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Research Article

Integration of Nurturing Care Framework for Early Childhood Development in the Care of HIV-Exposed Infants in Yaounde

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Abstract

Background: Malaria is the leading cause of hospital admission in Africa and constitutes the greatest disease burden in the region. More than one hundred nations are affected worldwide with children and pregnant women being mostly vulnerable. Children under the age of five years suffer severest forms. Malaria is said to be severe when the acute illness is associated with life threatening event (s). Several organ systems including the kidney can be involved. In most cases, severe malarial if untreated tends to result in Acute kidney injury. Therefore, the objective of this study is to examine kidney function in children with severe malaria seen at the University of Ilorin Teaching Hospital (UITH), Ilorin. A prospective case-control study was conducted in Emergency Paediatrics Unit (EPU), the Children's ward and the General Out Patient Department (GOPD) of the UITH over a period of one year. A total of 164 children were recruited into the study out of which 82 had severe malaria served as subject and another 82 uncomplicated malaria, serving as controls. The male: female ratio was 1:1 in the subjects and 1.4:1 in the controls. The median age was 36.0 months in the subjects and 36.0 months in the controls, both groups were comparable ($p>0.05$). Children between ages 1 to 5 years constituted 62.2% of the entire population studied. The estimated Glomerular Filtration Rate (eGFR) in children with severe malaria was compromised in 30% of cases. Improved Global Outcomes (KDIGO) and World Health Organization (WHO) criteria; an increase in serum creatinine value of 0.3mg/dl(5.4mmol/l) within 48 hours of admission was applied. Correspondingly the serum urea and creatinine were compromised in same group of patients. The prevalence of acute AKI in this study was 30.5%. The mean eGFR, potassium, sodium, urea and creatinine at admission were 74.6±56.3 ml/min/1.73 m^2, 5.4±0.5 mmol/l, 143.9±12.3 mmol/l, 117.2± 27.5 µmol/l and 6.3±5.6 mmol/l respectively. Outside sodium, these parameters were higher in subjects than controls.

Keywords: Kidney function; Acute kidney injury; Severe malaria; Creatinine; Estimated Glomerular Filtration Rate; Nigeria

Introduction

The World Health Organization (WHO) World Malaria report 2019 estimates 228 million cases of malaria worldwide, causing 405,000 deaths in the year 2018, many under the age of 5 years [1]. In 2018, nineteen sub-Saharan African countries and India carried approximately 85% of the global malaria burden [1,2]. Malaria is said to be severe when the acute illness is associated with life threatening event(s) [2-5]. Several organ systems including the kidney can be involved [8-14]. The main manifestations of severe malaria among semi-immune, residents of malaria-endemic countries are cerebral malaria and severe anaemia. Acute kidney injury is not uncommon [3,15-25]. In some cases of kidney involvement malaria, damage to the kidneys might persist beyond the acute illness, as has been described in *P. malariae* infection and this could progress to nephrotic syndrome [3,4].

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More children particularly under-fives are now observed to present with renal impairment as a component of severe malaria despite improvements in case management and malaria control programmes, in Nigeria, [1,19,26-28] Survivors are commonly left with long term morbidities [5]. Determination of the presence of acute kidney injury in severe malaria is essential for appropriate clinical management of patients with malaria as it may determine the subsequent use of drugs and fluid. The Estimated Glomerular Filtration Rate (eGFR), which is the volume of plasma that can be completely cleared of a particular substance by the kidneys in a unit of time remains the best indicator of kidney function [29-39].

Malaria constitutes about 25% of the disease burden in children in Nigeria with its attendant effects on virtually all organs of the body [19,28]. The extent to which renal function is affected in Nigerian children particularly in north central region is not known, hence, this study which aims at determining the effects of severe malaria on the kidneys. The understanding of the degree of renal involvement in children with severe malaria will enhance case management through use of appropriate therapies with a view to preventing renal damage, particularly in our sub region where facilities for Renal Replacement Therapy (RRT) are not within easy reach (Table 1).

Objective of the paper

The specific objectives of the paper:

(1) Estimate glomerular filtration rate, serum electrolyte, urea and creatinine of children with severe malaria.

(2) Find out the prevalence of AKI in children with severe malaria.

Table 1: Definitions of Acute Kidney Injury.

RIFLE, 2004		Pediatric RIFLE, 2007		AKIN, 2007		KDIGO, 2012		Urine output
Criteria	Creatinine Definition	Criteria	Creatinine Definition	Criteria	Creatinine Definition	Criteria	Creatinine Definition	
Risk	≥1.5x increase in SCr from baseline or decrease in GFR ≥25%	Risk	Decrease in GFR ≥25	Stage 1	≥0.3 mg/dL increase in SCr within 48hrs or ≥1.5x increase in SCr from baseline	Stage 1	≥0.3 mg/dL increase in SCr within 48 hrs or ≥1.5x increase in SCr from baseline	<0.5 mL/kg/h for >6hrs
Injury	≥2x increase in SCr from baseline or decrease in GFR ≥50%	Injury	Decrease in GFR ≥50%	Stage 2	≥2x increase in SCr from baseline	Stage 2	≥2x increase in SCr from baseline within 7 days	<0.5 mL/kg/h for ≥12 hrs
Failure	≥3x increase in SCr from baseline or decrease in GFR ≥75%, SCr ≥4.0 mg/dL with an acute increase of >0.5 mg/Dl	Failure	Decrease in GFR ≥75% or an eGFR<35 mL/min per 1.73m2	Stage 3	≥3x increase in SCr from baseline, SCr ≥4.0 mg/dL with an acute increase of >0.5mg/dL or initiation of KRT	Stage 3	≥3x increase in SCr from baseline within 7 days, SCr ≥4.0 mg/dL with an acute increase of >0.5 mg/dL or initiation of KRT	<0.3 mL/kg/h for ≥24hrs or anuria for ≥12hrs
Loss	Failure for >4 weeks	Loss	Failure for >4 weeks					
ESRD	Failure for >3 months	ESRD	Failure for >3 months					

