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CKD is the Major Cause of Death in Uddanam: A Population-Representative Study Using Smart Verbal Autopsy

Balaji Gummidi¹, Vaishali Gautam¹, Renu John¹, Rohina Joshi^{1,4}, Oommen John^{1,2} and Vivekanand Jha^{1,2,3,5}

¹The George Institute for Global Health India, UNSW, New Delhi, India; ²Manipal Academy of Higher Education, Manipal, India; ³Faculty of Medicine, Imperial College London, London, UK; ⁴School of Population Health, University of New South Wales, Sydney, Australia; and ⁵Faculty of Medicine, University of New South Wales, Sydney

Introduction: Uddanam is an agricultural area with a high burden of chronic kidney disease of unknown etiology (CKDu). Despite reports of many deaths due to CKD in the lay press, the exact contribution of CKD to deaths remains uncertain because most deaths occur outside medical care.

Methods: We used SmartVA automated verbal autopsy tool to ascertain the cause-specific mortality fractions among a 2419 subject-strong general population cohort of adult subjects in Uddanam between 2018 and 2022. Verbal autopsy interviews were conducted twice with the family members of the deceased.

Results: A total of 133 deaths were recorded, giving a crude death rate of 5.5%, 10 times higher than that recorded in national surveys. CKD was responsible for 45% of all deaths, followed by ischemic heart disease (15%) and respiratory disease (6%).

Conclusion: This study confirms CKD as the leading cause of mortality in this high CKD burden area and provides crucial data for public health decision-making and resource allocation.

Kidney Int Rep (2024) **9**, 108–113; https://doi.org/10.1016/j.ekir.2023.10.026 KEYWORDS: cause of death; chronic kidney disease; CKD of unknown etiology; SmartVA; uddanam nephropathy; verbal autopsy

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See Commentary on Page 10

• KD is the third fastest growing cause of death (COD) ✓ worldwide and is projected to rise in the rank of CODs from 16th in 2016 to 5th by 2040.¹ The greatest increases in CKD deaths are forecast in low and lowermiddle-income countries. In India, from 2001-2003 to 2011–2013, there was a 50% increase in the contribution of CKD to all deaths among persons aged 15 to 69 year.² COD reporting is problematic in many jurisdictions, including India, and the Global Burden of Disease study has admitted to having a high proportion of garbage codes (codes that are not useful for public health analysis) in ascertaining a CKD diagnosis.³ Many deaths occur at home for which the COD is either not reported at all or reported by untrained persons.⁴ Only 22.3% of the total registered deaths in 2020 were medically certified.⁴ Therefore, the true contribution of various conditions to

deaths remains uncertain. Tools such as verbal autopsy have been used to reduce this uncertainty.⁵

Population clusters with higher than usual prevalence of CKD not associated with traditional risk factors such as diabetes, hypertension, and other known etiological categories have been reported in many parts of the world. This CKDu is mostly encountered among rural agricultural communities.⁶ One such region is in the coastal district of Srikakulam in Andhra Pradesh, India, known as Uddanam (population 5.5 million).⁷ The age-adjusted and sex-adjusted prevalence of CKD in this area is estimated at 18% to 22%,^{8,9} 2.5 to 3.3 times higher than the population prevalence of CKD reported from other regions of India.¹⁰

More than 4500 deaths due to kidney disease were reported in Uddanam in the lay press in 2015.⁹ However, there has been no formal ascertainment of the COD in this population, which is critical for gaining actionable insights. We conducted this study to ascertain the cause-specific mortality fractions to overcome the key data gap in COD estimates using the SmartVA automated verbal autopsy tool¹¹ in a population-based cohort of adults in Uddanam.

