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Initial factors associated with in-hospital mortality in both critically ill and non-critically ill hospitalized patients with acute kidney injury in Northern Tanzania: a single center cohort study

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ABSTRACT

Acute kidney injury (AKI) is prevalent in Intensive Care Unit settings, with rates exceeding 50%. While many studies from sub-Saharan Africa focus on critically ill AKI patients, limited data exist on non-critically ill patients, hindering effective dialysis prioritization. Studies from developed countries suggest AKI is also common in non-critical settings. This study aimed to assess mortality rates among critically ill and non-critically ill hospitalized AKI patients and identify early mortality predictors at the time of AKI diagnosis. A single-center prospective cohort study was conducted at Kilimanjaro Christian Medical Center between September 2023 and February 2024. Patients admitted to the internal medicine ward were assessed, with critical illness determined using the Universal Vital Assessment (UVA) score. Cox regression identified predictors of in-hospital mortality, and Kaplan-Meier curves assessed survival time. Out of 1,211 admissions, 139 patients met inclusion criteria. Overall hospital mortality was 39.6%, higher in critically ill patients (57.1% vs. 21.7%, $p<0.001$). Predictors of mortality included critical illness (aHR 3.44, $p<0.001$), traditional herbal medicine (THM) intoxication (aHR 5.99, $p=0.002$), volume depletion (aHR 1.95, $p=0.028$), referral from regional hospitals (aHR 2.78, $p=0.002$), and age >60 (aHR 2.46, $p=0.001$). Critically ill patients had shorter median survival (12 vs. 20 days; $p=0.001$), which declined with higher UVA risk. While critical illness predicts AKI in-hospital mortality, non-critical AKI patients—often affected by THM, volume depletion, or regional hospital referrals are also at risk. Older age (>60 years) is a non-modifiable predictor of in-hospital mortality in AKI.

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Introduction

Acute kidney injury (AKI) results from an abrupt loss of kidney function that is usually reversible [1]. The disease is of public health concern as it affects nearly a quarter of the hospitalized population globally with global incidence reported at 21.6%–23.9% [2]. Limited data from sub-Saharan Africa (SSA) show similar findings where AKI incidence of 22.4% was reported from a hospital in Cameroon [3].

The kidney disease improving global outcomes (KDIGO) has provided guidelines for AKI diagnosis and disease severity staging. AKI is staged into KDIGO stages 1, 2 and 3 with KDIGO 3 being severe AKI [1]. AKI is also often categorized into; pre-renal, intrinsic and post-renal AKI depending on the determined etiology. Sepsis, volume depletion, heart failure and acute nephrotoxicity are some of the most commonly recognized risk factors pre-disposing to AKI [4]. Treatment is mainly conservative while dialysis is reserved for disease presenting with complications or when it is warranted to remove toxins [1,5]. Where warranted, dialysis is a costly procedure, and usually several treatment sessions are required when

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indicated. This further burdens the already under-funded healthcare infrastructure in lower and middle income countries (LMICs) [6–8].

Critical illness refers to a state of high mortality risk due to vital organ dysfunction, which is often associated with the need for critical care in an intensive care unit (ICU) [9]. AKI is particularly prominent among the critically ill, affecting more than half of intensive care unit (ICU) patients in SSA [10–12].

The outcome of AKI in the critically ill patients varies across settings. In some high resource settings, the hospital mortality of AKI patients in the ICU (ICU-AKI) was reported at 19.4% in the USA [13] while in SSA similarly conducted studies showed great variation, ranging from 31.8% in South Africa [11] and 58.2% in the Democratic Republic of Congo (DRC) [14] to as high as 94.1% in Tanzania [12]. Data from the developed world also showed that ICU-AKI patients were more than seven times more likely to die during the admission period compared to non ICU-AKI patients with corresponding mortality rates of 15.7% vs. 2.1%, respectively [15].

The mortality associated with AKI is linked to the AKI severity [16–18], AKI complications [19,20] as well as limited access to dialysis treatment in SSA [21]. Challenges impeding access to dialysis treatment in SSA were likely attributed to shortage of specialists (nephrologists), limited availability of dialysis services and the overall lack of medical insurance cover. Previous studies had reported relatively lower coverage of dialysis among ICU-AKI patients from SSA (18.0% from South Africa [11], 6.5% from the DRC [14], and 5.1% in Tanzania [10] when compared to the more developed Middle East region (20.4% in Jordan [22] and 35.4% in Pakistan [23]. Pooled data from SSA also reported a low population medical insurance coverage rate at 10.6% and 14.0% for males and females, respectively [24]. For the uninsured, the cost of AKI treatment in SSA is prohibitive to many as it was estimated to be in excess of $ 1,700 per person [25] in a developing region where the average daily income was $ 1.90 per head per day [8]. Higher mortality rates among ICU-AKI is also reported to be attributed to inter-organ crosstalk mechanisms [26] which result to multi-organ failure (MOF) compared to a single-organ failure observed in a non ICU setting.

Given the known variation in AKI outcomes across settings, it was important to identify other important and contextual factors that may be responsible for explaining this wide variation in hospital mortality in critically and non-critically ill keeping in mind that a wide range of factors, including; AKI severity, etiological factors, the presence of chronic diseases and supportive treatments for organ failure have also been reported to influence poor mortality outcomes in ICU-AKI [3,10–14].

The terms 'critically ill AKI' and 'ICU-AKI' can therefore be considered synonymous in this context since inpatients are usually assessed and determined to be critically ill based on a particular mortality risk stratification score. Most studies done prior to the present study had reported only on critically ill AKI, mostly through sampling ICU-AKI patients [10–14]. There is a general scarcity of data non-critically ill AKI, especially from SSA. Data pertaining to non-critically ill AKI is important and could contribute to guide treatment prioritization in AKI, especially for dialysis which is often associated with high cost and limited access in LMICs [8,25].

The main objective of this study was to assess the in-hospital mortality rates of critically ill and non-critically ill hospitalized AKI patients as well as to determine initial factors present at the time of AKI diagnosis that are predictive of in-hospital mortality in the overall hospitalized AKI patients. This would make it possible to both; assess the burden of critical illness in hospitalized AKI patients as well as to assess the non-critically ill AKI group for any association with initial factors that predict in-hospital mortality in AKI. These predictors would give foresight to poor outcomes and could also be used to gauge those with a high chance of survival or mortality at the time of AKI diagnosis in order to guide prioritization of AKI treatments including dialysis. Maximum treatment resources could then be directed to those patients with a predicted favorable survival profile.

