteristics and explore whether a similar burden of CKDu exist in our region as well.

METHODS

In the first phase (hospital-based registry) of the study, an observational registry was established (CKD Registry) for all patients with CKD who presented to the nephrology outpatient clinic at our institution in the year 2014. Data of all consecutive incident adult patients with CKD per Kidney Disease: Improving Global Outcomes (KDIGO) criteria presenting to the renal clinic was entered prospectively in the registry. Data of all enrolled patients between January 1, 2015, and December 31, 2018, were analyzed as part of this study.

The following definitions were used for identification of the possible etiology of CKD in our cohort. Diabetes mellitus, identified using American Diabetes Association (ADA) criteria for fasting and postprandial blood glucose levels or if the patient was receiving hypoglycemic agents, was presumed to be the cause of CKD when present (diabetic kidney disease). CKD was attributed to hypertensive nephrosclerosis if the patient had documented systemic hypertension for >5 years before the diagnosis of CKD or with severe hypertension (requiring more than 2 antihypertensives or blood pressure >160/100 mm Hg) at any time in the absence of other causes of CKD. Chronic glomerulonephritis was diagnosed if kidney biopsy showed glomerulonephritis or if a patient with CKD had a history of long-standing edema and/or proteinuria > ++ or >1.5 g/d. The diagnosis of chronic tubulointerstitial disease was made either on histology or based on a compatible history, the presence of vesicoureteral reflux, and/or recurrent urinary tract infection. Obstructive uropathy and cystic disease were diagnosed if there were confirmatory findings seen on imaging studies. The diagnosis of renovascular disease was from Doppler study or angiography. Kidney disease in association with specific "syndromes" was diagnosed by characteristic clinical findings, family history, and laboratory abnormalities. A diagnosis

Table 2. Etiologic profile of chronic kidney disease patients attending the tertiary care center, 2015–2018

Etiology	Patients *n* (%)
Diabetic nephropathy	525 (21.66)
Hypertensive nephropathy	349 (14.40)
Chronic glomerulonephritis	182 (7.51)
Cystic disease	20 (0.83)
Obstructive uropathy	67 (2.76)
Undetermined	1254 (51.73)
Others	27 (1.11)
Total	2424

