Rate of Progression of Chronic Kidney Disease(CKD) in Children-Spectrum and Determinants: A Longitudinal Study

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Abstract:

Objectives: The objectives of the study were to study the rate of progression of CKD stages II to IV, to assess the risk factors associated with progression and study the quality of life in these children.

Materials and methods: A prospective longitudinal study was conducted including children with eGFR 15-90 ml/min/1.73m^2. The demographic details were noted. The estimated GFR was calculated using the modified Schwartz formula at recruitment and yearly for a follow up period of two years. The non modifiable and modifiable risk factors for progression of CKD were assesed. The mean time to reach ESRD and the influence of the risk factors on the progression of CKD was studied. The quality of life (QoL) was assessed using the PedsQL questionnaire for children and parents.

Results:Seventy eight children were recruited. The median GFR of the cohort was 34.67 ml/min/1.73m^2. Of the 65 children who were followed up, 26% progressed to ESRD in the first year of follow up. Glomerular disease and baseline GFR were significant non modifiable risk factors, proteinuria, anemia, hyperparathyroidism and acidosis were significant modifiable risk factors for progression of CKD in our cohort. The QoL in our cohort significantly correlated with height z score, eGFR and socioeconomic status.

Discussion and Conclusions: Our study showed that the baseline GFR of our population at recruitment was lower than other similar studies. The rate of progression to ESRD was higher in our cohort. Glomerular disease, baseline GFR and proteinuria were the risk factors in our study and in other similar studies like the CKiD study. We did not find dyslipidemia and hypertension as significant risk factors for progression in our study. The factors affecting the quality of life in our study were comparable to other studies.

Introduction:

Burden of CKD:Adult versus Children

Chronic kidney disease (CKD) in adults is currently estimated to have an averagecrude and age-adjusted incidence ratesof 151 and 232 per million population, respectively from a population based study in India[1]. In children, the prevalence of CKD has been reported to be ranging from 15-74.7 cases per million children[2]. The incidence of children 0-19 years of age initiating dialysis has significantly increased from 5.9 to 15 per million population in the United States.[3]The second annual report of the Pediatric CKD registry in India, provided the following details: 1229 patients were registered, of which 76.5% were males. The mean age of patients was 7.32 $\pm$ 4.57 years. The mean duration of symptoms was 3.5 $\pm$ 4 years and 65.3% of patients presented in or beyond stage IV CKD, emphasizing the delay in presentation and increased burden of co-morbidities in these children. Around 47% of patients had a monthly income< 5000 rupees and 77.3% of the patients had to rely on self-funding to bear the cost of health care, highlighting the burden imposed by the cost of health care on the family.[4]

Progression of CKD in Children:

There is little prospective data on progression of CKD in children and the risk factors associated with it.TheNorth American Pediatric Renal Collaborative Trials (NAPRTCS) data show a progression rate to ESRD of 17% at1 year and 39% at 3 years with median time to ESRD being4.5 years[5]. Age, primary disease, stage of CKD, hypertension, anemia (haematocrit), nutrition (albumin), mineral bone disease (corrected calcium, phosphorous) were found to be independent risk factors for progression of CKD[6]. The ESCAPE trial showed that intensified blood pressure controlreduced progression of CKD in children[7].
Cross sectional data from the Chronic Kidney Disease in Children (CKiD) study showed that nephrotic range proteinuria, high phosphate, high potassium, elevated BP, anemia and dyslipidemia were predictors of progression in both non glomerular and glomerular diseases.The longitudinal data showed that proteinuria, blood pressure, dyslipidemia and anemia were significant risk factors for progression of CKD[8].

Quality of life of children with CKD:

Chronic kidney disease has a significant impact on the physical, social and emotional well being of the child. It also has a significant impact on the care givers and the family dynamics. Studies have shown that the physical and psychosocial quality of life scores are significantly lower in children with CKD when compared to the general population[9]. The long duration of CKD, short stature and poor socio economic status were important determinants of quality of life[10]. There is no published literature on the quality of life in children with chronic kidney disease from developing countries.

Need for the study

Children with CKD have a high risk of mortality, morbidity and a significant reduction in lifespan. Children with CKD who progress to End stage renal disease (ESRD) and are on dialysis have 30 to 50 times higher mortality when compared to the general population[11].

