Research Article

Acute Childhood Cardiorenal Syndrome and Impact of Cardiovascular Morbidity on Survival

Wasiu A. Olowu

Paediatric Nephrology and Hypertension Unit, Obafemi Awolowo University Teaching Hospitals Complex, PMB 5538, Ile-Ife, Osun State 234, Nigeria

Correspondence should be addressed to Wasiu A. Olowu, yetundeolowu@yahoo.com

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Cardiorenal syndrome (CRS) clinical types, prevalence, aetiology, and acute cardiovascular morbidity impact on the outcome of acute kidney function perturbation were determined. Forty-seven of 101 (46.53%) patients with perturbed kidney function had CRS. Types 3 and 5 CRS were found in 10 and 37 patients, respectively. Type 3 CRS was due to acute glomerulonephritis (AGN; $n = 7$), captopril ($n = 1$), frusemide ($n = 1$), and hypovolaemia ($n = 1$). Malaria-associated haemoglobinuria ($n = 20$), septicaemia ($n = 11$), lupus nephritis ($n = 3$), tumour lysis syndrome ($n = 2$), and acute lymphoblastic leukaemia ($n = 1$) caused Type 5 CRS. The cumulative mortality in hypertensive CRS was similar to nonhypertensive CRS (51.4% versus 40.9%; $P = .119$). Mortality in CRS and non-CRS was similar (45.7% versus 24.5%; $P = .053$). Type 5 survived better than type 3 CRS (66.7% versus 12.5%; $P = .001$). Risk factors for mortality were Type 3 CRS ($P = .001$), AGN-associated CRS ($P = .023$), dialysis requiring CRS ($P = .008$), and heart failure due to causes other than anaemia ($P = .003$). All-cause-mortality was 34.2%. Preventive measures aimed at the preventable CRS aetiologies might be critical to reducing its prevalence.

1. Introduction

The cardiorenal syndrome (CRS) is a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other [1, 2]; it is a recognized morbidity and mortality multiplier in critically ill children [3]. While heart failure (HF) is a clinical syndrome in which heart disease reduces cardiac output, increases venous pressures, and is accompanied by molecular abnormalities that cause progressive deterioration of the failing heart and premature myocardial cell death [4], acute kidney injury (AKI) is an abrupt clinical and/or laboratory manifestation of kidney dysfunction usually within 48 hours of bilateral kidney insult of any kind. Failure of both organs commonly coexists in critically ill children [5–7]. Congestive HF is a highly prevalent AKI comorbidity and a major indication for acute dialysis in children [5]. Recently, the 7th Acute Dialysis Quality Initiative (ADQI) workgroup classified CRS into five distinct clinical types, [1, 2] namely: acute CRS (Type 1)—acute worsening of heart function leading to kidney injury and/or dysfunction; chronic CRS

(Type 2)—chronic abnormalities in heart function leading to kidney injury and/or dysfunction; acute renocardiac syndrome (Type 3)—acute worsening of kidney function (AKI) leading to heart injury and/or dysfunction; chronic renocardiac syndrome (Type 4)—chronic kidney disease leading to heart injury, disease, and/or dysfunction, and secondary CRS (Type 5)—systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney. While a lot of data have been published on chronic kidney disease as risk factor for cardiovascular morbidity and mortality in both children and adults (reviewed in [1–3]), there is paucity of specific data on acute cardiac dysfunction leading to AKI and vice versa in children especially [8]; in this study, an attempt was made to determine the prevalence, aetiology, clinical types of CRS, and impact of acute cardiovascular morbidity on the outcome of childhood acute kidney injury.

2. Patients and Methods

Clinical charts of patients managed for AKI-associated HF and acute glomerulonephritis (AGN)—associated HF in our

paediatric nephrology and hypertension unit were reviewed. It was a retrospective case-control study; patients who had either AKI or AGN without HF served as control (non-CRS). The objectives were to determine the prevalence, aetiology, clinical types of CRS, and impact of acute cardiovascular morbidity on the outcome of childhood AKI. The study period ranged between January 2005 and December 2009. Our hospital's Ethics and Research Committee approved the research protocol. The study conformed to the provisions of the revised Declaration of Helsinki, Edinburgh, 2000.