Methods

Study design

This was a prospective, single center, observational cohort study.

Setting

This study was conducted at the internal medicine department of the Kilimanjaro Christian Medical Center (KCMC), Northern Tanzania from September 2023 to February 2024. KCMC is a tertiary zonal level specialized hospital located in the municipality of Moshi, Kilimanjaro, Tanzania.

Population

KCMC hospital has a 630 bed capacity and serves a catchment area of 15 million persons.

Data collection

Daily surveys of both newly admitted patients and those continuing with care were conducted and we diagnosed AKI using the earliest abnormal serum creatinine (SCr) test result that fitted AKI criteria when compared with the participants' known or estimated baseline SCr level. Consent was sought from those fulfilling the KDIGO criteria for AKI. Those medical ward inpatients having age ≥18 years, KDIGO stage ≥1 and provided informed consent were consecutively included in the study. No participants were excluded. Critical illness was considered the main exposure, however other socio-demographic, etiological and treatment related exposures were also analyzed. The main outcome of interest was in-hospital mortality.

Data was collected using case report forms (CRF) containing socio-demographic, clinical and outcome characteristics. Initial data were collected at the time of AKI diagnosis (within 24 h of a new admission or within 24 h of critical SCr results reporting for the inpatients continuing with care). The initial data included; the etiology of AKI, severity of AKI, unit of triage, presence of chronic diseases, presence of a critically ill state, and receiving dialysis treatment. Participants were henceforth followed up daily until the final outcome was determined to be either in-hospital mortality or survival at hospital discharge.

Operational definitions

AKI was defined using the KDIGO serum creatinine (SCr) criteria by a rise in SCr level of equal to or more than 1.5 times the individual's baseline SCr level [1]. When available, a previous normal range SCr test result taken in the prior 7–365 was considered as baseline [27]. In the absence of previously documented SCr test results, the baseline SCr was estimated by back calculation using the MDRD formula and the glomerular filtration rate assumed at 75 mL/min/1.73m^2 [28]. Chronic kidney disease was ruled out using historic, clinical laboratory and/or radiological evidence of CKD in addition to consulting a nephrologist. Critical illness was defined by a high risk universal vital assessment (UVA) score of ≥5 and/or receiving vasopressor treatment and/or mechanical ventilation at the time of AKI diagnosis [9]. The UVA score is a tool for mortality risk stratification that has been validated for use in SSA in addition to being user-friendly in the low income setting [29]. Given the definition of critical illness, those participants with UVA score of <5 and receiving neither vasopressor treatment nor mechanical ventilation at the time of AKI diagnosis were considered non-critically ill. In-hospital mortality was defined as any death of a participant during the hospital admission period. The documented date and time of death obtained from patient's clinical notes was used to timestamp the event. Initial factors were those individual socio-demographic, etiological or clinical characteristics of participants determined to be present at the time of AKI diagnosis. Initial factors were assessed at the time of AKI diagnosis (as opposed to the time of hospital admission) in order to fully capture factors from both community acquired AKI (CA-AKI) and hospital acquired AKI (HA-AKI) populations at one uniform time-point in AKI. CA-AKI was defined as any AKI occurring within 48 h of being in a hospital [30]. HA-AKI was defined as any AKI occurring after 48 h of hospitalization in a patient who was AKI-free at the time of admission [31]. Sepsis was defined by a sequential organ failure assessment (SOFA) score of ≥2 in the population suspected of infection [24]. Infection was suspected in any participant who had had a simultaneous sampling of body fluid for microbiology testing and initiated on empiric antibiotics [32]. Heart failure was defined by the presence of typical symptoms and/or specific signs of heart failure with echocardiographic evidence of functional and/or structural cardiac abnormalities [33]. Traditional herbal medicine (THM) intoxication was defined as a reported use

of plant-based treatments within seven days prior to the onset of acute kidney injury (AKI) [34,35]. THM use can lead to kidney injury through; direct nephrotoxicity of its constituents (including aristolochic acid, chromium and germanium), additives and adulterants (including heavy metals) and/or interactions between allopathic medicines and THMs if used together [34]. Volume depletion was defined by historical presence of risks for hypovolemia, including; hemorrhage, vomiting, diarrhea, and over-diuresis in the 7 days leading to AKI onset [36]. Acute stroke was defined by the development of new neurological dysfunction persisting > 24 h with imaging evidence of cerebral infarction and/or intra-cerebral hemorrhage [37]. HIV disease was diagnosed by testing positive on the rapid diagnostic test for HIV, or evident records of enrollment to a care and treatment center for people living with HIV (CTC). Hypertension, diabetes mellitus and chronic heart failure were diagnosed by considering past history of morbidity with each individual disease along with current drug history of using anti-hypertensive drugs, oral hypoglycemic drugs/insulin therapy and anti-failure treatment for each, respectively. Dialysis treatment was defined by initiation of hemodialysis treatment within 24 h of AKI.

Study outcome

In-hospital mortality was the outcome of interest.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 23 software package (SPSS Inc, Chicago IL, USA). Descriptive statistics were summarized using frequency and percentage for categorical data and mean and standard deviation or median and interquartile range for continuous data. The Pearson chi square test (x^2) or Fischer's exact test (where applicable) were used to compare differences categorical data. The independent t test was used to compare differences in means for continuous data. The level of significance was set at $p \leq 0.05$. Survival analysis was done using a cox regression model to determine predictors of in hospital mortality in AKI patients. The tested effect was set to be in-hospital mortality. The survival time was set to be the duration in days from the time of AKI diagnosis to the time of either death or live discharge. An initial univariate analysis was done to determine crude hazard ratios (cHR) for each independent variable to determine covariates of the final model whereby 7 variables showed association with mortality at $p < 0.20$ and were eligible for inclusion in the final model. To avoid omitting potential confounders known to influence mortality, additional clinically important covariates were retained for entry into the final model and the final model included 18 covariates. Because the number of outcome events ($n = 55$) limited the number of parameters that could be reliably estimated (EPV = 3.06), a stepwise-forward procedure (entry criterion $p < 0.05$) was deemed appropriate to identify the most parsimonious combination of independent predictors in the final model. Collinearity of covariates was avoided by purposefully not including KDIGO stage 3 and high oxygen target ($FiO2 \geq 0.6$) as these covariates showed substantial overlap with critical illness through cross tabulation as well as clinical reasoning. The overall model fit was significant (global Wald test = $p = 0.033$), indicating that the included covariates jointly predict mortality in patients with AKI. Covariates with $p \leq 0.05$ were considered to be independent predictors of in-hospital mortality in AKI. Kaplan Meier curves with respective log rank tests were used to determine survival time. Data is presented using figures, tables, and narration.