Hence early detection of CKD, early interventions to reduce morbidity and delay or prevent progression to ESRD are crucial. In a resource limited country like ours, the challenges of managing chronic diseases like CKD are of delay in diagnosis, lack of expertise, lack of logistic and financial support from the health care system and poor compliance to treatment.There is a scanty literature on the progression, determinants of progression, associated morbidities and outcomes of children with CKD from developing countries like India. Hence, there is a need for a prospective study on pediatric CKD in India.

Objectives:

Primary objectives

- To study the rate of progression of CKD in children with stages II-IV
- To identify the risk factors associated with progression of CKD

Secondary objective:

- To assess the quality of life in children with CKD

Materials and methods:

Study design: Prospective longitudinal study

Study duration: October 2013 to October 2016. Recruitment was over one year and follow up over two years

*Sample size:*The slope of GFR decline in a group of patients with hypertension was compared with the slope of decline in GFR in patients without hypertension in a pilot data set at our centre. The ratio of this decline was 1.7 which was found to be within 95% confidence intervals of the ratio obtained in other studies on progression of GFR. Based on this and the assumption that the overall annual decline in GFR would be 5 ml/1.73m^2/min a sample size of 85 patients should be recruited to achieve a 5% level of significance and power of 80%. Considering 20% drop out rate during the course of the study, the total sample size required would be 100.

Inclusion criteria:

All children 2-16 years of age with CKD stages II to IV (estimated glomerular filtration rate between15-90 ml/1.73m^2/min by modified Schwartz formula) attending the CKD Clinic.

Exclusion criteria:

Children who have undergone renal transplantation

Children who require maintenance dialysis (hemodialysis/peritoneal dialysis for> 3 months)

Children in the acute phase of AKI on CKD

Children with any other co-existing chronic disease

Children with IQ <40

Methodology:

The ethical clearance for the study was obtained from the institutional ethical review board(IERB No 134/2013). Children who fulfilled the inclusion criteria were enrolled in the study after obtaining informed consent from the parents or legal guardians and assent from children older than 8 years of age. They were subsequently followed up at 6 monthly intervals for a minimum period of two years.

At recruitment, a performa was used to gather information regarding details of native kidney disease. Physical examination included assessment of height or length using stadiometer/ infantometer and weight using a standard weighing scale. The height and BMI percentiles and z scores for age were calculated using the CDC growth charts. The BMI for height age was calculated

The investigations done at recruitment and follow up are given in Table 1.

Children who had a follow up of less than 6 months after recruitment were considered defaulters and only the data at recruitment was used for cross sectional analysis.

Estimation of GFR and staging of CKD:

The estimated GFR was calculated at recruitment and follow up using the modified Schwartz formula (eGFR = 0.413 x height (cm)/Serum creatinine(mg/dl). The KDOQI classification was used classify the stages of CKD based on eGFR[12]. Creatinine was measured using modified Jaffe Kinetic method which is traceable to isotope dilution mass spectrometry. The metabolic panel included electrolytes and bicarbonate estimation.

Cystatin C was estimated at recruitment using immunoturbidimetric assay (Roche Diagnostics). Cystatin C based GFR calculation was done using the new CKid combined creatinineand cystatin formula[13]eGFR = $39.8 \times [ht/Scr]^{0.456} \times [1.8/cysC]^{0.418} \times [30/BUN]^{0.079} \times [1.076^{male}]\ [1.00^{female}] \times [ht/1.4]^{0.179}$

Progression of CKD:

Progression of CKD was defined as a 50% reduction in eGFR or aeGFR<15 or initiation of chronic dialysis(>3 months) or renal transplantation. The presence of any of these was considered as an event for survival analysis.

Risk factors for progression of CKD:

Non modifiable:

Demographic variables like age, sex, etiology of CKD and baseline GFR were examined as non modifiable risk factors influencing progression of CKD.

Modifiable risk factors:

Proteinuria:

The urine protein to creatinine ratio (UPCr) was measured at recruitment and follow up and the baseline UPCr was studied as a co-variate influencing progression of CKD.