Methods

Study design

This was a prospective case-control observational study that was conducted in Emergency Paediatrics Unit (EPU), the Children's ward and the General Out Patient Department (GOPD) of the UITH over a period of one year. Improved Global Outcomes (KDIGO) and World Health Organization (WHO) criteria; an increase in serum creatinine value of 0.3mg/dl(5.4mmol/l) within 48 hours of admission was applied.

Study site

UITH is located within north central Nigeria, situated in Southern Guinea Savannah belt of Nigeria, a sub humid zone, enjoys two climatic seasons, dry and wet seasons, with mean temperature range of 21.5-38.5°C and an annual rainfall of 1,080 mm and length of growing period of 175 to 190 days, both of which favours plasmodium and vector development and survival [1-4].

Study subjects

The study was conducted among children between the ages of 6 months and 14 years with severe malaria, and children of same ages with uncomplicated malaria served as controls.

Inclusion criteria (Cases)

(a) Children with clinical features suggestive of severe malaria

(b) Children with laboratory features suggestive of severe malaria

Inclusion criteria (Controls)

Children with clinical and/or laboratory features of malaria with no life-threatening event(s).

Exclusion criteria cases and controls

(a) Children with history of renal illness before the onset of malaria.

(b) Children on drugs that affect renal function such as aminoglycosides.

(c) Children with concomitant illnesses.

Sample cize

The minimum sample size was determined using the formula

$$n = \frac{Z^2 Pq}{d^2}$$ [8]

Where;

n=desired sample size

Z=the standard normal deviate usually set at 1.96% (or simply at 2.0) which corresponds to 95% confident interval.

P=the proportion in the target population estimated to have a particular characteristic (renal impairment in severe malaria).

A reasonable estimate mean was 5.9% (WHO, 1996). The quoted estimate was that of renal involvement in severe malaria as reported by several authors in the earlier studies [11,25-29].

d=tolerable margin of error usually set at 0.05

q=1.0-p

=1.0 -0.05 = 0.95

Thus, the minimum sample size:

$$n = \frac{1.96 \times 1.96 \times 0.059 \times 0.95}{0.05 \times 0.05}$$

$$n = \frac{3.8416 \times 0.0475}{0.0025}$$

n= 73.074= 74

The minimum sample size was 74

Allowing for an attrition rate of 10%, a total of 82 children with severe malaria and 85 children with uncomplicated malaria were recruited into the study.

Ethical considerations

Ethical clearance was obtained from the Ethics and Research Committee (ERC) of the Hospital. Informed consent was obtained from the mother, parents, or caregiver before subject recruitment after

clearly explaining the study in the language they best understood.

Subject recruitment

Children between the ages of 6 months and 11 years presenting in the EPU with features of severe malaria were recruited consecutively as they presented. Those with features of uncomplicated malaria presenting in the General Outpatient Department (GOPD) as well as EPU between the ages of 6 months to 11 years were recruited as controls.

Severe malaria is commonest in children under the age of five years when the morbidity and mortality are highest. Children older than five years are, however, not spared even though at lower rate when compared to children aged 5 years and below [3,5,8-12]. It was not the intention of the researcher to restrict the subject to under-five as older children have been known to have cerebral malaria. This informed the decision to also study children above five years up to 11 years.

Recruitment procedures

Detailed history of the illness in each child recruited into the study was obtained from a reliable informant(s). A thorough physical examination was carried out on each child and features of severe malaria such as; severe anaemia, cerebral malaria, hyperpyrexia, prostration, and jaundice among others were noted in a proforma, where they were found. Glasgow coma scoring was done where appropriate. The height of children aged one to eleven years was assessed using stadiometer. The length of children less than one year was assessed using an infantometer. The weight assessment was done using weighing scale as appropriate for the age of the child. The weighing scale was standardized using standard weight periodically. The length of children (irrespective of age) who were unconscious was also determined as described above. The weight of unconscious patients was estimated by weighing each patient with the mother or the care giver, subsequently the mother's (care giver's) weight was subtracted from the sum to arrive at the patient's weight. The height/length measurement of the subjects were documented sequentially. The essence of detailed anthropometric measurements was to aid appropriate drug and fluid management of the patients, it was also needed for the estimation of eGFR in each subject. Details of home interventions and/or remedies were documented appropriately. The social class of each child was determined using Social Classification model, [27] by estimating the mean of four scores, to the nearest whole number of the parental (mother and father) educational attainments and professions. The controls were recruited consecutively at Children Emergency Unit and General Out Patient Department of UITH.

