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ORIGINAL ARTICLE

The Indian Chronic Kidney Disease (ICKD) study: baseline characteristics

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ABSTRACT

Background. Chronic kidney disease (CKD) is an important cause of morbidity and mortality worldwide. There is a lack of information on epidemiology and progression of CKD in low–middle income countries. The Indian Chronic Kidney Disease (ICKD) study aims to identify factors that associate with CKD progression, and development of kidney failure and cardiovascular disease (CVD) in Indian patients with CKD.

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Methods. ICKD study is prospective, multicentric cohort study enrolling patients with estimated glomerular filtration rate (eGFR) 15–60 mL/min/1.73 m^2, or >60 mL/min/1.73 m^2 with proteinuria. Clinical details and biological samples are collected at annual visits. We analysed the baseline characteristics including socio-demographic details, risk factors, disease characteristics and laboratory measurements. In addition, we compared characteristics between urban and rural participants.

Results. A total of 4056 patients have been enrolled up to 31 March 2020. The mean ± SD age was 50.3 ± 11.8 years, 67.2% were males, two-thirds of patients lived in rural areas and the median eGFR was 40 mL/min/1.73 m^2. About 87% were hypertensive, 37% had diabetes, 22% had CVD, 6.7% had past history of acute kidney injury and 23% reported prior use of alternative drugs. Diabetic kidney disease, chronic interstitial nephritis (CIN) and CKD-cause unknown (CKDu) were the leading causes. Rural participants had more occupational exposure and tobacco use but lower educational status and income. CIN and unknown categories were leading causes in rural participants.

Conclusions. The ICKD study is the only large cohort study of patients with mild-to-moderate CKD in a lower middle income country. Baseline characteristics of study population reveal differences as compared with other cohorts from high-income countries.

Keywords: alternative drugs, chronic kidney disease, chronic interstitial nephritis, cohort study, rural health, socioeconomic factors

INTRODUCTION

Global Burden of Disease collaboration identifies chronic kidney disease (CKD) as a major contributor to global morbidity and mortality [1]. Between 1990 and 2017, the global all-age prevalence and mortality from CKD increased by 29.3 and 41.5%, respectively [1]. In India, there was a 38% increase in the proportion of deaths attributable to kidney failure between 2001–03 and 2010–13 [2]. CKD is also an important cardiovascular disease (CVD) risk factor, the leading cause of premature deaths and disability-adjusted life years. Opportunities for secondary and tertiary prevention in CKD are often missed in developing countries like India [3]. Patients seek medical attention when they are symptomatic, usually late in the course of disease. CKD only comes to light in earlier stages when kidney function evaluation is done for either other health conditions or, less commonly, for routine screening [4]. When coupled with the fact that the major burden of CKD is concentrated in regions with lower socio-demographic indices [1], it becomes clear that risk factor identification and mitigation strategies in CKD will be globally successful only when the unique challenges of these regions are addressed.

The development and outcomes of CKD are impacted by local factors like aetiological spectrum influenced by local risk factors, genetic differences, socio-demographic variables and access to healthcare resources. Cohort studies in patients with CKD have been established in the USA, Germany, Canada, France, Spain, Japan, Republic of South Korea and China [5–11]. These have allowed compilation of a wealth of scientific data that have informed local research and clinical care priorities, as well as international cooperation and comparisons such as the International Network of CKD cohort studies of the International Society of Nephrology [12–14].

The Indian CKD (ICKD) study [15] is a publicly funded cohort study that aims to explore risk factors for progression of CKD, development of CVD and differences in outcomes based on gender, socio-demographic profile and regions, and quality of life and cost of care in a CKD population representing all parts of India. In the present manuscript, we report baseline characteristics of participants enrolled in the ICKD study.

MATERIALS AND METHODS

Study design and setting

The ICKD study is a multicentric, prospective cohort study of patients with mild-to-moderate CKD in India. Participants are recruited in large nephrology services across 11 centres distributed throughout the country (Supplementary Appendix S1: map showing location of centres across India). The study procedures were developed, harmonized and adapted to ensure comparability of data with other International cohorts of patients with CKD. Expert consultations were held to decide on questions about possible risk factors in CKD perceived to be relevant in local context. The study has a distributed biobank, with a local biobank at each centre and the central one at Post-graduate Institute of Medical Education and Research, Chandigarh. The detailed design and methods of the study have been published [15]. The study has been approved by Ethics Committees at each participating centre.

Study population

Clinically stable adult patients aged between 18 and 70 years with estimated glomerular filtration rate (eGFR) by creatinine-based CKD Epidemiology Collaboration (CKD-EPI_{Cr}) equation of either 15–60 mL/min/1.73 m^2, or >60 mL/min/1.73 m^2 and proteinuria (urine protein to creatinine ratio >500 mg/g or albumin to creatinine ratio >300 mg/g or equivalent) were approached for consent and recruitment. Organ transplant recipients, pregnant females or those with malignancy, life expectancy <1 year or on current immunosuppressive drug therapy were excluded.