Ethical consideration

This study was granted a research ethical clearance certificate from the Kilimanjaro Christian Medical University college research ethics committee (CREC), certificate no. PG 51/2023 as well as being granted written permission to collect data from KCMC. Written consent was obtained from participants after they had been informed of the purpose and benefit of the study. Confidentiality was maintained throughout the study duration and data was stored not containing participant identifiers. Participants who did not consent were not denied access to medical care.

Results

There were a total of 1,211 admissions in the internal medicine departments between 15 September 2023 and 27 February 2024 and of these, 152 (12.6%) fulfilled the KDIGO criteria for AKI. 13 participants did not consent to participate in the study. The remaining 139 participants were included in the study (Figure 1).

The mean age of hospitalized patients presenting with AKI was 52.9 (SD 18.6) years, and male was the predominant gender (61.9%). Majority of AKI patients were referred from district level hospitals (45.3%) and a larger proportion did not have medical insurance (69.8%). All the participants were of the black race (Table 1).

Close to a third (28.8%) of hospitalized AKI patients were triaged to the ICU. Hypertension was the commonest co-morbidity comprising 29.5% of the cases, followed by diabetes mellitus (16.5%), HIV disease (15.1%) and chronic heart failure (10.8%). About a third of the AKI population (32.4%) received high target oxygenation ($FiO2 \geq 0.6$) with a larger proportion in the critically ill group (54.3% vs. 10.1%, $p \leq 0.001$, respectively) (Table 1)

Community acquired AKI (CA-AKI) comprised the majority of cases (89.2%), while the remainder 10.8% were hospital acquired AKI (HA-AKI). The median serum creatinine at the time of AKI diagnosis was 187 µmol/L (IQR 136–449 µmol/L) and in the majority (69.1%) baseline SCr level were estimated using back calculation of the MDRD formula. The median baseline serum creatinine was 76 µmol/L (IQR 71–81 µmol/L). Most AKI presented in KDIGO stage 3 (38.8%) with pre-renal AKI being predominant (84.9%). Intrinsic AKI was in low proportion in the critically ill group compared to the non-critically ill. (8.6% vs. 21.7%, $p = 0.030$, respectively) (Table 1).

Sepsis was the most frequent cause of AKI attributing to 43.9% of all AKI cases and the mean SOFA score was 7(4) among those with sepsis. Other frequent causes of AKI included volume depletion (30.2%), heart-failure related AKI (17.3%) and traditional herbal medicine (THM) intoxication (5.0%). Less frequently, AKI resulted from; acute pesticide poisoning (APP), nephrotoxic drugs, contrast exposure, rhabdomyolysis, malaria-associated AKI (MA-AKI) as well as obstructive causes. Together, these less frequent causes of AKI comprised 14.4% of all causes. Less than a quarter (18.0%) of the AKI patients received hemodialysis. There was no significant difference in hemodialysis uptake between the critically ill and non-critically ill groups. Majority (92.0%) of KDIGO stage 3 received dialysis while in the older AKI patients of ≥60 years, only a small proportion (12.0%) received dialysis (Table 1)

The mean UVA score was 4 (SD 3) with high-risk UVA status being more common (46.8%) compared to intermediate risk (23.7%) and low risk (29.5%) UVA categories. Vasopressor and mechanical ventilation treatments uptake in the total population were 16.5% and 12.2%, respectively (Table 1).

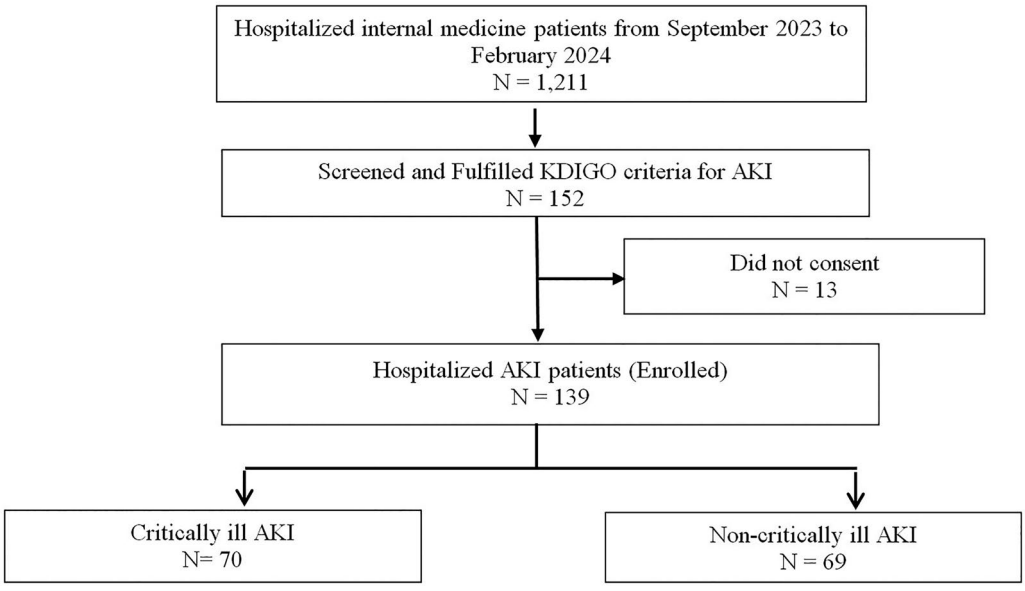

Figure 1. Participant's enrollment flow chart.

Table 1. Clinical characteristics of hospitalized AKI patients.

