Arab Journal of Nephrology and Transplantation. 2013 May;6(2):105-13

*Original Article*

# Epidemiology and Clinicopathologic Outcome of Pediatric Chronic Kidney Disease in Nigeria, a Single Cenetr Study

Wasiu Adekunle Olowu*, Olufemi Adefehinti, Theophilus Adesola Aladekomo

Pediatric Nephrology and Hypertension Unit, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Osun State, Nigeria.

## Abstarct

**Introduction**: Due to dearth of data, chronic kidney disease (CKD) outcome in African children has been dismal owing to poor understanding of its etiology, manifestations and management.

**Methods**: We retrospectively analyzed the records of 154 CKD children and adolescents who were managed at Obafemi Awolowo University Teaching Hospitals Complex between 2000 and 2009 to evaluate the epidemiology and clinicopathologic outcome of pediatric CKD in Nigeria.

**Results**: Overall mean incidence was 11 (6-20) per million children population (pmcp)/year while prevalence averaged 48 (8-101) pmcp. There were 86 males (55.8%). Median age was 10.0 (0.2-15.5) years with 83.8% ≥ 5 years old. Etiologies were glomerular disease (GMD, 90.26%), congenital and acquired urinary tract (7.79%) and hereditary disorders (1.95%). CKD stages at diagnosis were 45.5% CKD-1, 22.7% CKD-2, 10.4% CKD-3, 2.6% CKD-4 and 18.8% CKD-5. Median progression time through the CKD stages was 24.0 (3-108) months. Mean dialysis incidence and prevalence were 1 (0-4) pmcp/year and 4 (1-12) pmcp, respectively. Hypertension, heart failure (HF), malnutrition, anemia, acute-on-CKD, need for dialysis, azotemia, hypercreatininemia, and high calcium-phosphorous product (≥ 55 $mg^2/dL^2$) were mortality risk factors. CKD-1 survived significantly better than CKD stages 3-5 ($p < 0.05$) but not CKD-2 ($p=0.1$). Hypertensive CKDs without HF survived better (73.0%) than hypertensive CKDs with HF (16.0%) [Hazard ratio (HR): 0.34, 95% CI: 0.14-0.83]. GMD survived better (68.5%) than non-GMD patients (33.0%) [HR: 2.87, 95% CI: 1.16-7.06].

**Conclusion**: CKD was commoner among school than pre-school age children. GMD was the predominant etiology with better outcome than non-GMD. Comorbidity prevalence increased significantly with increasing severity of CKD stage.

* Corresponding author; Pediatric Nephrology and Hypertension Unit, Obafemi Awolowo University Teaching Hospitals Complex, PMB 5538, Ile-Ife, Osun State, Nigeria; E. mail: yetundeolowu@yahoo.com.

**Keywords**: Chronic Kidney Disease; Glomerular Disease; Mortality Risk Factors; Nigeria

***The authors declared no conflict of interest***

## Introduction

Chronic kidney disease (CKD) is a progressive disorder with serious systemic morbidities causing prolonged patient sufferings, increased treatment cost, and death inspite of much caring effort. Childhood and adolescent CKD, especially in its advanced form, poses serious cardiovascular, neurologic, metabolic, hematologic, endocrine and other varied clinical problems that stretch the financial capacity of parents to the limits. CKD management burden has increased over the years across the globe. The situation is worse in developing countries with limited resources [1, 2]. Developed countries with adequate resources have registered CKD as a major health problem [3-6] with huge financial implications for governments [3]. This became a source of concern both to the International Society of Nephrology and International Federation of Kidney Foundation that it was considered imperative to jointly launch a 'World Kidney Day' that has been held yearly since 2006 [7]. NKF-K/DOQI (National Kidney Foundation-Kidney Disease Outcome Quality Initiative) has formulated comprehensive CKD clinical practice guidelines to promote early disease detection, delay disease progression, prevent related complications and improve outcome [8].

Published K/DOQI-based data on pediatric CKD are few [2, 9-20]. Most of them are from centers outside Africa [9-20]. At the time of writing only one published K/DOQI-based report is from Africa [2]. Dearth of information on CKD from Africa has led to dismal outcome owing to poor understanding of its etiology, clinicopathologic manifestations, leading to late diagnosis and management including preventive measures. This study sought to expand the available K/DOQI-based CKD data from Africa by determining CKD incidence, prevalence, etiologies, stages, clinicopathologic

**Table 1: Classification and staging of chronic kidney disease in children < 2 years of age in the studied group**

| Age group | Normal glomerular filtration rate (NGFR) | Stage-1 CKD: lower limit of NGFR reduced by 0.0% | Stage-2 CKD: lower limit of NGFR reduced by 33.3- 1.1% | Stage-3 CKD: lower limit of NGFR reduced by 66.7-34.4% | Stage-4 CKD: lower limit of NGFR reduced by 83.3-67.8% | Stage-5 CKD: lower limit of NGFR reduced by >83.3% |
|---|---|---|---|---|---|---|
| **1 week** | 26-56 | ≥ 26 | 17.3-25.7 | 8.7-17.1 | 4.3-8.4 | <4.3 |
| **2-8 weeks** | 41-91 | ≥ 41 | 27.3-40.5 | 13.7-26.9 | 6.8-13.2 | <6.8 |
| **9 weeks to 2 years** | 74-118 | ≥ 74 | 49.3-73.2 | 24.6-48.5 | 12.0-24.0 | <12.0 |

manifestations, and outcome in Nigerian children and adolescents managed at our center.