Hypertension:

Blood pressure was measured using a mercury sphygmomanometer according to the guidelines. Blood pressure between 90^{th} to 95^{th} centile was considered pre-hypertension, from 95^{th} to 99^{th}+5 mm Hg as stage I hypertension and >99^{th} centile+5 mm Hg as stage II hypertension[14]. Any child on anti-hypertensive drugs, irrespective of the blood pressure was considered hypertensive.

Anemia:

Hemoglobin levels less than the recommended haemoglobin level for age was considered as anemia[15]. Iron status (ferritin, transferrin saturation) assessment was done every six months. The cut off for all parameters as provided by the KDIGO guidelines for management of anemia in children with CKD were used[16]. A ferritin level <100 ng/ml and transferrin saturation <20% was considered as iron deficiency.

Mineral bone disease:

Serum levels of calcium, phosphate, alkaline phosphatase, Parathormone (PTH) and Vitamin D levels were assessed and classifiedaccording to the KDIGO guidelines[17].

Cardiovascular disease:

Lipid profile, echocardiography and Carotid intima- media thickness were done annually. Dyslipidemia was defined by the presence of one of the following: serum triglycerides >130 mg%, HDL< 40mg/dl, LDL >160 mg/dl, cholesterol >200 mg/dl or use of lipid lowering medications[18].

The M mode and Doppler echocardiography was performed in all children at recruitment and subsequently after one year. The left ventricular mass was calculated using the Devereaux formula and indexed to height ($m^{2.7}$). Left ventricular hypertrophy was defined as left ventricular mass index (LVMI) >95^{th} percentile for age and sex.

The carotid intimal medial thickness was measured using B mode ultrasound in children older than four years. Two readings of the intimal medial thickness of the carotid artery 1-2 cm above the carotid bulb were taken and the mean of the two readings on each side was noted.The carotid intimal thickness was compared to age specific nomograms in children and to a cohort of age matched normal population[19]. The children were treated in accordance with the standard guidelines (KDIGO/KDOQI).[16,17]

Quality of life:

Quality of life was assessed using Health related quality of life (HRQOL) questionnaire. The questionnaire could be used only in patients who were able to read and understand English. The questionnaire was answered by the patient and also by the parents (depending on the age and educational status of child and parents). The PedsQL version 4.0 end stage renal disease module for age 5-18years was used[20]. The questionnaire has two major aspects – the physical score and the psychosocial score. The psychosocial score was a combination of the scores in the emotional, social and school category scores.

Statistical analysis:

All continuous data are described as Median (quartile1, quartile3). Categorical data are described as number and percentage.The association of GFR with other patient characteristics were examined using scatter plot, Spearman's rank correlation and Mann-Whitney U test. The various co-morbidities were compared between stages of CKD using the Kruskal Wallis test. The correlation of co-morbidities with other variables was done using Spearman's correlation coefficient.

The mean time to reach ESRD and the 95% confidence interval were reported. Kaplan Meier survival curve was plotted for the time to progression and was compared between glomerular and non glomerular disease using the log rank test. Cox proportional hazard model was used to find the significant predictors oftime to progression.Statistical significance was considered at $p < 0.05$ and all analysis were performed using SPSS version 24.

Results:

The demographic details of the study cohort (n=78) at recruitment and follow up are described in Figure 1.

Demographic profile:

The median age of the cohort was 108 (69, 156) months.The median duration of CKD was 12 (0,21) months. Twenty eight children (35.89%) were newly diagnosed to have CKD at the time of recruitment and the median GFR of this subset was 32 ml/min/1.73m^2. When the cystatin C GFR was compared to the estimated GFR (modified Schwartz), it was found that there was a significant agreement between the two and the agreement was best seen between eGFR 30-75 ml/min (Intra class correlation coefficient 0.884).Prematurity/low birth weight was found in 14 (19%) children. Around 60% of the families had an income below rupees 10,000 per month.

Etiology of CKD (n=78):

Glomerular diseases were the cause of CKD in 12 (15.03%) children. CAKUT (hypodysplasia, reflux nephropathy and obstructive uropathy) was the most common cause (50%) of CKD in our cohort. The details of the etiological diagnosis of kidney disease causing CKD in our cohort are described in Table 2.