Characteristic	Total $n=139$	Critically ill $n=70$	Non-critically ill $n=69$	p-Value
Age ≥ 60 years[b] *n* (%)	61 (43.9)	35 (50.0)	26 (37.7)	0.143
Male[b], *n* (%)	86 (61.9)	42 (60.0)	44 (63.8)	0.647
Referral origin				
Home n (%)	38 (27.3)	21 (30.0)	17 (24.6)	0.478
Health center *n* (%)	15 (10.7)	5 (7.1)	10 (14.5)	0.163
District hospital[b] *n* (%)	63 (45.3)	34 (48.6)	29 (42.0)	0.439
Regional hospital[b] *n* (%)	23 (16.5)	10 (14.3)	13 (18.8)	0.470
Medical insurance[b] *n* (%)	42 (30.2)	17 (24.3)	25 (36.2)	0.125
ICU admission[b] *n* (%)	40 (28.8)	31 (44.3)	9 (13.1)	**<0.001**
Chronic diseases				
Diabetes mellitus[b] *n* (%)	23 (16.5)	11 (15.7)	12 (17.4)	0.790
Hypertension[b] *n* (%)	41 (29.5)	21 (30.0)	20 (28.9)	0.896
CHF *n* (%)	15 (10.8)	7 (10.0)	8 (11.6)	0.626
HIV disease[b] *n* (%)	21 (15.1)	13 (18.6)	8 (11.6)	0.251
Vital signs				
Normal BP *n* (%)	70 (50.4)	31 (44.3)	39 (56.5)	0.149
Hypotension *n* (%)	34 (24.4)	25 (35.7)	9 (13.0)	**0.002**
HR, mean (SD)	103 (24)	113 (24)	94 (20)	<0.001
RR, mean (SD)	24 (7)	27 (8)	22 (6)	<0.001
GCS <10, mean (SD)	31 (22.3)	28 (40.0)	3 (4.3)	**<0.001**
High target oxygenation (FiO2 ≥ 0.6)	45 (32.4)	38 (54.3)	7 (10.1)	**<0.001**
AKI				
CA-AKI *n* (%)	124 (89.2)	56 (80.0)	68 (98.6)	**<0.001**
HA-AKI[b] *n* (%)	15 (10.8)	14 (20.0)	1 (1.4)	
SCr at diagnosis, median (IQR)	187 (136, 449)	188 (133, 452)	186 (142, 433)	
Baseline SCr estimation				
MDRD formula used *n* (%)	96 (69.1)	44 (62.9)	52 (75.4)	0.111
Mean (SD)	75 (9)	75 (10)	76 (7)	0.272
KDIGO stage				
KDIGO stage 1 *n* (%)	44 (31.7)	21 (30.0)	23 (33.3)	0.673
KDIGO stage 2 *n* (%)	41 (29.5)	19 (27.1)	22 (31.9)	0.540
KDIGO stage 3 *n* (%)	54 (38.8)	30 (42.9)	24 (34.8)	0.239
AKI type				
Pre-renal *n* (%)	118 (84.9)	65 (92.9)	53 (76.8)	**0.008**
Intrinsic *n* (%)	21 (15.1)	6 (8.6)	15 (21.7)	0.030
Post renal *n* (%)	7 (5.0)	2 (2.9)	5 (7.2)	0.237
AKI etiology				
Volume depletion[b] *n* (%)	43 (30.2)	20 (28.6)	23 (33.3)	0.544
Heart failure[b] *n* (%)	24 (17.3)	11 (15.7)	13 (18.8)	0.262
Sepsis[b] *n* (%)	61 (43.9)	42 (60.0)	19 (27.5)	**<0.001**
SOFA mean (SD)	7 (4)	8 (3)	5 (3)	<0.001
Acute stroke[b] *n* (%)	12 (8.6)	5 (7.1)	7 (10.1)	0.529
THM intoxication[b] *n* (%)	7 (5.0)	2 (2.9)	5 (7.2)	0.237
Others causes[a,b] *n* (%)	20 (14.4)	6 (8.6)	14 (20.3)	**0.049**
Received dialysis[b] *n* (%)	25 (18.0)	12 (17.1)	13 (18.8)	0.794
UVA score median (IQR)	4 (0,6)	7 (6,8)	2 (0,4)	
UVA risk categories				
Low risk *n* (%)	41 (29.5)	1 (1.4)	40 (58.0)	<0.001
Intermediate risk *n* (%)	33 (23.7)	4 (5.7)	29 (42.0)	<0.001
High risk *n* (%)	65 (46.8)	65 (92.6)	0	
Received vasopressor treatment *n* (%)	23 (16.5)	23 (32.9)	0	
Received mechanical ventilation *n* (%)	17 (12.2)	17 (24.3)	0	
In-hospital mortality rate *n* (%)	55 (39.6)	40 (57.1)	15 (21.7)	**<0.001**

Bold: Indicates a significant p-value.

[a]Other causes: comprises; APP (1.4%); Nephrotoxic allopathic drugs (3.6%); Contrast exposure (0.7%); RI-AKI (2.9%); MA-AKI (1.4%); Pelvic tumors (2.9%); Faulty catheterization (1.4%).

[b]Variable included in the cox regression analysis.

Abbreviations: APP: acute pesticide poisoning; BP: blood pressure; CA-AKI: community acquired acute kidney injury; CHF: chronic heart failure; FiO2: fraction of inspired oxygen; GCS: Glasgow comma score; HA-AKI: hospital acquired acute kidney injury; HIV: human immune-deficiency virus; HR: heart rate; ICU: intensive care unit; IQR: interquartile range; KDIGO: kidney disease improving global outcomes; MA-AKI: malaria associated acute kidney injury; RI-AKI: rhabdomyolysis induced acute kidney injury; RR: respiratory rate; SCr: serum creatinine; SD: standard deviation; SOFA: sequential organ failure assessment score; THM: traditional herbal medicines; UVA: universal vital assessment

The overall in-hospital mortality rate among AKI patients was high at 39.6%, and much higher among the critically ill vs. non-critically ill (57.1% vs. 21.7%, $p \leq 0.001$), respectively. The median duration of hospital stay was 8 (IQR 4–16) days (Table 1).

