Original Clinical Research Quantitative

Burden and Risk Factors of Contrast-Associated Acute Kidney Injury in Hospitalized Zambian Children: A Prospective Cohort Study at the University Teaching Hospitals

Hellen M'hango[1] (iD), Chishiba Kabengele[2], Veronica Sukuntu[3], and Chisambo Mwaba[1,4]

Abstract

Background: Contrast-associated acute kidney injury (CAAKI) is defined as acute kidney injury (AKI) occurring within 72 hours of administration of contrast media (CM) and is linked to adverse outcomes including longer hospital stay, increased hospital mortality, and a higher risk of chronic kidney disease in later life. Risk factors for the development of CAAKI in the Zambian pediatric population have not been well studied.

Objectives: The objective of this study was to assess the burden of CAAKI, ascertain its risk factors, and describe short-term outcomes in hospitalized children at the University Teaching Hospitals (UTH) undergoing contrast-enhanced radiological investigations.

Methods: This was a prospective observational study of in-patients undergoing contrast-enhanced radiological procedures, between September 2020 and September 2021. The participants were recruited from the Children's Hospital, the Cancer Diseases Hospital, and the Pediatric Surgical Ward at the University Teaching Hospital in Lusaka, Zambia. The primary outcome variable was occurrence of AKI at 48 hours post CM administration. We used 2 criteria to define CAAKI in our study—the European Society of Urogenital Radiology (ESUR) and the Kidney Disease Improving Global Outcomes (KDIGO) 2012 criteria. Multivariable logistic regression models were formulated to assess for risk factors of CAAKI.

Results: Of the 201 enrolled participants, 123 (61.2%) were male and the median age of the participants was 5 years (interquartile range [IQR] = 3-10). The mean hemoglobin was 103 g/L (standard deviation [SD] = 26), median creatinine was 30.9 µmol/l (IQR = 22.6-43), and the glomerular filtration rate (GFR) was 102.5 mL/min/1.73 m^2 (IQR = 76.2-129.4). Forty-six (22.9%) developed CAAKI using the ESUR compared with 4.5% (9/201) using the KDIGO criteria. Independent risk factors of CAAKI were receiving a higher dose of CM (adjusted odds ratio [aOR] = 2.54; 95% confidence interval [CI] = [1.12-5.74]), prematurity (aOR = 4.6; 95% CI = [1.05-16.7]), and a higher eGFR (aOR= 1.01; 95% CI = [1.01-1.02]). Females had higher odds of CAAKI (aOR = 2.48; 95% CI = [1.18-5.18]) when compared with males. One CAAKI participant (2.2%) died; none of the participants who developed CAAKI and survived required dialysis and most of them (90%) were discharged before day 7. Day 7 eGFR results had returned to or near baseline values for those whose creatinine results were available.

Conclusions: Using the ESUR criteria, a significant proportion (22.9%) of children undergoing contrast-enhanced computed tomography (CT) scans at the UTH developed CAAKI. In contrast, using the KDIGO criteria only 4.5% had CAAKI. Being born as a preterm baby, being female, having a higher eGFR at baseline, and receiving a higher dose of CM were found to be independent risk factors for CAAKI development in Zambian children. Most of the cases of CAAKI in children were transient and of little clinical significance as only a minority of patients developing CAAKI required kidney replacement therapy and all resolved by day 7 post administration of CM.

Abrégé

Contexte: L'insuffisance rénale aiguë associée aux produits de contraste (IRA par produits de contraste) est définie comme une IRA survenant dans les 72 heures suivant l'administration d'un produit de contraste. L'IRA par produits de contraste est associée à des résultats de santé indésirables comme un séjour prolongé à l'hôpital, une mortalité hospitalière accrue et un risque plus élevé de souffrir d'insuffisance rénale chronique plus tard dans la vie. Les facteurs de risque de l'IRA par produits de contraste dans la population pédiatrique zambienne n'avaient pas fait l'objet d'études approfondies.

Objectifs: Évaluer le fardeau de l'IRA par produits de contraste, déterminer ses facteurs de risque et décrire les résultats de santé à court terme chez les enfants hospitalisés dans des hôpitaux universitaires et subissant des examens radiologiques avec produit de contraste.

Méthodologie: Il s'agit d'une étude observationnelle prospective examinant des patients hospitalisés ayant subi des procédures radiologiques avec rehaussement de contraste entre septembre 2020 et septembre 2021. Les participants ont été recrutés dans trois hôpitaux de Lusaka en Zambie : l'Hôpital pour enfants, le Cancer Diseases Hospital et le University Teaching Hospital (service de chirurgie pédiatrique). Le principal critère d'évaluation était la survenue d'une IRA dans les 48 heures suivant l'administration du produit de contraste. Nous avons défini l'*IRAPC* à l'aide de deux critères, soit celui de la Société européenne de radiologie urologique et celui de KDIGO (Kidney Disease Improving Global Outcomes) de 2012. Des modèles de régression logistique multivariés ont été formulés afin d'évaluer les facteurs de risque de l'IRA par produits de contraste.

Résultats: Des 201 participants inscrits, dont l'âge médian était de 5 ans (ÉIQ : 3 - 10), 123 (61,2%) étaient des garçons. Le taux d'hémoglobine moyen s'établissait à 103 g/L (écart-type : 26), le taux de créatinine médian à 30,9 umol/L (IQR : 22,6 – 43) et le DFGe à 102,5 ml/min/1,73 m^2 (ÉIQ: 76,2 – 129,4). Le taux d'IRA par produits de contraste était de 22,9% (46 patients) selon le critère de la Société européenne de radiologie urologique, et de 4,5% (9/201) avec le critère KDIGO. Les facteurs de risque indépendants de développer une IRAPC étaient : l'administration d'une dose plus élevée de produit de contraste (rapport de cote ajusté [RCc] = 2,54; IC 95% : 1,12 – 5,74), une naissance prématurée (RCc = 4,6; IC 95% : 1,05 – 16,7) et un DFGe plus élevé (RCc = 1,01; IC 95% :1,01 – 1,02). Les filles étaient plus susceptibles de développer une IRA par produits de contraste (RCc = 2,48; IC 95% : 1,18 – 5,18) que les garçons. Un patient qui avait développé une IRA par produits de contraste (2,2%) est décédé; aucun des survivants à une IRA par produits de contraste n'a eu besoin de dialyse, et la plupart des patients (90%) avaient reçu leur congé de l'hôpital avant le septième jour. Chez les patients dont les résultats de créatinine étaient disponibles, les valeurs de DFGe au septième jour étaient de retour aux valeurs initiales, ou proches de celles-ci.