Progression of CKD (n=65):

Twenty five children reached ESRD within a follow up period of 2 years. Five children had a decline in GFR of >50% from baseline, eight children had a GFR less than 15, 4 were initiated on dialysis and one underwent renal transplantation.

Rate of progression of CKD

The median rate of decline in GFR was 3.50 (-1.71, 11.00) ml/min/1.73m^{2}in the first year and for those who continued to be on follow up, the median rate of decline in GFR was 2.94(0, 11.64) ml/m^2/1.73m^2 in the second year.

The mean time to reach ESRD in our cohort was 22.98 (20.56, 25.41) months(Figure 2). The mean time to reach ESRD for children with glomerular disease (15.45months (9.64, 21.25)) was significantly lower than that fornon glomerular disease (24.43months (20.56, 25.41))(p=0.021). (Figure 3)

Risk factors for progression of CKD

Non-modifiable risk factors:

Glomerular versus non glomerular etiology:

Glomerular disease was associated with a 2.65 times higher risk of progression to ESRD (58.3% of glomerular disease versus 30.1% with non glomerular disease progressed to ESRD) (p=0.021)

The median decline in GFR was significantly higher in children with glomerular disease when compared to non glomerular disease in the first year of follow up (11.36 ml/year vs 2.38 ml/year)

(p=0.007). As most of the children with glomerular disease had progressed within two years, the rate of decline was not comparedin the second year.

As urological disease accounted for the majority of cases of CKD in our cohort, the risk factors associated with progression were studied. The rate of decline in GFR over one year was similar in both the groups (4.3 ml/year in those with normal lower tract versus 4.6 ml/year in those with abnormal lower tract). The presence of VUR, abnormal lower urinary tract did not influence the rate of progression.

Baseline GFR:

An eGFR<45 ml/min at recruitment was associated with a 3.3 times increased risk of progression (p=0.009)There was no significant correlation of progression of CKD with age and sex of the subjects.

Modifiable risk factors:

The prevalence and correlations of the modifiable risk factors associated with CKD are described in Table 3. The comparison of co-morbidities between stages of CKD is given in Table 4. When the co-morbidities associated with CKD were compared between stages II, III and IV, it was found that height z score, hemoglobin and PTH levels significantly changed with reduction in GFR.

Proteinuria: (n=78)

Proteinuria was found to be a significant risk factor with a urine PCr>2 at baseline being associated with a 2.8 times increased risk of progression (p=0.012). In the subgroup analysis of children with urological disease, proteinuria was a significant predictor of progression of CKD (p=0.02). ACEi were used only in 4 children.

Hypertension: (n=78)

Among the 46 children with hypertension, twenty one children (45.6%) were on antihypertensive medications.Fourteen children (66%) had uncontrolled hypertension despite medications. Angiotensin converting enzyme inhibitors (ACEi) were used in only 4(19%) of children receiving antihypertensive drugs.The presence of hypertension, systolic or diastolic blood pressure z scores were not significant predictors of progression.

Other risk factors: (n=78)

Low hemoglobin was associated with a significant risk of progression to CKD (p=0.003). Among the mineral bone disease parameters assessed, low calcium (p=0.001), high phosphate (p=0.028) and high PTH(p<0.001) were associated with a significant risk of progression to CKD.The presence of dyslipidemia, left ventricularhypertrophy or abnormal CIMT were not associated withsignificant risk of progression. Metabolic acidosis was a significant predictor for progression (p=0.048)

Growth:

The median height z score was -2.17 (-3.31,-1.16) which corresponded to a median of 2nd percentile (0.12, 25). Fifty one children (65.4%) had short stature, i.e height <3rd centile for age. None of our patients received growth hormone therapy. The Median BMI score in our cohort was -1.00(-2.00,-0.12). Twenty children (25.64%) were undernourished (BMI<-2SD). None of the patients in our cohort were overweight or obese.In the 33 children who were in the pre-pubertal and pubertal ages (10-16 years), 22 (66%) had delayed pubertal development for age.

Impact of disease on Quality of life:

The quality of life was measured in 45 children who were able to read and comprehend English. Forty seven parents were able to answer the quality of life questionnaire. The mean scores of the child and parent are given in the table 5.