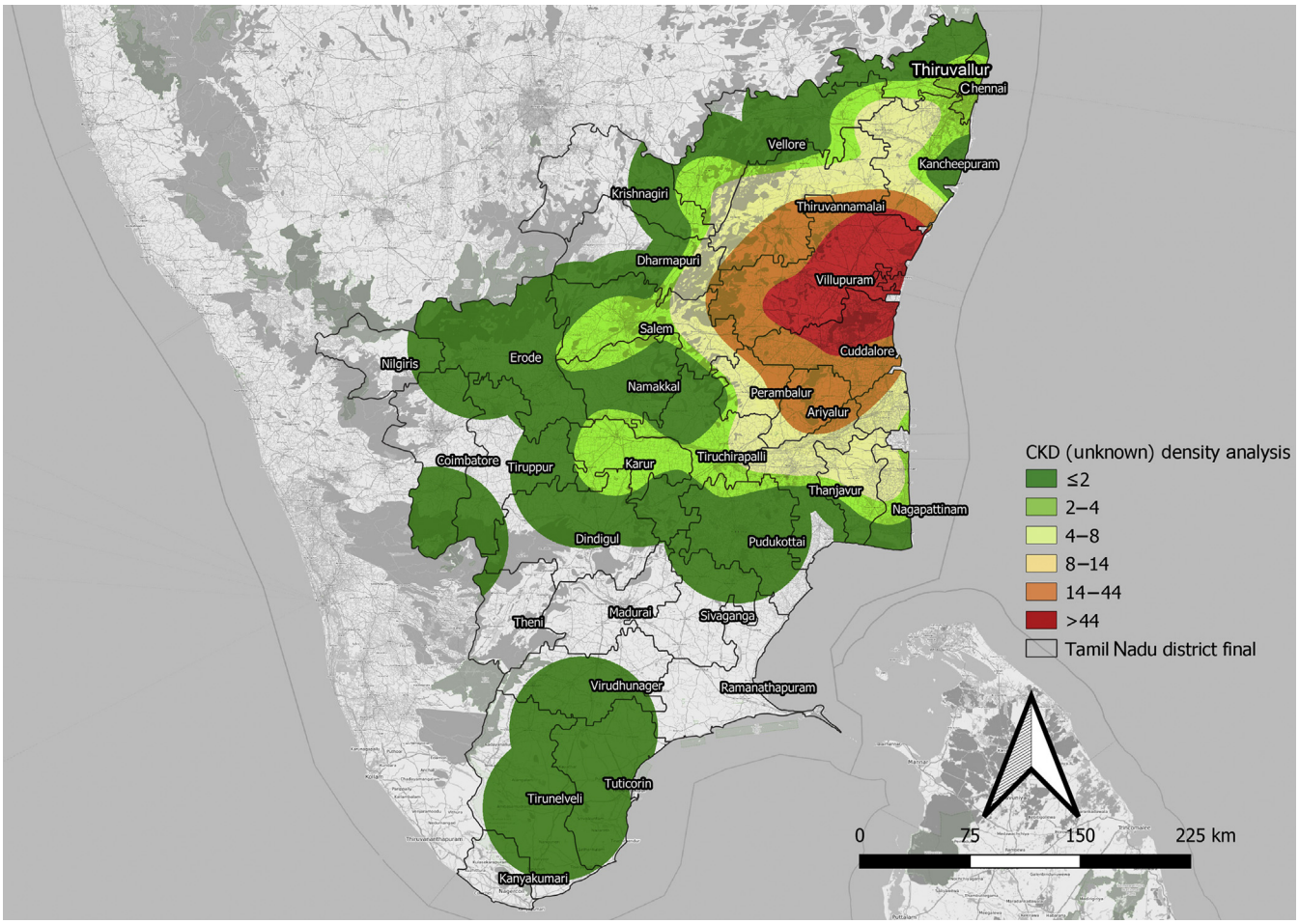

Figure 1. Districts in Tamil Nadu state from where majority of patients were enrolled on the chronic kidney disease (CKD) registry and the distribution of cases.

of CKDu was made, as a diagnosis of exclusion, in the absence of any of these potential identifiable causes of CKD and when the blood pressure was less than 160/100 mm Hg or if the patient required only 2 or fewer antihypertensive drugs. All patients underwent imaging of the kidneys by ultrasonography to assess kidney size. Kidney biopsy was performed only in patients with nondiabetic CKD with kidney size >9 cm.

Contact information of the patients, including postal address and mobile numbers, demographic and socioeconomic profile, and clinical and laboratory data were collected. Using the address, geolocalization of the patients was done using a geographic information system (GIS) software (QGIS) to determine if there was any geographic clustering of CKDu.

In the second phase, a voluntary medical camp for CKD screening was conducted in a village identified to be in a geographic area with large number of CKDu cases in the district of Villupuram. All adults in the village were offered testing for CKD on a voluntary basis, with the participation of a local NGO. Demographic, socioeconomic, and clinical data were collected using a predefined form, and blood and urine samples were collected for measuring hemoglobin, random blood glucose, serum creatinine, and urine albumin (dipstick). On a second visit to this village after 3 months, the estimated glomerular filtration rate was rechecked to confirm the diagnosis of CKD in those individuals with low estimated glomerular filtration rate at the first screening.

Proportions were used to summarize categorical variables. Mean (SD) was used to summarize continuous variables. Data entry and statistical analysis was done using EpiData, version 3.1, and SPSS, version 22, respectively. A P value < 0.05 was used as the threshold for statistical significance. The study was approved by the institute ethics committee.

RESULTS

A total of 2424 patients with CKD were recruited in the first phase of the study (hospital-based registry). The patients were predominantly (75.3%) male with a median age of 52 years (Table 1). Most patients, >75%, were in advanced CKD stages (i.e., 4 and 5).