Conclusion: Selon le critère de la Société européenne de radiologie urologique, une proportion significative des enfants (22,9%) avait développé une IRA associée aux produits de contraste à la suite d'une tomodensitométrie avec rehaussement de contraste à l'University Teaching Hospital. Cette proportion s'établissait à 4,5% avec les critères de KDIGO. Dans cette population pédiatrique de Zambie, le fait d'être né prématurément, d'être de sexe féminin, d'avoir un DFGe initial plus élevé et de recevoir une dose plus élevée de produit de contraste se sont avérés des facteurs de risque indépendants de développer une IRA par produits de contraste. La plupart des cas d'IRA par produits de contraste étaient transitoires et peu significatifs sur le plan clinique puisque seuls quelques patients ont eu besoin d'une thérapie de remplacement rénal et que tous les cas se sont résolus dans les sept jours suivant l'administration du produit de contraste.

Introduction

Contrast-associated acute kidney injury (CAAKI) is a general term used to describe the sudden deterioration in kidney function that occurs within 72 hours following the administration of intravascular contrast media (CM).[1] Contrast-induced nephropathy (CIN) is defined as the abrupt worsening of kidney function after exposure to radio-CM in the absence of any other acute kidney injury (AKI) etiologies. While CIN suggests that the AKI is a direct result of the CM, with CAAKI, on the contrary, other etiologies, other than the CM, may explain the deterioration in kidney function.[2] Contrast-associated acute kidney injury has repeatedly been linked with adverse outcomes, such as increased length of hospital stay, in-hospital mortality, and risk of chronic kidney disease (CKD) in later life.[1]

The incidence rates of CAAKI are further modulated by the population under study with rates ranging from 3% among low-risk groups to as high as 30% among high-risk

[1]Department of Paediatrics, University Teaching Hospitals – Children's Hospital, Lusaka, Zambia
[2]Rwanda Zambia Health Research Group, Emmasdale, Zambia
[3]Department of Radiology, University Teaching Hospitals – Adult Hospital, Lusaka, Zambia
[4]Department of Paediatrics and Child Health, School of Medicine, University of Zambia, Lusaka, Zambia

Corresponding Author:
Hellen M'hango, Department of Paediatrics, University Teaching Hospitals – Children's Hospital, Private Bag RW1X, Nationalist Road, Lusaka 10000, Zambia.
Email: hellenmhango26@gmail.com

groups.[1,3-5] This wide variation in the incidence rates is influenced by varying CAAKI definitions, the type of radiological procedures performed, and the amount and kind of radio-contrast agent administered.[2,6] There is an on-going debate about the ideal definition of CAAKI in children; different definitions have been used by different authors which include pediatric reference change value optimized for AKI in children (PROCK), the pediatric risk, injury, failure, loss of function (PRIFLE), acute kidney injury network (AKIN), the Kidney Disease Improving Global Outcomes (KDIGO) criteria, and the European Society of Urogenital Radiology (ESUR) criteria was mostly used to define CIN in older studies and this was mostly in adults.[4,6] The incidence of CAAKI seems similar in children and adolescents to that in adults, and different incidences have been found depending on the definition used.[7]

A 25% increase in serum creatinine (SCr) from baseline or a 44 µmol/l increase in absolute SCr value within 72 hours of contrast administration is defined as CAAKI by the ESUR[5] whereas in the KDIGO classification system, AKI is defined as an SCr increase of >26.4 µmol/l within 48 hours or of >150% from baseline presumed to have occurred within the prior 7 days or as urine output of <0.5 mL/h for 6 hours.[8]

The Contrast Media Safety Committee (CMSC) of the ESUR updated its 2011 definition and guidelines on postcontrast AKI, and these guidelines are recommended for use in adults but may also be used in children and adolescents. In essence, ESUR has since adopted the KDIGO 2012 AKI criteria and only modified the duration in which the 50% change in creatinine occurs from 48 to 72 hours. The modified criteria have not been validated in the pediatric population.[7] The use of both the KDIGO and ESUR criteria to define and quantify the burden of CAAKI in this cohort of children allows us to compare the 2 measures in children.

Some recent studies say that the risk of CAAKI with the use of modern intravenous CM in imaging studies among people with reduced kidney function has been exaggerated to the detriment of those in need of diagnostic imaging. Patients with reduced kidney function have commonly been denied or had delayed computed tomography (CT) imaging because of concerns of iodinated contrast-induced AKI, such delays potentially lead to delay in diagnosis or even misdiagnosis.[9]

Few studies have individually examined CAAKI in pediatric populations. Two recent trials reported incidences of pediatric CIN between 4% and 10%.[6,10-12] These studies have been done in developed countries, so no data regarding the prevailing situation in sub-Saharan Africa is available. It is possible that the incidence of CAAKI in low-resource settings could be even higher than the estimates in the Western countries due to the limited health care resources to prevent, diagnose, and treat CAAKI and the reduced awareness of the impact of the resulting CAAKI on patient outcomes.[4,13]

We conducted a prospective cohort study to determine the rates of CAAKI in children at a large teaching hospital in Zambia and identified the risk factors for its development. We also determined the short-term (7 days) outcomes of children who developed CAAKI.

Methods

Study Design, Setting, Population and Ethical Approval

This study was a prospective cohort study conducted at the University Teaching Hospitals Children's Hospital, Cancer Diseases Hospital, and Pediatric Surgery departments in Lusaka, Zambia, from September 2020 to September 2021.