Table 2. Cox regression analysis for predictors of AKI in-hospital mortality.

	cHR	95% CI	*p*-Value	aHR	95% CI	*p*-Value
Age ≥ 60	2.50	1.45 – 4.29	0.001	2.46	1.45 – 4.29	**0.001**
Male	0.81	0.47 – 1.38	0.435			
District hospital referral	0.73	0.42 – 1.26	0.258			
Regional hospital referral	2.00	1.10 – 3.64	0.022	2.78	1.48 – 5.23	**0.002**
No medical insurance	1.19	0.65 – 2.19	0.568			
ICU admission	1.51	0.88 – 2.59	0.138			
HA-AKI	1.35	0.70 – 2.61	0.365			
Volume depletion	1.31	0.75 – 2.31	0.343	1.95	1.08 – 3.54	**0.028**
Heart Failure	0.57	0.23 – 1.43	0.228			
Sepsis	1.27	0.74 – 2.18	0.384			
THM intoxication	1.96	0.70 – 5.47	0.198	5.99	1.97 – 18.21	**0.002**
Other causes[a]	0.30	0.09 – 0.97	0.044			
Stroke	0.97	0.39 – 2.45	0.952			
Diabetes mellitus	1.05	0.49 – 2.23	0.896			
Hypertension	0.88	0.48 – 1.59	0.663			
HIV disease	1.32	0.64 – 2.71	0.450			
Critical illness	2.69	1.48 – 4.89	0.001	3.44	1.83 – 6.47	**<0.001**
Received dialysis	0.53	0.25 – 1.13	0.100			

Bold: Indicates a significant p-value.
[a]Other causes: comprises; APP (1.4%); Nephrotoxic allopathic drugs (3.6%); Contrast exposure (0.7%); RI-AKI (2.9%); MA-AKI (1.4%); Pelvic tumors (2.9%); Faulty catheterization (1.4%).
Abbreviations: APP: acute pesticide poisoning; BP: blood pressure; CA-AKI: community acquired acute kidney injury; CHF: chronic heart failure; FiO2: fraction of inspired oxygen; GCS: Glasgow comma score; HA-AKI: hospital acquired acute kidney injury; HIV: human immune-deficiency virus; HR: heart rate; ICU: intensive care unit; IQR: interquartile range; KDIGO: kidney disease improving global outcomes; MA-AKI: malaria associated acute kidney injury; RI-AKI: rhabdomyolysis induced acute kidney injury; RR: respiratory rate; SCr: serum creatinine; SD: standard deviation; SOFA: sequential organ failure assessment score; THM: traditional herbal medicines; UVA: universal vital assessment

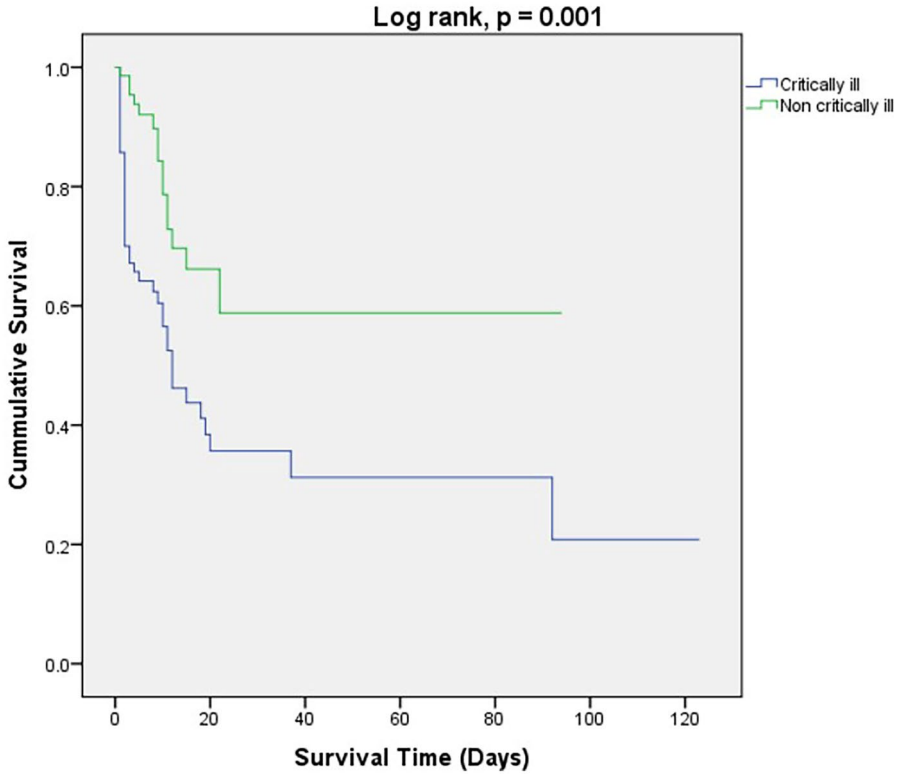

Figure 2. Kaplan Meier curve demonstrating the relationship between critical illness and AKI in-hospital mortality.

Survival analysis revealed critical illness to be an independent predictor of in-hospital mortality in AKI (aHR 3.44, p = <0.001) along with other four predictors including; older age (≥60 years) (aHR 2.46, $p = 0.001$), referral from a regional hospital (aHR 2.78, $p = 0.002$), volume depletion associated AKI (aHR = 1.95, $p = 0.028$) and THM intoxication (aHR 5.99, $p = 0.002$) (Table 2). The median survival time was shorter among the critically ill AKI patients (12 ± 3 days) compared to the non-critically ill AKI patients (20 ± 9 days) (log rank $p = 0.001$) (Figure 2). The median survival time also declined with increasing UVA risk category