Table 3. Districtwise distribution of patients (Tamil Nadu and Puducherry)

District	CKDu, *n* (%)	CKD from other causes, *n* (%)	Total,[a] *n* (%)	Population of the District (2011 Census) in hundred-thousands	% of OPD patients at JIPMER from the same district
Villupuram	404 (40.8)	268 (29.8)	672 (35.6)	34.59	37.2
Cuddalore	199 (20.1)	186 (20.7)	385 (20.4)	26.1	15
Puducherry	89 (9)	125 (13.9)	214 (11.3)	12.44	17
Tiruvannamalai	58 (5.9)	60 (6.7)	118 (6.2)	24.64	13
Ariyalur	63 (6.4)	29 (3.2)	92 (4.9)		
Kanchipuram	17 (1.7)	18 (2)	35 (1.9)		
Nagapattinam	13 (1.3)	22 (2.4)	35 (1.9)		
Thanjavur	13 (1.3)	13 (1.4)	26 (1.4)		
Salem	9 (0.9)	15 (1.7)	24 (1.3)		
Others	124 (12.5)	163 (18.1)	287 (15.2)		
Total[a]	989	899	1888		

CKD, chronic kidney disease; CKDu, CKD of undetermined etiology; OPD, outpatient department; JIPMER, Jawaharlal Institute of Postgraduate Medical Education and Research.
[a]Native district is available for only 1888 patients.

Diabetic kidney disease accounted for 21.7%, hypertensive nephrosclerosis 14.4%, chronic glomerulosclerosis 7.5%, and cystic diseases 0.8%. The single largest diagnostic category was CKD of undetermined etiology (CKDu), with 51.7% of patients having no identifiable cause for CKD (Table 2).

The geographic region where the patient lived is depicted in Figure 1 and Table 3. More than half (56%) of the patients were from the districts of Villupuram and Cuddalore in the state of Tamil Nadu. Nearly 50% of affected individuals, on whom information was available on employment, reported working either in farming (53.6%) or other blue-collar jobs. Rice paddy, sugarcane, and groundnut were the predominant crops cultivated by the patients engaged in farming. Approximately two-thirds (65.2%) of individuals with CKD reported a family income of less than 5000 (US$77) per month.

The characteristics of patients with a diagnosis of CKDu were compared with those of patients with CKD from identifiable causes (Tables 4 and 5). CKDu comprised a significantly higher proportion of kidney disease among farmers and other farm-related laborers compared with other causes of CKD. In addition, the proportion of CKDu patients was significantly higher among the uneducated population, and the proportion of CKDu patients was significantly higher in the lower-income group compared to those with higher incomes. There were no significant differences between CKDu and non-CKDu categories regarding age and gender distribution.

Table 4. Distribution of comorbid conditions in the study papulation

Comorbidities, treatment expense, and CKD stage	CKDu, *n* (%)	CKD from other causes, *n* (%)	Total, *n* (%)	*P* value
Hypertension				<0.001
Present	672 (53.9)	936 (83.1)	1608 (67.8)	
Absent	574 (46.1)	191 (16.9)	765 (32.2)	
Total	1246	1127	2373	
CVD				<0.001
Present	180 (18)	211 (26.1)	391 (21.6)	
Absent	821 (82)	597 (73.9)	1418 (78.4)	
Total	1001	808	1809	
Expense of treatment borne by				<0.001
Self	799 (64.1)	911 (78.7)	1710 (71.1)	
Employer	57 (4.6)	32 (2.8)	89 (3.7)	
Insurance	5 (0.4)	6 (0.5)	11 (0.5)	
Other	385 (30.9)	209 (18)	594 (24.7)	
Total	1246	1158	2404	
Stages of CKD				<0.001
Stage 1	43 (3.4)	55 (4.7)	98 (4)	
Stage 2	17 (1.4)	14 (1.2)	31 (1.3)	
Stage 3	234 (18.7)	160 (13.7)	394 (16.3)	
Stage 4	314 (25.1)	238 (20.4)	552 (22.8)	
Stage 5	644 (51.4)	701 (60)	1345 (55.6)	
Total	1252	1168	2420	

CKD, chronic kidney disease; CKDu, CKD of undetermined etiology; CVD, cardiovascular disease.