Study measurements and conduct

Details of socio-demographic status, family history, history of CKD risk factors, CVD, acute kidney injury (AKI), comorbidities, occupation, addictions and treatment details including the use of alternative drugs were recorded (Supplementary Appendix S2: baseline questionnaire, Supplementary data, Table S1: definitions/interpretations used for the present analysis in context of data captured in baseline questionnaire). The responses were

either self-reported by participants or captured from the records of previous encounters with the healthcare system. Residence was classified as rural or urban. History of pregnancy-related complications was recorded in the case of females. Participants were questioned about past history of any rapid deterioration in kidney function or requirement of dialysis from which they had recovered. Anthropometric measurements (height, weight and waist/hip ratios) and resting blood pressure (BP) were taken, and quality of life based on Kidney Disease Quality of Life Instrument survey was recorded . Serum, plasma and second-morning spot urine samples were collected and stored at −80°C.

Serum creatinine was measured using assays traceable to isotope dilution mass spectrometry reference standards at participating centres. GFR was estimated using the creatinine-based CKD-EPI$_{Cr}$ equation. Spot urine protein to creatinine ratio (expressed as mg/g) or semi-quantitative urine albumin testing by dipstick (expressed as trace, 1+, 2+ or >2+) was converted to urine albumin to creatinine ratio (uACR) as described by Sumida *et al.* [16]. Proposed models adjusted for sex, diabetes and hypertension were used for calculation. Hazardous occupational exposure was recorded as regular exposure to sand, saw, dust, cement, pesticides, other chemicals, animals or need for working barefoot in fields. Household income was defined as net annual income of family from all sources. Medical expenditure included costs incurred on medicines and ancillary expenses (travel, stay, etc.) on account of hospital visits. Physical activity was defined as exercise equivalent to 30 min of brisk walk at least five times every week. Other diseases and comorbidities were diagnosed as per prevailing standards. Patients with a primary diagnosis of hypertension or diabetes and/or on anti-hypertensives or anti-diabetic drugs, respectively, were assigned the respective diagnoses. These diagnoses were either self-reported or physician diagnosed based on review of prescription. CVD was defined as history or previous recorded documentation of heart failure, coronary artery disease, prior revascularization, stroke, peripheral vascular disease or any form of atherosclerotic vascular disease. The causes of CKD in the study population were recorded as chronic glomerulonephritis (CGN), chronic interstitial nephritis (CIN), diabetic kidney disease (DKD), hypertensive nephropathy (HTN), polycystic kidney disease (PKD), unknown or miscellaneous. The cause was recorded by the treating physician based on his/her clinical judgement. Unknown cause was recorded in the absence of any known risk factors that could lead to CKD.

Statistical considerations

Data were cleaned, edited and analysed using Stata statistical software version 14 (Stata Corp LP, College Station, TX, USA). Both descriptive and quantitative analyses were performed showing socio-demographic, clinical and biochemical characteristics of participants. Distribution based on gender has been presented in the study. Characteristics of participants from rural and urban regions were compared.

Data for continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range, as appropriate. In the case of categorical variables, data were presented in terms of count and percentage. All the presented data are based on the available values only and percentages have been calculated from total number of available values. Comparison of baseline characteristics between rural and urban participants has been done by Student's *t*-test, Mann–Whitney U-test, one way Analysis of variance (ANOVA) or chi-square test as appropriate. Two-sided $P < 0.05$ were considered significant.

RESULTS

A total of 4056 participants were enrolled in the cohort between 1 April 2016 and 31 March 2020 in Phase I of the study. The socio-demographic characteristics of the participants are shown in Table 1. The average age at recruitment is 50.3 ± 11.8 years, with 67.2% of the population being males. Two-thirds of the population lived in rural areas, and 73% had received some formal education. About 35% were vegetarians. Among those classified as non-vegetarians, the frequency of meat consumption (includes meat, fish and fowl) was 4.5 times every month. About 43% of the study population was physically active, and 7.5% and 18.6% participants were current alcohol and tobacco users, respectively. The median (25–75th percentiles) annual expenditure on medical care was US$286 (84–571), which represented ∼17% of the median total annual household income of US$1680 (1008–4200). Only 32.1% of the participants had any medical insurance. About 83% incurred out-of-pocket expenditure for CKD care. Only 10.6% of the participants admitted to missing scheduled hospital visits or drugs on account of financial constraints.