## Methods

we performed a retrospective analysis of baseline and follow-up data of pediatric CKD patients in the pediatric nephrology and hypertension unit, Obafemi Awolowo university teaching hospitals complex, ile-ife, Osun state, Nigeria. Records between January 1st, 2000 and December 31st, 2009 were reviewd. In our locality, the population of children and adolescents (≤ 16 years old) is 1 530 000. The study was approved by research and ethical committee of our institution.

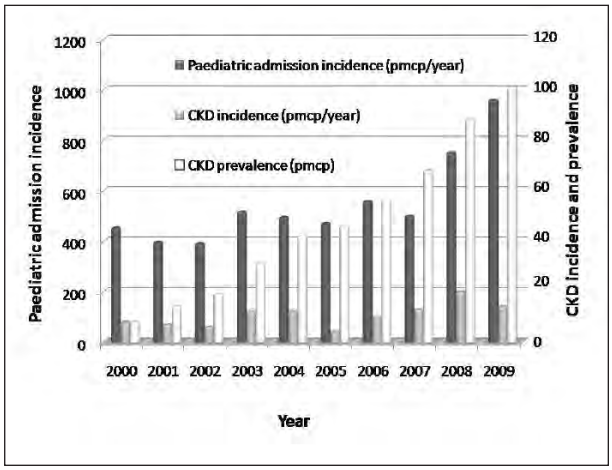
All patients with laboratory and/ or radiologic evidence of CKD, who were followed-up for ≥ 3 months, were included. Patients with insufficient laboratory data were excluded. Estimated glomerular filtration rate (eGFR) was determined using the Schwartz formula [21]. We diagnosed CKD based on K/DOQI diagnostic and staging criteria [8]. Significant proteinuria was defined as a dipstick proteinuria of 1+ or more or ≥4 mg/m$^2$/ hr in a 24-hour urine sample or UPCR ≥ 20 mg/mmol. Hematocrit < 33.0% was regarded as anemia. Hospital presentions >3 months after onset of symptoms were regarded as late presentaions. Hypertension (HTN) was defined and staged according to the task force report on high blood pressure in children and adolescents [22]. Considering that all patients had at least one end-organ damage, post treatment control of HTN was regarded as good, fair, and poor if systolic and/ or diastolic blood pressure (BP) was ≤ 50th percentile, >50th but < 90th percentile, and > 90th percentile for age, gender and height, respectively.

Chronic glomerulonephritis markers were hypertension, azotemia, reduced eGFR, red blood cell cast, proteinuria, hematuria, symmetrically shrunken kidneys on ultrasound, and renal histopathologic features. Sickle cell anemia nephropathy markers comprised hemoglobin-S on electrophoresis, proteinuria with or without urine sediments and renal histopathologic features. Long standing history of bilateral flank pains, fever, dysuria, white blood cell casts and persistently low specific gravity on urinalysis, significant bacteriuria, and asymmetrically shrunken kidneys on ultrasound indicated chronic pyelonephritis. Obstructive uropathies due to posterior uritheral valve (PUV) and urinary bladder rhabdomyosarcoma were diagnosed based on poor urine stream, urinary retention and abnormal voiding cystourithrogram (VCUG). Urethrocystoscopy and histopathologic features confirmed rhabdomyosarcoma. Poor urine stream and stenotic external urethral meatus confirmed post circumcision meatal stenosis. Systemic lupus erythematosus and Churg-Strauss syndrome associated nephropathy was diagnosed using the American College of Rheumatology criteria [23, 24]. Diagnoses of infant polycystic kidney disease (IPKD), solitary multi-cystic dysplastic kidney, and fused crossed ectopic kidney were made by ultrasound.

Because K/DOQI recommendation is not applicable to children < 2 years old, the CKD stages for this age group was, therefore, computed by applying the same percentage reduction of the eGFR from the lower limit of normal range for each of the five K/DOQI CKD stages to the lower limits of normal eGFR for each of the age groups under 2 years (Table-1).

To analyze data, SPSS Version 15.0 (SPSS Inc., Chicago, IL, USA) was used. The comparative statistics used were chi-square test, odds ratio (OR), hazard ratio, Wilcoxon signed ranks test, Pearson correlation, Cox regression analysis, Kaplan-Meier survival analysis and the log-rank test. Data of patients who presented with CKD-5 and remained so for ≥ 3 months were excluded from renal survival analysis. The diagnostic accuracy of identified mortality risk factors, including laboratory tests, in predicting mortality was determined using the AUROC curve test. The sensitivity, specificity, positive and negative predictive values as well as the positive and negative LR for the categorical mortality risk factors and diagnostic (continuous) test variables was calculated.