Table 5. Proteinuria

Urine protein	CKDu, *n* (%)	CKD from other causes, *n* (%)	Total, *n* (%)
Nil	98 (21.1)	60 (9.4)	158 (14.3)
Trace	90 (19.4)	47 (7.4)	137 (12.4)
+	137 (29.5)	120 (18.8)	257 (23.3)
++	140 (30.1)	155 (24.3)	295 (26.7)
+++	0	191 (29.9)	191 (17.3)
++++	0	66 (10.3)	66 (6)
Total	465	639	1104

CKD, chronic kidney disease; CKDu, CKD of undetermined etiology.

Approximately one-fourth of the study participants (24%) were being conservatively managed for CKD, with diuretics, antiemetics, oral hematinics, antihypertensives, and other symptomatic measures, without renal replacement therapy. One-fifth of the study participants were undergoing renal replacement therapy (19.6%). Among the CKD patients who had a glomerular filtration rate of less than 8 ml/min, 54 patients (7%) were not receiving renal replacement therapy.

Figures 2 and 3 depict the geographical distribution of patients with CKD and CKDu from the state of Tamil Nadu. Sixty-two percent of patients hailed from the districts of Villupuram, Cuddalore, Thiruvannamalai, and Kancheepuram, and 11.3% were from the Puducherry district of the union territory of Puducherry. CKDu accounted for more than 40% of CKD patients from these districts, with the highest proportion of CKDu observed in Villupuram and Ariyalur districts (Table 3). There was apparent clustering of CKDu in certain taluks (a smaller administrative unit of a district in India) within the district of Villupuram (Figure 1).

Residents of Nainakuppam village (Ulundurpet Taluk, Villupuram district, Tamil Nadu), a region where a large number of patients with CKDu were identified, were screened for CKD as part of an outreach effort. Among the 983 inhabitants of the village, 670 were older than 18 years. Of these, 447 individuals participated in the CKD screening program. Eight percent were hypertensive, 6.8% were diabetic, and 19% (n = 85) had an estimated glomerular filtration rate of <60 ml/min (19%). Based on glomerular filtration rate criteria, 19% of individuals had CKD. Only 7 individuals were aware of their kidney disease before

