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ISSN 2380-5498

International Journal of Nephrology and Kidney Failure

Research Article | Volume: 2.1 | Open Access

Renal and Patients' Survival in Children with Hypertensive Chronic Kidney Disease

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Received date: 19 May 2015; **Accepted date:** 24 August 2015; **Published date:** 28 August 2015.

Citation: Olowu WA, Aladekomo TA, Ajite AB, Aderounmu T (2015) Renal and Patients' Survival in Children with Hypertensive Chronic Kidney Disease. Int J Nephrol Kidney Failure 2(1): doi http://dx.doi.org/10.16966/2380-5498.110

Abstract

The impact of hypertension on renal and patients' survival was retrospectively determined in children with chronic kidney disease (CKD).

Seventy-seven of 154 CKD patients were hypertensive with 23 (30%) and 54 (70.0%) having stages I (123.0 ± 12.5/ 82.4 ± 10.6 mmHg) and II hypertension (161.0 ± 32.3/111.0 ± 23.0 mmHg), respectively. Seventy percent received two or more anti-hypertensive medications to achieve satisfactory blood pressure (BP) control. BP control was good, fair and poor in 43 (56.0%), 18 (23.4%), and 16 (20.6%) patients, respectively. Post-treatment BP in hypertensive CKD (hCKD) with good control was similar to normotensive CKD (nCKD), p=0.541. One/5 years renal survivals in nCKD (97.0/80.0%) were similar to hCKD with good BP control (96.2/63.0%, Log-rank p=0.362). nCKD, however, demonstrated significantly better one/five years renal survival (97.0/80.0%) than hCKD with fair (75.0/25.0%, p=0.014) and poor BP control (50.0/0.00%, p=0.003). hCKD with good BP control survived (66.7%) significantly better than hCKD with either fair (24.1%; p=0.002) or poor (0.0%; p=0.000) control. nCKD (90.4%) and hCKD with good BP control (66.7%) survived similarly, p=0.198. Cumulative mortality was significantly higher in hCKD (62.4%) than in nCKD (9.5%) [*Hazard ratio: 0.54, 95% CI: 0.35-0.83, p=0.005*].

Stage II occurred more frequently than stage I hypertension. Hypertension is a significant risk factor for poor renal survival and mortality in childhood CKD. Renal and patients' survival was significantly better in hCKDs with post-treatment BP level ≤ 50th percentile compared to hCKDs with post-treatment BP level >50th percentile for age, gender, and height.

Keywords: Chronic kidney disease; Children; Hypertension; Mortality; Renal survival

Introduction

Compared to the normal paediatric and adolescents' population [1-3], the prevalence of hypertension (HTN) in childhood chronic kidney disease (CKD) is frequently higher [4-7]. CKD-associated hypertension (CKD/HTN) develops by a large variety of complex and interwoven pathophysiological mechanisms. Fluid overload, renin-angiotensin-aldosterone-system activation, sympathetic nervous system hyper activation, vascular endothelial dysfunction, chronic hyperparathyroidism are important pathomechanisms for CKD/HTN [8]. HTN develops very early in childhood CKD [9,10] and has been associated with rapid CKD progression and significant target-organ damage. Left ventricular hypertrophy (LVH) is the most prominent evidence of target-organ damage in hypertension [11]. Children with chronic renal failure with systolic blood pressure (SBP) >120 mm Hg were observed to have significantly faster decline in the glomerular filtration rate (GFR) [12]. Furthermore, hypertension was a strong predictor of accelerated GFR decline [13] and graft loss [14,15] in children who have received a kidney transplant. Therefore, when blood pressure (BP) is consistently above the 90th percentile for age, gender, and height in non-dialyzing hypertensive CKD (hCKD) children, it is advised that antihypertensive medications should be started to limit disease progression and comorbidities [16]. Furthermore, it was recommended that the therapeutic BP target in such children, particularly those with proteinuria, should be less than the 50th percentile for age, gender and height unless achieving this target is limited by signs or symptoms of hypotension. Apart from escalating disease progression, HTN is an established risk factor for comorbidities like cardiovascular abnormalities, proteinuria, seizures, and stroke [11].

There has been no previous study on the impact of hypertension on renal and patients' survival in children with CKD in sub-Saharan Africa. This study was, therefore, conducted to determine the impact of hypertension on renal and patients' survival in children with CKD.