Clinical characteristics

The most common cause of CKD was DKD (24.9%), followed by CIN and unknown in 23.2 and 19.5%, respectively (Table 2). The mean duration of kidney disease at the time of recruitment into the study was 38.3 ± 53.0 months (Table 1). Family history of hypertension, diabetes mellitus and stroke were recorded in 43.1%, 37.4% and 14%, respectively. In terms of risk factors, 87% were hypertensive and 37.5% had diabetes, whereas 22.9% reported history of using alternative drugs (local or indigenous forms of medicine). History of nephrolithiasis and recurrent urinary tract infections (UTIs) were present in 11.8 and 11%, respectively. About 9% of the participants reported a family history of kidney disease. Prior history suggestive of AKI was recorded in 6.7% of study population. About 33% of females reported adverse outcome events during pregnancy. Only 21.8% of participants had prior CVD. The median (25–75th percentiles) body mass index (BMI) and waist/hip ratio in study population were 24.4 (21.6–27.4) kg/m^2 and 1.05 (1.02–1.09), respectively (Table 1).

Laboratory characteristics

The median (25th–75th percentiles) serum creatinine and eGFR were 1.7 (1.5–2.0) mg/dL and 40.5 (33.7–50.8) mL/min/1.73 m^2, respectively (Table 3). Albuminuria (trace or more) by urine dipstick examination was present in 41.4% of the participants, with the calculated uACR being >300 mg/g in 25.5%. Median (25–75th percentiles) haemoglobin (Hb), serum albumin, calcium, inorganic phosphorus and uric acid were 11.8 (10.5–13.2) g/dL, 4.0 (3.5–4.4) g/dL, 9.0 (8.5–9.4) mg/dL, 4.0 (3.3–4.5) mg/dL and 6.4 (5.2–7.6) mg/dL, respectively. About 6.3% and 6.5% of the participants had positive hepatitis B surface antigen and antibodies against hepatitis C virus, respectively (Table 3).

Rural–urban comparisons

The socio-demographic, clinical and biochemical characteristics of the rural and urban participants are described in Tables 4 and 5. Age was similar between the groups. Compared with urban participants, those from rural areas had more occupational exposure (54.6% versus 41.5%, $P < 0.001$), higher tobacco use (20.6% versus 15.1%, $P < 0.001$), lower level of education (66.8% versus

Table 1. Socio-demographic characteristics of participants in the study cohort

Characteristic	Females ($n = 1331$)	Males ($n = 2725$)	Total ($n = 4056$)	Missing, n (%)	P-values
Age, years	49.0 ± 11.6	50.9 ± 11.9	50.3 ± 11.8	0 (0)	<0.001
Duration of kidney disease, months	40.8 ± 55.6	37.1 ± 51.6	38.3 ± 53.0	32 (0.8)	0.039
BMI, kg/m^2	25.3 (22.1–29.0)	24.0 (21.5–26.7)	24.4 (21.6–27.4)	103 (2.5)	<0.001
Waist/hip ratio	1.06 (1.02–1.21)	1.05 (1.01–1.08)	1.05 (1.02–1.09)	964 (23.8)	<0.001
Place of residence					
Rural	845 (65.2)	1781 (66.5)	2626 (66.0)	80 (2.0)	0.407
Urban	452 (34.8)	898 (33.5)	1350 (34.0)		
Education					
Illiterate	524 (39.6)	564 (20.8)	1088 (26.9)	18 (0.4)	<0.001
School level education	582 (44.0)	1330 (49.0)	1912 (47.4)		
Went to college	216 (16.4)	822 (30.2)	1038 (25.7)		
Occupational exposure[a]	629 (47.6)	1406 (51.8)	2035 (50.4)	18 (0.4)	0.013
Sand/dust	228 (17.3)	618 (22.8)	846 (21.0)		
Cement	7 (0.5)	81 (2.98)	88 (2.2)		
Saw dust	34 (2.6)	112 (4.1)	146 (3.6)		
Working barefoot in field	58 (4.4)	204 (7.5)	262 (6.5)		
Pesticide spray	41 (3.1)	186 (6.9)	227 (5.6)		
Others	356 (56.6)	593 (42.2)	949 (46.6)		
Current tobacco user	87 (6.6)	660 (24.5)	747 (18.6)	43 (1.1)	<0.001
Current alcohol user	1 (0.1)	300 (11.1)	301 (7.5)	43 (1.1)	<0.001
Physically active	479 (36.4)	1239 (45.9)	1718 (42.8)	43 (1.1)	<0.001
Non-vegetarian diet	830 (63.5)	1771 (66.2)	2601 (65.3)	75 (1.9)	0.090
Access to piped water supply	693 (52.4)	1282 (47.2)	1975 (48.9)	18 (0.4)	0.003
Annual household income (USD)	1680 (840–4200)	1680 (1008–4200)	1680 (1008–4200)	41 (1.0)	0.176
Annual household medical expenditure (USD)	269 (84–571)	302 (84–571)	286 (84–571)	0 (0.0)	0.742
Medical insurance	432 (33.2)	844 (31.5)	1276 (32.1)	77 (1.9)	0.284
Incurred out of pocket medical expenditure	1115 (84.3)	2237 (82.4)	3352 (83.0)	18 (0.4)	0.034
Missed hospital visit/drugs due to financial constraints	135 (10.2)	293 (10.8)	428 (10.6)	18 (0.4)	0.577

Data are presented as mean ± SD, median (25–75th percentile) or n (%).
[a]Occupational exposure—has multiple responses.