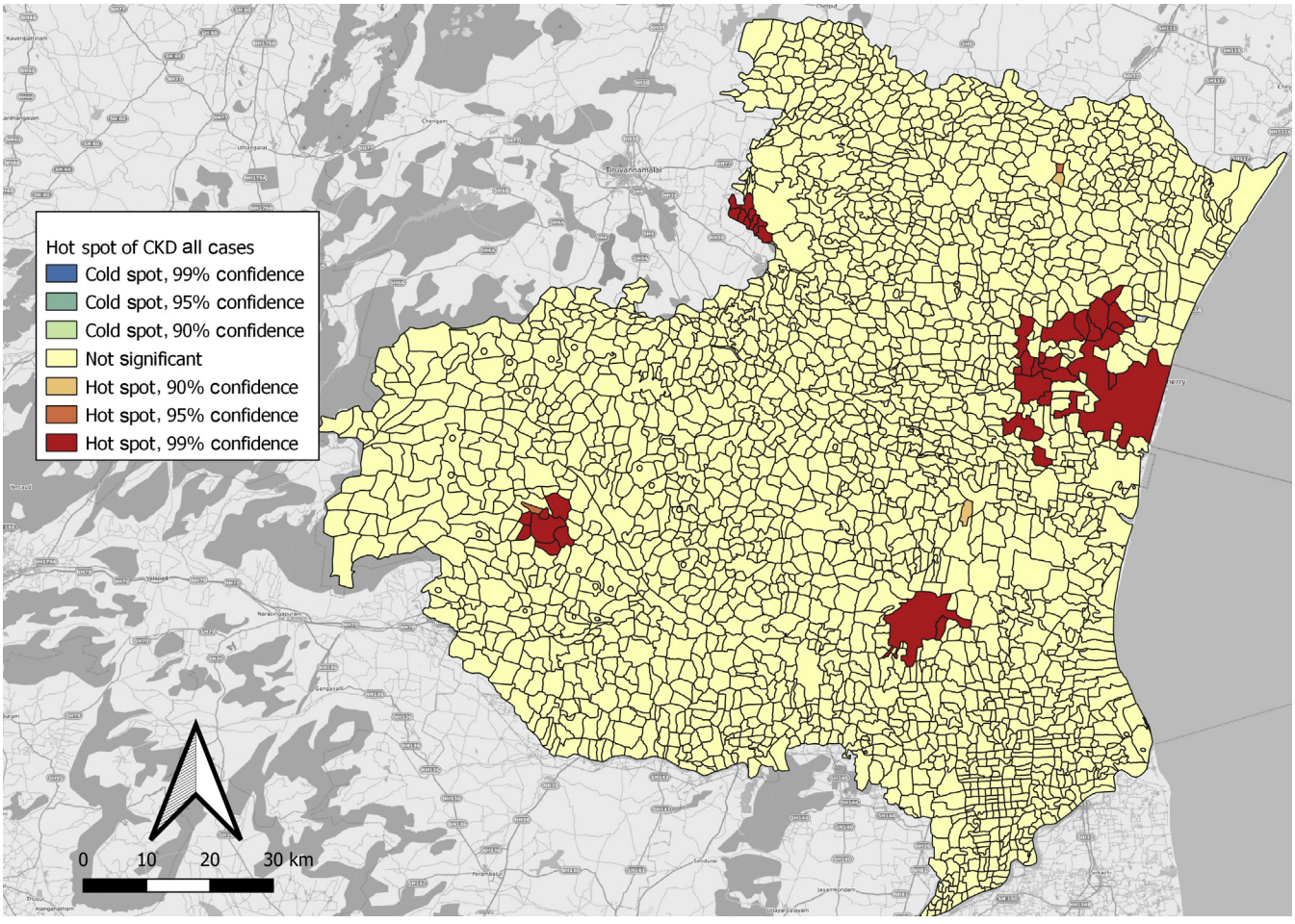

Figure 2. Distribution of chronic kidney disease (CKD) of undetermined etiology (CKDu) patients from the districts of Tamil Nadu in the CKD registry.