Sample collection

(1) Blood Sample and Laboratory Procedure

(2) Sampling was done in aseptic manner using a sterile 23G needle attached to a 5mls syringe. The researcher collected 5mls of blood with the assistance of the registrars working in EPU. Of this, random blood sugar was determined by glucometer using a drop of whole blood; the test strips used were the ACCU-CHEK [28-31] following standard operational procedure as prescribed by the manufacturer, two milliliters was dispensed into a specimen bottle containing dipotassium salt of Ethylene Diamine Tetra-Acetic Acid (EDTA) for complete blood count and malaria parasite identification and quantification. The World Health Organisation [28,29] procedure was adopted for detection and identification of malaria parasite. Thin and thick blood smears were made. The thin film was fixed in methanol. Thick film was stained in 2% Giemsa stain for 30 minutes while thin film was stained in Leishman stain. The slides were rinsed in phosphate buffer (PH 7.2) for three seconds, dried and examined with x 100 objective for malaria parasites. Parasite count was done via a count of parasites in a field containing 200 White Blood Cells (WBC) in the thick film, and the number of asexual forms per microlitre calculated from the WBC count using the formula

$$\frac{\mathbf{PC \times TLC}}{200}$$

Where

PC=Parasite count

TLC=Total leucocytes count

An observation of a parasitaemia rate of 5% and above for the Red Blood Cells (RBC) was regarded as severe. The counting was done under supervision of the Chief Laboratory Technologist in the Hematology Laboratory of UITH.

The Packed Cell Volume (PCV) was expressed as the volume of erythrocytes per litre of whole blood, so that it indicated the relative proportions of plasma and red cells. A heparinized capillary tube was used to take blood from the EDTA specimen bottle and centrifuged using the microhaematocrit centrifuge at 1,000 revolutions per second for five minutes. The capillary tube was transferred to the haematocrit reader and the column of the Red Blood Cells (RBCs) was measured and this corresponded to the PCV [29].

Serum electrolytes urea and creatinine estimation

The remaining three milliliters of venous blood was collected in a plain specimen bottle for serum creatinine, urea, sodium and potassium. The estimation of serum creatinine was done by a Laboratory scientist at the UITH Chemical Pathology Laboratory using the Jaffe's method on Corning colorimeter reading at 520 nanometers [30-33]. The serum sodium and potassium were analysed by the flame photometry method [15-18] using the Galenkamp flame photometer. The serum urea and creatinine were determined by the diacetyl monixime method on a Corning colorimeter reading at an Optical Density (OD) of 520 nanometers [15-17].

Coefficient of variation was ± 2% for within run samples and ±4% for between day's samples using serum. When analysis was not done on the day of sample collection; blood was stored in refrigerator at 40C without freezing and then sent to the laboratory the next working day. Creatinine estimation was done both in acute phase of illness and at fourth week for each child. The Estimated Glomerular Filtration Rate (eGFR) was determined using Schwartz's formula33 as shown below in order to overcome the problems associated with accurately timed urine collection in the estimation of GFR. The eGFR was determined at the onset and four weeks later, clinical and laboratory recovery was expected before this time [16-26].

Schwartz's formula:

$$GFR = \frac{kL\ ml/min/1.73m^2}{Scr}$$

Where:

k = Constant of proportionality

k = 0.55 for children less than 13 years

k = 0.77 for children greater than 13 years

L = Body height in cm.

Scr = Serum creatinine in mg/dl.

Urinalysis

About 15-20mls of freshly voided urine was collected from each child into a sterile universal bottle. Urinalysis was performed immediately by the investigator using dipstick method. Ten milliliters of urine was tested, using Multistix 10SG (Bayer Diagnostics, with sensitivity of 98.5%) [9,10].

(A) Physical characterization of urine

Urine collected in the Universal bottle was subjected to direct observation for

1. Colour

2. Clarity

(B) Dipstick reagent strip

Procedure

Part (10mls) of the collected uncentrifuged urine was properly mixed before testing.

All reagent pads of the strip were immersed in the urine specimen and the strip was removed immediately.

The edge of the strip was run against the rim of the container to remove excess urine.

The test strip was held horizontally and the colour changes on the test areas were compared closely with colour chart on the container.

The colour changes were read at the times specified by the manufacturer.

All instructions as regarding the storage and handling of the reagent strip were observed as stipulated by the maker [9,10].

Statistical analysis

Data were analyzed using SPSS 13.0 software. Data collected on the study proforma were entered using numeric codes. Frequency distribution tables of demographic variables were generated. Measures of central tendency and dispersion of quantitative variables were determined. Chi-square test (with Yates correction or Fisher's exact where applicable) and student t-test were used to test for significance of the difference between categorical variables and continuous variables respectively. Level of significance was put at p value less than 0.05.

General characteristics of study population

A total of 164 children were recruited into the study out of which 82 (50%) had severe malaria and another 82, without severe malaria, serving as controls. The male: female ratio was 1: 1 in the subjects and 1.4:1 in the controls. The median age was 36.0 months in the subjects and 36.0 months in the controls, both groups were comparable (p>0.05). Children between ages 1 to 5 years constituted 62.2% of the entire population studied (Table 2).