**Figure-1: The yearly incidence and prevelance of CKD in the studied population**




Cut-point value that most predict mortality for each of the diagnostic test variables was determined using the Youden's index [25]. Statistically significant p value was set at <0.05.

## Results

Of 8 393 pediatric admissions, 154 (1.83%) had CKD. The incidence of chronic kidney disease (CKD) increased with increasing incidence of pediatric admission. CKD prevalence also increased from year to year (Figure-1). Table-2 summarizes the demographic and anthropometric characteristics of the patients.

Table-3 summarizes the CKD etiology pattern while Figure-2 shows the prevalence of CKD etiology by age group. Disease progression occurred over a median time of 24.0 (30.3 ± 3.2; range 3-108) months in 16 patients who required no dialysis. Four (2.6%) patients were under 2 years of age. One of these was in stage 1 and three were in stage 5 CKD, due to rapidly progressive glomerulonephritis, infantile polycystic kidney disease (IPKD), and PUV (in two cases). Their eGFR ranged between two and 82 mL/min/1.73m$^2$.

Prevalence of major comorbidities by chronic kidney disease (CKD) stage is shown in Figure-3. The risk of elevated calcium-phosphorous product [odds ratio, OR: 2.5, 95% CI: 1.76-3.56], malnutrition [OR: 1.74, 95% CI: 1.40-2.16], anemia [OR: 2.16, 95% CI: 1.83-2.56], hypertension [OR: 2.09, 95% CI: 1.76-2.49], and heart failure [OR: 2.24, 95% CI: 1.80-2.81] increased significantly from CKD stage 1 to 5. Other comorbidities were water intoxication (n=3), stroke (n=5) and hypertensive encephalopathy (n=22). Seven patients had varying grades of hypertensive retinopathy. The prevalences of malnutrition in social classes II, III, IV and V were 12.5%, 28%, 21% and 41.3% respectively. Seventeen patients were growth retarded.

Forty-nine of 121 (40.5%) patients, who survived beyond 6 months, were lost to follow-up. Median follow-up period was 6.0 (16.8 ± 22.6, range: 0.25-127) months. CKD-1 was significantly associated with better patients' survival than stages 3-5 but not CKD-2 (Figure-4). Renal survival at 1 and 5 years were 94.1% and 63.4%, respectively. Overall patients' survival at 1 and 5 years were 80.7% and 66.0% respectively. Hypertension (HTN), heart failure (HF), Protein energy malnutrition (PEM), anemia, superimposed acute kidney injury, need for dialysis, azotemia, hypercreatinemia, and high Ca x P (≥ 55 mg$^2$/dL$^2$) were mortality risk factors. The continuous risk factors had similar AUROCs implying that any of the test variables can reasonably predict mortality in childhood CKD. But low hematocrit cut-point ≤ 22.5% was most predictive of mortality with 94% sensitivity, 78% specificity, 58.5% positive and 97.5% negative predictive value as well as positive LR of 4.3 and negative LR of 0.1.

Forty-one patients required dialysis but only 17 patients were dialyzed (three by peritoneal dialysis and fourteen by hemodialysis), giving an overall median dialysis incidence and prevalence of one (0-4) pmcp/year and four (1-12) pmcp, respectively. Non-dialysis was due to financial constraints in 12 patients (50.0%), diuresis onset (12.5%), death (12.5%), positive human immune deficiency virus testing (8.3%), and other factors (16.7%). Eight incident dialysis patients died owing to inability to afford further dialysis; similarly, financial constraints precluded kidney transplant in the prevalent dialysis patients.

There were 139 patients with glomerular disease (GMD) and 15 patients with non-GMD. Median illness duration before presentation was two and 48 months for GMD and non-GMD, respectively (p= 0.001). Estimated GFR at presentation was significantly lower in non-GMD than GMD patients (12.4 versus 64 ml/min/1.73m$^2$, p=0.0016). One-year renal survival in GMD and non-GMD was 95.4% and 80.0%, respectively [hazard ratio (HR): 8.12, 95% CI: 1.44-46.0; p=0.02]. GMD patients (68.5%) survived better than non-GMD (33.0%) [HR: 2.87, 95% CI: 1.16-7.06; p=0.02].