Participants in this study were hospitalized pediatric patients who had a medical or surgical indication to undergo contrast-enhanced radiological examinations as prescribed by the primary care physicians. Total enumerative sampling was used for the study period as all children who met the set eligibility criteria were included in the study.

Written informed consent and assent were obtained from the participant's legal guardians and participants older than 8 years old, respectively. We excluded participants who had evidence of end-stage kidney disease (ESKD), prior receipt of CM within the previous 7 days, and insufficient data.

Ethical approval was obtained from the University of Zambia Biomedical and Research Ethics Committee (UNZABREC reference No. 990-2020). Permission to conduct the study at the University Teaching Hospital was sought from the Medical Superintendents of the University Teaching Hospitals – Children's Hospital, Cancer Diseases Hospital, and Pediatric Surgery. Further approvals were sought from the National Health Research Authority.

Study Procedures

Data were collected, using a semi-structured data collection tool and review of clinical and radiological information from patient files. The questionnaire was translated in Nyanja and Bemba, the most commonly spoken local languages in Lusaka. Potential participants were identified by attending physicians and nurses on the respective wards as patients booked to undergo contrast-enhanced imaging. The research team obtained written informed consent from the legal guardians of the patients before enrollment. Where applicable, assent was also obtained.

On day 1, baseline creatinine, full blood count, liver function tests, and urine for dipstick were collected by the attending physician before the patient underwent the radiological procedure. After the imaging procedure, blood samples for postcontrast creatinine were collected on day 2 for all participants and day 7 creatinine in participants who had developed CAAKI. Admission beyond day 7 was considered prolonged. Serum creatinine was analyzed using the

ILab Aries chemistry analyzer. The Schwartz formula was used to determine estimated glomerular filtration rate (eGFR). All CT scan and angiography procedures used either of the 2 contrast agents: iopromide or iohexol. Participants with raised creatinine that met AKI criteria were referred to the renal unit for management of the AKI.

Study Variables

The primary outcome was the occurrence of CAAKI, defined as an SCr increase of >25% from baseline or an absolute increase of 44 μmol/L assessed within 48 to 72 hours post CM administration as per the 2011 updated ESUR guidelines. This was compared to the latest KDIGO criteria to define CAAKI as an increase in SCr by 26.5 μmol/L within 48 hours or an increase in SCr to 1.5 times baseline after CM administration, which is known or presumed to have occurred within the prior 7 days. The secondary outcome variables were need for dialysis and duration of hospitalization obtained from patient records and death. Seven days were arbitrarily considered as prolonged hospitalization because based on our local hospital experience, the majority of patients are discharged before then.

The independent variables included the continuous variables such as age, amount of contrast used, baseline creatinine, hemoglobin, and blood pressure (BP) (normal BP in children is BP less than the 90th centile for age and sex, low BP is BP less than the 5th centile for age and sex, and high BP is BP above the 90th centile for age and sex). The categorical variables included were sex, birth history (whether born full-term or preterm and prematurity refers to the broad category of neonates born <37 weeks gestational age), pre-existing medical condition, hydration status, indication of radiological procedure, and HIV status being either HIV negative, positive, or exposed. An HIV exposed infant is one born to or breastfed by an HIV positive mother and whose true HIV status can only be determined by molecular testing using DNA PCR or serologically after 18 months when the maternal antibodies acquired trans-placentally have completely weaned off. Supplemental Table 1 summarizes both the dependant and independent variables.

Statistical Analysis

Stata version 16 (StataCorp, College Station, Texas) was used for analysis. Descriptive statistics were used to present the continuous variables; mean values and standard deviations were reported for normally distributed variables and medians and interquartile ranges for variables that were not normally distributed. Categorical variables were presented as frequencies and percentages.

To assess the association between radiological CM and CAAKI, potential confounders were carefully considered. Age, sex, baseline kidney function, hypertension, and the presence of pre-existing kidney disease were collected as important confounders in this analysis. Independent *t*-tests were used to determine differences in normally distributed continuous variables between patients with CAAKI and those without. For non-normally distributed continuous variables, Mann-Whitney tests were employed. The association between the outcome (CAAKI or no CAAKI) and categorical variables was evaluated using the chi-square test. In instances where any cell count was <5, Fisher's exact test was applied.

To account for potential confounding variables and detect the presence of effect modifiers in the relationship between radiological CM and CAAKI, the Mantel-Haenszel odds ratios were calculated. Finally, a multiple logistic regression model was employed to determine the association of CAAKI with baseline or clinical variables, while adjusting for the identified confounders. After fitting the model, we used the likelihood ratio test, using the "lrtest" command to assess the model fit, and the goodness of fit of the logistic regression model was evaluated using the Hosmer-Lemeshow test. Statistical significance was set at a $P < .05$, allowing for a comprehensive analysis that accounted for potential confounding factors in the relationship between radiological CM and CAAKI.

Results

Recruitment into the Study

In this study, 226 children were screened to participate in the study, but only 206 were recruited because 20 children were excluded as they did not meet the eligibility requirements. Of the 206 children enrolled into the study, only 201 (97.6%) had sufficient follow-up data and were thus included in the analysis. This information is illustrated in Figure 1.

Baseline Characteristics of the Study Participants

Table 1 shows the baseline demographic, clinical, and laboratory characteristics of the recruited participants. Of the children included in the study, 173 (86.1%) were referred from the Children's Hospital, whereas 25 (12.4%) were referred from the Cancer Diseases Hospital, and only 3 (1.5%) came from the Pediatric Surgery unit.

Most of the participants, 123 (61.2%), were male, giving a male-to-female ratio of 2:1. However, the proportion of CAAKI differed by sex ($P = .009$). The median age in years was 5 (3-10). The mean age in years was not significantly different between participants with contrast-associated AKI (7.1 years) and those without CAAKI (6.3 years) ($P = .366$).