Socio-economic classification, anthropometric measurements and clinical features in the study population.

There was no statistically significant difference in the socio-economic classification of the subjects and the controls. (p=0.08).

The mean weight of the subjects was 15.1±6.9 kg, while the mean length or height was 98.4±15.5 cm. There were no statistically significant differences when compared with those obtained in the controls (p=0.06).

The leading clinical feature in the study population was fever which occurred in 69 (82.0%) subjects and 75 (95.1%) controls (p=0.48). This was closely followed by pallor in 79.3% subjects and was significantly higher than what was obtained in the control (p=0.001). Other clinical features of note included difficulty in breathing 50.0%, oliguria 28.1%, vomiting 25.1% and convulsion 20.7% (Table 3).

Home remedy in the study population

Several forms of remedies were offered to the subjects before presenting in the hospital, ranging from chloroquine (12.2%), paracetamol (18.3%), artesunate (11.0%), quinine (4.9%) and herbal preparations (15.9%). Herbal preparations were mostly used in the subjects (9.8%) than in the controls (2.4%) (χ^2=7.2, p=0.001) (Table 4).

Malaria Parasite density observed in the study population

The mean parasite density in the subjects was 243,235±19.4/200 WBC, while the mean in the controls was 107, 257±21.0/200 WBC and the difference was significant (p=0.001). Most of the children in the study population, 46 (56.1%) had a parasite density <50,000/200 WBC, while only 7 (8.5%) had hyperparasitaemia. The parasite density in the subjects was significantly higher than that in the controls. (Yates corrected χ^2 =5.37, p=0.020), (Table 5).

Biochemical profiles in the study population at admission

The mean serum sodium of the study population was 143.9±12.3 mmol/l compared to 133.6±12,9 mmol/l in the control group (p=0.555). The mean serum potassium was 5.4±0.5 mmol/l compared to 3.2±0.7 mmol/l in the controls (p=0.002). The mean serum urea and creatinine in the subjects were 6.3±5,6 mmol/l and 117.2±27.5 µmol/l respectively while values for the controls were 3.1±2.3 mmol/l and 91.1±8.6 µmol/l respectively. The serum potassium, urea and creatinine of the subjects were significantly higher in the subjects than in the controls (p<0.05) (Table 6).

Biochemical profiles in the subjects at admission and fourth week.

The means potassium (5.7±0.5 mmol/l) and creatinine (118.2±27.5 µmol/l) were significantly higher at admission but had returned to values within the normal range by the fourth week. There was a statistically significant difference in the values obtained at admission

Table 2: Gender and age distribution of the study population.

Sex	Total	Subject n=82 (%)	Controls n=82 (%)
Male	88	40(45.5)	48(54.5)
Female	76	42(55.3)	34(44.7)
M: F	**01:01**	**01:01**	**1.4:1**
Age in months			
6-12	25	11(44.0)	14(56.0)
13-24	48	22(54.9)	26(45.1)
25-36	39	19(48.7)	20(51.3)
37-48	26	16(40.6)	10(59.4)
49-60	13	8(61.5)	5(38.5)
61-72	8	4(50.0)	4(50.0)
≥73	5	2(40.0)	3(60.0)
Total	164	82(50.0)	82(50.0)

Table 3: Clinical features in the study population.

Clinical Feature	Subject N=82(%)	Control n=82(%)	χ^2	P
Vomiting	21(25.1%)	15(18.3%)	2	0.157
Pallor	**65(79.3%)**	**38(46.3%)**	**14.16**	**0.001**
Difficulty with				
breathing	41(50.0%)	0(0.0)		
Fever	69(84.0%)	75(91.5%)	0.5	0.48
Convulsions	17(20.7%)	0(0.0)		
Yellowness of eyes	18(22.0%)	0(0.0)		
Passage of dark				
urine	16(19.5%)	0(0.0)		
Oliguria	23(28.1%)	0(0.0)		
Severe dehydration	12(14.6%)			

Table 4: Home remedies in the study population.

Home Remedies	Subjects n=82(%)	Controls n=82(%)	χ^2	P
Paracetamol(PCM)	15(18.3)	13(15.9)	0.29	0.593
Chloroquine	10(12.2)	14(17.1)	1.33	0.248
Artesunate	3(3.7)	6(7.3)	2	0.157
Herbal preparation	**8(9.8)**	**2(2.4)**	**7.2**	**0.001**
Chloroquine+PCM	20(24.4)	22(26.8)	0.98	0.332
Artesunate +PCM	6(7.3)	9(11.0)	1.2	0.273
Herbal preparation +PCM	10(12.2)	5(6.1)	3.33	0.067
Q uinine	4(4.9)	0(0.0)		
Fansidar		6(7.3)	2	0.157
No remedy	3(3.7)	5(6.1)	1	0.317
Total	3(3.7)	82(100.0)		
	82(100.0)			

Table 5: Malaria parasite density of the study population.

Parasite density	Subjects n=85(%)	Controls n=85(%)	χ^2	p
0-50000	48(56.5)	76(89.4)	13.07	0.003
50001-100000	12(14.1)	3(3.7)	9.14	0.003
100001-150000	10(12.2)	4(4.7)	7.54	0.006
150001-200000	4(4.9)	2(2.4)	0.33	0.564
200001-249999	4(4.9)	0(0)	8	0.005
≥ 250000	7(8.5)	0(0)	14	0
Total	85(100.0)	85 (100.0)		

χy^2 = 5.37, p = 0.020.