Materials and Methods

A retrospective analysis of data of 154 pediatric CKD patients, seen between January 1, 2000 and December 31, 2009, in the Pediatric Nephrology and Hypertension Unit of our hospital was carried out after approval of our institution's research and ethical committee.

All children with laboratory and/ or radiologic evidence of CKD, who were followed-up for ≥ 3 months, were included. The aetiology of CKD in the hypertensive children were glomerular disorder (n=54), systemic lupus erythematosus (n=7), obstructive uropathy (n=6), infantile polycystic kidney disease (n=2), sickle cell anaemia (n=2), and human immunodeficiency virus-associated nephropathy (n=2). Chronic pyelonephritis, Burkitt's lymphoma nephropathy, Henoch-Schonlein purpura nephritis, and Churg-Strauss syndrome accounted for a case each. Estimated glomerular filtration rate (eGFR) was determined using the Schwartz formula [17]. We diagnosed CKD based on K/DOQI diagnostic and staging criteria for patients who are 2 years old or older [18]. Staging of CKD in children younger than 2 years of age (n=4) was performed according to the method we earlier described [9]. The auscultation method of BP measurement, using the mercury gravity sphygmomanometer, was routinely employed with patients placed in the sitting position. Eighty to hundred percent of the cuff bladder length, of appropriate size for age, was wrapped round the right arm as recommended by the 1996 update

on high BP in children and adolescents [19]. The lower boarder of the cuff was placed 2-3 cm above the ante-cubital fossa to allow for auscultation with the bell of the stethoscope. Upon deflation of cuff bladder, the tapping first Korotkoff sounds (K1) defined the SBP while the disappearance of the Korotkoff sounds (K5) defined the diastolic blood pressure (DBP). However, in a few of the children muffling of the Korotkoff sounds (K4) was taken as the DBP when the Korotkoff sounds were heard up to 0 mmHg. The age, gender and height standardized BP percentile charts published by the task force on high BP in children and adolescents [11] were used to determine whether or not a child was hypertensive. The charts were also used for the staging of HTN. HTN was defined and staged according to the fourth report on high BP in children and adolescents [11] as a SBP and/or DPB that was ≥ 95th percentile for age, gender and height. Stage I HTN was defined as a SBP and/or DBP that was >95th but not >99th percentile for age, gender and height by more than 5 mmHg. A SBP and/or DBP that was >99th percentile for age, gender and height by more than 5 mmHg was regarded as stage II HTN [11]. Post treatment control of HTN was good if SBP and/ or DBP was ≤ 50th percentile for age, gender and height while it was fair and poor if >50th but <90th and >90th percentile, respectively.

Poor renal survival is a progressive decline in kidney function determined by the eGFR. A 28.0% reduction from the lower limits of normal eGFR value for age group was defined as poor renal survival in this study. Therefore, eGFRs that were persistently <18.7, <29.5, <53.3, and <65 mL/min /1.73 m^2 for ≥ 6 months were regarded as poor renal survival in children aged 1 week, 2-8 weeks, 9 weeks to 2 years and >2 years, respectively. The lower limits of normal eGFR value as reported by K/DOQI are 26.0, 41.0, 74.0, and 90.0 mL/min /1.73 m^2 for the age-groups 1 week, 2-8 weeks, 9 weeks to 2 years and >2 years, respectively [18].

To analyze data, SPSS Version 15.0 (SPSS Inc., Chicago, IL, USA) was used. The comparative statistics used were hazard ratio (*HR*), Wilcoxon signed ranks test, Pearson correlation (*r*), Cox regression analysis, Kaplan-Meier survival analysis and the log-rank test. Data of hCKD patients with insufficient laboratory data (n=5), who were lost to follow up (n=11), and those who presented with CKD stage 5 and remained so for ≥ 3 months (n=6) were censored during renal survival analysis. Data of normotensive CKD (nCKD) were similarly treated. The diagnostic accuracy of SBP, DBP, and mean arterial pressure (MAP) cut-points in predicting mortality was determined using the receiver operating characteristic (ROC) statistics. The sensitivity, specificity, positive and negative predictive values of the test variables was calculated. Cut-point value that predicted mortality most for each of the diagnostic test variables was determined using the Youden's index [20]. Statistically significant p value was set at <0.05.