Regarding laboratory characteristics, the mean hemoglobin for the participants was 103 g/l (SD = ±26), median albumin 36.1 g/L (IQR = 31.9-40.1), median alanine transferase (ALT) 18.5 U/L (IQR = 12.5-32.7), and aspartate transferase (AST) 40.8 U/L (29.3-65.5). Clinical assessment
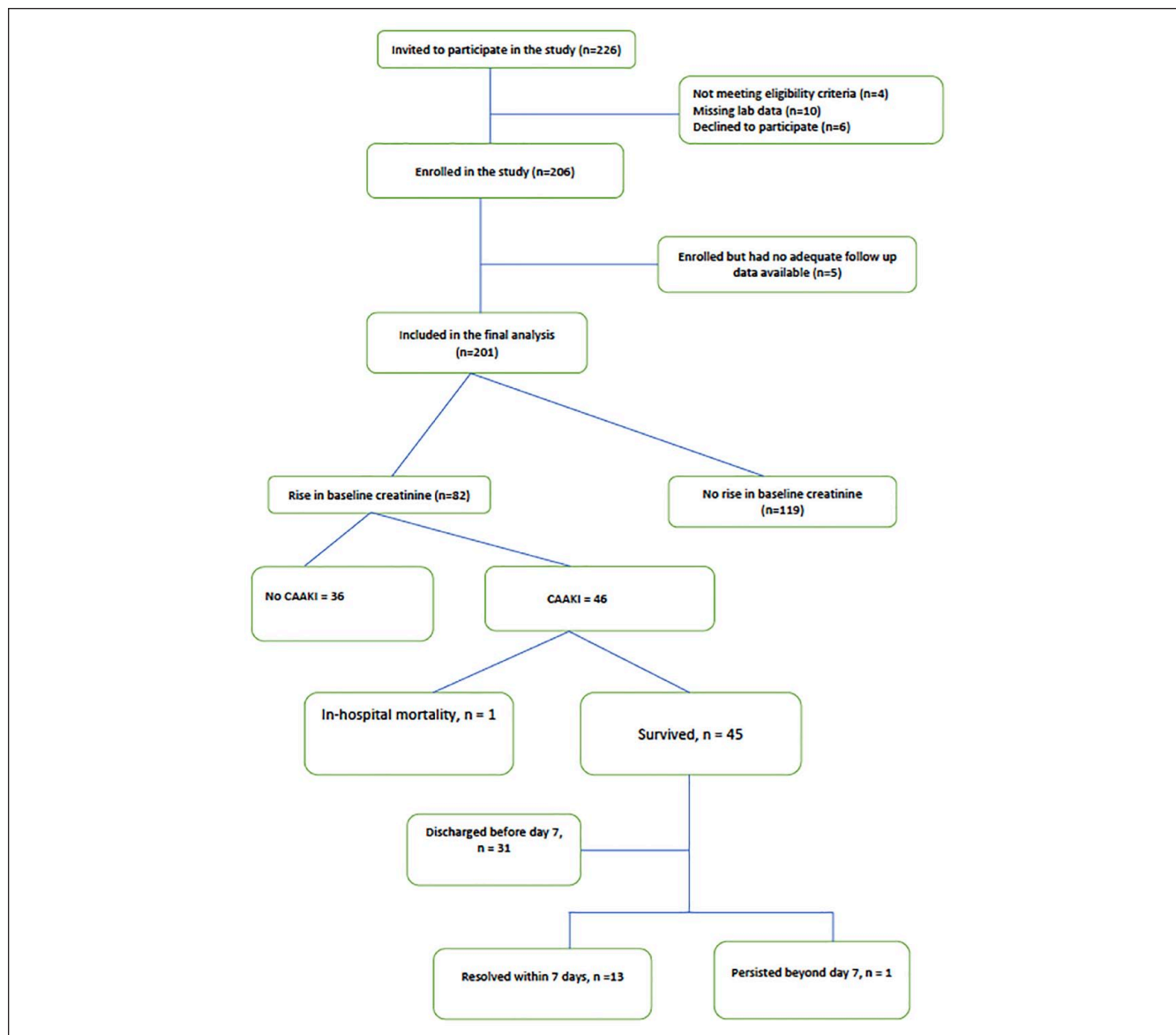
Figure 1. Study flowchart; contrast-associated acute kidney injury (CAAKI) using the European Society of Urogenital Radiology (ESUR) criteria.

of the participants showed 12 (5.9%) were HIV positive, and 10 (4.9%) were HIV exposed. Of the total participants, only 7 (3.5%) were born at a gestational age <37 weeks. There were no significant differences in the levels of hemoglobin, albumin, ALT, and AST between the children who developed CAAKI and those who did not. Furthermore, no significant association was noted between HIV infection and development of CAAKI.

Over half 109 (54.2%) received iopromide as CM for their radiological procedures as opposed to 92 (45.8%) who received iohexol. The median contrast amount used for the participants was 15 mL (10-30), and the median contrast dosage was 1.02 mL/kg (IQR = 0.9-1.2). The median dose of contrast (mL/kg) was higher in children who acquired CAAKI 1.3 (1.0-1.5) vs 1.1 (1.0-1.1) ($P = .013$) for those who did not develop CAAKI, and this difference was significant. Contrast-associated acute kidney injury was more common in children with lower baseline creatinine values than in children with higher baseline creatinine values; in those with CAAKI, the median creatinine was 27.3 µmol/L, whereas, in those without CAAKI, the median creatinine was 39.1 µmol/L ($P = .0017$). Concerning the glomerular filtration rate (GFR), a high GFR was observed in children with CAAKI 126.3 mL/min/1.73 m^2 (105.6-198.1) as opposed to 91.7 mL/min/1.73 m^2 (74.2-115.3) in children without CAAKI ($P < .001$).

Table 1. Baseline Characteristics of the Study Participants.