QOL score of the child:

The total score of the child correlated significantly with the parent's total score. (p=0.01). The physical and psychosocial scores of the child correlate with each other (p=0.001,r=0.572) and were significantly lower in the children belonging to the lower socioeconomic status (p=0.035) (p=0.024). There was no difference in the QOL scores among glomerular and non-glomerular disease and across various stages of CKD. The need for CIC did not alter the quality of life in children with CKD.

QOL score by parent proxy:

The parent proxy physical score correlates significantly with the height z score of the child (p=0.002, r=0.485), eGFR (p=0.003, r=0.475) and parent proxy psychosocial score (p<0.001, r=0.796).

The parent proxy psychosocial score(emotional and social domains) correlated with the height z score (p=0.004, r=0.459), eGFR (p=0.025, r=0.367) and psychosocial score of the child (p=0.001, r=0.73). The psychosocial score was also significantly lower in patients belonging to lower socioeconomic group and was different in different stages of CKD.

Discussion:

This study is a prospective longitudinal follow up of the rate of progression and the risk factors associated with progression in children with CKD from a developing country.

At the outset, the median eGFR of the cohort was lower than that observed in CKiD and the Italkid project 34.67(24.3, 65.4) ml/min/1.73m^2 versus 44 and 41.7 ml respectively[21,22].One third of our cohort were newly diagnosed to have CKD (stage IIIb) at the time of recruitment and and this reflects the delay in diagnosis of CKD in our population which has not been emphasized in other studies.

Looking at the etiology of CKD in our cohort, we found that like most other studies[22,23], our study showed that hypodysplasia, obstructive uropathy and reflux nephropathy together account for about 50% of cases. A high prevalence of neurogenic bladder was found as an important cause of CKD in children that has not been mentioned in other studies.

Glomerular diseases accounted for only 15% of CKD in our cohort as compared to 22% in the CKiD cohort. Among the glomerular diseases, FSGS has been reported as the most common cause of CKD in most studies including CKiD; however, in our study we found that atypical hemolytic uremic syndrome was the most common glomerular disease leading to CKD in children.

Two other studies from India, showed that obstructive uropathy was the most common cause of CKD in their cohort, followed by glomerulonephritis which accounted for a third of the cases of CKD.[24,25]In contrast to the studies from the rest of the world, the studies from the Asia Pacific region have found glomerulonephritis to be the most common disease leading to CKD in their population.[26]

Rate of Progression of CKD:

The rate of progression of CKD in our study was higher than the rate in other similar studies. We found that26% of ourchildren with CKD progressed to ESRD during the first year offollow up and 32 % progressed at 2 years. This is higher than the rate of progression of 17% in one year and 39% by 3 years recorded by the NAPRTCS 2012 data. The ItalKid project showed that the rate of progression was 7.3% per year.[5,21]

The median rate of decline in GFR was 3.5 ml/min/1.73m^2 per year in our study and this almost twice the rate found in the CKiD study(1.8 ml per year)[27].The mean time to reach ESRD in our study was 1.8 years, which was much shorter than the median time of 4.5 years in the NAPRTCS study.[5]The ItalKid project found that the risk of ESRD was 68% by 20 years of age.[21]

Non-modifiable risk factors for decline in GFR:

The major non modifiable risk factors for progression in our cohort were –glomerular disease as etiology of CKD and a lower baseline GFR. The median rate of decline of GFR was 4.7 times higher in the children with glomerular disease when compared to non glomerulardisease.The median decline in GFR for glomerular disease versus non glomerular disease (11.8 ml versus 2.38 ml) in our study was much higher than that seen in the CKiD study(4.3 ml versus 1.5ml)[27].

Our study showed that a baseline GFR <45 ml/min/1.73m2 was associated with a 3.3 times increased risk of progression to CKD.The CKiD study also showed that the baseline GFR was a significant risk for progression. They also showed that the trajectory of decline in GFR was non-linear, especially when the baseline GFR was low.[28]

A multivariate analysis of retrospective data from NAPRTCS 2010 showed that age, primary disease, stage of CKD were significant risk factors for progression of CKD. The etiology of CKD and pre-existing GFR have been found to be important risk factors in several other studies.[6]

Modifiable risk factors for decline in GFR:

Proteinuria:

The median urine protein:creatinine (PCr) ratio in the CKiD study was 0.53 (0.2,1.27) and proteinuria was seen in 76% of their cohort. Our study showed that proteinuria was seen in a majority of the cohort and the degree of proteinuria was four times that seen in the CKiD cohort. The higher prevalence of proteinuria and the higher degree of proteinuria in our cohort is probably due to the delay in the diagnosis of CKD and lower prevalence of ACE inhibitor use in our population.[6]Only five percent of our patietnsrecived ACE inhibitors as compared to fifty five percent of patients with proteinuria were receiving ACEi in the CKiD study.