Table 2. Clinical characteristics and diagnosis of CKD in the study cohort

Parameter	Females ($n = 1331$)	Males ($n = 2725$)	Total ($n = 4056$)	Missing, n (%)	P-values
Clinical characteristics					
Hypertension	1130 (86.1)	2357 (87.5)	3487 (87.0)	49 (1.2)	0.240
Diabetes	473 (36.6)	1012 (37.9)	1485 (37.5)	96 (2.4)	0.436
CVD	255 (19.4)	621 (23.0)	876 (21.8)	33 (0.8)	0.009
Renal stone disease	139 (10.5)	335 (12.4)	474 (11.8)	27 (0.7)	0.092
Recurrent UTI	144 (10.9)	298 (11.0)	442 (10.9)	27 (0.7)	0.940
Alternative drug use	284 (21.5)	639 (23.5)	923 (22.9)	16 (0.4)	0.150
Ayurvedic	108 (38.0)	256 (40.0)	364 (39.5)	—	—
Homoeopathic	51 (18.0)	158 (24.7)	209 (22.6)	—	—
Siddha	21 (7.4)	30 (4.7)	51 (5.5)	—	—
Unani	8 (2.8)	5 (0.8)	13 (1.4)	—	—
Others	96 (33.8)	190 (29.8)	286 (31.0)	—	—
NSAID use	251 (19.1)	375 (13.9)	626 (15.6)	43 (1.1)	<0.001
History of AKI	91 (6.9)	177 (6.6)	268 (6.7)	43 (1.1)	0.668
Required dialysis for AKI	88 (6.7)	143 (5.3)	231 (5.8)	43 (1.1)	0.076
Underwent renal biopsy	228 (17.3)	458 (17.0)	686 (17.1)	43 (1.1)	0.774
Family history					

(continued)

Table 2. (continued)

Parameter	Females ($n = 1331$)	Males ($n = 2725$)	Total ($n = 4056$)	Missing, *n* (%)	P-values
Hypertension	525 (43.0)	1088 (43.1)	1613 (43.1)	309 (7.6)	0.141
Diabetes	475 (39.4)	915 (36.4)	1390 (37.4)	337 (8.3)	0.200
Kidney disease	127 (9.6)	231 (8.5)	358 (8.9)	30 (0.7)	0.502
Kidney stones	22 (17.3)	41 (17.7)	63 (17.6)	–	–
Dialysis	35 (27.6)	71 (30.7)	106 (29.6)	–	–
Kidney transplant	5 (3.9)	13 (5.6)	18 (5.0)	–	–
Cause of CKD					
DKD	333 (25.0)	678 (24.9)	1011 (24.9)	0 (0)	–
CIN	319 (24.0)	621 (22.8)	940 (23.2)		–
Unknown	243 (18.3)	545 (20.0)	788 (19.5)		
CGN	216 (16.2)	382 (14.0)	598 (14.7)		0.224
Hypertensive nephrosclerosis	94 (7.1)	226 (8.3)	320 (7.9)		–
PKD	49 (3.6)	90 (3.3)	139 (3.4)		–
Others	77 (5.8)	183 (6.7)	260 (6.4)		–

Data are presented as *n* (%).
NSAID, non-steroidal anti-inflammatory drugs.

Table 3. Physical and biochemical characteristics of participants in the study cohort