Characteristic	Category	Total (N = 201)	CAAKI (N = 46)	No CAAKI (N = 155)	P
Sex	n (%) Male	123 (61.2)	20 (44.4)	103 (66.1)	.009
	n (%) Female	78 (38.8)	25 (55.7)	53 (33.9)	
Age (y)	Median (Q1-Q3)	5 (3-10)	7.1 (4.8)	6.3 (4.5)	.366
Admitting hospital	Children's Hospital	173 (86.1)	40 (23.1)	133 (76.9)	.857
	Pediatric Surgery	3 (1.5)	1 (33.3)	2 (66.7)	
	Cancer Diseases Hospital	25 (12.4)	5 (20)	20 (8)	
Hemoglobin (g/L)	Mean (SD)	103 (26)	102 (26)	104 (22)	.683
Albumin (g/L)	Median (Q1-Q3)	36.1 (31.9-40.1)	35.9 (31.2-38.9)	36.5 (32.0-40.4)	.140
ALT (U/L)	Median (Q1-Q3)	18.5 (12.5-32.7)	16.7 (11.5-33.5)	19.6 (13.1-32.7)	.401
AST (U/L)	Median (Q1-Q3)	40.8 (29.3-65.5)	38.8 (26.1-38.5)	41.7 (30.3-65.5)	.091
White cell count	Mean (SD)	9.43 ($\pm$5.2)	11.0 (8.8)	10.9 (6.2)	.924
Contrast amount, median (mL) (IQR)	Median (Q1-Q3)	15 (10-30)	15 (10-25)	15 (10-30)	.462
Contrast dose (mL/kg)	Median (Q1-Q3)	1.02 (0.9-1.2)	1.3 (1.0-1.5)	1.1 (1.0-1.1)	.013
GFR (mL/min/1.73 m^2)	Median (Q1-Q3)	102.5 (76.2-129.4)	126.3 (105.6-198.1)	91.7 (74.2-115.3)	<.001
Creatinine (μmol/L)	Median (Q1-Q3)	30.9 (22.6-43.0)	27.3 (16.0-29.5)	39.1 (26.7-45.0)	.0017
Blood pressure	Low	11 (5.5)	0 (0.0)	11 (100)	.168
	Normal	171 (85.1)	42 (24.6)	129 (75.4)	
	High	19 (9.5)	4 (21.0)	15 (79.0)	
Contrast type used	Iopromide	109 (54.2)	26 (23.9)	83 (76.1)	.722
	Iohexol	92 (45.8)	20 (21.7)	72 (78.3)	
Nephrotoxic drugs	Yes	44 (21.9)	8 (18.2)	36 (81.8)	.401
	No	155 (78.1)	38 (24.2)	119 (75.8)	
HIV status	Positive	12 (5.9)	2 (4.4)	10 (6.4)	.541
	Negative	179 (89.2)	42 (93.3)	137 (87.8)	
	Exposed	10 (4.9)	1 (2.2)	9 (5.8)	
Gestation age (wk)	≥37	194 (96.5)	42 (93.3)	152 (97.4)	.142
	<37	7 (3.5)	3 (6.7)	4 (2.6)	

AKI = acute kidney injury; ALT = alanine transferase; AST = aspartate transferase; CAAKI = contrast-associated acute kidney injury; GFR = glomerular filtration rate; HIV= Human immunodeficiency virus; IQR = interquartile range; SD = standard deviation.

In this study, 171 (85.1%) participants had normal BPs. The CT procedures that were done ranged from CT brain to CT pelvis and CT angiogram. Although the indications for CT were varied, some indications were common and included seizures, meningoencephalitis, malignancies of various regions, and congenital malformations of the lungs and the heart. A summary of CT procedures and the indications for these procedures are shown in Supplemental Table 2. From the patients who had CAAKI, it was found that no specific disease condition or radiological procedure predisposed to development of CAAKI.

Burden of Contrast-Associated Acute Kidney Injury in Hospitalized Children

Of the total 201 participants, 46 (22.9%, 95% confidence interval [CI]: [17.1-29.1]) had CAAKI whereas 156 (77.6%, 95% CI = [70.9-82.9]) had no contrast-associated kidney injury by the ESUR criteria. By comparison, only 4.5%

(9/201) participants had CAAKI using the KDIGO criteria; participants who met the KDIGO criteria also met the ESUR criteria for CAAKI (Figure 2).