Analyzed data were age, gender, anthropometry, vital signs, admission diagnosis, time of onset of HF and AKI, final AKI stage, hospitalization period, follow-up duration, urine output, and management outcome. Relevant laboratory investigations including serum creatinine (Scr) both at baseline and at followup were reviewed.

2.1. Definitions. AKI was diagnosed based on the acute kidney injury network (AKIN) criteria [9] as an absolute increase in serum creatinine (Scr) level within 48 hours of bilateral kidney insult by ≥ 0.3 mg/dL (≥ 26.4 μ mol/L) or a 50% (1.5-fold) increase or more in Scr from the baseline. AKI was staged using the creatinine criteria of the AKIN workgroup [9]—Stage 1 AKI (AKI-1): rise in Scr by ≥ 0.3 mg/dL (26.4 μ mol/L) or an increase of >150 –200% (1.5- to 2-fold increase) from the baseline; Stage 2 AKI (AKI-2): rise in Scr by >200 –300% (>2 - to 3-fold increase) from baseline; Stage 3 AKI (AKI-3): rise in Scr by $>300\%$ (>3 -fold) from the baseline or Scr ≥ 4.0 mg/dL (≥ 354 μ mol/L) with an acute rise of at least 0.5 mg/dL (44 μ mol/L). Nonoliguric AKI was defined as urine output that was persistently >0.5 mL/kg/hour in the setting of an abnormal Scr level. Anuric AKI was defined as the urine output that was <0.039 mL/kg/hr for 12 hr or more in the absence of an obstructive uropathy. AKI was staged based on the peak Scr (pScr) level. pScr was the highest Scr level reached in any patient either before death or before gradual return to normal. Those who were initially diagnosed AKI-1 or AKI-2 but later required dialyses were upgraded to AKI-3 as recommended [9]. The predictive eGFR equation with corrections for age, gender, and race derived by the Modification of Diet in Renal Disease (MDRD) [10] study group was used to determine the baseline Scr for patients who do not have baseline Scr as recommended by the 2nd ADQI workgroup [11]. For such patients, the 2nd ADQI recommended that normal estimated glomerular filtration rate (eGFR) ranging from 75 to 100 mL/min per 1.73 m² should be used. In this study, all AKI patients without baseline measure of renal function were assumed to have eGFR value of 100 mL/min/1.73 m². By the MDRD equation, $eGFR = 186 \times ([Scr]^{-1.154} \times Age^{-0.203} \times 0.742 \text{ (if female)} \times 1.210 \text{ (if black)})$ [10].

Heart failure was diagnosed based on a combination of dyspnoea, tachycardia (heart rate >160 , >150 , >140 , >120 , and >100 beats/min for infants, children aged 1–3, 4–5, 6–12, and above 12 years, resp.), tachypnoea (respiratory rate >60 , >40 , >34 , >30 , and >20 breathes/min for infants, children aged 1–3, 4–5, 6–12, and above 12 years, resp.), tender hepatomegaly, and feeding difficulty with or without chest

X-ray evidence of cardiomegaly (abnormal cardiothoracic ratio $>60\%$ in under fives and $>55\%$ in older children). HF severity was assessed and classified according to the modified Ross heart failure classification for children [12]—Class I heart failure: asymptomatic; Class II heart failure: mild tachypnoea or diaphoresis with feeding in infants or dyspnoea on exertion in older children; Class III heart failure: marked tachypnoea or diaphoresis with feeding in infants, marked dyspnoea on exertion, and prolonged feeding times with growth failure; Class IV heart failure: symptoms such as tachypnoea, retractions, grunting, or diaphoresis at rest. Hypertension was diagnosed based on the update of the 1987 Task Force Report on High Blood Pressure in Children and Adolescents [13]. CRS was classified based on the 7th ADQI consensus conference report [2].