Results

Seventy-seven of 154 CKD patients were hypertensive. Their mean age was 10.1 ± 3.4 (1.0-15.0) years. There were 37 boys and 40 girls. The overall mean SBP, DBP, and MAP for hCKD were 150.4 ± 33.0 (110.0-240), 103.4 ± 24 (60.0-160.0), and 120.0 ± 26.2 (80.0-187.0) mmHg, respectively. The pattern of hypertension by stage and anti-hypertensive medications used are summarized in Tables 1 and 2, respectively. CKD stages 1, 2, 3, 4, and 5 were associated with stage I HTN in 12, 5, 1, 2, and 3 patients, respectively. On the other hand, CKD stages 1, 2, 3, 4, and 5 were associated with stage II HTN in 15, 8, 7, 2 and 22 patients, respectively. BP control was good in 43 (56.0%), fair in 18 (23.4%) and poor in 16 (20.6%) patients. Patients with good BP control were significantly more than those with fair and poor control, *p=0.000*. Table 3 shows the impact of hypertension, as determined by echocardiography, on the heart geometry in childhood CKD. Comparison of median BP between normotensive CKD (nCKD) and hCKD with good BP control is shown in Figure 1.

The overall mean eGFR for hCKD was 66.4 ± 56.8 (4.0-280.0) mL/

Hypertension stage	Mean ± SD; Median [range]; Number (%)
Stage I Hypertension	23 (30)
Systolic blood pressure (BP), mmHg	123.0 ± 12.5; 120.0 [100.0-150.0]
Diastolic BP, mmHg	82.4 ± 10.6; 80.0 [60.0-100.0]
Mean arterial pressure, mmHg	96.0 ± 10.2; 93.3 [73.3-117.0]
Stage II Hypertension	54 (70)
Systolic BP, mmHg	161.0 ± 32.3; 150.0 [110.0-240.0]
Diastolic BP, mmHg	111.0 ± 23.0; 105.0 [70.0-160.0]
Mean arterial pressure, mmHg	128.0 ± 25.0; 120.0 [90.0-187.0]

Table 1: Pattern of hypertension by stage in childhood chronic kidney disease

Anti-hypertensives	Number (%)
One anti-hypertensive	30 (39)
Two anti-hypertensives	27 (35.0)
Three anti-hypertensives	13 (17.0)
More than three anti-hypertensives	7 (9.0)
Angiotensin converting enzyme inhibitor alone or in combination with other anti- hypertensives	26 (34.0)
Angiotensin receptor blocker alone or in combination with other anti-hypertensives	9 (12.0)
Other anti-hypertensives used in different combinations	42 (54.0)

Table 2: Number and pattern of anti-hypertensives used in children with chronic kidney disease

M-Mode/2D Echocardiography	Mean ± SD; Median [range]; Number (%) N=19
Left ventricular mass, g	130.0 ± 40.6; 123.4 [70.0-199.0]
Left ventricular mass index, g/m$^{2.7}$ (normal, <38.0)	52.0 ± 16.6; 50.4 [28.9-98.0]
Relative wall thickness (normal, <0.41)	0.56 ± 0.19; 0.52 [0.29-0.90]
Ejection fraction, % (normal, 64-83)	63.0 ± 11.3; 65.0 [35.6-81.3]
Altered Left Ventricular Geometry	
Concentric left ventricular hypertrophy	13 (68.4)
Eccentric LVH	3 (15.8)
Concentric remodeling	1 (5.3)
Normal Left Ventricular Geometry	2 (10.5)

Table 3: Impact of hypertension on the heart in chronic kidney disease in children

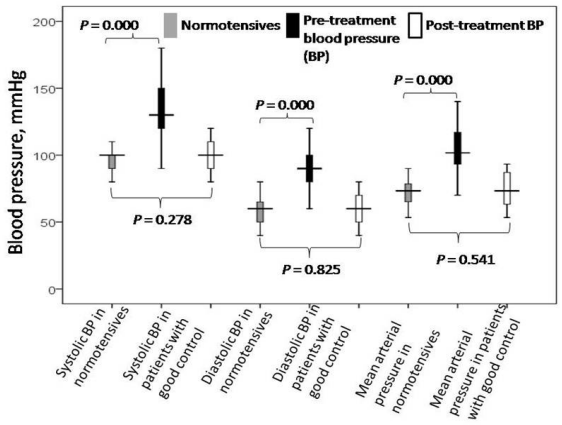

Figure 1: Comparison of median systolic, diastolic blood pressure (BP), and mean arterial pressure between normotensive chronic kidney disease (CKD) and hypertensive CKD patients with good BP control.