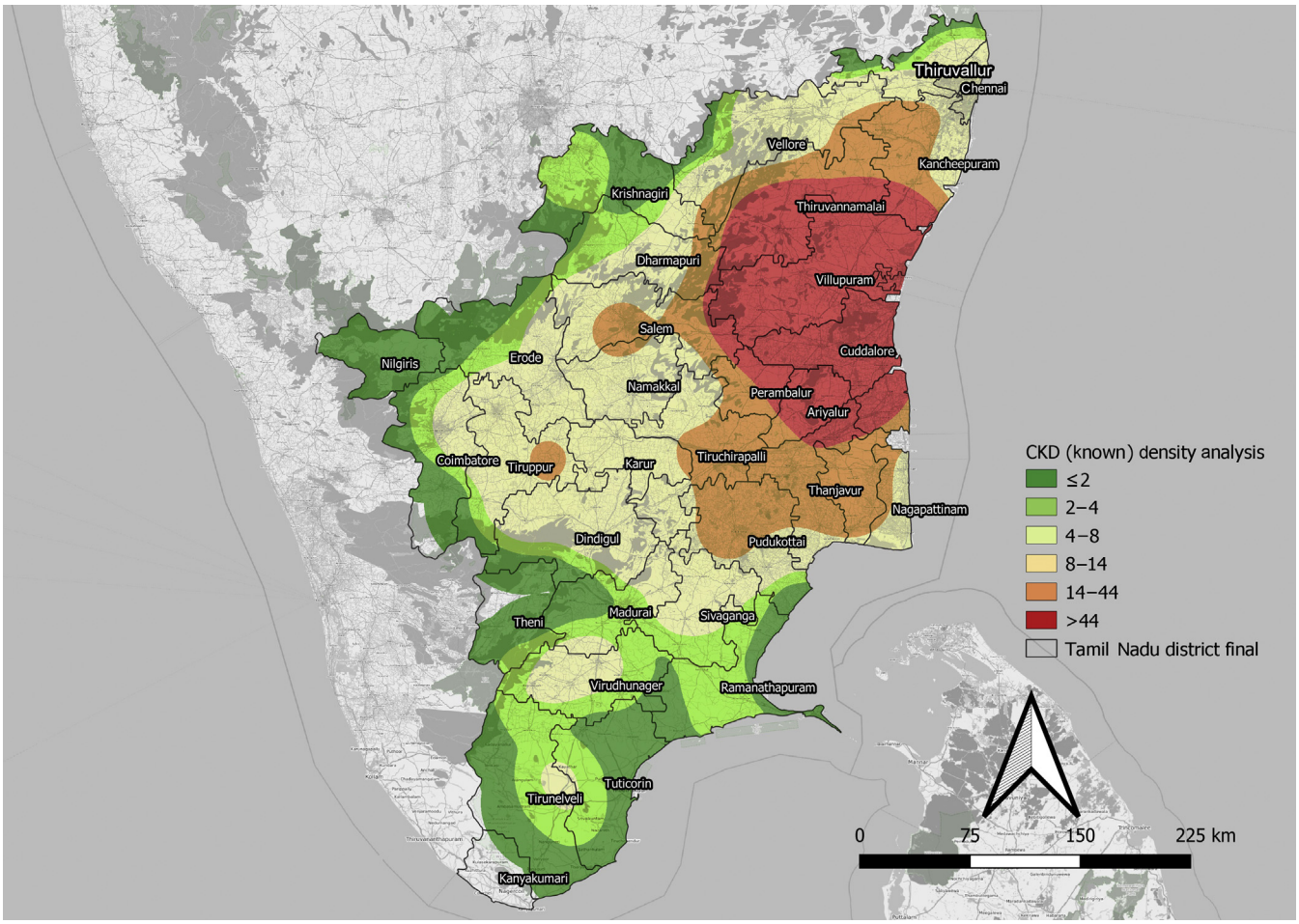

Figure 3. Geolocalization of CKD of undetermined etiology (CKDu) patients in the districts of Villupuram (TN) and Puducherry (Puducherry), showing clustering in certain regions.

the screening program. None of them had urinary symptoms or edema.

DISCUSSION

The relatively high proportion of CKDu among the CKD patient population from the geographical area studied suggests that CKDu is endemic in that region and has not been previously reported. We found that CKDu was the largest etiologic category among incident patients with CKD at our institution. CKDu was diagnosed in 51.7% of patients, and this is the highest proportion of CKDu reported among all studies from India thus far. We used the WHO SEARO consensus definition of CKDu[5] in the study. This definition uses a blood pressure >160/100 mm Hg as an exclusion criterion for CKDu. If the blood pressure criterion is not used, the proportion of CKD where etiology could not be identified increases to 74%. Along with this observation from the registry data, the high prevalence of CKD found in the village where CKD screening was undertaken strengthens our suspicion of the endemic nature of CKD in this region. The prevalence of CKD was found to be 19% in the village, higher than most CKD prevalence estimates for India[6,7] and similar to the prevalence reported from the Uddanam region in Andhra Pradesh[8] and from endemic areas in Sri Lanka.[3]

The only prior study that examined the etiology of CKD from our geographical region in India did so from a large urban center (Chennai) in 1993.[9] This study, using hospital data along with clinical and laboratory criteria to define etiologic categories of CKD, reported "chronic interstitial nephritis" to be the most common cause of CKD (27.9%). However, there are important differences between their report and our current study. In the earlier study, 70.7% of the patients reported a high socioeconomic status, compared to only 2% in our cohort. Chronic interstitial nephritis accounted for a significantly higher proportion of CKD in the lower-income group compared to the higher-income group (38.25% vs. 25.11%) in the prior study, which is consistent with the findings in our sample.