The Ital-Kid project also showed that children with P/Cr levels <0.9 showed a slower decline of renal function and a higher rate of renal survival than those with baseline P/Cr>0.9 at 5 years. ACEi did not significantly delay the progressive decline in renal function in children with lower proteinuria compared with matched controls.[21]

Hypertension:

Our study is comparable with the CKiD data which showed that the prevalence of hypertension was 54%, of whom 61% were receiving medication. Forty eight percent of patients had hypertension despite treatment. Uncontrolled hypertension in children receiving antihypertensive medications was independently associated with male gender, shorter duration of CKD, and the absence of ACEi/ARB use. Hence, the CKiD study concluded that ACEi must be the first line of therapy in children with CKD.[22]

Our study, in contrast to the CKiD study, did not show any difference in the prevalence of hypertension in children with glomerular disease. There was no significant correlation with the severity of proteinuria, durataion of CKD or eGFR. The presence of hypertension at recruitment did not influence the progression of CKD.

This is a significant finding suggesting that hypertension may be present even in stage II of CKD irrespective of the etiology of CKD. All children should be screened from stage II onward for the presence of hypertension and actively treated.

Similar to the ESCAPE trial data were results from the CKiD study which showed an association between lower casual BP (50th percentile for age, gender, and height) and improved renal outcomes.[22]A study on progression of CKD found that systolic hypertension was a significant risk factor.[5]

Anemia:
The mean haemoglobin in our cohort was lower than that found in the CKiD study, though the prevalence of anemia was similar.[29,30]The NAPRTCS data showed that there is an increase in prevalence of anemia with worsening GFR with a prevalence of 18% in CKD stage II to 68% in CKD stage V[23].

Anemia was found to be a significant predictor of progressionin ourstudy and this is comparable to the longitudinal datafrom the CKiD study showed that in children with non glomerular disease, anemia was a significant predictor of progression[8]. The NAPRTCS data also showed that a hematocrit <33% wassignificantly associated with risk of progression.[6]

Mineral bone disease:

The prevalence of vitamin D deficiency in our cohort is around 4 times that seen in the CKiD cohort.Low calcium, high phosphate and hyperparathyroidism were significant predictors for progression of CKD in our cohort and similar results were also obtained from the NAPRTCS data which found that inorganic phosphorus above 5.5 mg/dl, calcium below 9.5 mg/dl had a higher risk of progression ($p<0.001$).[26] High PTH was a significant predictor for progression in our study; however, this has not been highlighted in other similar studies. We presume that the high prevalence of vitamin D deficiency in our cohort may be a factor influencing the high prevalence of high PTH and this needs to be analysed further.

Cardiovascular disease:

The CKiD study found that forty-five percent of the children had at least one measure of dyslipidemia and 20% had combined dyslipidemia. This is similar to the prevalence of dyslipidemia observed in our cohort. Multivariate analysis of the CKiD study showed that lower GFR and obesity were independently associated with elevated triglycerides, low HDL cholesterol, and high non-HDL cholesterol.[31]Though none of our patients were obese, we found that serum cholesterol correlated with BMI and was higher in children with glomerular disease.

In contrast to the CKiD studywhich showed that dyslipidemia was a significant risk factor for progression in children with non glomerular disease, we did not find dyslipidemia as a predictor for progression in our cohort.[8]

The prevalence of LVH in our study was around 3 times higher than that seen in the CKiD study and was present even in early stages of CKD suggesting that cardiovascular screening should be done even in early stages of CKD.

