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Unlocking Mysteries: Smart Verbal Autopsy's Role in CKD of Unknown Etiology Research

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Chronic kidney disease (CKD) is a global health burden, affecting around 10% of the world's population, or approximately 850 million individuals.[1] CKD's prevalence varies from one region to another, with underserved communities bearing a disproportionate burden due in part to socioeconomic factors and limited access to healthcare. Of particular concern is CKD of unknown etiology (CKDu), which has been observed in many regions but particularly in Central America and South Asia.[2,3] Despite its significant impact, the exact prevalence of CKDu remains uncertain. This variant of CKD predominantly affects young to middle-aged men engaged in agricultural labor and distinguishes itself from traditional CKD cases by the absence of typical risk factors, such as diabetes or hypertension.[2,3] CKDu has raised important questions, leading to extensive research into its underlying causes.

In addition to Central America, CKDu hotspots have been identified in India, including regions such as Andhra Pradesh, Telangana, Goa, Orissa, Maharashtra, Tamil Nadu, Chhattisgarh, and Punjab. Among these, the Uddanam region, situated in the coastal district of Andhra Pradesh, has garnered particular attention, given its estimated CKD prevalence of 18%, which is 3 to 4 times higher than in other parts of the country.[4] However, the actual prevalence remains unestablished due to the absence of medical records, necessitating further investigation.

In regions where vital registration systems are deficient, and a substantial proportion of adult deaths occur outside medical facilities, a method called "verbal autopsy" (VA) has been used to estimate causes of death at the population level. A VA involves a structured interview with family or friends of the deceased to ascertain the symptoms and circumstances preceding the death. It operates on the premise that most causes of death manifest distinctive symptom patterns that lay people can recall and discuss. This technique has been refined through dedicated international workshops since 1989.[5] In recent years, computer algorithms have been integrated to reduce costs, save time, and enhance consistency, with the Smart Verbal Autopsy (SmartVA) tool standing out. SmartVA, validated by the Population Health Metrics and Research Consortium and endorsed by the World Health Organization's 2022 questionnaire, is half the length of other automated VA instruments and employs age-specific automated algorithms for accurate cause-of-death assessments.[6] For adults, it delves into symptoms, medical history, lifestyle factors, injuries, and women's health issues in cases of female decedents. It also transcribes data from death certificates and available medical records, making it a comprehensive and versatile tool for a better understanding of the causes of death (Figure 1).

SmartVA has been adopted and implemented in various countries as part of the Data for Health initiative, aimed at strengthening national civil registration and vital statistics systems. In a study conducted by Hazard and colleagues, SmartVA was deployed across 4 countries with varying levels of health statistical development, including Myanmar, Papua New Guinea, Bangladesh, and the Philippines.[6] The study compared its results with data from the Global Burden of Disease study, confirming the acceptability and reliability of these methods for broad implementation and the generation of accurate cause-of-death

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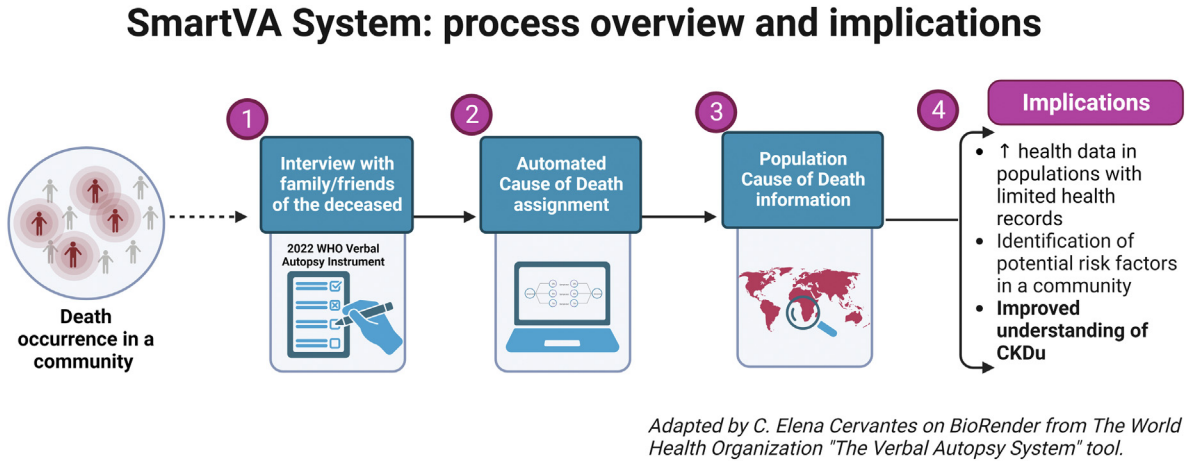

Figure 1. Smart Verbal Autopsy (SmartVA) System. CKDu, CKD of unknown etiology.

information in rural areas at different stages of VA program implementation.[6]