Characteristic	Females ($n = 1331$)	Males ($n = 2725$)	Total ($n = 4056$)	Missing, *n* (%)	P-values
SBP, mmHg	130 (120–141)	130 (120–145)	130 (120–144)	101 (2.5)	0.006
DBP, mmHg	80 (76–90)	80 (78–90)	80 (78–90)	133 (3.3)	0.010
eGFR, mL/min/1.73 m^2	36.3 (30.7–45.3)	42.9 (35.7–52.3)	40.5 (33.7–50.8)	0	<0.001
Hb, mg/dL	11.0 (10.0–12.0)	12.4 (11–13.7)	11.8 (10.5–13.2)	143 (3.5)	<0.001
Anaemia[a]	932 (73.2)	1607 (60.9)	2539 (64.9)	143 (3.5)	<0.001
Mild	329 (25.8)	976 (37.0)	1305 (33.4)	–	–
Moderate	579 (45.5)	597 (22.6)	1176 (30.1)	–	–
Severe	24 (1.9)	34 (1.3)	58 (1.5)	–	–
Serum urea, mg/dL	45 (35–56)	45 (34–56)	45 (34–56)	571 (14.1)	0.788
Serum creatinine, mg/dL	1.6 (1.4–1.9)	1.8 (1.5–2.1)	1.7 (1.5–2.0)	0	<0.001
Serum calcium, mg/dL	8.9 (8.4–9.4)	9.0 (8.6–9.5)	9.0 (8.5–9.4)	290 (7.2)	0.0001
Serum inorganic phosphorus, mg/dL	4.1 (3.6–4.6)	3.9 (3.2–4.4)	4.0 (3.3–4.5)	340 (8.4)	<0.001
Serum albumin, g/dL	3.9 (3.4–4.2)	4.0 (3.5–4.4)	4.0 (3.5–4.4)	225 (5.6)	<0.001
Serum uric acid, mg/dL	6.2 (5.0–7.3)	6.5 (5.4–7.7)	6.4 (5.2–7.6)	842 (20.8)	<0.001
Total cholesterol, mg/dL	173 (140–203)	162 (130–198)	166 (133–200)	1538 (37.9)	<0.001
Triglycerides, mg/dL	140 (112–180)	136 (108–175)	138 (110–177)	1647 (40.6)	0.202
HbsAg					–
Positive	–	170 (6.2)	255 (6.3)	6 (0.2)	
Negative	750 (56.5)	1614 (59.3)	2364 (58.4)		0.385
Not available	493 (37.1)	938 (34.3)	1431 (35.3)		–
Anti-HCV					–
Positive	97 (7.3)	167 (6.1)	264 (6.5)	6 (0.2)	–
Negative	707 (53.2)	1530 (56.2)	2237 (55.2)		0.132
Not available	524 (39.5)	1025 (37.7)	1549 (38.3)		
uACR, mg/g	45 (12–357)	26 (11–280)	29 (11–304)	272 (6.7)	<0.001
<30	573 (65.9)	1330 (68.4)	1903 (67.6)		–
30–299	296 (34.1)	616 (31.7)	912 (32.4)		–
300–1000	234 (18.9)	349 (13.70)	583 (15.4)		–
>1000	133 (10.8)	251 (9.8)	384 (10.1)		–

Data are presented as median (25–75th percentile) or *n* (%).
[a]Anaemia was classified as per World Health Organization criteria: mild anaemia, Hb 11.0–11.9 mg/dL for females and 11–12.9 mg/dL for males; moderate anaemia, Hb 8.0–10.9 mg/dL for females and males; and severe anaemia, Hb <8 mg/dL for females and males.
SBP, systolic BP; DBP, diastolic BP; HbA1c, glycosylated Hb; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

85.4%, $P < 0.001$) and non-vegetarian dietary status (68.2% versus 59.9%, $P < 0.001$). Compared with the urban participants, the median annual household income was almost half in the rural group [US dollars (USD) 1680 versus 3024, $P < 0.001$]. Fewer patients in the rural regions had medical insurance (27.8% versus 39.8%, $P < 0.001$). History of use of alternative drugs (26.4% versus 21.4%, $P < 0.001$), BMI and family history of hypertension or diabetes were more in the urban group. uACR was lower among rural participants (25.5 versus 41.0 mg/g, $P = 0.003$). CIN and unknown aetiologies were proportionally more in the

Table 4. Comparison of socio-demographic and clinical factors between rural and urban subgroups within the study cohort ($n = 4056$)