Correspondence: Vivekanand Jha, The George Institute for Global Health, 308, Third Floor, Elegance Tower, Plot No. 8, Jasola District Centre, New Delhi 110025, India. E-mail: vjha@georgeinstitute. org.in

Received 9 June 2023; revised 3 October 2023; accepted 23 October 2023; published online 31 October 2023

METHODS

This population-representative study was conducted in Uddanam as part of an ongoing research program, the Study to Test and Operationalize Preventive Approaches for Chronic Kidney Disease of Undetermined Etiology (STOP-CKDu), the details of which are published elsewhere.^{8,12} The study established a general population-based cohort of adult subjects in July 2018 using a cluster sample technique, and the participants are being followed-up with to determine the incidence and risk factors for kidney disease progression.

All households included in the study were surveyed between 2018 and 2022 to create a mortality list through active community surveillance. After obtaining verbal consent from the family members, health workers scheduled an appointment for a verbal autopsy interview. The primary informants for the interviews were the deceased's closest relatives. The George Institute Ethics Committee approved the study.

We used SmartVA, a computerized algorithm validated by Population Health Metrics and Research Consortium in various settings and included in World Health Organization 2022 questionnaire. The tool has been developed to interpret data from interviews conducted with family members or caregivers of a deceased individual using a set of standardized questions to collect information about the signs, symptoms, and circumstances of the individual's death and applies an automated algorithm to assign a probable COD based on the collected data.^{13,14} There are 3 age-specific modules and a general information module in the SmartVA questionnaire: neonatal fatalities (from birth to 28 days), child deaths (from 29 days up to 11 years), and adult deaths (from 12 years and older). We used the adult deaths module for this study. The general information module collects data about the decedent's demographic details, education, household characteristics, and a list of their occupants. The adult module gathers information on the deceased's symptoms, past medical history, lifestyle (smoking and alcohol intake), injuries, and women's health issues if the deceased were a female. In addition, it transcribes data from death certificates and available medical records. We used modified Kuppuswamy scale to assess the socioeconomic status of the participants (Supplementary Material). This scale considers 3 key parameters: the education and occupation of the participant, as well as the total income derived from all sources within the family.

Verbal Autopsy Interview and Quality Maintenance

A trained interviewer collected data on android phones using a questionnaire developed by the Population Health Metrics and Research Consortium, translated into local language (Telugu) and implemented with the Open Data Kit software suite.¹⁵

Household members (aged 18 and older) who had cared for the deceased or were familiar with the illness were interviewed in-person. If medical records were accessible, the interviewee was asked to provide a transcription of the medical record's most recent summary. If a death certificate was provided, the interviewer was asked to note the reason for death as listed on the certificate.

Interviews lasted an average of 25 to 30 minutes, with a further 3 to 5 minutes required for the open narrative section. The completed questionnaires were saved on the tablets and transmitted to a central database following verification. To ensure the highest quality data were collected, this questionnaire was administered twice over 3 months by 2 independent, trained interviewers.

Data Analysis

The data were exported from Open Data Kit Collect using the Open Data Kit Briefcase tool as comma separated value files and uploaded into the SmartVA program, which assigns individual COD by using the Tariff Method 2.0 method,^{15,16} which uses an additive algorithm that assigns weights or scores to symptoms and signs reported during a verbal autopsy interview. These scores are based on their associations with different causes of death. The cumulative score for a particular set of symptoms and signs helps determine the most likely COD for the individual. In the few instances where symptoms were vague, contradictory, or mutually inconsistent, SmartVA could not determine the COD, and as a result, these deaths were deemed undetermined. Cohen's kappa statistic (K) was used to compare the agreement proportions between interviews.

COD Assignment

If the SmartVA-generated COD assignment matched between the 2 interviewers, it was considered the final COD. All unmatched results were reviewed by a trained, unbiased physician who had access to the decedent's verbal autopsy narratives and medical records. Assessment of the physician was considered the final COD in the case of unmatched records (Figure S1).