Table 6: Biochemical profiles in the study population at admission.

Biochemical Profiles	Subjects n= 85	Controls n= 85	T	P
Sodium in mmol/l				
Mean (SD)	146.9±11.3	136.8±10.9	0.583	0.55
Range	134.5-159.1	133.6-159.1		
Potassium in mmol/l				
Mean (SD)	**5.7±0.4**	**3.3±0.8**	**3.54**	**0.002**
Range	3.0-7.2	2.6-5.7		
Urea in mmol/l				
Mean (SD)	**6.3±5.6**	**3.1±2.3**	**4.791**	**0.001**
Range	1.0-31.0	1.6-15.4		
Creatinine in µmol/l				
Mean (SD)	**118.2±27.5**	**90.8±8.6**		
Range	17.0-678.0	82.5-102.7	**3.571**	**0.002**

and fourth week for the two parameters (<0.05). However, between admission and four weeks into recovery, urea levels were significantly higher, (t=7.57, p=0.001) though values remained within normal range. Serum sodium was within the normal range at admission and remained within the normal range at the fourth week. (p=0.524) (Table 7).

Study subjects with deranged biochemical profiles at admission

Elevated serum creatinine (creatinine >88 µmol/l) and azotaemia (serum urea >6.4 mmol/l) occurred in 25 (30.5%) and 24 (29.3%) subjects respectively. None of the controls had elevated serum creatinine, while 8 (9.8%) controls had azotaemia. The occurrence of elevated serum creatinine and azotaemia was significantly more in subjects as compared to the controls (t=50.0, p=0.001). However, hypernatraemia and hyponatremia occurred in 3.7% and 31.7% respectively, while hyperkalaemia occurred in 13.4% of the subjects. (Table 8).

Urinalysis in the study population at admission

Proteinuria occurred in 62(75.6%) of subjects and in 26(31.7%) controls (p=0.01). However, no massive proteinuria was observed in the study population. Twenty-two (26.8%) and 13(15.9%) subjects had haematuria and bilirubinuria respectively (p<0.05). The urine pH was normal in 90.3% of the subjects and 100% of the controls. Eight (9.8%) of the subjects had alkaline pH.0 The specific gravity was also normal in 86.6% of the subjects, while eleven (13.4%) of the subjects had high specific gravity. Specific gravity was normal in 95.1%, high in 3.7% and low in 1.2% of the control group (p<0.05).

There were significant differences in the urinalysis findings at fourth week and those obtained at admission. Sixty-nine (87.3%) of the subjects four weeks later had no protein in their urine (p=0.0001). The urine pH and specific gravity were normal in all subjects at four weeks (Table 9).

The mean eGFR of the study population

The mean eGFR of the subjects, 74.55±56.27 ml/min/1.73m^2 was significantly lower than that of the control, 164.6±71.10 ml/min/1.73m^2 (p=0.001) (Table 10 and Figure 1).

The mean GFR of the subjects at fourth week was significantly higher than the GFR at presentation, (p=0.001). (Table 11 and Figure 2).

Only 18 (22.0%) of the subjects had eGFR of >100 ml/min/1.73m^2 compared to 44 (53.7%) of control. The lowest eGFR was 11.6 ml/min/1.73m^2 in children with severe malaria. There were no significant differences in the mean eGFR of the subjects and the controls when eGFR of 50 ml/min/1.73m^2 and above were compared (Table 12).

eGFR of the subjects at admission and fourth week

The number of subjects with eGFR >100 ml/min/1.73m^2 increased from 18 (22.0%) at admission to 66 (78.5%) in the fourth week (p<0.05). Similarly, by the fourth week there was no subject with eGFR <50 ml/min/1.73m^2. However, 11 (13.9%) subjects had eGFR between 50-99 ml/min/1.73m^2 (Table 13).

Low eGFR in the subjects

Twenty-four (29.3%) children had low eGFR for age as well as azotaemia. Twenty-five (30.5%) children had elevated serum creatinine. The eGFR was normal in the remaining 58 (70.7%) children and the controls (Table 14).

Prevalence of acute kidney injury (AKI) using the three parameters of reduced eGFR, Azotaemia and elevated creatinine

The prevalence of AKI using the three parameters of reduced eGFR, azotaemia and elevated creatinine ranged from 29.3% and 30.5%.

Twenty-four children (29.3%) had low eGFR, azotaemia and elevated serum creatinine respectively, while a patient (1.4%) had elevated serum creatinine with normal eGFR (Table 15).

Table 7: Biochemical profiles in the subjects at admission and at four weeks into recovery.