Although estimates on the regional differences in the proportion of CKDu in the CKD population is not available from India, a high incidence of CKDu has been reported from the coastal areas of the state of

Table 6. Clinicoepidemiologic features of major globally reported regional nephropathies

	Mesoamerican nephropathy	Sri Lankan nephropathy	Uddanam nephropathy	Tondaimandalam nephropathy, Tamil Nadu, India
Geographic region	Rural, low-altitude, and coastal regions of Nicaragua and El Salvador mainly and to some extent Costa Rica and Guatemala	Rural, North Central Province	Rural, low-altitude, coastal belt in the eastern Indian state of Andhra Pradesh with tropical arid climate	Rural, low-altitude, northern coastal districts of Tamil Nadu, India, with tropical arid climate
Latitude and longitude	13.794185° N, 88.896530° E	7.8731° N, 80.7718° E	15.9129° N, 79.7400° E	11.1271° N, 78.6569° E
Epidemiology	Widely reported; cross-sectional community-based, and prospective cohort studies; variable prevalence based on sex and occupation	Cross-sectional community-based studies; point prevalence of CKD varies from 5.1% to 16.9% in the endemic region based on persistent albuminuria as the diagnostic criterion	Cross-sectional community-based study; CKD point prevalence in the endemic area close to 50% (unpublished estimates)	Previously not reported
Occupations affected	Sugarcane, cotton, and subsistence farming; fishing, mining, brick workers	Rice paddy and chena farming (vegetable and other crops)	Cashew nut, coconut, and rice paddy farming	Rice paddy, sugarcane, peanut farming; laborers engaged in herding animals, construction work
Age	Age range: 20–50 yr	Age range 40–50 yr; prevalence increases with age	Age range 30–60 yr	Age range 40–50 yr
Sex	M > F (3.4:1)	M > F (1.3:1)	M > F (—)	M > F (4:1)
Clinical features	Silent but progressive GFR decline; low-grade proteinuria (0.1 g/d); nephrotic syndrome rare; urinary sediment is bland; variable progression to ESRD; limited access to RRT	Slow progression, long asymptomatic period; bland urinary sediments; low-grade proteinuria (0.1 g/d); shrunken kidneys; elevated urinary biomarkers of tubular damage in early disease	Bland urine sediment, low-grade or absent proteinuria, information on progression not available at present	Clinical presentation in advanced stages of CKD possibly because of asymptomatic earlier stages; low-grade or absent proteinuria; bilateral small kidneys
Risk factors implicated	Male sex; increasing age; hypertension; family history of CKD; sugarcane, banana farming (in men only); mining/subsistence farming; NSAIDs, heavy metals, and agrochemical exposure (inconsistent)	Chena farmer; family history of CKD; use of traditional medications; ayurvedic medication use; cadmium exposure; pesticide use	Male sex; increasing age; agricultural job	Underprivileged socioeconomic status, farm-related labor, advancing age, male sex
Histopathologic features	Chronic tubulointerstitial disease with secondary glomerular and vascular damage; occasional global glomerulosclerosis from possible glomerular ischemia	Chronic tubulointerstitial fibrosis with nonspecific interstitial inflammation; rare glomerular collapse and sclerosis with fibrous intimal thickening and arteriolar hyalinosis	Tubular atrophy and interstitial fibrosis mainly with secondary glomerular and vascular changes	Not studied

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NSAIDs, nonsteroidal anti-inflammatory drugs; RRT, renal replacement therapy.