The inclusion criteria were patients with acute perturbation of kidney function (AKI or AGN or both) with or without HF. Patients with chronic renal failure or acute-on-chronic renal failure were excluded. To determine the impact of HF on survival, mortality was compared between CRS (AKI + HF and AGN + HF) and non-CRS patients. The cumulative all-cause-mortality and CRS-specific mortality rates were determined.

2.2. Statistical Analysis. Descriptive statistics used comprised mean, standard deviation, median, percentages, and proportions. The comparative statistics were Student's *t*-test, Chi-square test, Cox regression analysis for hazard ratio (HR), Wilcoxon statistics, Kaplan-Meier survival analysis, and Mantel-Cox pairwise comparisons (Log-rank test) using the SPSS 15.0 for Windows evaluation version (2006, SPSS Inc.). A *P*-value <0.05 was regarded as statistically significant.

3. Results

A total of 101 patients with acute perturbation of kidney function, namely, AKI and AGN were reviewed. There were 7 and 94 acute glomerulonephritis (AGN) and AKI patients, respectively. Forty seven of 101 (46.53%) patients with abnormal kidney function had HF-cardiorenal syndrome. HF was of the severest class (Class IV) in all the CRS patients. Age, gender, and blood pressure data are summarized in Table 1. Median age of 5.0 years (0.06–15.0) for controls was similar to that for CRS, *P* = .689. Types 3 and 5 CRS were found in 10 (21.3%) and 37 (78.7%) patients, respectively. Table 2 shows the relationship between the two CRS types in this study and their aetiologies. Two of 7 patients whose CRS was due to AGN had no associated AKI (AGN–AKI) while the remaining 5 had associated AKI. The pScr was 6.11 ± 4.0 (0.95–17.32) mg/dL. AKI-1, AKI-2, and AKI-3 accounted for 4 (8.50%), 5 (10.60%), and 36 (76.60%) CRS cases, respectively, while AGN-AKI accounted for the rest. Twenty-two (46.80%) of the CRS patients had oliguric AKI while nonoliguric and anuric AKI were seen in 11 (23.40%) and 14 (29.80%) patients, respectively. Oliguria duration in both CRS and controls was 6.9 ± 5.54 days and 7.5 ± 4.75 days, respectively (*P* = .654).

Anaemia was present in 43 of 47 CRS patients (91.5%). The haematocrit ranged from 4.0 to 32.0% with the 5th,

TABLE 1: Demographic and clinical characteristics of the cardiorenal syndrome patients ($n = 47$).

Demographic and baseline clinical characteristics	Results (%)
Age < 6 years	33 (70.21)
Age $\geq$ 6 years	14 (29.79)
Median age (range), years	4.0 (.3–14.5)
Gender	
Male	26 (55.32)
Female	21 (44.68)
Male to female ratio	1.24 : 1
Number with normal blood pressure (BP) ^a	26 (57.8)
Systolic BP range, mmHg	60–110
5th, 50th, and 95th percentiles in mmHg	63.5, 90, and 110
Diastolic BP range, mmHg	30–70
5th, 50th, and 95th percentiles in mmHg	33.5, 50, and 70
Mean arterial pressure range, mmHg	43.3–83.3
5th, 50th, and 95th percentiles in mmHg	44.49, 66.7, and 82.85
Number with hypertension	19 (42.2)
Systolic BP range, mmHg	90–190
5th, 50th, and 95th percentiles in mmHg	90, 120, and 190
Diastolic BP range, mmHg	60–130
5th, 50th, and 95th percentiles in mmHg	60, 80, and 130
Mean arterial pressure range, mmHg	73.3–150
5th, 50th, and 95th percentiles in mmHg	73.3, 93.3, and 150

^aBlood pressure data available in 45 of 47 patients.

TABLE 2: Relation between cardiorenal syndrome types and their aetiologies.