RESULTS

The STOP-CKDu cohort consisted of 2419 adult participants (Table 1). During a median follow-up of 3.9 years, there were 133 deaths (crude death rate 5.5%). A total of 100 (85.2%) were males, and 90 (67.7%) belonged to the lower-middle socioeconomic group. The median

Table 1.	Sociodemographic	characteristics	of the e	entire cohort	and the	deceased populat	ion
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Characteristics	Entire	Cohort	Deceased Population	
Variables	Male	Female	Male	Female
Number of cases	1193	1226	100	33
Age (yrs)				
18–30	156 (13.1)	169 (13.8)	2 (2)	0
31–40	242 (20.3)	326 (26.6)	3 (3)	3 (9.1)
41–50	318 (26.7)	343 (28.0)	19 (19)	8 (24.2)
51–60	267 (22.4)	244 (19.9)	25 (25)	11 (33.3)
>60	210 (17.6)	144 (11.8)	51 (51)	11 (33.3)
Level of education				
College	400 (33.5)	194 (15.8)	15 (15)	2 (6.1)
Attended school	487 (40.8)	411 (33.5)	43 (43)	9 (27.3)
No formal education	306 (25.7)	621 (50.7)	42 (42)	22 (66.7)
Occupation				
Not working	80 (6.7)	342 (27.9)	7 (7)	6 (18.2)
Sedentary workers	116 (9.7)	53 (4.3)	4 (4)	5 (15.2)
Manual workers/farmers	997 (83.6)	831 (67.8)	89 (89)	22 (66.7)
Socio-economic status				
Lower middle	515 (43.2)	856 (69.8)	64 (64)	26 (78.8)
Upper lower	677 (56.8)	370 (30.2)	36 (36)	36 (21.2)
Medical history (yes)				
Diabetes	186 (7.7)	131 (5.4)	28 (21.1)	2 (1.5)
Hypertension	408 (16.8)	312 (12.9)	60 (45.1)	22 (16.5)
Longstanding hypertension (≥5 yrs)	95 (3.9)	66 (2.7)	22 (16.5)	6 (4.5)
Heart disease	138 (5.7)	111 (4.6)	24 (18.1)	2 (1.5)
CKD	299 (12.4)	209 (8.7)	59 (44.4)	19 (14.3)
Place of death				
Home			77 (77)	29 (87.9)
Hospital			23 (23)	4 (12.1)

(interquartile range) age at death in the sample was 56 (48-66) and 55 (47-60) years for males and females, respectively. A total of 106 deaths were reported at home; the number was higher among females (87.9%) than males (77%). Cause specific mortality fraction from the STOP-CKDu cohort and global burden of disease estimates are depicted in Figure 1. CKD and chronic respiratory diseases were more prevalent in the study population, whereas burden of deaths due to neoplasm and TB was higher at the national level. Age-specific death rates from the STOP-CKDu cohort compared with vital statistics death rate of Andhra Pradesh are summarized in Supplementary Table S1. There was a high level of agreement between the COD determined in the 2 independent interviews (86.5%), with a Cohen's kappa (K) statistic score of 0.85.

The 15 leading COD by sex, before and after redistribution of undetermined causes are reported in Table 2. Tariff assigned a specific COD for 94.7% of deaths, with the COD being undetermined in approximately 5.3% of cases. The leading COD was CKD in 60 (45.1%), followed by ischemic heart disease (20, 15%), respiratory disease (8, 6%), and stroke (7, 5.3%). The COD distribution was similar between males and females. Table 3 shows the characteristics of the persons who died of CKD and those due to other causes among the cohort.

DISCUSSION

This first-of-its-kind study confirms CKD as the dominant COD in this rural agricultural population, long identified as a high CKD prevalence area. The proportion of individuals with CKD as the COD was significantly greater than that reported from the global burden of disease estimates for the state. In addition, the annual all-cause and sex-specific mortality rates were nearly 10 times higher than that documented in the sample registration survey report for Andhra Pradesh¹⁷ among adults of age 20 years and older. The COD ascertainment was made with high confidence because the data were collected twice by independent interviewers, and any disagreements resolved by an independent physician.