Biochemical Profiles	Subjects at admission n=82	Subjects at four weeks n=79	T	P
Sodium in mmol/l				
Mean (SD)	**143.9±12.3**	**135.2±2.7**	**0.64**	**0.524**
Range	134.5-159.1	132.6-139.7		
Potassium in mmol/l				
Mean (SD)	**5.4±0.5**	**3.2±0.5**	**3.15**	**0.002**
Range	4.9-5.8	2.7-4.5		
Urea in mmol/l				
Mean (SD)	**6.3±5.6**	**3.3±2.9**	**7.57**	**0.001**
Range	1.0-31.0	0.4-6.1		
Creatinine in µmol/l				
Mean (SD)	**117.2±27.5**	**54.4±50.2**	**5.4**	**0.001**
Range	19.0-680	4.1-112.7		

Table 8: Derangements of biochemical profiles in the study population at admission.

Biochemical Indices	Subjects n = 82(%)	Controls n = 82(%)	χ^2	P
Sodium in mmol/l				
Hypernatraemia (>145mmol/l)	3 (3.7)	1 (1.2)	0.04	0.243
Hyponatraemia (<138mmol/l)	26 (31.7)	25 (30.5)	0.17	0.843
Normal (138-145mmol/l)	53 (64.6)	56 (68.3)	0.18	0.684
Potassium in mmol/l				
Hyperkalaemia (>4.7mmol/l)	11(13.4)	10 (12.2)	0.1	0.757
Hypokalaemia (<3.4mmol/l)	**0 (0)**	**2 (2.4)**	**12.46**	**0.001**
Normal (3.4 – 4.7mmol/l)	71 (86.6)	70 (85.4)	0.01	0.905
Urea in mmol/l				
Azotaemia (>6.4mmol/l)	**24 (29.3)**	**8 (9.8)**	**16**	**0.001**
Normal Urea (1.8- 6.4mmol/l)	58 (70.7)	74 (90.2)	3.88	0.049
Creatinine in µmol/l				
Elevated (>88µmol/l)	**25 (30.5)**	**0 (0)**	**50**	**0.001**
Normal (27 – 88µmol/l)	**57 (69.5)**	**82 (100)**	**8.99**	**0.001**

Table 9: Urinalysis in the study population at admission and four weeks into recovery.

Urinalysis	Subject at admission n=82(%)	Subject at fourth week n =79 (%)	χ^2	P
Proteinuria				
nil	**20(24.4)**	**69(87.3)**	**53.96**	**0.001**
1+	**50(61.0)**	**9(11.4)**	**56.98**	**0.001**
2+	**12(14.6)**	**1(1.3)**	**18.62**	**0.001**
Urinary Ph				
Normal pH	74(90.3)	79(100.0)	0.33	0.567
Acidic pH	0(0.0)	0(0.0)		
Alkaline pH	8(9.8)	0(0.0)		
Specific gravity (SG)				
Normal (1015-1030)	71(86.6)	79(100.0)		
High (>1030)	11(13.4)	0(0.0)		
Low (<1010)	0(0.0)	0(0.0)		
Haematuria	13(15.9)	0(0.0)		
Bilirubinuria	22(26.8)	0(0.0)		

Table 10: The estimated glomerular filtration rate (eGFR) of the study population at admission.

	Subject n = 82	**Control** n = 82	T	P
Mean (SD)	**74.6±56.2**	**164.6±71.1**	**7.841**	**0.001**
Range	11.6-259.0	50.7- 258.7		

The socio-demographic (and biochemical) characteristics of the twenty-five children with AKI in the study population

Most of the children 15(60%) with AKI belonged to the lower social classes IV and V, while 5 (20.0%) children belonged to social class III and the rest 5 (20%) children belonged to social classes I and II. Majority of the children were also females 13(52%) while the rest 12(48%) were males. The age range of the children was 11-135 months. Majority of them 15(60%) were >5years old, while the rest 10 children were <5years. All the 25 children except two had received one form of home remedy or the other and these ranged from paracetamol to chloroquine, herbal remedies, artesunate and quinine. There was no indication for dialysis in any of the children with AKI, as they all recover following effective malaria treatment and intravenous fluid management.

Table 11: The eGFR of the study population at presentation compared with the eGFR at fourth week.

	Subject at admission n=82	Subject at 4weeks n=79	t	P
GFR ml/ min / 1.73 m^2 Mean (SD)	**74.6±56.3**	**123.8±73.6**	**5.737**	**0.001**
Range	11.6-259.0	14.7-263.7		

Table 12: Classification of eGFR of the study population at admission.

eGFR ml/ min/1.73m^2	Subject n=82(%)	Control n=82(%)	χ^2	P
≥100	**18(22.0)**	**56(68.3)**	**14.37**	**0.001**
75-99	14(17.1)	25(30.5)	0.15	0.695
50-74.9	28(34.2)	**1(1.2)**	**10.89**	**0.001**
25-49.9	16(19.5)	0 (0.0)	**28.13**	**0.001**
< 25	6(7.3)	0 (0.0)	**8.33**	**0.001**

Table 13: Classification of eGFR of the subjects at admission and fourth week.

eGFR Ml/ min/1.73m^2	Subject at admission n=82(%)	Subject at fourth week n=79(%)	χ^2	P
≥100	**18(22.0)**	**66(83.5)**	**54.86**	**0.001**
75-99	**14(17.1)**	**11(13.9)**	**0.72**	**0.4**
50-74.9	**28(34.2)**	**0(0.0)**	**5.2**	**0.001**
25-49.9	**16(19.5)**	**0(0.0)**	**28.13**	**0.001**
< 25	**6(7.3)**	**0(0.0)**	**8.33**	**0.002**

Table 14: Comparison of estimated eGFR with the normal value for age.