Half the patients were hypertensive. Blood pressure control was good, fair and poor in 56%, 23.4% and 20.6% of patients respectively. The number of antihypertensive medications used was one, two, three or more in 39%, 35%, 17% and 9% respectively. By Kaplan-Meier pairwise comparisons and the log-rank test, patients with good BP control survived (66.7%) better than patients

**Table 2: Demographic and clinical characteristics of studied patients (N=154)**

| Demographic and clinical characteristics of studied patients | Results |
|---|---|
| Overall paediatric admission incidence, pmcp/year (N [range]) | 549 [391-959] |
| Overall mean CKD incidence, pmcp/year (N [range]) | 11 [6-20] |
| Overall mean CKD prevalence, pmcp (N [range]) | 48 [8-101] |
| **CKD incidence at diagnosis (pmcp/year)** | |
| CKD stage 1 | 5 |
| CKD stage 2 | 3 |
| CKD stage 3 | 2 |
| CKD stage 4 | 1 |
| CKD stage 5 | 2 |
| **CKD prevalence at diagnosis (pmcp)** | |
| CKD stage 1 | 46 |
| CKD stage 2 | 23 |
| CKD stage 3 | 11 |
| CKD stage 4 | 3 |
| CKD stage 5 | 19 |
| **Socioeconomic class [N (%)]** | |
| II | 8 (5.2) |
| III | 18 (11.7) |
| IV | 24 (15.6) |
| V | 104 (67.5) |
| Late presentation (N (%) | 71 (46.1) |
| Pre-diagnosis duration of illness symptoms, months (median [range]) | 3.0 [0-132] |
| Male gender, (N (%)) | 86 (55.8) |
| Age, years (mean ± SD) | 9.2 ± 3.7 |
| **Age group, years (N (%))** | |
| < 5 | 20 (13.0) |
| 5-9 | 53 (34.4) |
| 10-14 | 76 (49.4) |
| 15-19 | 5 (3.2) |
| Weight , kg (mean ± SD) | 27.7 ± 10.6 |
| Height, cm (mean ± SD) | 127.3 ± 19.7 |
| Body mass index, kg/m$^2$ (mean ± SD) | 17.0 ± 3.6 |

CKD: chronic kidney disease; pmcp: per million children population

with either fair (24.1%; p=0.002) or poor (0.0%; p=0.000) BP control. Hypertensives with good BP control (66.7%) and normotensives (90.4%) survived similarly, p= 0.2. Normotensives survived (90.4%) better than patients with either stage I (46.8%, p=0.01) or stage II (49.3%, p=0.000) HTN. Stages 1 and 2 HTN patients survived similarly (p=0.4). Cox regression analysis revealed a 55.5% (6/13) cumulative mortality rate among non-hypertensive HF compared with 2.4% (1/63) in patients without HF and HTN (HR: 0.16, 95% CI: 0.07-0.37; p=0.000). The cumulative mortality in patients with both HTN and HF was 84.0% (17/33) compared with 27.0% (7/43) in hypertensives without HF (HR: 0.34, 95% CI: 0.14-0.83; p=0.02).

Normotensives demonstrated significantly higher one/five years renal survival (97.0/80.0%) than patients with fair (75.0/25.0%, p= 0.01) and poor (50.0/0.00%, p=0.003) BP control. Normotensives (97.0/80.0%) and hypertensives with good BP control (96.2/63.0%, p=0.4) had similar one/five years renal survival. Median renal survival times of patients who received either angiotensin antagonist medications (ACEi or ARB) or patients treated with other anti-hypertensives were similar (47 versus 33 months; p=0.6).

## Discussion

Mean CKD incidence in our center increased from 3.43 to 11 pmcp/year, three times more, from 1995-1999 [1] to 2000-2009 eras, emphasizing the importance of prevention. Other centers have observed similar rising incidence of CKD (8-14.3 pmcp/year) [18, 19, 26-29] and massive increase in CKD prevalence (49.0-96.1 pmcp) [18, 19, 26-29]. The increased prevalence (48.0 pmcp) observed in this study concurs with the rising global CKD burden. This, in our setting, calls for facility expansion if qualitative patients care is not to be compromised. CKD stages prevalence pattern vary from study to study [2, 9, 10, 13, 18, 19]. Our results show the dynamic nature of CKD with sixteen patients progressing through the stages without needing dialysis while seventeen progressed to ESRD and received dialysis. At diagnosis CKD-5 constituted 18.8% of the entire CKD stage spectrum agreeing with the statement that, 'CKD-5 represents the tip of CKD iceberg' [6].

In most studies, about 56.3-86.8% of the patients were aged 5 years and above [2, 12, 26, 30-33] with average diagnosis age being 6.9-11.29 years [2, 9, 12, 29-34]. Our findings did not contradict this global CKD age trend suggesting that CKD is commonly a school age disease. Non-GMDs, largely due to congenital anomalies of the kidney and urinary tract (CAKUT) and non-CAKUT, were not diagnosed during infancy in majority of our