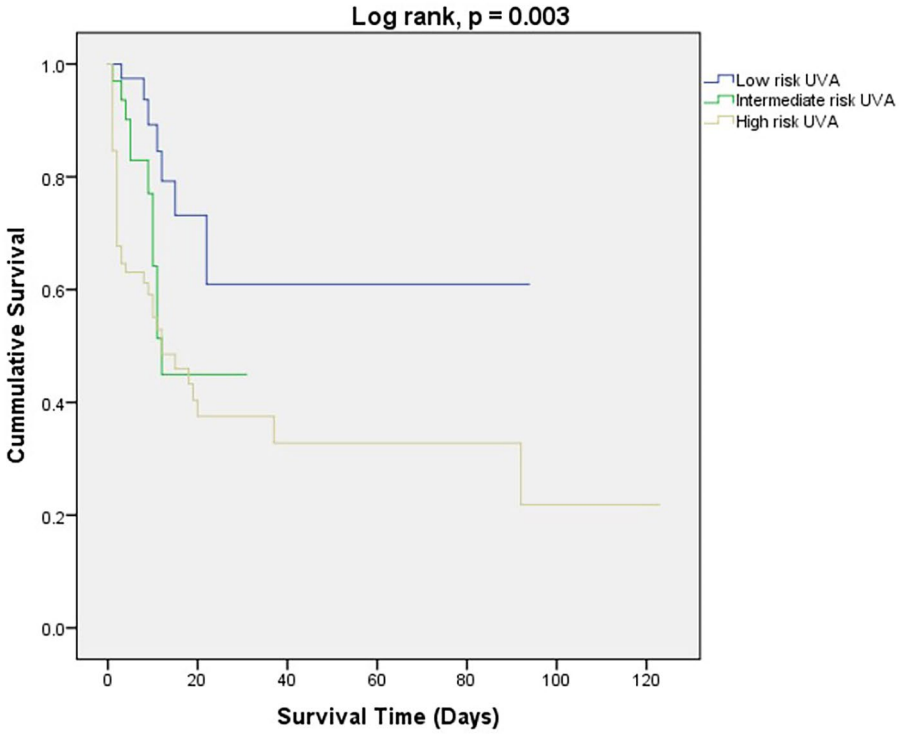

Figure 3. Kaplan Meier curve demonstrating the relationship between UVA risk categories and AKI in-hospital mortality. UVA: Universal vital assessment.

Table 3. Description of the relationship between predictors of AKI mortality with critical illness and dialysis treatment.

Predictor	Total (*n*)	Prevalence (%)	Critically ill, *n* (%)	Non critically ill, *n* (%)	In-hospital Mortality rate, *n* (%)	Received dialysis, *n* (%)
Critical illness[a]	70	50.4	N/A	N/A	40 (57.2)	12 (17.1)
THM intoxication[a]	7	5.0	2 (28.6)	5 (71.4)	4 (57.1)	4 (57.1)
Volume depletion[a]	43	30.9	19 (44.2)	24 (55.8)	19 (44.2)	4 (9.3)
Regional hospital referral[a]	23	16.5	10 (43.5)	13 (56.5)	15 (65.2)	6 (26.1)
Age > 60 years[a]	61	43.9	35 (57.4)	26 (42.6)	33 (54.1)	3 (4.9)

[a]Variable included in the cox regression analysis.
Abbreviation: THM: traditional herbal medicines

in the hospitalized AKI patients, from 20 ± 9 days in the low risk group to 12 ± 5 days in the high risk group (log rank 0.003) (Figure 3).

Of the five predictors of mortality in AKI, critical illness was the most prevalent in AKI (50.4%). Traditional herbal medicine was the least prevalent predictor (5.0%) but one with the highest hazard (aHR 5.99, $p = 0.002$) as well as the highest coverage for dialysis (57.1%). The THM intoxication group also had a higher proportion (71.4%) of non-critical presentation at the time of admission. Patients who had AKI secondary to volume depletion and those that came as referral from regional hospitals also had higher proportions of non-critical presentation at the time of admission (55.8% and 56.5%, respectively). Patients with AKI secondary to volume depletion and the older patients (age ≥60 years) had the lowest coverage of dialysis (9.3% and 4.9%, respectively) (Table 3).

Discussion

In the context of a data-scarce environment in SSA, this was an important study comparing hospital mortality in the critically ill versus the non-critically ill AKI patients, examining the burden of critical illness and early factors associated with AKI in-hospital mortality.

The proportions of the AKI population were nearly equally distributed in the critically ill and non-critically ill groups, indicating that the non-critically ill AKI group is of proportional significance.

A similar distribution of hospitalized AKI patients was reported from the USA at 51.1% and 48.9% for ICU-AKI and non-ICU AKI, respectively [15]. AKI has by far been mostly studied in the critically ill state or critical care setting [10–14] leaving a gap for AKI in the non-critically ill state being relatively unexplored. Previously published predictors and recommendations currently guiding AKI treatment have lacked the contribution of data from the non-critically ill AKI group, therefore the predictors and recommendations in use today cannot be generalized to a wider AKI population. This warrants further studies where broader populations of in AKI are sampled to include AKI in the non-critically ill setting as well as community settings in order to enrich the pool of data available from this group of AKI population.

A major part of our main objective had been to assess the burden of critical illness in hospitalized patients with AKI in the overall medical ward. Indeed our analysis revealed that critical illness was a significant predictor of in-hospital mortality in AKI, along with other four etiological and socio-demographic factors.

The critically ill AKI patients were more than three times likely to die during the hospital admission compared with the non critically ill. A similar pattern was reported from the USA in that ICU-AKI had a higher in-hospital mortality rate compared to non-ICU AKI (15.9% vs. 2.0%, respectively) [15]. The fact that a state of critical illness predicts hospital mortality in AKI is plausible given the fact that the very nature of critical illness is defined by a high risk of death due to vital organ failure, including kidney failure.

Despite wide searches across different databases, our attempts to find previously published data describing critical illness as an independent predictor of mortality in AKI were unsuccessful and as a result we faced challenges while comparing our survival data. As described earlier, this comes about as most previous studies have been focused mainly on ICU-AKI leaving the non-critically ill AKI group under-researched. An alternative but similar perspective was sought by considering the fact that previously published studies on ICU-AKI populations from SSA had described many hallmarks of critical illness as being independent predictors of mortality. Receiving vasopressor treatment was described as an independent predictor of AKI mortality from Tanzania (aOR 3.78, $p=0.01$) [10] while receiving mechanical ventilation was reported as an independent predictor of AKI mortality from South Africa (aHR 2.08, $p=0.029$)[11] and Tanzania (aHR 1.54, $p=0.046$) [12]. These findings show similarities with our findings as vasopressor treatment and mechanical ventilation treatments were absolute criteria for defining critical illness in our study. Likewise, a study from the DRC had identified that respiratory distress (aHR 1.60, $p=0.018$), oxygen desaturation (aHR 1.53, $p=0.006$) and multi-organ failure (aHR 1.63, $p=0.006$) as predictors of AKI mortality [14] while in South Africa a high SAPS 3 score was among the predictors of mortality in ICU-AKI (aHR 1.04, $p\leq 0.001$) [11]. From the latter two studies, similarities with our findings are also seen since multi-organ failure was assessed using the UVA score and a high risk UVA score (≥5) was a criteria to define critical illness in our study. Using this alternative perspective, our findings are considered to resonate with previously published data, especially from SSA.