Characteristic	Rural ($n = 2626$)	Urban ($n = 1350$)	P-value
Age, years	50.5 ± 11.6	49.8 ± 12.1	0.096
BMI, kg/m^2	23.8 (21.0–26.8)	25.3 (23.0–28.4)	<0.001
Waist/hip ratio	1.05 (1.02–1.10)	1.04 (1.00–1.08)	<0.001
Education			
Illiterate	872 (33.21)	197 (14.6)	<0.001
Some schooling	1262 (48.1)	624 (46.2)	
Graduate or above	492 (18.7)	529 (39.2)	
Occupational exposure[a]	1434 (54.6)	560 (41.5)	<0.001
Sand/dust	644 (24.5)	195 (14.4)	0.000
Cement	64 (2.4)	22 (1.6)	0.097
Saw dust	123 (4.7)	22 (1.6)	0.000
Working barefoot in field	238 (9.1)	21 (1.6)	0.000
Pesticide spray	213 (8.1)	12 (0.9)	0.000
Others	586 (40.9)	330 (58.9)	
Current tobacco user	536 (20.6)	203 (15.1)	<0.001
Current alcohol users	193 (7.4)	104 (7.8)	0.691
Physically active	1047 (40.2)	656 (48.9)	<0.001
Non-vegetarian diet	1765 (68.2)	805 (59.9)	<0.001
Access to piped water supply	1229 (46.8)	710 (52.6)	<0.001
Annual household income (USD)	1680 (840–3360)	3024 (1512–6720)	<0.001
Annual household medical expenditure (USD)	268.8 (84–521)	336 (84–672)	<0.001
Has medical insurance	721 (27.8)	531 (39.8)	<0.001
Out-of-pocket medical expenses	2254 (85.8)	1049 (77.7)	<0.001
Clinical characteristic			
Hypertension	2207 (85.2)	1226 (91.2)	<0.001
Diabetes	933 (36.3)	530 (40.0)	0.026
CVD	592 (22.7)	257 (19.2)	0.010
Renal stone disease	283 (10.8)	183 (13.6)	0.010
Recurrent UTI	293 (11.2)	144 (10.7)	0.647
Alternative drug use	561 (21.4)	357 (26.4)	<0.001
Ayurvedic	222 (39.6)	141 (39.5)	
Homoeopathic	135 (24.1)	72 (20.2)	
Siddha	27 (4.8)	24 (6.7)	
Unani	10 (1.8)	3 (0.8)	
Others	167 (29.8)	117 (32.8)	
NSAID use	395 (15.2)	217 (16.2)	0.397
History of AKI	167 (6.4)	98 (7.3)	0.283
Required dialysis for AKI	158 (6.1)	70 (5.2)	0.284
Underwent kidney biopsy	417 (16.0)	264 (19.7)	0.004

Data are presented as mean ± SD, median (25–75th percentile) or *n* (%).
[a]Occupational exposure—has multiple responses.

rural group, whereas DKD and CGN were more in the urban group.

DISCUSSION

This is the first paper to provide a comprehensive description of a nationwide cohort of patients with mild-to-moderate CKD from a developing country like India. The enrolled cohort is representative of the general Indian population in terms of age, sex ratio, representation of rural population, income and education levels, and other socio-economic characteristics according to the National Census [17].

The ICKD cohort is younger as compared with western cohorts (Table 6). It is worth noting that except for the CKD Japan Cohort (CKD-JAC), other Asian cohorts are younger than Western cohorts by 5–20 years. This finding is consistent with previous descriptions of CKD in India [21], and could be due to number of factors such as differential exposure to environmental risk factors, maternal malnutrition leading to development of kidney disease earlier in life, differences in genetic background or delayed recognition leading to faster disease progression [22]. Data from the nationally representative mortality survey of India in the Million Death Study have shown that the highest burden of age-standardized renal deaths was seen in the 45–69 years age group [2]. Approximately two-thirds of participants in our study cohort are males. A similar observation was noted in a multicentric hospital-based registry of patients with CKD in India [21]. This finding contradicts the global observation of a higher prevalence of milder stage CKD among females [20], and might reflect a systematic barrier in presentation to healthcare facilities for females in India, likely due to socio-cultural reasons.

The average BMI in our cohort was lower than that reported in the western cohorts [5, 19]. We report a higher

Table 5. Physical, biochemical characteristics and diagnosis between rural and urban subgroups within the study cohort ($n = 4056$)