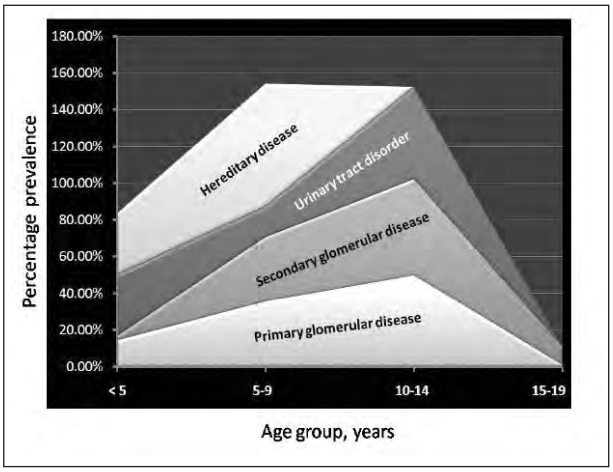
**Table 3: Pattern of etiology of chronic kidney disease in the studied group**

| Etiology | Number within category (%) | % of total CKD patients (N=154) |
|---|---|---|
| **Primary Glomerular Disease (n=99)** | | 64.29 |
| Nephrotic syndrome | 69 (69.7) | 44.80 |
| Chronic glomerulonephritis (GN) | 30 (30.3) | 19.50 |
| **Secondary Glomerular Disease (n=40)** | | 25.97 |
| Lupus nephritis | 15 (37.5) | 9.70 |
| Hepatitis B virus nephritis | 6 (15.0) | 3.90 |
| Sickle cell nephropathy | 6 (15.0) | 3.90 |
| Churg-Strauss syndrome nephritis | 3 (7.5) | 1.95 |
| Rapidly progressive GN (Henoch-Schonlein purpura) | 3 (7.5) | 1.95 |
| Human immune deficiency virus-associated nephropathy | 2 (5.0) | 1.30 |
| Bee stings | 1 (2.5) | 0.65 |
| Rhabdomyosarcoma (paraneoplastic syndrome) | 1 (2.5) | 0.65 |
| Burkitt's lymphoma nephropathy | 1 (2.5) | 0.65 |
| Addison's disease | 1 (2.5) | 0.65 |
| Mixed connective tissue disease | 1 (2.5) | 0.65 |
| **Urinary Tract Disorder (n=12)** | | 7.79 |
| Posterior urethral valves (PUV) | 4 (33.3) | 2.60 |
| Crossed fussed ectopic kidney with severe hypospadias and meatal stenosis | 1 (8.35) | 0.65 |
| Solitary dysplastic multicystic kidney with PUV | 1 (8.35) | 0.65 |
| Prune Belly syndrome with PUV | 1 (8.35) | 0.65 |
| Post circumcision meatal stenosis | 4 (33.3) | 2.60 |
| Chronic pyelonephritis | 1 (8.35) | 0.65 |
| **Hereditary (n=3)** | | |
| Infantile polycystic kidney disease | 3 (100.0) | 1.95 |

CKD: chronic kidney disease

patients. The peak age groups at diagnosis of IPKD, and CAKUT/non-CAKUT in this study were 5-9 years and 10-14 years, respectively. This contradicts the age group pattern in European countries where diagnoses and treatment of these conditions are commonly made during infancy [10, 19]. Poorer renal and patients' survival in non-GMD compared with GMD patients was significantly due to severer renal function impairment at diagnosis, late hospital presentation and management in the former. This explains why mortality risk was approximately three times higher in non-GMD than GMD patients. Elsewhere, non-GMD survived better than GMD because of early diagnosis and treatment [29]. These facts underline the need for deliberate prenatal and neonatal screening for CAKUT in Nigeria for early diagnosis, management and better outcome. Unlike in Australia/ New Zealand, Turkey, Canada and some European countries, where non-GMD predominantly cause CKD (67.5-97.0%) [9, 10, 12, 18, 19, 26, 28, 29], GMD was the predominant etiology in our patients (90.3%) and other centers in Nigeria and some developing countries [2, 31, 33, 34]. High prevalence of bacterial, viral, and parasitic infections that commonly affect the kidneys in developing countries was considered responsible for this [35]. The low ESRD burden in this study emanated from our extremely low incidence and prevalence rates

**Figure-2: Prevalence of the etiology of chronic kidney disease by age-group**




of renal replacement therapy by dialysis. This is similar to findings in Serbian and Vietnamese children [18, 33]. Low socio-economic class of the majority of the patients largely contributed to this as the burden of healthcare delivery cost is borne totally by patients in Nigeria.

The overall prevalence of high Ca x P, a significant mortality risk factor in this study, was 15%. This is similar to the 27.1% prevalence reported for Turkish children [12]. Vascular calcifications have been associated with high Ca × P with increased risk of cardiovascular morbidity and mortality [37].

Protein energy malnutrition (PEM) prevalence ranges between 6% and 65% in childhood CKD [19, 38]. It is more pronounced when dialysis is initiated, because of associated increased catabolism, loss of nutrients and anti-oxidants, and dietary restrictions [39]. In this study, PEM prevalence increased from 32.4% for CKD-1 to 50% and 41.4% for CKD -4 and -5, respectively. In this and another study, PEM was a risk factor for mortality [40].

An overall 36.6% anemia prevalence rate that increased from 31% for CKD-1 to 93.3% for CKD -4 and -5 was found in Canadian children [9]. A higher overall prevalence (58.4%) that increased from 41.4% for CKD-1 to 100% for CKD-4 and 97.0% for CKD-5 was found in this study. Anemia is 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 [41].