In our study less than a quarter of the critically ill AKI patients received dialysis, this proportion was nearly the same for the non-critically ill AKI as well, indicating that critical illness did not necessarily warrant dialysis. Similar and even lower dialysis coverage rates among ICU-AKI were reported from South Africa (18.0% of all ICU-AKI) [11], the DRC (6.5% of KDIGO 3 ICU-AKI) [14] and Tanzania (9 out of 177 – 5.1% of all ICU-AKI) [10]. In the two former studies, dialysis was reserved for KDIGO stage 3 only. Data from the Middle East region showed greater dialysis coverage among ICU-AKI at 20.4% and 35.4% from Jordan and Pakistan, respectively [22,23].

While critical illness is not a specific indication for dialysis in AKI, we see varied dialysis coverage rates across different regions of the world [10–12,14,22,23] Greater availability of appropriate dialysis modalities in the middle-east region may explain this relative variation in RRT rates. Continuous renal replacement therapy (CRRT) characterized by a continuous low filtration rate is recommended as the choice of dialysis for critically ill patients as it is better suited for the hemodynamic unstable patients [38]. Currently, CRRT services are scarce in SSA [39] and most if not all dialysis provided consist of intermittent hemodialysis (IHD), which in some circumstances may be a risky undertaking for the critically ill. Wide availability of CRRT in SSA could widen the dialysis coverage among critically ill AKI in need.

The second aspect of our main objective had been to determine whether there were other factors (apart from critical illness) that were significantly associated with in-hospital mortality in AKI and whether or not such factors would be prevalent in the non-critically ill AKI group.

Our efforts proved to be fruitful as among the other predictors of hospital mortality in AKI, the majority were found to be mostly prevalent in the non-critically ill AKI group. These included traditional herbal medicine (THM) intoxication, volume depletion and referrals from a regional hospital. The exception was older age (≥ 60 years) which was found to be more prevalent in the critically ill group.

In our study, THM intoxication was a rare and yet the strongest modifiable predictor of in-hospital mortality among hospitalized AKI patients. AKI patients who had THM intoxication as the cause of AKI were six times more likely to die compared with patients who had AKI due to other causes, however nearly three quarters of AKI patients with THM intoxication were not critically ill at the time of admission. The likely explanation for this phenomenon is that those with THM intoxication do not initially present with features of critical illness but nevertheless they deteriorate during the hospital stay and die. Aristolochic acid is the most recognizable nephrotoxic component present in many THM preparations worldwide [34]. While comparing our findings with those of others, an interesting observation was made, that there has been a significant drop in the overall prevalence of THM induced AKI in SSA over the past 2 decades. In 2002, THM intoxication had been implicated to cause as much as 35% of all cases of AKI in South Africa [40]. Around that time, the WHO had reported that 80% of the population in Africa used THM to treat different diseases [41]. Data published more than two decades ago also indicated that THM-AKI was associated with a mortality rate as high as 75% [42]. Since then, the prevalence of THM intoxication as a cause of AKI in SSA seems to have declined as recently the prevalence of THM intoxication as a cause of AKI in overall SSA was reported at 0.8% [43]. The same prevalence as the later (0.8%) was also recently reported from South Africa [11].

Our findings regarding THM intoxication resonated the most with those from a recent study from Goma, the DRC, where traditional herbal medicine intake was a significant modifiable predictor of in-hospital mortality in severe AKI requiring dialysis (aHR 5.1, $p \leq 0.0001$) with death occurring in 26 out of 57 (45.6%) of patients with THM intoxication [44]. Different from our findings was that, the DRC study reported an alarmingly high prevalence of THM intoxication being documented in 57 out of the total 131 (43.5%) studied AKI population [44]. This finding deviated significantly from both the low overall prevalence reported in SSA as well as with our findings. The Goma region of the DRC is situated far (more than 1800 km away) from country's main port of Matadi and the Goma region in particular has been burdened with an ongoing civil war for many years. Interrupted supply chains in this region may have resulted to regular scarcity of basic commodities including allopathic medicines. Such an environment has likely driven these deprived communities toward preference of THM compared to western medicines. In another region of Africa, a study from Morocco reported a high prevalence (50.7%) of herbal medicine use among patients with varying degrees of kidney diseases, with the preference for herbal medicine use among patients with kidney disease being driven mostly by personal beliefs, relative ease of access compared to allopathic medicines as well as the lower cost of herbal medicines [42]. While the Moroccan study [42] did not report AKI patients separately and had considered the general population with kidney disease in the nephrology unit, the prevalence of herbal medicines among the AKI in their population can be reasonably estimated to be significantly higher than the rates reported for overall SSA [43] and South Africa [11]. In the Moroccan study [42], the prevalence of herbal medicine use among AKI is likely to resonate more with the prevalence reported from the DRC study [44].

THM intoxication can therefore be considered as a 're-emerging' important cause of both AKI and AKI mortality in some regions of SSA and shouldn't be considered uniformly rare as reported by some recent studies. Being that THM intoxication is predominantly a feature of the non-critically ill and yet bears a significantly high in-hospital mortality risk is a demonstration that the understudied non-critically ill AKI population does contribute some modifiable factors that are associated with high mortality in AKI. This justifies further research into both THM intoxication and non-critically ill AKI populations of SSA. In comparison to the other predictor groups, THM intoxication comprised the group with the highest proportion that received dialysis, with more than half receiving dialysis. This is reassuring as it likely implies that THM intoxication is a recognized high risk AKI state by local practitioners in northern Tanzania. However, this coverage rate is still suboptimal as it is likely that all patients with THM intoxication required dialysis since 'intoxication' with nephrotoxins is a recognized absolute indication of dialysis in AKI. In the DRC study [44] all patients with THM intoxication received dialysis, as the study was set in a hemodialysis center. Low economic status and lack of medical insurance among patients were likely the barriers

toward receiving dialysis in our study. THM intoxication should be recognized as a high risk state in AKI regardless of the initial mortality risk categorization at the time of admission and such patients may benefit more with liberal dialysis treatments to reduce hospital mortality in AKI.