Predictors of CAAKI

After controlling for possible confounders, being female, prematurity, having a higher baseline eGFR and receiving a higher dose of contrast were found to be predictors of CAAKI (Table 2). The odds of CAAKI among the female sex were 2.48 times higher than their male counterparts (CI = [1.18-5.18]). Similarly, participants with a higher eGFR were more likely to develop CAAKI. For every 10 mL/min/1.73 m^2 increase in eGFR, the odds of developing CAAKI increased by 10.1 times (CI = [1.01-1.02]). Furthermore, for participants born at a gestation age <37 weeks, the odds of CAAKI were 4.6 times higher than those born at a gestation age equal to or more than 37 weeks (CI = [1.05-16.7]). Finally, 1 unit increase in the amount of contrast used (mL/kg) was
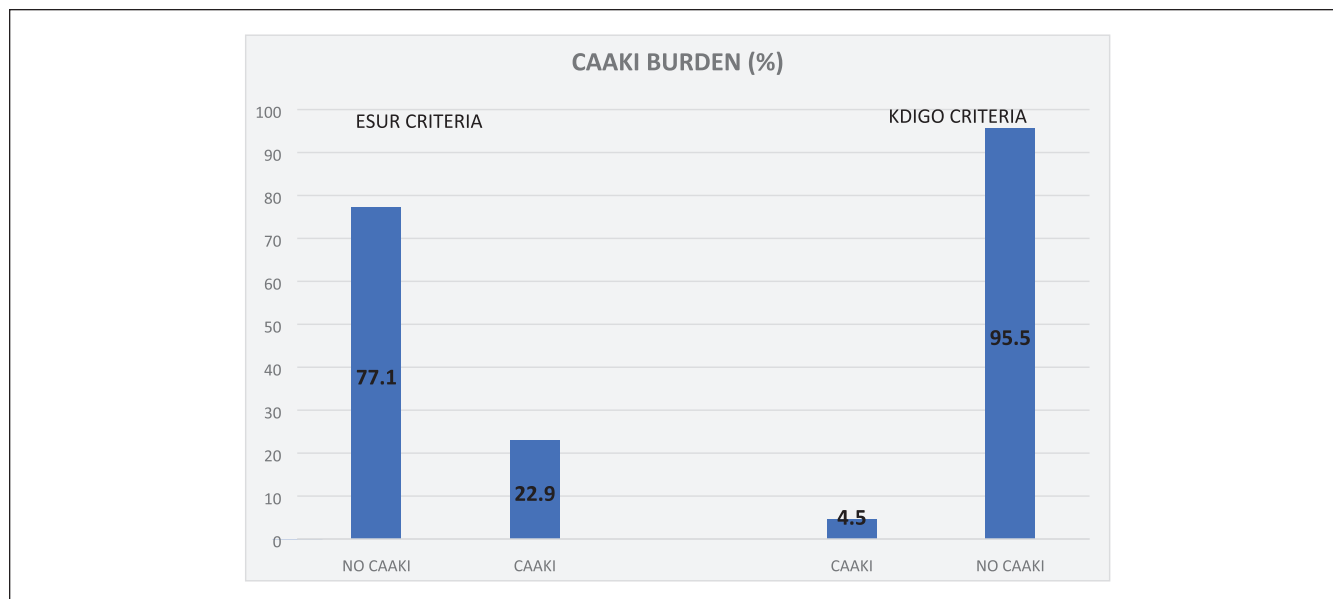
Figure 2. Burden of CAAKI in hospitalized children at the University Teaching Hospitals, Lusaka, Zambia.
CAAKI = contrast-associated acute kidney injury; ESUR = European Society of Urogenital Radiology; KDIGO = Kidney Disease Improving Global Outcomes.

Table 2. Multivariable Logistic Regression Model for the Predictors of Contrast-associated AKI in Children.

Characteristics	aOR	95% CI	P
Sex*			
Male	Ref	1.18-5.18	
Female	2.48		
Gestational age (wk)*			
≥37	Ref	1.05-16.7	
<37	4.6		
eGFR*	1.01	1.01-1.02	
Creatinine	0.99	0.97-1.03	.989
Albumin (U/L)	0.96	0.91-1.01	.150
AST (U/L)	1.01	0.99-1.07	.094
Contrast dose (mL/kg)*	2.54	1.12-5.74	

OR = adjusted odds ratio; AST = aspartate transferase; eGFR = estimated glomerular filtration rate; Ref = reference category; CI = confidence interval.
*$P < .05$.

Table 3. Clinical Outcomes of CAAKI (n = 46).

Variable	N	%
CAAKI (ESUR criteria)		
Yes	46	22.9
No	155	77.1
Hospital stay beyond day 7		
Yes	4	9.1
No	42	90.9
Requiring dialysis		
Yes	0	0
No	46	100
In-hospital mortality		
Yes	1	2.2
No	45	97.8
Discharged before day 7		
Yes	42	90.9
No	4	9.1

CAAKI = contrast-associated acute kidney injury; ESUR = European Society of Urogenital Radiology.

associated with 2.54 times higher odds of CAAKI (CI = 1.12-5.74).

Outcomes in Patients Who Developed CAAKI

Out of the 46 participants who developed CAAKI (ESUR criteria), only 1 participant died. The cause of death was multiple organ failure secondary to sepsis as confirmed by the attending physicians in the intensive care unit. None of the remaining participants who survived required dialysis, and only 4 (9.1%) required hospitalization beyond day 7

(Table 3). Hospitalization beyond day 7 was due to other diseases and not CAAKI. Regarding the GFR levels on day 7, all but 1 had their GFR levels return to baseline or close to baseline levels (Figure 3).

The chart in Figure 3 shows the evolution of eGFR levels at baseline, after contrast administration, and on day 7 for the 22 participants who had remained hospitalized up to day 7. The chart also includes those who did not develop CAAKI but had raised Scr post CM administration. Of note, from the
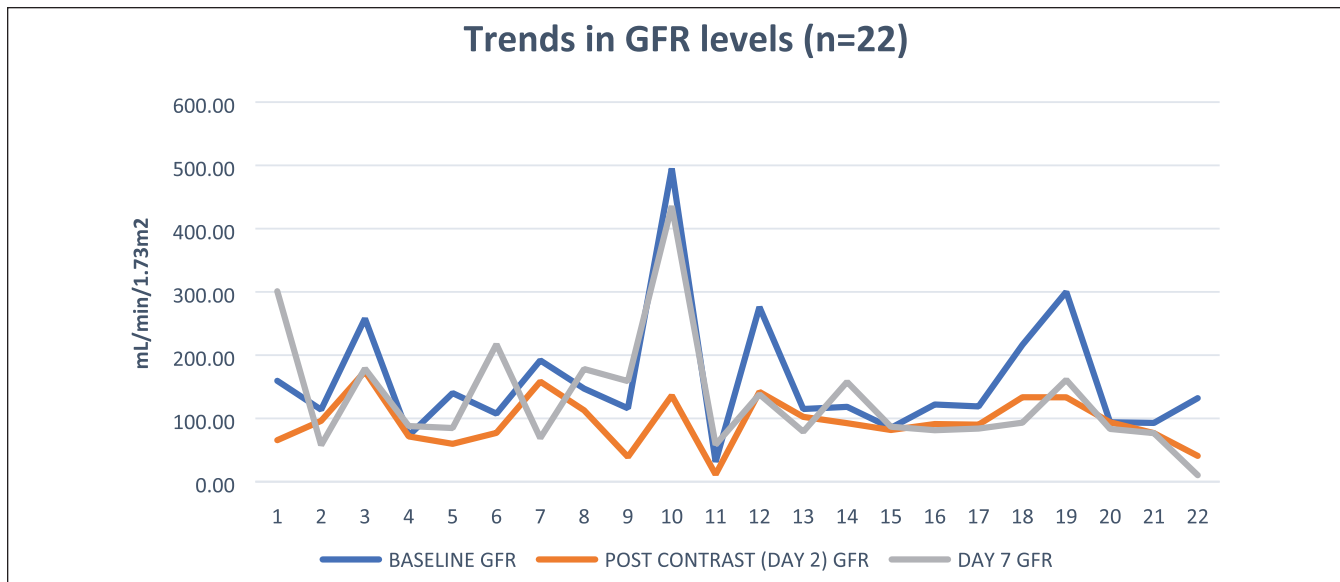
Figure 3. Changes in GFR levels for the selected 22 participants with day 7 creatinine results available.
Note. This chart also includes participants who did not develop CAAKI based on the ESUR and KDIGO criteria. CAAKI = contrast-associated acute kidney injury; ESUR = European Society of Urogenital Radiology; GFR = glomerular filtration rate; KDIGO = Kidney Disease Improving Global Outcomes.