Andhra Pradesh.[8] We found that the clinical characteristics of our patient population was comparable with the characteristics of CKDu patients from endemic areas in Sri Lanka and Central and South America as well as Uddanam in Andhra Pradesh, India. The patients were mostly from an underprivileged background, were engaged in farm labor or other forms of labor requiring significant physical activity, working in hot and humid climate, had shrunken echogenic kidneys with minimal proteinuria, and often presented with advanced CKD, with presumably minimally symptomatic or asymptomatic early stages (Table 6). The geographical areas where our patients belong have a tropical arid climate, with average ambient temperatures during the summer of 30 °C–41 °C and during winter of 30 °C–35 °C, with high humidity round the year. This region shares climatic, cultural, and possibly genetic characteristics with Uddanam, Andhra Pradesh, and regions of Sri Lanka where CKDu is endemic. The Uddanam area is located 1100 km north of Tamil Nadu, on the eastern coast of the Indian peninsula.

On the basis of our observations, we believe that the burden of CKD and CKDu in this region is much higher than currently appreciated. The patients enrolled in our CKD registry likely represent only a fraction of patients with CKD in this region. Only those patients referred for specialized nephrology care reach our center, and patients also seek treatment from other well-established centers offering kidney care in this region. This hypothesis coupled with the fact that one-fifth individuals sampled in one village had CKDu suggests the possibility that there is a higher prevalence of CKDu in the region. Almost 80% of patients in the CKD registry presented in advanced stages of CKD. In contrast, the patients detected to have early stages of CKD during the screening program in the village were asymptomatic. It appears that the kidney disease is asymptomatic in the earlier stages, leading to the disease going undetected till advanced stages of CKD. We believe that these observations of possible high burden of CKD in the community, asymptomatic earlier stages of the disease and presentation in advanced stages of kidney failure are all compelling reasons to establish a community-based CKD surveillance and prevention program in this region.

Our study has several strengths. Our registry employed a rigorous approach of data collection and diagnosis adjudication by using predefined clinical criteria for defining the cause of CKD. Initial spatial clustering noted among patients presenting to the

clinic was confirmed by a community-based CKD screening program in the region suspected to be experiencing the case clustering that found a CKD prevalence of 19%.

There are some limitations of our study. The primary data collection relied on a hospital-based registry that may not be representative of the population at large. With respect to geolocalization, comparison with distant districts or even other neighboring states may have experienced similar clustering of CKDu in these geographical regions, but such comparative data were not available. The addresses of patients had information only up to the village or town level address and not street addresses. The screening of a single village was based on voluntary participation in a medical camp and hence may have its inherent limitations in terms of sampling bias.

Further studies in the form of community-based studies with systematic stratified sampling are needed to confirm high burden of CKD from CKDu in this region and the possible factors contributing to the high CKD burden. We propose that all medical institutions caring for patients with kidney disease in the state of Tamil Nadu should maintain a CKD registry and all cases of CKD should be reported, including the home address and etiology of CKD. This will allow identification of regions with clustering of CKD in the state of Tamil Nadu and in turn will facilitate establishing a community-based CKD surveillance and prevention program in regions with high CKD burden. The surveillance program should be coupled with studies on environmental factors that might be contributing to the high prevalence of CKDu in the region. It is also possible that there are other, yet unrecognized regions with clustering of CKD (CKD hot spots) in India. Implementing a similar strategy in other parts of the country may identify such regions, and we believe there is a strong case for establishing a comprehensive national CKD registry in India (Supplementary Table S1).[10]

In conclusion, we found a high prevalence of CKDu in the southeastern coastal districts of India, in the states of Tamil Nadu and Puducherry, similar to the Uddanam region of Andhra Pradesh that is approximately 1100 kilometers further north. The geographical area of the state of Tamil Nadu and Puducherry to which our patients belong roughly corresponds to the historical region referred to as "Tondaimandalam,"[11] and hence we propose the name "Tondaimandalam Nephropathy" for this entity. Further large-scale prospective studies are needed to improve our understanding of the factors contributing to the remarkably high prevalence of chronic kidney disease in this rural socioeconomically underprivileged region in South India.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1. Proposed strategy for identifying and studying CKD hot spots.

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