min/1.73 m^2. Figure 2 compares the overall 1 and 5 years renal survivals between nCKD and hCKD. nCKDs demonstrated significantly higher one/five years renal survivals (97.0/80.0%) than hCKD with fair (75.0/25.0%; *Log-rank p=0.014*) and poor (50.0/0.00%; *Log-rank p=0.003*) BP control. One and 5 years renal survival was, however, similar in both nCKDs (97.0/80.0%) and hCKDs with good BP control (96.2/63.0%; *Log-rank p=0.362*). Median renal survival times of patients who received either angiotensin converting enzyme inhibitor (ACEi) or angiotensin-II receptor blocker (ARB) and patients treated with other anti-hypertensives were similar (47 versus 33 months, *p=0.639*). Figure 3 shows the Kaplan-Meier survival curves comparing patients' outcome with regards to BP control. By Kaplan-Meier pair wise comparisons and the Log-rank test, survival in hCKD with good BP control (66.7%) was significantly better compared with patients with either fair (24.1%; *p=0.002*) or poor (0.0%; *p=0.000*) BP control. Patients outcome was similar in hCKD with fair and poor BP control, *p=0.284*. Correlation of mean BPs with CKD stages in hCKD is shown in Figure 4. Worsening eGFR significantly correlated inversely with SBP (*r=– 0.510*; *p=0.000*), DBP (*r=– 0.523; p=0.000*), and MAP (*r=– 0.530; p=0.000*). By Cox regression analysis, nCKD patients (90.4%) survived significantly better than hCKD patients with either stage I (46.8%) or stage II (49.3%) hypertension (*HR: 0.56; 95% CI: 0.224-0.883; p=0.004*). BP cut-point values that were most predictive of mortality are shown in Table 4. The diagnostic accuracy of cut-point values of SBP (≥ 135 mmHg), DBP (≥ 83 mmHg), and MAP (≥ 102 mmHg) in predicting mortality is compared in Figure 5. The cumulative mortality in hCKD patients with heart failure (HF) was 84.0% (17/33).

The mean renal survival follow up time was 11.4 ± 18.7 (0.25-108.0) months. Eleven hCKD patients were lost to follow up while the rest was followed up for 25-127 (13.1 ± 20.8) months. The overall cumulative hypertension-specific mortality in hCKD was 62.4% (n=26) compared to 9.5% (n=7) in nCKD (*HR: 0.54; 95% CI: 0.35-0.83, p=0.005*).

Discussion

The prevalence of HTN in this study was very high; it was commonly of the severe type as 70.0% of the patients had stage II HTN. Unlike in the normal paediatric and adolescents' population where HTN prevalence is low (3.2-3.6%) [1-3], the prevalence is frequently high (20-80%) in CKD depending on the degree of renal dysfunction and underlying renal disease [4,6,7]. HTN is often difficult to control in CKD. Monotherapy

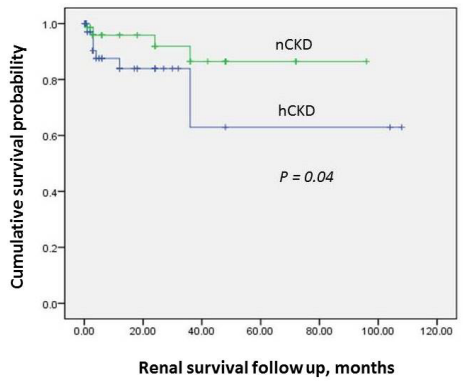

Figure 2: Kaplan-Meier surviva1curves comparing 1 and 5 years renal survival in normotensive chronic kidney disease (nCKD) and hypertensive chronic kidney disease (hCKD).