Age in Months	Normal Range eGFR for age ml/min/1.73m^2	No of pts n (%)	Normal eGFR n (%)	Low eGFR n (%)
6mo-23mo	74-118	31(37.8)	22(71.0)	9(29.0)
24mo-60mo	106-160	45(54.9)	31(68.9)	14(31.1)
61mo-144mo	106-160	6(7.3)	5(83.3)	1(16.7)
Total		**82 (100.0)**	**58(70.7)**	**24(29.3)**

Table 15: Prevalence of acute renal failure (AKI) in the study population.

Parameter	No. of children with AKI	Prevalence
↓eGFR (ml/min/1.73m^2)	24	29.30%
Azotaemia	24	29.30%
Elevated serum creatinine µmol/l)	25	30.50%

Table 16: Summary of the outcome of subjects in the study population.

Total number of patients:	**82**
Discharged and followed up:	**79**
Death:	**3**
Case fatality for severe malaria in the study:	**4%**

The outcome of the patients with severe malaria in the study population

Out of the 82 subjects recruited into the study, 79 were managed and discharged, while 3 patients died in the course of the study, two children died from severe anaemia while the third had cerebral malaria given a case fatality of 4% (Table 16).

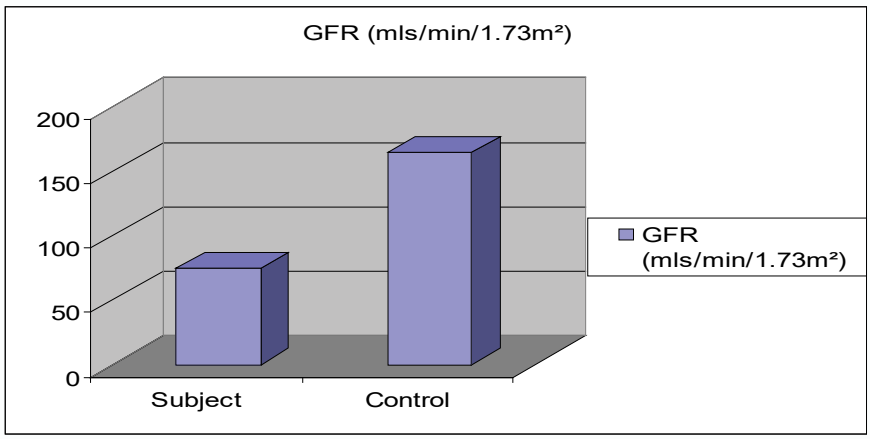

Figure 1: Bar chart showing the mean eGFR of the subjects and controls.

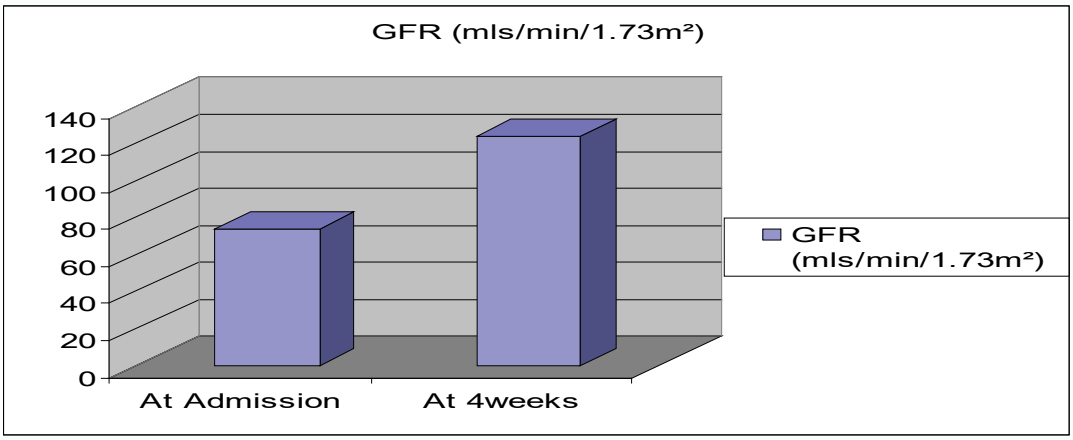

Figure 2: Bar chart showing the mean eGFR of the subjects at admission and four weeks later Classification of eGFR of the study population at admission

Discussion

The prevalence of AKI of 30.5% in children with severe malaria in this study is higher than the findings of other scholars [14,16,18-23]. This may be related to late presentation by the subjects in this study [34-36]. Most patients in the study would have tried home remedies before presentation [38,39]. This assertion is corroborated by the findings that as much as 96.3% of the subjects had used chloroquine, quinine, Sulfadoxine-Pyrimethermine (SP) combinations, herbal preparations, paracetamol (PCM) and artesunate before presentation. The prevalence of AKI of 30.5% in this study is lower than that of 58% prevalence reported by Folake et al, when only eGFR is used in determining the prevalence of AKI in children with severe malaria [25]. Studies have shown that when these initial home remedies are applied, they are administered at sub-optimal doses due to ignorance or lack of sufficient funds to procure the full dosage [18-23]. The study indicated that most of the children had received one form of home remedy or the other. Most of these children who received home remedy also belonged to the low socio-economic class families.