graph, is that the decrease in GFR levels for the participants in whom the data were sufficient and available, the reduction in the eGFR returned to near baseline levels at day 7.

Discussion

This study was aimed at determining the burden of CAAKI in hospitalized children aged between 1 month and 18 years, from the UTH Children's Hospital, Cancer Diseases Hospital, and Pediatric Surgery departments who underwent various contrast-enhanced radiological imaging studies. We found that the incidence of CAAKI in hospitalized pediatric patients at the UTH was 22.9% (95% CI = [17.3%-29.3%]) based on the ESUR criteria and 4.5% (95% CI = [2.1%-8.3%]) based on the KDIGO criteria. A higher baseline eGFR was an independent predictor of CAAKI. Almost all the children who developed CAAKI and survived had their SCr levels return to baseline or near baseline levels at day 7, and only 1 participant died from non–kidney-related causes. Using the KDIGO definition, the rate of CAAKI was slightly lower than what has been previously reported in children[8] and adults.[4]

The use of both the KDIGO and ESUR criteria to define and quantify the burden of CAAKI in this cohort of children allows us to compare the 2 measures and other studies in children. The ESUR criterion is more sensitive than the KDIGO criteria, which explains why we observed a higher burden of CAAKI using this criterion compared to the KDIGO criteria. One finding of note is that all our participants who met the KDIGO criterion for CAAKI also met the classification of CAAKI using the ESUR criterion.

The incidence of CAAKI reported by various authors, whether in children or adults, varies greatly. This variation is because of the definitions and criteria of CAAKI used, underlying comorbid conditions, and differences in the population studied. In both adult and pediatric populations, CAAKI incidence has ranged from 3% to 30%.[14-17] Despite the differences in the rates of CAAKI and different methods of defining CAAKI, recent observational studies have reported a low incidence of CAAKI among hospitalized patients. Guo et al, using the KDIGO criteria, found an AKI incidence of 29.7% in pediatric patients who had preoperative exposure to CM before undergoing cardiac surgery with cardiopulmonary bypass, but following propensity score adjustment, no difference in risk for AKI was observed between the patients who were exposed to CM and those not exposed to CM.[18] Using the PRIFLE classification for the AKI that resulted from contrast administration, one study found an incidence of 18.75% in 80 children having cardiac angiography,[19] whereas another study showed a 15% incidence after intravenous urographic investigations.[20] McGaha et al, using the AKIN criteria, found an AKI incidence of 7.3% in severely injured pediatric patients who had undergone contrast-enhanced CT scans compared with 8.5% of severely injured pediatric patients who did not undergo contrast-enhanced CT scans; there was no significant difference between the 2 groups.[21] Two recent trials revealed incidences of pediatric CAAKI ranging from 4% to 10%, but a lack of control groups in these studies precluded the authors from ascertaining causality.[1,22]

Rather than using SCr, many new studies employ more sensitive novel biomarkers to diagnose and quantify the burden of CAAKI. These biomarkers include neutrophil

gelatinase–associated lipocalin (NGAL), Kidney Injury Molecule (KIM)-1, and cystatin-C. Biomarkers detect significant kidney injury promptly, unlike creatinine, which is a marker of kidney function rather than damage and may not rise even if the GFR decreases by about 50%.[23,24] Furthermore, the serum concentration of creatinine is influenced by non-kidney variables such as age, race, sex, muscle mass, hydration status, and protein consumption. As a result, determining what change in creatinine defines substantial AKI has been problematic. To this effect, Tkaczyk et al[24] and Agwaral et al[25] used NGAL to predict CAAKI. They, however, had conflicting findings; Tkaczyk et al noted a significant change in serum NGAL occurred at 6 hours post contrast administration, whereas Agarwal et al found that 6 hours post contrast plasma, NGAL did not predict the CAAKI. Nonetheless, when both sets of authors computed CAAKI incidence using the PRIFLE criteria, they found incidences between 10% and 35% between 24 and 48 hours post contrast administration. In this study, the incidence of CAAKI by the ESUR criteria (22.9%) is comparable to that of Agarwal et al and Tkaczyk et al, despite different criteria to define CAAKI.

The independent predictors of CAAKI in this study were a higher baseline eGFR, prematurity, female sex, and a higher CM dose. However, as only 3.5% (7) participants were born at a gestational age of <37 weeks, a larger data set would be required to make a conclusive comment on the effect of prematurity. Our findings contrast with those of Cantais et al[8] who found no independent risk factor for CAAKI and Agarwal et al[25] who found that a younger age at the time of contrast administration was a risk factor for CAAKI. The variations in risk factors noted by different authors depend on the criteria used to define CAAKI and the composition of the study population.