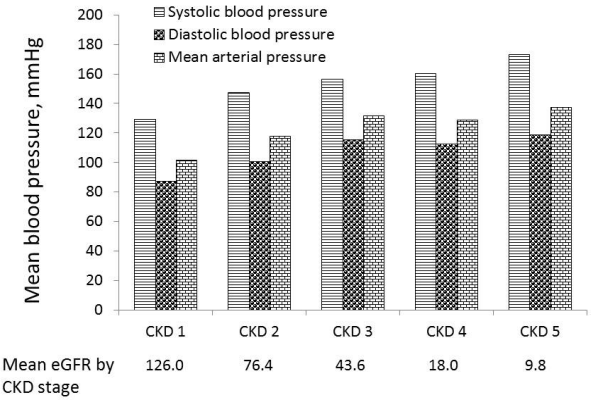

Figure 4: Correlation of mean systolic blood pressure (BP), diastolic BP, and mean arterial pressure with chronic kidney disease (CKD) stage in hypertensive CKD. eGFR, glomerular filtration rate in mL/min/1.73 m^2.

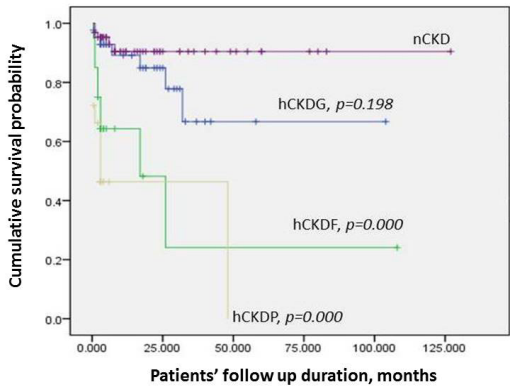

Figure 3: Kaplan-Meier survival curves comparing patients' outcome in normotensive chronic kidney disease (nCKD) with hypertensive chronic kidney disease (hCKD) in relation to degree of blood pressure (BP) control. hCKDG, hCKDF, and hCKDP refer to hCKD with good, fair, and poor BP control, respectively.

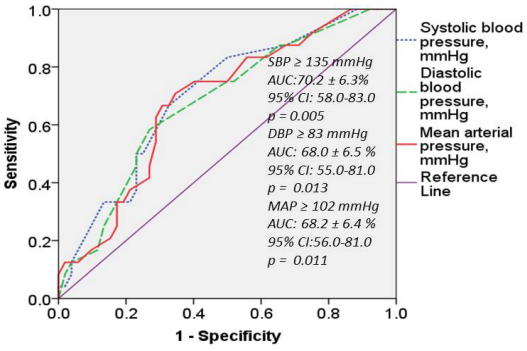

Figure 5: Receiver operating characteristic (ROC) curves comparing the discriminatory ability of the test variables to predict mortality in hypertensive chronic kidney disease. Systolic blood pressure (SBP) had the largest statistically significant area under the ROC curve (AUC). SBP is most discriminatory and the cut-point value of ≥ 135 mmHg on the SBP ROC curve is most significantly predictive of mortality (Sensitivity 83.3%; specificity 57.1%).

Outcome	At Systolic BP cut-point ≥ 135 mmHg		At Diastolic BP cut-point ≥ 83 mmHg		At MAP cut-point ≥ 102 mmHg	
	≥ 135	<135	≥ 83	<83	≥ 102	<102
Died	20	4	21	3	20	4
Alive	18	24	26	16	24	18
Sensitivity (95% CI)	83.3 (62.6-95.3)		87.5 (67.6-97.3)		83.3 (62.6-95.3)	
Specificity (95% CI)	57.1 (41.0-72.3)		38.1(23.6-54.4)		43.0 (28.0-59.0)	
Positive predictive value (95% CI)	53.0 (35.8-69.0)		44.7 (30.2-60.0)		45.5 (30.4-61.2)	
Negative predictive value (95% CI)	85.7 (67.3-96.0)		84.2 (60.4-97.0)		82.0 (60.0-95.0)	

Table 4: Blood pressure cut-point values that were most predictive of mortality in the patients