Furthermore, it is known that there is already high level of resistance to some of these remedies like chloroquine and S-P combination. The content and efficacy of the herbal remedies are questionable and indeed there is the probability that some could have nephrotoxic effect. The higher prevalence of AKI in this study may also be related to the fact that other workers did not use age related eGFR, urea and creatinine standards in determining the presence of renal impairment. It is well established that an arbitrary adult cut off values cannot be extrapolated to the paediatric age group. The eGFR, serum creatinine, urea and other biochemical indices possess age related standard values. Above all, the findings of a study conducted by Kwambele, et al (2023) reveal that there is a high prevalence of acute kidney injury among children with severe malaria in Kiryandongo General Hospital [16]. Acute kidney injury among children with severe malaria was associated with low level of education of caretakers, young age of children (less than 5 years), history of receiving NSAIDs, and anemia (moderate and severe) [26,34-36,40,41].

The same group of children had elevated creatinine, azotaemia and low eGFR accounting for between 29.3% to 30.5% prevalence of renal insufficiency in the study. While this was reassuring or heartwarming, it was also surprising because serum creatinine is known not to be sensitive to substantial decline in eGFR [16]. Glomerular filtration rate may be reduced by up to 50% before serum creatinine becomes elevated [4,21,23,25]. The fact that it is filtered and excreted by the

kidney makes it an imperfect measure of eGFR. However, it remains the most widely used indirect measure of eGFR. It is easy and inexpensive to measure even though it is not accurate. Serum urea has a similar problem as it could be elevated in a state of dehydration and after consumption of protein.

There were strong negative correlations between eGFR and serum potassium, urea, creatinine and parasite density. A positive correlation existed between serum sodium and eGFR; as sodium continues to accumulate in acute kidney injury there is associated water retention resulting in hyponatraemia. The failed kidneys cannot excrete potassium so it accumulates resulting in hyperkalaemia. Similarly, there is a buildup of serum urea resulting in azotememia or uraemia. Creatinine also builds up due to failure of its excretion as the kidney begins to fail. The higher the parasite density, the lower was the eGFR. This perhaps may be due to lyses of parasitized red cells resulting in release of substantial amount of haemoglobin which plugs the tubules thereby interfering with tubular excretion. Similarly, heavy parasitemia is associated with accentuation of symptoms of malaria such as vomiting which results in loss of fluid causing hypovolemia which could produce a pre-renal failure [8,19].

Four weeks into recovery, eGFR had increased and returned to normal in keeping with the findings of other workers [18-22]. Similarly, the elevated serum creatinine returned to normal and azotaemia normalized in agreement with the findings of other workers [18-20]. The renal dysfunction associated with severe malaria is reversible when there is prompt and accurate intervention as all our patients did recover.

The urine pH and specific gravity remained largely within normal limit at admission and in the fourth week indicating that tubular function may not have been as compromised as glomerular function. This is in keeping with the findings of other workers [16,18]. However, proteinuria was observed in the subjects. This was in agreement with the findings of Weber [19] and Shieban, [18] however, massive proteinuria was not recorded in any of the patients. The proteinuria could be due to fever or may reflect the transient glomerular dysfunction due to severe malaria. The latter reason is plausible because the proteinuria returned to normal by the fourth week. The three deaths recorded in the study population were not due to renal impairment as the three children had normal renal function. Two children died from severe anaemia while the third had cerebral malaria. AKI does occur following severe malaria. It is reversible once prompt and adequate treatment of malaria and conservative management of AKI are offered. Renal replacement therapy may not be required as seen in this study.

This study was conducted over a decade ago; when the world was facing the challenge of high level of resistance of malaria parasites. It is believed that with introduction of newer antimalaria drugs based on the advises from the outcome of interventional researches such as Africa Quinine versus Artesunate Trial (AQUAMAT), [26] the prevalence of AKI may be lower currently than the finding of this study.

Conclusion

Based on the findings in this study the following conclusions and inferences can be drawn:

The eGFR in children with severe malaria was compromised in 30% of cases, correspondingly the serum urea and creatinine were compromised in same group of patients.

The prevalence of acute renal failure in this study was 30.5%. The mean eGFR, potassium, sodium, urea and creatinine at admission were 74.6±56.3 ml/min/1.73m^2, 5.4±0.5 mmol/l, 143.9±12.3 mmol/l, 117.2±27.5 µmol/l and 6.3±5.6 mmol/l respectively. Outside sodium, these parameters were higher in subjects than controls.

Deteriorating eGFR correlated strongly with presence of jaundice and proteinuria and rising potassium, creatinine, urea and increasing parasite density.

The features of AKI noticed at inception had normalized four weeks unto recovery.

Recommendations

1. More studies would need to be carried out particularly in other geopolitical zones of the country to determine the prevalence of AKI secondary to malaria.

2. Renal compromise occurs sufficiently enough in children with severe malaria (30%) to warrant screening.

3. Routine serum creatinine evaluation would be of relevance as it correlated well with eGFR which could be tasking and cumbersome.

4. Severe malaria predisposes to AKI and measures to reduce its incidence would be invaluable tool in preventive nephrology in the region and perhaps other parts of the tropics.

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