In childhood CKD, hypertension prevalence may range between 20% and 80% depending on degree of renal dysfunction and underlying renal disease [42, 43]. About 50% of our patients were hypertensive with majority (70%) having stage 2 HTN. HTN was an independent mortality risk factor and was associated with escalation of mortality from 55.5% in non-hypertensive HF patients to 84% in hypertensive HF patients. Concentric left ventricular hypertrophy was a major HTN related cardiovascular morbidity in those with echocardiogram results. Monotherapy was rarely effective in controlling CKD-associated HTN as 61% of our patients were treated with two or more anti-hypertensives. Good BP control had better renal and patients' survival than patients with either fair or poor BP control. Post-treatment BP in hypertensives with good BP control was similar to the normotensives'. Furthermore, both had similar renal survival, emphasizing the importance of HTN as a risk factor for disease progression and the need to tame it effectively.

CKD mortality rate is higher in developing (20.3-58.3%) [1, 2, 30-32, 34, 44] than developed countries (3-20.0%) [10, 45, 46]. In this study the five year all-cause cumulative mortality is 34.0% , a rate which is considered high and similar to findings in developing countries [2, 30-33]; the high mortality rate was sequel to poor dialysis access and severe co-morbidities.

## Conclusions

CKD was commoner among school than pre-school age children. GMD was the predominant etiology with better renal and patient outcome than non-GMD. Comorbidity prevalence increased significantly with increasing severity of CKD stage.

## References

1. Olowu WA. Renal failure in Nigerian children: factors limiting access to dialysis. 2003 Dec;18(12):1249-54.

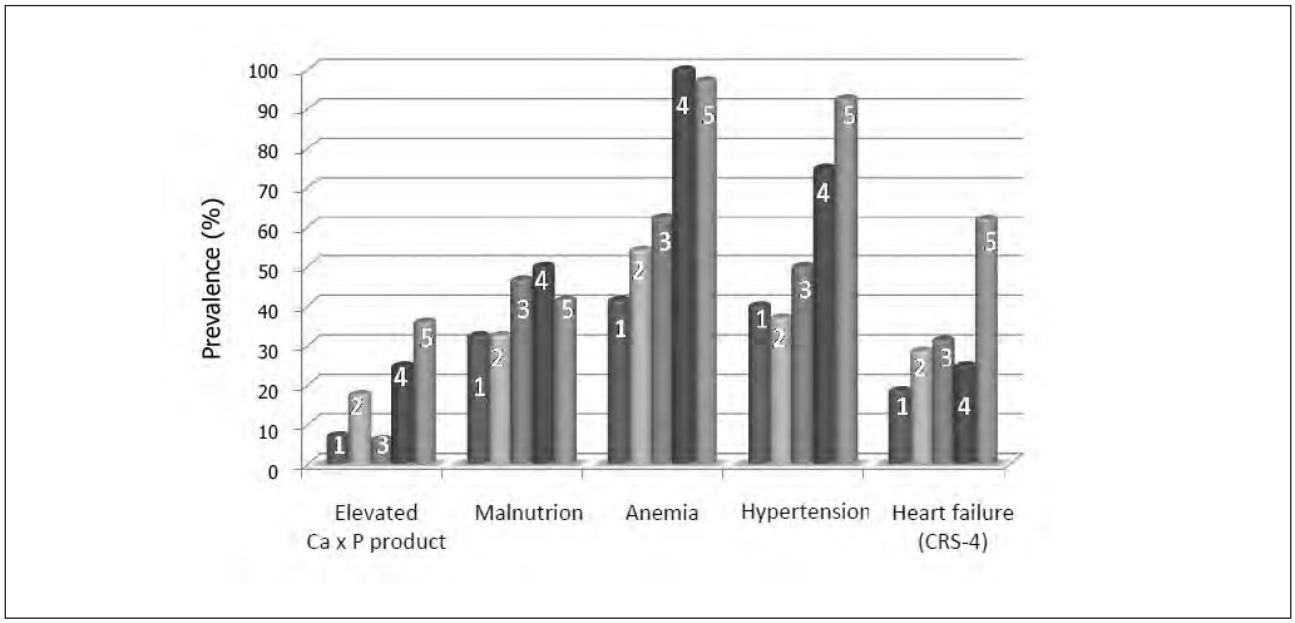
2. Bhimma R, Adhikari M, Asharam K, Connolly C. The spectrum of chronic kidney disease (stages 2-5) in KwaZulu-Natal, South Africa. Pediatr Nephrol. 2008 Oct;23(10):1841-6. doi: 10.1007/s00467-008-0871-5.

3. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol. 2002 Jan;13 Suppl 1:S37-40.

4. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet. 2005 Jan 22-28;365(9456):331-40.

5. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, Hallan HA, Lydersen S, Holmen J. International comparison of the relationship of chronic

**Figure-3: Prevalence of major comorbidities by chronic kidney disease (CKD) stage**




kidney disease prevalence and ESRD risk. J Am Soc Nephrol. 2006 Aug;17(8):2275-84.

6. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003 Jan;41(1):1-12.

7. International Society of Nephrology and International Federation of Kidney Foundation. World Kidney Day. [Cited 2012 Feb 22]. Available at: http://www.worldkidneyday.org/page/history-of-wkd.

8. National Kidney Foundation. Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. K/DOQI clinical practice guidelines. Am J Kidney Dis. 2002;39 (Suppl 1):S1-S266.

9. Wong H, Mylrea K, Feber J, Drukker A, Filler G. Prevalence of complications in children with chronic kidney disease according to KDOQI. Kidney Int. 2006 Aug;70(3):585-90.

10. Mong Hiep TT, Ismaili K, Collart F, Van Damme-Lombaerts R, Godefroid N, Ghuysen MS, Van Hoeck K, Raes A, Janssen F, Robert A. Clinical characteristics and outcomes of children with stage 3-5 chronic kidney disease. Pediatr Nephrol. 2010 May;25(5):935-40.

11. Foster BJ, Kalkwarf HJ, Shults J, Zemel BS, Wetzsteon RJ, Thayu M, Foerster DL, Leonard MB. Association of chronic kidney disease with muscle deficits in children. J Am Soc Nephrol. 2011 Feb;22(2):377-86.

12. Bek K, Akman S, Bilge I, Topaloğlu R, Calişkan S, Peru H, Cengiz N, Söylemezoğlu O. Chronic kidney disease in children in Turkey. Pediatr Nephrol. 2009 Apr;24(4):797-806.

13. Koshy SM, Garcia-Garcia G, Pamplona JS, Renoirte-Lopez K, Perez-Cortes G, Gutierrez ML, Hemmelgarn B, Lloyd A, Tonelli M. Screening for kidney disease in children on World Kidney Day in Jalisco, Mexico. Pediatr Nephrol. 2009 Jun;24(6):1219-25.

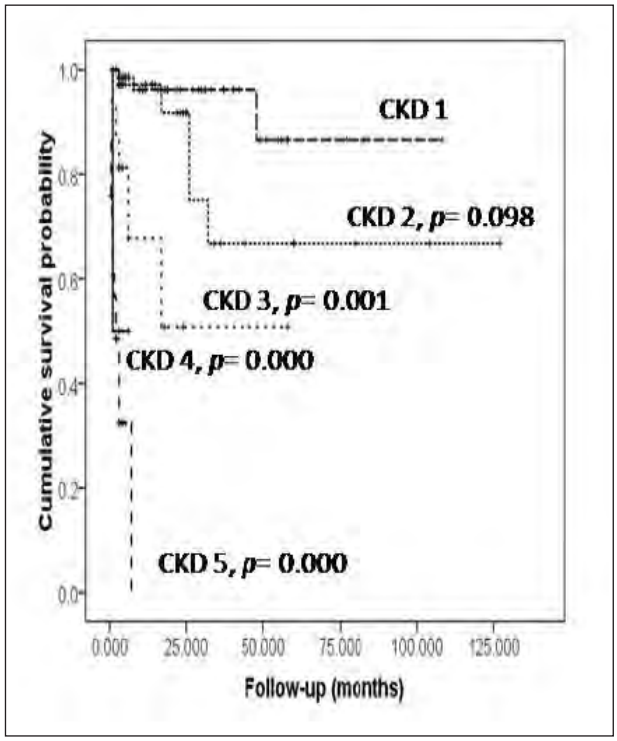
15. Armstrong JE, Laing DG, Wilkes FJ, Kainer G. Smell and taste function in children with chronic kidney disease. Pediatr Nephrol. 2010 Aug;25(8):1497-504.

16. Hari P, Gupta N, Hari S, Gulati A, Mahajan P, Bagga A. Vitamin D insufficiency and effect of cholecalciferol in children with chronic kidney disease. Pediatr Nephrol. 2010 Dec;25(12):2483-8.

16. Marciano RC, Soares CM, Diniz JS, Lima EM, Silva JM, Canhestro MR, Gazzinelli A, Melo CC, Dias CS, Simões e Silva AC, Correa H, Oliveira EA. Behavioral disorders and low quality of life in children and adolescents with chronic kidney disease. Pediatr Nephrol. 2011 Feb;26(2):281-90.

17. Heath J, Mackinlay D, Watson AR, Hames A, Wirz L, Scott S, Klewchuk E, Milford D, McHugh K. Self-reported quality of life in children and young people

**Figure-4: Impact of chronic kidney disease stage at diagnosis on patients' survival**




with chronic kidney disease. Pediatr Nephrol. 2011 May;26(5):767-73.

18. Peco-Antic A, Bogdanovic R, Paripovic D, Paripovic A, Kocev N, Golubovic E, Milosevic B; Serbian Pediatric Registry of Chronic Kidney Disease (SPRECKID). Epidemiology of chronic kidney disease in children in Serbia. Nephrol Dial Transplant. 2012 May;27(5):1978-84.