Our study showed an alarmingly high proportion of CKD deaths in this community. The burden of CKD mortality is more than the national and state average (2.37% and 2.08% of total deaths, respectively), and the neighboring states that report CKDu clusters, such as Tamil Nadu (5.16%), Kerala (4.89%), Goa (3.66%), and West Bengal (2.97%). The high burden of CKD deaths could be related to poor access to care pathways.¹⁸

High mortality burden among communities with high CKDu burden is also reported from Central America (60–

verbal Autopsy (CKDu conort)	cause of death	Global buraen of alsease, India
45.1	Chronic kidney disease	18.4
15.0	Ischemic heart disease	11.3
6.0	Chronic respiratory diseases	8.5
5.3	Stroke	5.1
3. <mark>0</mark>	Cancer	3.3
3. <mark>0</mark>	Diabetes	3.3
3. <mark>0</mark>	Road traffic accidents	2.7
3. <mark>0</mark>	Suicide	2.7
1.5	Cirrhosis	2.2
7.5	Other Infectious diseases	14
0.7	Other NCDs	10.7
0.8	Tuberculosis	12.5
0.8	Other injuries	4.9
5.3	Undetermined	0

*Other infectious diseases include deaths due to COVID-19.

*Other Non communicable diseases and Other injuries are as categorized from SmartVA tool.

#Other NCDs deaths include deaths due to cardiovascular diseases (excluding Ischemic heart disease, Stroke), Musculoskeletal disorders, digestive disorders, neurological and mental health disorders, substance use disorders, and skin and subcutaneous diseases.

#Other injuries include deaths due to unintentional injuries and interpersonal violence.

#Other infectious diseases include deaths due to communicable diseases excluding Tuberculosis

#All calculations were done after excluding maternal deaths

Figure 1. Cause-specific mortality fractions for leading causes of death from verbal autopsy data in the STOP-CKDu cohort, Uddanam region (N = 133) compared with Global Burden of Disease estimates for India (age >20 years).

70/100,000 population)^{19,20} and Sri Lanka (67.6% of total deaths).²¹ This high burden of CKD cases and associated mortality underscore the need for systematic efforts to establish the cause of CKDu and generate evidence on locally acceptable and scalable primary and secondary preventative strategies.

We used an automated tool for COD assessment, SmartVA. High reliability scores for COD ascertainment were observed from existing studies using similar tools

 Table 2. Leading cause-specific mortality fractions for all verbal autopsy deaths

Cause of death	Males	Females	Total
Chronic kidney disease	43 (43)	17 (51.5)	60 (45.1)
Ischemic heart disease	14 (14)	6 (18.2)	20 (15)
Chronic respiratory disorders	7 (7)	1 (3.0)	8 (6.0)
COVID-19	8 (8)	0	8 (6)
Stroke	4 (4)	3 (9.0)	7 (5.3)
Undetermined	4 (4)	4 (12.1)	7 (5.3)
Neoplasm	4 (4)	0	4 (3)
Diabetes	4 (4)	0	4 (3)
Transport accidents	4 (4)	0	4 (3)
Suicide	3 (3)	1 (9.0)	4 (3)
Cirrhosis	2 (2)	0	2 (1.5)
Other infectious diseases	1 (1)	1 (3.0)	2 (1.5)
Other injuries	1 (1)	0	1 (0.8)
Other NCDs	0	1 (3.0)	1 (0.8)
TB	1 (1)	0	1 (0.8)
Total	100 (75.2)	33 (24.8)	133 (100)

NCDs, non-communicable diseases; TB, tuberculosis.

in community settings of Uganda,²² Indonesia,²³ China,²⁴ and Philippines.²⁵ Our finding of favorable agreement scores, the minimal proportion of undermined deaths, and low disagreement rate between the 2 interviewers indicate SmartVA can generate high-quality verbal autopsy data in rural settings and has the potential to be used as a tool for medical certification of deaths in community settings.²⁶ These findings have implications for improving the quality of death reporting from rural communities which is vital for developing meaningful policies.