Characteristic	Rural ($n = 2626$)	Urban ($n = 1350$)	P-value
SBP, mmHg	130 (120–143)	130 (120–145)	0.092
DBP, mmHg	80 (78–90)	80 (78–90)	0.981
eGFR, mL/min/1.73 m^2	40.0 (33.6–49.7)	42.0 (34.4–52.7)	<0.001
Hb, g/dL	11.6 (10.4–13.0)	12.1 (10.8–13.5)	<0.001
Anaemia	1712 (67.8)	771 (58.8)	<0.001
Mild	858 (34.0)	422 (32.2)	
Moderate	814 (32.2)	332 (25.3)	
Severe	40 (1.6)	17 (1.3)	
Serum urea, mg/dL	46.0 (35.3–56.0)	43.0 (33.1–53.8)	<0.001
Serum creatinine, mg/dL	1.8 (1.5–2.0)	1.7 (1.4–2)	<0.001
Serum calcium, mg/dL	9.0 (8.5–9.4)	9.0 (8.5–9.5)	0.982
Serum inorganic phosphorus, mg/dL	4.0 (3.3–4.5)	3.9 (3.3–4.5)	0.978
Serum albumin, g/dL	4.0 (3.5–4.4)	4.0 (3.6–4.4)	0.203
Serum uric acid, mg/dL	6.5 (5.3–7.6)	6.2 (5.1–7.5)	0.024
Total cholesterol, mg/dL	171 (137–202)	156 (128–194)	<0.001
Triglycerides, mg/dL	138 (110–176)	137 (107–178)	0.717
HbA1c, %	5.7 (5.1–6.9)	5.6 (5.0–6.6)	0.092
HbsAg-positive status	190 (7.3)	53 (3.9)	<0.001
Anti HCV-positive status	195 (7.4)	57 (4.2)	<0.001
uACR, mg/g	25.5 (10.7–304.3)	41.0 (11.7–304.3)	0.003
<30	1255 (69.0)	613 (64.9)	–
30–299	563 (30.97)	332 (35.1)	–
300–1000	364 (15.0)	206 (16.2)	–
>1000	251 (10.3)	123 (9.6)	–
Cause of CKD			<0.001
DKD	620 (23.6)	370 (27.4)	–
CIN	630 (24.0)	283 (21.0)	–
Unknown	570 (21.7)	209 (15.5)	–
CGN	362 (13.8)	220 (16.3)	–
Hypertensive nephrosclerosis	196 (7.5)	123 (9.1)	–
PKD	92 (3.5)	45 (3.3)	–
Others	156 (5.9)	100 (7.4)	–

Data presented as mean ± SD, *n* (%) and median (25–75th percentile).
SBP, systolic BP; DBP, diastolic BP; HbA1c, glycosylated Hb; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Table 6. Salient characteristics of major CKD cohort studies in adult population

Characteristic	ICKD ($n = 4056$)	CRIC [5, 18] ($n = 3612$)	CKD-JAC [6] ($n = 2977$)	GCKD [19] ($n = 5217$)	CanPREDDICT [7] ($n = 2402$)	C-STRIDE [11] ($n = 3168$)	KNOW-CKD [10] ($n = 2238$)	NEFRONA [8]
Age (years), mean ± SD	50.3 ± 11.8	58.2 ± 11.0	60.8 ± 11.6	60.1 ± 12.0	68.1 ± 12.7	48.2 ± 13.7	53.7 ± 12.2	57.9 ± 12.8
Female sex, %	32.8	46.0	38.0	40.0	37.0	41.0	38.8	42.3
BMI, kg/m^2, mean ± SD	24.4 ± 5.8	32.1 ± 7.9	23.5 ± 3.8	29.8 ± 6.0		24.5 ± 3.6	24.6 ± 3.4	28.3 ± 5.2
eGFR, mL/min/ 1.73 m^2, mean ± SD	40.6 ± 17.2	43.4 ± 13.5	28.6 ± 11.8	47.0 ± 17.0	28.0 ± 9.0	50.7 ± 30.0	53.1 ± 30.7	CKD Stage 3–5D
Diabetes, %	37.5	47.0	37.6	35.3	48.0	22.8	33.7	25.7
Hypertension, %	87.0	86.0	81.5	95.0	Not available	77.8	96.1	89.3
CVD, %	21.8	33.0	25.6	32.2	22.0	9.8	6.0	NA
Tobacco use, %	18.6	14.0	16.4	14.9	Not available	38.2	15.7	19.4
Major cause of CKD	DKD (24.9) CGN (14.7) HTN (7.9) CIN (23.2) Unknown (19.4)	DKD (25.5) HTN (14.5) Other (13.7) Do not know (46.3)	DKD (20.6) CGN (31.9) Others (47.5)	DKD (15.0) CGN (19.0) Vascular nephropathy (23.0) Interstitial nephropathy (4.6) Unknown [20]	DKD (29.0) CGN (11.0) HTN (27.0) PKD (4.0) Others (29.0)	DKD (13.9) CGN (60.6) Others (25.6)	DKD (23.2) CGN (36.2) HTN (18.3) PKD (16.3) Unknown (6.1)	DKD (14.4) CGN (15.6) Vascular nephropathy (19.3) tubulointerstitial (11.7) Unknown (16.7)

proportion of tobacco users, a potentially modifiable CKD risk factor [23] than that in the Chronic Renal Insufficiency Cohort (CRIC), CKD-JAC and German CKD (GCKD) cohorts [5, 6, 19]. Consumption of tobacco, especially in smokeless forms, is a deeply ingrained cultural practice in many parts of India [24]. The Chinese Cohort Study of CKD (C-STRIDE) has reported an even higher prevalence of tobacco use, at 38.2% [11].