Interestingly, in this study, CAAKI patients had significantly higher precontrast eGFR and lower levels of precontrast creatinine compared with those who did not develop CAAKI. There was a positive trend associated with eGFR levels and the development of CAAKI. These findings are consistent with those of Buyan et al,[20] who observed that CAAKI incidence was higher in children with higher baseline eGFRs and lower creatinine levels. Cantais et al[8] attributed this finding to an amplified renal clearance, also described in trauma and septicemic patients, as possibly accounting for the finding, especially in seriously sick children.[26,27] This may hold in our study as infectious causes served as some of the most common indications for contrast-enhanced CT procedures.

In this study, children who were born as preterm babies were 4.6 times more likely to develop CAAKI when compared with those who were born at term; although due to the small numbers of preterm infants in our cohort, this would have to be verified in a larger study. Prematurity is a well-established risk factor for AKI, regardless of the source of the insult to the kidneys.[28-30] Our finding is in agreement with recent evidence that shows that prematurity harms future kidney health, and babies born prematurely have an increased risk of CKD.[31] The postulated causes for this increase in risk include incomplete nephrogenesis and reduced nephron bulk, which renders the kidneys susceptible to tubular damage when exposed to nephrotoxic substances postnatally.[1]

The significant negative correlation between gestational age and AKI development observed in this study is consistent with Shalaby et al[32] and Carmody et al,[33] who reported higher AKI burden in low birth weight neonates and infants, respectively. According to the AWAKEN cohort study, babies born at a later gestational age are similarly at risk of AKI. They discovered a U-shaped distribution of AKI incidence by gestational age category, with the highest rates in the youngest and oldest neonates.[34] This intriguing finding, showing a greater frequency of AKI among older infants with no complications, has not been reported by other studies and warrants further research.

We found that a higher dose of CM was significantly associated with the development of AKI. This is in tandem with earlier studies that reported a higher incidence of nephropathy associated with an increased contrast per kilogram body weight. Three previous studies have identified contrast volume as a predictor of nephropathy. Freeman et al,[35] Verghese,[36] and McCullough et al[37] reported increased incidences of nephropathy following in patients who received higher doses of radiographic CM, quantifying the amount of CM received per kg allowed us to adjust for weight objectively and ensured that the subjective volumes received did not influence the outcome findings.

Female sex was also a significant predictor of CAAKI in our study. Previous research in the adult population has revealed that the risk of AKI is higher in women undergoing percutaneous intervention procedures.[38,39] The link between female sex and CAAKI in children is yet to be documented. A lower glomerular capacity in women relative to men has been hypothesized as a possible explanation for their increased susceptibility to acute kidney failure. However, based on our literature search, this has not been demonstrated in children.[40]

We found a high discharge rate and resolution of CAAKI in our cohort. Only 1 participant died due to sepsis and multiorgan failure. For the rest of the patients who developed CAAKI and survived, no one required renal replacement therapy, and the majority were discharged by day 7. For those still hospitalized by day 7, we observed that the GFR had risen to or near baseline levels by day 7. Despite having a limitation of only following up our patients up to day 7, our findings are concordant with previous research that has confirmed that CAAKI may be transient and dialysis is required in <1% of the children who develop contrast-associated nephropathy.[41,42]

The favorable outcomes observed in this study could be because nearly all the children included in the study had an excellent kidney function before receiving CM. This

is similar to the report by Gilligan et al,[43] who found that hospitalized children with stable kidney function who underwent CT with intravenous iodinated contrast material had the same frequency of AKI following imaging as those who were not exposed to iodinated contrast material. Intravenous contrast material was not independently linked with AKI in children with an eGFR greater than 60 mL/min/1.73 m^2.

Due to the many definitions and variables used for CAAKI in the literature and in this study and the fact that we defined our results using the ESUR criterion, comparisons between our results and those of others may not be warranted and should be regarded as speculative. There is an urgent need for future research to modify diagnostic criteria and develop a uniform definition for CAAKI that can be used in different study populations.

The urine output was not available for most patients as the cohort included many non–pediatric intensive care unit (PICU) patients. Therefore, we did not use the urine output criteria to diagnose AKI. This may have led to an under-estimation of the AKI incidence.

We did not follow up on those who received CM and did not develop CAAKI in this study to serve as a control group. This limited our ascertainment of outcomes in CAAKI patients in this study. Furthermore, we had a short follow-up 7-day period in this study. Our ability to determine outcomes was limited by the brief follow-up period.

Our study consisted of a heterogeneous group of children whose ages ranged from 1 month to 18 years. The heterogeneity of the participants in the study meant that they might have had differing factors that were not uniformly distributed and were not adjusted for in the analysis.

The strength of this study is its prospective nature and reasonably large sample size. In addition, to ensure sufficient assessment and comparability of our data, we employed both the ESUR and the KDIGO definitions of CAAKI, which are relatively recent and are valid for use in pediatric settings.[8,34,45] The 2 criteria are equally helpful for measuring the kidney effects of CM administration. However, the ESUR criteria is highly sensitive, as evidenced by the high burden of CAAKI when compared with the KDIGO criteria in this study.

Future studies in Zambia on CAAKI which have a larger sample size, and more a robust design are needed to better ascertain outcomes of CAAKI. In addition, the diagnosis of CAAKI could be improved using biomarkers such as NGAL, KIM-1, and cystatin-C given that creatinine takes 24 to 48 hours to rise after a kidney insult has occurred.

Conclusions

This study demonstrated that the burden of CAAKI at the UTH is 22.9% and 4.5% by the ESUR and KDIGO criteria, respectively. Female children, a higher dose of CM received, having a higher GFR, and being born as a preterm baby were significant risk factors for developing CAAKI.

The occurrence of CAAKI was transient in our cohort of patients as almost all had reverted to baseline kidney function by day 7.

Ethics Approval and Consent to Participate

The study was carried out under the approval of the University of Zambia Biomedical and Research Ethics Committee (UNZABREC reference No. 990-2020), in accordance with the declaration of Helsinki. Informed written consent of the participants was obtained before participation.

Consent for Publication

Consent for publication was obtained from all authors.

Availability of Data and Materials

Not available.

Declaration of Conflicting Interests

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ORCID iD

Hellen M'hango   https://orcid.org/0000-0002-4917-9481

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