Cardiorenal syndrome type and aetiology	Proportion of patients (%)
Type 3	7.0 (70.0)
Acute glomerulonephritis	
Captopril	1.0 (10.0)
Frusemide	1.0 (10.0)
Hypovolaemic shock due to gastroenteritis	1.0 (10.0)
Type 5	20.0 (54.05)
Malaria-associated haemoglobinuria	
Septicaemia	11.0 (29.73)
Lupus nephritis	3.0 (8.11)
Tumour lysis syndrome in Burkitt's lymphoma patients	2.0 (5.41)
Acute lymphoblastic leukaemia	1.0 (2.70)

50th, and the 95th haematocrit percentiles for the anemic CRS being 5.2%, 15.0%, and 27.6%, respectively. Severe, moderate, and mild anaemia occurred in 38 (88.37%), 2 (4.65%), and 3 (6.98%) patients, respectively, ($P = .000$). Malaria-associated haemoglobinuria (MAH), septicaemia, AGN, lupus nephritis and tumour lysis syndrome accounted

FIGURE 1: Kaplan-Meier survival curves showing that survival was not significantly higher in controls than in cardiorenal syndrome (75.5% versus 54.3%). Similarly, the survival times were not significantly different.

for 20 (46.51%), 10 (23.25%), 4 (9.30%), 3 (6.97%), and 2 (4.65%) anaemia cases, respectively. Hypovolaemia due to gastroenteritis, acute lymphoblastic leukaemia, captopril, and frusemide accounted for one (2.33%) case each, ($P = .000$). Anaemia was absent in 1 septicaemia and 3 AGN cases.

3.1. Followup and Outcome. The mean CRS hospitalization period was 21.90 ± 16.42 days (controls: 25.1 ± 19.7 ; $P = .361$). Both the CRS and non-CRS patients were, respectively, followed for 67.2 ± 90.97 (1.0 – 398.0) days and 128.96 ± 240.61 (1.0–1319.0; $P = .106$) days. Survival in CRS patients who were <6 years old was similar to older patients (14 versus 10 survivors; HR:.483, 95% CI: .157–1.488; $P = .205$). Cumulative mortality was higher in hypertensive (51.4%) than nonhypertensive (40.9%) CRS, but the difference did not reach statistical significance (HR:.476, 95% CI: .183–1.240; $P = .129$). Survival comparison between non-CRS (controls) and CRS patients revealed no statistically significant difference (HR:.496, 95% CI: .239–1.031; Figure 1). Figure 2 shows that patients with Type 5 CRS survived better than Type 3 CRS (HR:.479, 95% CI: .299–.768). The cumulative survival for MAH, septicaemia, and acute glomerulonephritis was 81.4%, 39.8%, and 21.4%, respectively; none of the patients with AKI due to hypovolaemia, frusemide, captopril, and leukaemia survived. CRS due to aetiologies other than AGN was significantly less associated with mortality compared with CRS due to AGN (40.4% versus 78.6%; HR: .544; 95% CI: .322–.919; $P = .023$). A pairwise comparison statistics (Wilcoxon) revealed that MAH survived significantly better than other CRS causes ($P = .014$). No death occurred in AKI-1, but there were 2 and 15 deaths in AKI-2 and AKI-3, respectively; AGN-AKI had one death. Mortality was similar in all AKI stages (HR: 1.872, 95% CI: .761–4.603) as well as in all the three AKI types (HR: 1.385, 95% CI: .799–2.400) of CRS. Survival comparisons among the AKI types in both CRS and non-CRS revealed no significant differences

FIGURE 2: Kaplan-Meier survival curves showing significantly better survival in Type 5 compared to Type 3 cardiorenal syndrome (72.3% versus 12.5%).

FIGURE 4: Kaplan-Meier survival curves comparing survival in cardiorenal syndrome patients with anaemia and those without anaemia. Patients with anaemia had significantly higher survival rate compared to nonanaemic patients (61.4% versus 25.0%).

FIGURE 3: Comparisons between controls and patients with cardiorenal syndrome with regard to survival in the acute kidney injury (AKI) types. The number of patients surviving in oliguric, nonoliguric, and anuric AKI was similar in both groups of patients.

FIGURE 5: Kaplan-Meier survival curves for dialysis-requiring and non-dialysis requiring cardiorenal syndrome patients. Dialysis-requiring-cardiorenal syndrome had significantly lower survival rate compared to those who required no dialysis (35.5% versus 70.6%).