Sedentary life style is another modifiable risk factor for CVD and CKD [25]. Just 43% of participants in our cohort reported physical activity corresponding to brisk walk for 30 min on at least 5 days in a week. In the Korean Cohort Study for Outcomes in Patients With CKD (KNOW-CKD) study, physical activity equivalent to that in our cohort was reported by 38.4% of participants [26], and 50% of C-STRIDE participants exercised >3.5 h/week [11]. Taken together, these data show that sedentary habits are common in patients with CKD. As exercise can favourably modulate renal function and control of hypertension in patients with CKD [27], it represents an important intervention that has potential to improve outcomes.

A total of 23% of our cohort participants had used alternative drugs, both before and after the diagnosis of CKD. India has several traditional medical systems that use herbal remedies, but the contribution of these medicines in the development and/or progression of CKD in India is not known. Most of the published data come from China and Taiwan, where higher rates of CKD are documented among consumers of indigenous Chinese herbal medicines [28, 29]. However, recent data from large insurance databases suggest that the associations may be complex and need well-structured exploration [30–33].

Diabetes was the most common cause of CKD (25%). An important finding was the emergence of CIN as the second most common, followed by CKDu. The 2012 Indian CKD Registry report showed DKD to be the designated aetiology in 31%, followed by CKDu at ∼19% and CGN at 14% [21]. CIN and CKDu have an almost identical phenotype and there are no clear criteria that allow distinction between the two. Usually, patients with no apparent risk factors are assigned a diagnosis of 'unknown'. In the setting of long-standing hypertension (>5 years) without other risk factors, a diagnosis of hypertensive nephrosclerosis was assigned. The aetiological distribution in our cohort is consistent with the recent population-based reports on CKD in India [34–37]. Elucidating the cause in these cases with unknown cause is an important research agenda. The possibility to do additional studies using platform technologies on the biobanked samples holds promise to improve our understanding of potential causes and risk factors.

Only about one-third of the patients enrolled in the study had any medical insurance. Furthermore, >80% of the participants ended up paying the majority of their healthcare costs from their own pocket, which suggests that even when insurance is available, it does not cover all aspects of CKD care.

Almost two-thirds of the ICKD participants were rural, which reflects the population distribution in India. There were some differences between participants from urban and rural areas. Rural participants were less educated, had lower earnings with lower insurance coverage, were more likely to be engaged in manual work and had more hazardous occupational exposure. Tobacco use was also higher among rural participants, while self-reported physical activity was lower in the rural group. Consistent with previous reports, CKDu was identified more frequently in the rural participants. Such findings are being increasingly described from other studies in rural populations in India [38]. Taken together, these data reinforce differences in epidemiology of CKD between urban and rural regions and suggest dominant tubulo-interstitial injury on account of as yet unknown risk factors in rural communities. Elucidation of differences in the characteristics and risk factor profile set the stage for further exploration of causality and development of customized strategies for management and prevention of CKD in rural regions.

Table 6 shows the comparison between selected features of the ICKD cohort and CRIC, GCKD, CKD-JAC, the Canadian study of prediction of death, dialysis and interim cardiovascular events (CanPREDDICT), C-STRIDE, KNOW-CKD and Observatoria Nacional de Aterosclerosis en Nephrologia (NEFRONA). The frequency of CVD was somewhat lower compared with the western cohorts, but greater than in the Asian cohorts. Proportionally higher representation of males, CIN as one of the dominant causes and lack of clinically apparent cause for CKD in one-fifth of participants are other differences in comparison with other cohorts.

While the ICKD cohort offers a unique opportunity to explore the natural history and progression factors for CKD in Indian subjects, a few limitations should be acknowledged. Except for two, all participating centres in our study are public sector hospitals. Therefore, there may be proportionally more representation of patients belonging to lower socio-economic status. Also, our cohort is hospital-based and may not be reflective of CKD in patients who do not present to nephrologists. The latter population might disproportionately include disadvantaged people living in both urban and rural areas. In addition to population differences, variability in practice patterns and access to healthcare services may be responsible for some of the observed differences.

These limitations notwithstanding, the ICKD study is the only large cohort study of patients with mild-to-moderate CKD in a lower middle income country. Its strengths are the pan-India nature, detailed phenotyping, biobanking and rigorous follow-up. The baseline characteristics show unique features that differentiate this population from patients with CKD enrolled in other cohort studies. Given the high and growing disease burden, a relatively rapid rate of progression, the high cost of care and the impact on quality of life [39], data from this study will provide important information to help the national strategy to manage CKD in India. In addition to defining outcomes and finding factors that associate with adverse outcomes in patients with CKD in low-resource settings, the ICKD study offers opportunities for international comparisons to further the goals of the global nephrology community.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

V.J. has research grants from Baxter, GlaxoSmithKline and reports consultancy and advisory board honoraria from Baxter Healthcare and AstraZeneca, outside the published work. All other authors reported no conflict of interest.

DATA AVAILABILTY STATEMENT

The study data is not publicly available but can be made available on request.

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