Another modifiable predictor of in-hospital mortality in AKI was volume depletion AKI, bearing a 2 fold increased risk of mortality. It was the second most frequent etiology of AKI (after sepsis) affecting nearly one third of the hospitalized AKI patients and bearing a significant in hospital mortality of nearly fifty percent. Similar to THM intoxication, the majority of patients in this group were not critically ill. A study from Cameroon reported that volume depletion had a prevalence of 36.1% among hospitalized medical ward patients with AKI and was also the second most frequent cause of AKI following sepsis [3]. This resonated with our findings. Another study from the UK reported that among the elderly (age ≥65 years) hospitalized patients with AKI, dehydration occurred in 710 out of 1,525 AKI patients, corresponding to a relatively higher prevalence (46.2%) compared to our findings [45]. The mortality rate among the dehydrated patients was also observed to increase with the duration following AKI incidence at 12.8%, 14.7%, 17.0%, and 25.3% for in-hospital mortality, 30 day mortality, 90 day mortality and one year mortality, respectively [45]. Dehydration is more prevalent among the elderly than in younger adults due to a combination of age-related physiological changes including reduced thirst sensation, low fluid intake as well medication induced dehydration [46,47]. The relatively lower in-hospital mortality rate of the dehydrated elderly AKI patient seen from the UK [45] can be explained by the fact that the UK is a developed country with better healthcare infrastructure and treatment resources compared with Tanzania.

More importantly is that our findings resonated with the UK study in that dehydration was reported as a significant predictor of 30-day mortality among AKI patients (HR 1.61, $p \leq 0.001$) [45].

In our study, a striking observation made on the volume depletion group is that it had the second lowest proportion of patients that received dialysis compared to patients in other predictor variables. The low uptake of dialysis in this group could be attributed to the reluctance of practitioners to provide dialysis to AKI patients with volume depletion, as current treatment guidelines advocate for rehydration therapy as the mainstay treatment for pre-renal AKI. Another possible scenario may be that volume depletion is often present with concomitant hypotension, which may further limit the possibilities of a prompt initiation of hemodialysis. In the later scenario, CRRT with concomitant cardiovascular support treatments could be considered as a first line dialysis option to improve dialysis tolerability and overall survival of volume depletion associated AKI patients.

Being a referral from a regional hospital was another modifiable predictor of in-hospital mortality among patients with AKI. Patients in this group were nearly three times more likely to die during the admission duration. Despite the fact that the majority of patients in this group were not critically ill at the time of admission, this group presented the highest in hospital in-mortality rate among all the predictors, as well as more than a quarter receiving dialysis. This was yet another revelation that the non-critically ill AKI patients manifested some factors associated with in-hospital mortality. At the time of data collection, the majority of regional hospitals in northern Tanzania were not yet equipped with dialysis treatment facilities and this likely explains the need for referral to a tertiary center. Previously published data describing the characteristics of AKI referrals from regional hospital were lacking. Alternatively, in an attempt to learn more about referral patterns in Tanzania, the characteristics of referrals from regional hospitals observed in other disease conditions were studied. We found that surgical case referrals from regional hospitals suffered more from lack of medical supplies and consumables as a reason for referral (16.0%) compared to health centers (1.1%) and district hospitals (4.7%) [48]. Lack of medical supplies and consumables is likely to affect medical patients more than surgical patients, therefore posing a risk for under-treatment and/or treatment delays in AKI. Treatment delays, especially delays in initiating dialysis (when indicated) had likely resulted to the need for more intensive and prolonged treatments for AKI, creating a higher risk of mortality. AKI patients coming in as referral from regional hospitals in Tanzania should be carefully examined for disease severity and presence of AKI complications while being given consideration for liberal dialysis.

Lastly, older age (≥60 years) was found to be a non-modifiable predictor of in-hospital mortality in AKI. Older patient were a significant AKI sub population as they comprised more than 40% of the AKI cohort and were also more than twice likely to die during the admission period. More than half of the older patients were also critically ill at the time of admission. There is biologic plausibility to this finding, in that age-related organ decline (including kidneys) adds vulnerability in the setting of an acute illness,

increasing the risk of death in older individuals. Similar findings across the globe resonated with our findings regarding the mortality predictability of older age, from Sweden (age ≥65 years, aHR 1.90, $p \leq 0.001$) [16], Pakistan (age > 65 years, aOR 3.16, $p = 0.006$) [23] as well as from the neighboring DRC (age ≥ 60 years, aHR 15.89, $p \leq 0.0001$) [44]. As older age is a non-modifiable factor, conservative treatments rather than aggressive dialysis should be considered given the factor's irreversible nature. In our study, the older age group had the lowest coverage of dialysis (less than five percent received dialysis) and this is in keeping with our recommendations.

Strength and limitations

This study sampled a wider population of medical AKI, and was not limited to ICU-AKI as many studies have done previously. Also, being a prospective cohort study, missing data were minimized whist maximizing data quality. The main limitation of the study was that it was a single center hospital based study of medical-AKI as well as not including surgical-AKI, so the findings may not be generalized to the wider population as a whole. A larger, multicenter prospective study is needed to further validate the findings from this study. Another limitation relates to the possibility of a selection bias introduced by including both CA-AKI and HA-AKI populations which tends to underestimate the CA-AKI proportion. Lastly, baseline SCr estimation relied mostly on back calculation using the MDRD formula as many participants lacked previously documented normal range SCr records. This has potentially resulted to either a slight underestimation or overestimation of the actual AKI burden.

Conclusions

A significant proportion of hospitalized AKI patients present as non-critical at the time of AKI diagnosis. While critical illness continues to be a predictor of in-hospital mortality in AKI, other important predictors including THM intoxication, volume depletion and referral from a regional hospital have higher proportions of non-critical presentation at the time of admission. THM intoxication is also reemerging as an important cause of AKI in some regions of Africa while volume depletion AKI is among the most frequent causes of AKI as well as an underserved group in terms of receiving dialysis. Older age (≥60 years) is a non-modifiable predictor of hospital mortality in AKI. These predictors should inform treatment decisions and guide dialysis prioritization in hospitalized AKI.

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Ethical approval

This study was conducted in accordance with the principles stated in the *Declaration of Helsinki* (World Medical Association, 2013). Ethical approval was obtained from the Kilimanjaro Christian Medical University college research ethics committee (CREC), certificate no. PG 51/2023. Informed consent was obtained from all participants prior to inclusion.

Authors' contributions

CRediT: **Huda Akrabi**: Writing – review & editing; **Kajiru Kilonzo**: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Writing – original draft.

Disclosure statement

The authors have no conflict of interests to declare.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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