19. Areses Trapote R, Sanahuja Ibáñez MJ, Navarro M; Investigadores Centros Participantes en el REPIR II. [Epidemiology of chronic kidney disease in Spanish pediatric population. REPIR II Project]. Nefrologia. 2010;30(5):508-17.

20. Rinat C, Becker-Cohen R, Nir A, Feinstein S, Algur N, Ben-Shalom E, Farber B, Frishberg Y. B-type natriuretic peptides are reliable markers of cardiac strain in CKD pediatric patients. Pediatr Nephrol. 2012 Apr;27(4):617-25.

21. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987 Jun;34(3):571-90.

22. [No authors listed] Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Pediatrics. 1996 Oct;98(4 Pt 1):649-58.

23. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982 Nov;25(11):1271-7.

24. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, *et al*. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990 Aug;33(8):1094-100.

25. Bewick V, Cheek L, Ball J. Statistics review 13: receiver operating characteristic curves. Crit Care. 2004 Dec;8(6):508-12.

26. Orr NI, McDonald SP, McTaggart S, Henning P, Craig JC. Frequency, etiology and treatment of childhood end-stage kidney disease in Australia and New Zealand. Pediatr Nephrol. 2009 Sep;24(9):1719-26.

27. USRDS 2008 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda (MD); 2008.

28. van der Heijden BJ, van Dijk PC, Verrier-Jones K, Jager KJ, Briggs JD. Renal replacement therapy in children: data from 12 registries in Europe. Pediatr Nephrol. 2004 Feb;19(2):213-21.

29. Ardissino G, Daccò V, Testa S, Bonaudo R, Claris-Appiani A, Taioli E, Marra G, Edefonti A, Sereni F; ItalKid Project. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics. 2003 Apr;111(4 Pt 1):e382-7.

30.Vachvanichsanong P, Dissaneewate P, McNeil E. Childhood chronic kidney disease in a developing country. Pediatr Nephrol. 2008 Jul;23(7):1143-7.

31. Anochie I, Eke F. Chronic renal failure in children: a report from Port Harcourt, Nigeria (1985-2000). Pediatr Nephrol. 2003 Jul;18(7):692-5.

32. Ali el-TM, Abdelraheem MB, Mohamed RM, Hassan EG, Watson AR. Chronic renal failure in Sudanese children: aetiology and outcomes. Pediatr Nephrol. 2009 Feb;24(2):349-53.

33. Huong NT, Long TD, Bouissou F, Liem NT, Truong DM, Nga do K, Chien TT, Bascands JL. Chronic kidney disease in children: the National Paediatric Hospital experience in Hanoi, Vietnam. Nephrology (Carlton). 2009 Dec;14(8):722-7.

34. Michael IO, Gabreil OE. Chronic renal failure in children of benin, Nigeria. Saudi J Kidney Dis Transpl. 2004 Jan-Mar;15(1):79-83.

35. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012 Mar;27(3):363-73.

36. Kidney Disease: Improving Global Outcomes (KDIGO). Chapter 1: Introduction and definition of CKD–MBD and the development of the guideline statements. Kidney Int. 2009 Aug;76 (Suppl 113):S3-8.

37. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000 May 18;342(20):1478-83.

38. Sylvestre LC, Fonseca KP, Stinghen AE, Pereira AM, Meneses RP, Pecoits-Filho R. The malnutrition and inflammation axis in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2007 Jun;22(6):864-73.

39. Beşbaş N, Ozdemir S, Saatçi U, Coşkun T, Ozen S, Topaloğlu R, Bakkaloğlu A, El Nahas AM. Nutritional assessment of children on haemodialysis: value of IGF-I, TNF-alpha and IL-1beta. Nephrol Dial Transplant. 1998 Jun;13(6):1484-8.

40. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990 May;15(5):458-82.

41. Silverberg DS, Wexler D, Iaina A, Steinbruch S, Wollman Y, Schwartz D. Anemia, chronic renal disease and congestive heart failure--the cardio renal anemia syndrome: the need for cooperation between cardiologists and nephrologists. Int Urol Nephrol. 2006;38(2):295-310.

42. Seeman T, Šimková E, Kreisinger J, Vondrák K, Dušek J, Gilík J, Feber J, Dvořák P, Janda J. Control of hypertension in children after renal transplantation. Pediatr Transplant 2006 May; 10 (3):316-22.

43. Lingens N, Dobos E, Witte K, Busch C, Lemmer B, Klaus G, Schärer K. Twenty-four-hour ambulatory blood pressure profiles in pediatric patients after renal transplantation. Pediatr Nephrol. 1997; 11:23-26.

44. Al-Mosawi AJ. The etiology of chronic renal failure in 54 Iraqi children. Pediatr Nephrol. 2002 Jun;17(6):463-4.

45. U.S. renal data system. Annual data report: Atlas of end-stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda (MD); 2004.

46. McDonald SP, Craig JC; Australian and New Zealand Paediatric Nephrology Association. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004 Jun 24;350(26):2654-62.