Working collaboratively with trained staff and supplementing the COD results with adjudication from an independent physician are the principal strengths of our work. The proportion of undetermined deaths was minimal, indicating a high quality of verbal autopsy narratives, which was achieved by adequately training the investigators, utilizing medical records, and using an automated verbal autopsy method. The limitations include the lack of a comparator for verbal autopsy records collected solely by the SmartVA tool. The delay between the time of death and verbal autopsy interviews might have introduced a recall bias, especially where the interval was relatively long. In addition, given that CKD is endemic in the region, the families could have inappropriately attributed the deaths to CKD. The latter was minimized by collecting comprehensive medical information, verifying the informant's narratives with medical records, and conducting the interviews twice by

 $\label{eq:constraint} \textbf{Table 3.} \ \textbf{Characteristics of the persons who died of CKD versus} \\ \textbf{non-CKD among the cohort}$

Variables	CKD death ($n = 60$)	Non-CKD deaths $(n = 73)$
Gender		
Male	43 (71.7)	57 (78.1)
Female	17 (28.3)	16 (21.9)
Age (yrs)		
18–30	0 (0)	2 (2.7)
31–40	5 (8.3)	6 (6.8)
41–50	11 (18.3)	18 (24.6)
51–60	18 (30)	21 (28.7)
>60	26 (43.3)	37 (36.9)
Level of education		
College	3 (5)	14 (19.2)
Attended school	37 (61.7)	27 (37)
No formal education	20 (33.3)	32 (43.8)
Occupation		
Not working	52 (86.7)	59 (80.8)
Sedentary workers	5 (8.3)	8 (11)
Manual workers/farmers	3 (5)	6 (8.2)
Socio-economic status		
Lower middle	46 (76.7)	44 (60.3)
Upper lower	14 (23.3)	29 (39.7)
Medical history (yes)		
Diabetes	7 (5.3)	15 (11.3)
Hypertension	37 (61.7)	41 (56.7)
Longstanding hypertension (\geq 5 yrs)	11(18.3)	17 (23.3)
Heart disease	12 (20)	14 (19.2)
CKD	35 (58.3)	11 (15.1)
Place of death		
Home	53 (88.3)	53 (72.6)
Hospital	7 (11.7)	20 (27.4)

CKD, chronic kidney disease.

independent interviewers. Furthermore, our study was not powered enough to estimate any association or generate a hypothesis of no causal inference; therefore, these findings should be confirmed in larger studies. Lastly, factors associated with lower mortality rates for deaths attributable to tuberculosis and neoplasm in STOP-CKDu cohorts need to be explored further.

In conclusion, using a validated automated verbal autopsy tool, this population-based study provides accurate information on cause-specific mortality rates for the adult population of the Uddanam region. The burden of mortality attributable to CKD is high, which indicates that policymakers need to address this concern and develop region-specific policies to prevent and manage CKD through prompt and accurate screening and diagnosis of CKD cases. Equally important would be to act on improving community awareness of the significance of early diagnosis and management.

DISCLOSURE

VJ has received grant funding from GSK, Baxter Healthcare, and Biocon and honoraria from Bayer, AstraZeneca, Boehringer Ingelheim, NephroPlus, and Zydus Cadilla, under the policy of all honoraria being paid to the organization. All the other authors have declared no competing interest.

ACKNOWLEDGMENTS

The Open Access Fees was paid from the Imperial College London Open Access Funds.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Data collection flow.

 Table S1. Age and sex disaggregated mortality data of

 Andhra Pradesh and STOP-CKDu study.

Population Health Metrics and Research Consortium General module.

Population Health Metrics and Research Consortium shortened verbal autopsy questionnaire adult verbal autopsy module.

Modified Kuppuswamy classification, socio economic status scale.

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