was rarely effective in controlling CKD/HTN as 61% of our patients were treated with two or more anti-hypertensives. Following treatment with combination anti-hypertensives, 44% of hCKD children were not able to achieve good post-treatment BP control (≤ 50th percentile for age, gender and height) in this study. This is similar to findings in other reports in which more than 50% of children with end-stage renal disease (ESRD) have uncontrolled hypertension, despite widespread use of antihypertensive drugs [21-23]. Although not captured in the objective of this study, the difficulty encountered in achieving good BP control in hCKD in this and other studies might be due to comorbid conditions like chronic anaemia, volume overload, endothelial dysfunction, arterial media calcification, and metabolic derangements like secondary hyperparathyroidism, hyperphosphataemia, and calcitriol deficiency. Sometimes the toxic effects of medications like erythropoietin, cyclosporine, tacrolimus, corticosteroids and non-steroidal anti-inflammatory drugs could make BP control difficult. In a cohort of ESRD children, poor BP control was associated with very young age, post dialysis fluid overload, and hyperphosphataemia. In that report, only 23.5% of treated patients were able to achieve a BP target of <90th percentile according to KDOQI [23]. Target-organ abnormalities are common features of HTN in children and adolescents. Even less severe hypertension has been associated with target-organ damage in CKD [24-26]. LVH, a marker of HTN, has been reported in 34-38% of children and adolescents with mild, untreated HTN [27-29]. In this study, 17 of 19 hCKD who had echocardiogram investigation showed evidence of altered cardiac geometry with concentric LVH, pressure overload, being the major HTN related cardiovascular morbidity. All the 17 patients had HF demonstrating the deleterious cardiac impact of HTN.

This study revealed that the overall renal survival was significantly better in nCKD than hCKD showing HTN as a strong risk factor for renal disease progression. But further analysis revealed that 1 and 5 years renal survivals in nCKD and hCKD patients with good BP control were similar showing that with good BP control in hCKD, as demonstrated in Figure 1, disease progression could be retarded. In Figure 1, post-treatment BP in hCKD with good BP control (SBP and/ or DBP ≤ 50th percentile for age, gender and height) was similar to BP in nCKD. On the other hand, renal function performed poorly in hCKD patients with both fair and poor BP control. Studies have shown that children with hCKD tend to have a more rapid decline in eGFR than those without hypertension [30-32]. Data from the Chronic Kidney Disease in Children (CKiD) [16] study show that among 425 children with repeated measures of GFR, having SBP >90th percentile for age, gender, and height was associated with faster progression of CKD as compared with lower BP [32]. In that study, the annualized percent change in GFR among those with SBP>90th percentile was −7.5 ml/min/1.73 m^2 (*95% CI:−16.6-0.1*), compared to −3.8 (*95% CI −11.8-3.8*) in those with SBP between the 50th and 90th percentiles and −2.5 (*95% CI: −8.9-3.9*) in those with SBP below the 50th percentile. Although an ACEi or ARB is the suggested treatment of choice in non-dialyzing children with CKD in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria [16], our data showed that treatment with either ACEi or ARB conferred no added advantage on renal survival when compared with other anti-hypertensives. It appears from this study that a good BP control (post-treatment BP target ≤ 50th percentile for age, gender, and height) irrespective of the anti-hypertensives used is all that is important to achieve a good renal survival in childhood hCKD. While the ItalKid Project database did not show clear evidence of ACEi efficacy in slowing CKD progression [33] another study demonstrated the superiority of anti-hypertensive regimens containing an ACEi or ARB in controlling BP in childhood CKD [6]. Patients' survival followed a pattern similar to renal survival in this study. While patients' outcome was similar in both hCKD with good BP control and nCKD, outcome was significantly poor in hCKD patients with fair and poor BP control. This again emphasized the importance of good BP control in ensuring better renal and patients' survival in hCKD. The need to diagnose and manage CKD early and appropriately was shown by the progressive worsening of the mean BPs with increasing severity of the CKD stages as hypertension severity significantly correlated negatively with the eGFR. Going by our findings that mortality hazard was 0.56-fold higher in both stages I and II HTN than in nCKD, we then determined the BP cut-point values that were most predictive of mortality using the Youden's index [20] and compared their diagnostic accuracy by ROC analysis. SBP ≥ 135 mmHg was found to be most discriminatory and predictive of mortality of the three BP test variables; it was also associated with the highest diagnostic accuracy with the area under the ROC curve, sensitivity and specificity being 70.2%, 83.2%, and 57.1%, respectively. The overall mortality hazard was 0.54-fold (*95% CI: 0.35-0.83*) higher in hCKD than in nCKD.

This study is limited by its retrospective nature and the small sample size. It should, however, serve as a template for a larger future prospective study in sub-Saharan Africa.

It is concluded that Stage II hypertension occurred more frequently than stage I. Hypertension is a significant risk factor for poor renal survival and mortality in childhood CKD. Renal and patients' survival could definitely be improved if post-treatment BP level of ≤ 50th percentile for age, gender, and height can be achieved.

Conflict of Interest

None to declare

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