VA has had limited utilization in the field of nephrology until now. In the Uddanam region of India, although many deaths were attributed to kidney disease, there was a lack of a formal cause-of-death determination. To address this gap, Gummidi *et al.*[7] conducted a comprehensive analysis of cause-specific mortality in the general adult population of Uddanam spanning from 2018 to 2022. The primary tool used for identifying the causes of death was SmartVA. Over the study's 3.9-year median follow-up period, a total of 133 deaths occurred among a cohort of 2419 participants. Notably, CKD emerged as the leading cause of death, affecting 45.1% of the deceased, followed by ischemic heart disease (15%), respiratory diseases (6%), and strokes (5.3%).[7]

Individuals whose deaths were attributed to CKD exhibited certain distinguishing characteristics compared to non-CKD deaths. In both groups, a significant proportion were males (72% vs. 78%) and were generally older than 50, with the majority being over 60 years of age (43% vs. 37%).[7] Interestingly, most individuals' occupation was reported as "not working" (87% vs. 81%), and there was a low proportion of agricultural workers (5% vs. 8%). Similar to other CKDu literature, a higher proportion of patients with CKD-related deaths belonged to low-middle socioeconomic groups (77% vs. 60%) and had a low prevalence of diabetes (5% vs. 11%) and long-standing hypertension (lasting more than 5 years) (18% vs. 23%). Notably, the majority of individuals with CKD-related deaths had a history of CKD (58% vs. 15%). The occurrence of heart disease was fairly similar in both groups (20% vs. 19%). Not surprisingly, most deaths occurred at home in both groups (88% vs. 72%).[7]

The study's notable strengths include rigorous data collection conducted independently by 2 trained interviewers over 3 months, ensuring data quality. These interviewers engaged with household members who had cared for the deceased or were familiar with the illness. In cases where these interviewers reached an agreement on the cause of death, that determination was considered final. However, in instances where there was no consensus, a total of 16 cases were reviewed by an impartial physician.[7] This physician analyzed the data alongside VA narratives and medical records to establish the final cause of death. When the cause of death remained unclear or contradictory, SmartVA labeled these cases as "undetermined," resulting in 94.7% of cases with a primary cause of death determination and 5.3% left undetermined.[7]

This important study also presents some limitations worth mentioning. One of them is the lack of information regarding the time frame between the occurrence of death and the caregiver interview. A shorter time frame would have been preferable to reduce potential recall bias. It is unclear how many cases involved access to medical records or death certificates for the validation of the cause of death. These omissions leave a gap in understanding the robustness of the cause-of-death determinations. Furthermore, the assessment of socioeconomic status was done using the "modified Kuppuswamy scale" , which introduces some ambiguity. This is a widely used tool to assess socioeconomic status in India; however, in the international setting, specifying income levels would have helped improve understanding of the socioeconomic context. Lastly, providing a more comprehensive definition of medical variables, such as how diabetes diagnoses were established (self-reported, based on medical records, or medication reviews), would have been valuable.

CKDu's specific etiology continues to elude the medical community, although various potential triggers have been suggested. These include heat stress, pesticide exposure, consumption of water contaminated with agrochemicals and heavy metals, excessive use of nonsteroidal anti-inflammatory drugs, and genetic predisposition.[2,3]

In this study by Gummidi *et al.*,[7] the male predominance and low proportion of diabetes and hypertension, are similar to prior studies characterizing CKDu. Although the mean age of patients with CKDu is between 40 and 50 years, the age of individuals who die with CKDu has not been previously reported and can be hypothesized to affect older individuals similar to the cohort observed in this study. Another difference is that this population had a very low proportion of agricultural workers, in fact, many of them were not engaged in any labor. These findings may be attributed to their older age and potentially compromised health. The sex difference observed in this study still suggests a risk factor related to working conditions, but missing information about the prior occupations of men with CKD-attributed deaths adds an element of uncertainty.

The Uddanam region is a fertile, subtropical, low-altitude area known for coconut and cashew farming. Tatapudi and colleagues aimed to characterize CKD in this region and attributed more than 50% of the cases to CKDu.[4] The authors did not find a significant association between CKDu and sex disparity, education, farming, contact with pesticides, or habits such as tobacco smoking and alcohol consumption.[4] The authors conducted further investigations to explore potential risk factors for CKDu in Uddanam, uncovering high silica levels in the local water supply.[4] Despite this, the precise etiology of CKDu in Uddanam is yet to be determined.

SmartVA has emerged as a powerful tool in unraveling the causes of death, particularly in regions where CKDu prevails. This study in Uddanam, India, serves as an example of how SmartVA can illuminate the prevalence of CKD-related deaths and other contributing factors. By harnessing the capabilities of SmartVA in CKD research, particularly in regions with limited healthcare access, we can increase our understanding and response to the CKD burden, both locally and globally (Figure 1). The results of this study stand as an invitation to explore, adapt, and apply this tool, transforming the landscape of kidney disease research and paving the way for innovative solutions.

DISCLOSURE

All the authors declared no competing interests.

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