Our study also found a significant correlation of LVH with hemoglobin and PTH level. Anemia hasbeen linked to poor cardiovascular outcomes in children with CKD [32,33]Multivariate analysis of the CKiD study showed that hypertension, lower hemoglobin, and female gender were independent predictors of LVH. LVH was more frequent in children with confirmed (34%) and masked (20%) systolic or diastolic hypertension than in children with normal BP (8%). As ambulatory blood pressure was not performed in our study, perhaps it is difficult to obtain a correlation between LVH and hypertension in our study.

The CIMT in our study was significantly higher in children with higher systolic and diastolic blood pressures. This is comparable with the results from the CKiD study which found that hypertension and dyslipidemia were significant risk factors for abnormal CIMT.[34]

Growth:

The median height z scorewas -2.175 and this was much lower than the height z scores seen in other studies[35]. Almost half of our cohort had severe short stature. The height of children with CKD was plotted on the CDC charts given the lack of normative data in the Indian population. This may exaggerate the prevalence of short stature in our cohort. However, the delay in diagnosis, lack of growth hormone use in our patients could explain the poor growth in our cohort.

The BMI of our cohort and the median BMI z score was -1.415 was also extremely low. None of the children in our study were overweight or obese. This is in contrast to the CKiD study which found that 24% had a BMI >90th percentile and 15% were found to be obese.[35]

Quality of Life:

Our study showed that the QoL correlated significantly with short stature, eGFR and socioeconomic status.The CKiD study showed that children with longer duration of CKD, older age had higher scores in the physical, social and emotional domains, but was associated with significantly lower school domain scores. Short stature was significantly associated with poor scores in the physical function domain.[10,36]The severity of disease and height of the child had significant impact on the quality of life on children with CKD.

What this study adds:

This prospective, longitudinal study shows that the profile of children with CKD stages II-IV in a developing country is different from the published data which is mostly based on studies in developed countries. Our cohort has a lower median GFR and a significant proportion present in late CKD, suggesting a delay in the diagnosis of CKD in our cohort. A significant proprtion of our cohort being severely growth retarded, raises a question regarding the validity of estimated GFR as a true measure of the actual GFR in our population.

The rate of progression of CKD is much higher in our cohort, particularly in those with glomerular disease suggesting that the risk factors associated with progression of CKD need to be identified early and treated adequately.

Proteinuria was found to be a significantrisk factor for progression even in the subset of our cohort with non glomerular disease. The prevalence of short stature, undernutrition, anemia, vitamin D deficiency and LVH were higher in our cohort underscoring the role that these factors may play in the progression of CKD.

The QoL analysis empahsises how CKD affects the life of the afflicted children and also on the role of socioeconomic status which in turn influences the ability to seek and avail medical care on the quality of life.

Limitations ofthe study:

Albumin-creatinine ratio would have been a better marker to estimate proteinuriacompared to protein creatinine ratio.The difference in proteinuria between glomerular and non glomerular disease could not be elucidated in our study. As albuminuria was not measured, the recent KDIGO staging of CKD could not be used.

Ambulatory blood pressure measurement would help to detect the true burden of hypertension and the prevalence of masked hypertension. The interpretation of various parameters like left ventricular mass index may be inaccurate in the absence of age appropriate, population specific normative data.

Our study was not sufficiently powered to run a multivariate analysis of the various predictors for progression of CKD.

Conclusions:

- The rate of progression of CKD in our study was found to be high, with more than one third of our cohort reaching ESRD during the two year follow up period.
- The mean time to reach ESRD for the cohort was 22 months and was significantly lesser in those with glomerular disease.
- Glomerular disease and baseline eGFR were significant non modifiable predictors of progression
- Proteinuria, low hemoglobin, acidosis, low calcium, high phosphate and hyperparathyroidism were significant modifiable predictors of progression
- The quality of life in our cohort was significantly affected by eGFR, height and socioeconomic status.