(Figure 3). Figure 4 shows that mortality in nonanaemic CRS patients was significantly higher compared to anaemic CRS (HR: 4.637, 95% CI: 1.496–14.370). The outcome was significantly better among CRS patients who required no dialysis than those who required dialysis (HR: .284, 95% CI: .106–.765; Figure 5). A stratification to CRS type showed that dialysis-requiring Type 3 CRS had significantly higher cumulative mortality rate than dialysis-requiring Type 5 CRS (100% versus 51.1%; Log rank $P = .049$). This was similarly so for those not requiring dialysis (Type 3 CRS: 70.0%

versus Type 5 CRS: 19.1% mortality; Log rank $P = .039$). Further stratification for aetiology showed poorer survival with regards to Type 3 CRS compared to Type 5 as all Type 3 patients who required dialysis died ($n = 5$); all had AGN that was associated with poorer outcome compared to either MAH or septicaemia (Wilcoxon, $P = .001$). Eighteen CRS patients died at the end of 398 follow-up days, while 28 survived, and one took voluntary discharge. The cumulative CRS-specific mortality was 45.7%. Thirty

patients died overall (both CRS and controls) thus bringing the cumulative all-cause-mortality to 34.2%.

4. Discussion

This study revealed CRS as a highly prevalent clinical event in acute perturbation of kidney function with hypertension as a common cardiovascular comorbidity. Given the spectrum of CRS aetiology in this study, hypertension was probably the result of intravascular congestion brought about by oliguria seen in 76.6% of the patients on one hand, and activation of the renin-angiotensin-aldosterone-system following renal hypoperfusion secondary to acute proliferative changes of AGN on the other hand. Interestingly, hypertension was found not to be a significant risk factor for mortality in this study (HR: 0.476, 95% CI: 0.183–1.240).

The acute nature of the CRS and the accompanying hypertension, as well as, prompt response to anti-hypertensive treatment, and vascular decongestion following diuretic phase onset could be responsible for this. Left ventricular hypertrophy and congestive HF are common in childhood AGN and CKD with high mortality rate [7, 14–16]. In this study, HF was highly prevalent and mortality rate from CRS was equally high but was not significantly different from controls; this is not withstanding the fact that the HF was of the severest class (Class IV). Anaemia is a highly prevalent comorbidity in both AKI [5, 6, 17] and CKD [18]; it has been associated with increased severity of congestive HF, increased hospitalization, worse cardiac function and functional class, the need for higher doses of diuretics, progressive worsening of renal function, and reduced quality of life [19]. Anaemia occurred in 91.5% of our patients with anaemia-specific mortality rate of 38.6%. Nonanaemic CRS patients were, however, 4.6 times more likely to die than their anaemic counterparts (95% CI: 1.496–14.370). This is because the majority of the anaemic cases were due to malaria that responded rapidly to treatment; the acute nature of the accompanying congestive anaemic HF that responded promptly to blood transfusion also contributed to better survival in the anaemic CRS compared to nonanaemic CRS that was largely due to poor outcome septicaemia and AGN. While AKI stage and type did not influence the outcome in this study, Type 5 CRS was found to protect against mortality. The positive impact of Type 5 CRS on survival was due to the fact that the majority of the patients in this class had MAH that was significantly associated with the highest survival rate compared to Type 3 CRS in which majority of the patients had AGN that was significantly associated with very low survival rate. The fact that CRS patients who required no dialysis survived better than those who required dialysis (HR: 0.28; 95% CI: 0.106–0.765) could mean more severe structural kidney pathology and dysfunction in those needing dialysis. This was particularly more evident when CRS was stratified for CRS types and outcome.

It is concluded that CRS was a very common clinical event with high mortality rate in critically ill children. Compared to controls, CRS mortality rate was not significantly higher; risk factors for mortality in CRS were CRS Type 3, AGN-associated CRS, dialysis-requiring CRS, and heart

failure not associated with anaemia. Preventive measures aimed at some of the preventable aetiologies of CRS might be critical to reducing its prevalence.

Conflict of Interests

The authors declare that there is no conflict of interests.

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