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Tables:

Table 1: Evaluation of the patient at recruitment and follow up:

Evaluation	**Recruitment**	**6 months**	**1 year follow up**	**18 months**	**2 year follow up**
History	Symptoms	*	#	*	#
Examination	Height Weight BMI Tanner stage Blood pressure	*	#	*	#
GFR estimation	Creatinine (eGFR) Cystatin C	* -	# #	* -	# #
Renal	Urine Protein/creatinine ratio Metabolic panel		# #		# #
Mineral bone disease	Calcium Phosphate Alkaline phosphatase Vitamin D PTH	*	# # #	*	# # #
Cardiovascular	Lipid profile Carotid intimal medial thickness Echocardiography		#		#

- * Clinical details and GFR estimation done 6 monthly
- # Investigations repeated at yearly intervals

Table 2: Etiology of chronic kidney disease

Disease	**N=78(Percentage)**
Non Glomerular disease	**54 (69.23%)**
Renal hypoplasia/dysplasia/aplasia	20 (25.6%)
Obstructive uropathy	12 (15.3%)
Neurogenic Bladder	13(16.6%)
Reflux Nephropathy	5(6.4%))
Cystinosis	4(5.1%)
Glomerular disease	**12 (15.3%)**
Hemolytic uremic syndrome	7(8.9%)
Focal Segmental glomerulosclerosis	4 (5.1%)
IgA Nephropathy	1(1.2%)
Miscellaneous(Nephronophthisis, Familial hypercalciuria, polycystic kidney disease)	**10(12.8%)**
Unknown etiology	**2(2.5%)**

Table 3: Modifiable risk factors at baseline:

Risk factor	**Prevalence: N(percentage)**	**Correlations**
Proteinuria	73 (93.48%) UPCr>2- 36(46%)	Inversely with GFR Positive correlation with durationof CKD
Hypertension	Hypertension – 46(59%) Treated- 21 (45.6%) Pre-hypertension -10 (12.8%) Stage I – 18(23.2%) Stage II – 11(14.1%)	No correlation with GFR, stage of CKD
Anemia	29(37.17%) Iron deficiency -44(56.4%)	Positive correlation with GFR, serum iron,inversely with proteinuria
Mineral bone disease	Symptoms- 14(19%) Hypocalcemia -36 (46.1%) Hyperphosphatemia- 25 (32.05%) Vitamin D deficiency – 72(92.3%) Hyperparathyroidism -44 (56.4%)	Calcium- correlated with GFR Vitamin D- Inversely withPTH PTH- Inversely with GFR, calcium, Vitamin D
Cardiovascular	Dyslipidemia- 50 (64%) LVH- 34 (44.72%) Concentric hypertrophy -18 (25%) Concentric remodeling – 18(25%) Eccentric hypertrophy-13 (17%) Mean CIMT - 0.05$\pm$0.008 cm	Cholesterol – correlated with BMI, glomerular disease LVMI- inversely with Hemoglobin, direct- PTH CIMT- correlated with systolic and diastolic BP z scores
Growth	Median z score was-2.14(-3.31,-1.16) Short stature – 51(65.4%)	Correlated with GFR, bicarbonate levels
Acidosis	59 (75.67%)	Correlated with height z scores

Table 4: Comparison of risk factors and co-morbidities between various stages of CKD

Parameters	**Stage II**(n=21)	**Stage III**(n=26)	**Stage IV**(n=31)	**P value**
*Height z score	-2.25(-3.25,-0.51)	-1.53(-2.38,-0.68)	-2.67(-4.64,-2.01)	**0.017***
BMI z score	-1.06(-2.76,-0.19)	-1.61(-2.66,-0.43)	-1.61(-2.59,-0.22)	0.92
Systolic BP z score	1.18(0.87,1.88)	1.28(0.55,2.16)	1.07(0.43,2.01)	0.60
Diastolic BP z score	0.95(0.53,2.84)	1.1(0.59,1.92)	0.845(-0.08,1.44)	0.11
Urine protein/creatinine	1.44(0.34,11.3)	1.78(0.73,6.89)	2.83(1.27,17.46)	0.11
Bicarbonate	20.8(18.1,23.7)	19.6(17.8,21)	19.05(16.5,20.4)	0.11
***Hemoglobin**	11.8(10.1,13.2)	11.3 (10.5,13)	10.6(9,12.3)	**0.045**
Ferritin	38.7(24.2,77)	22 (15.3,41.5)	35(19.6,105.5)	0.15
Transferrin saturation	16.8(10.53, 30.12)	17.96 (12.63,22.41)	20.6(13.42,27.7)	0.47
Calcium	9.2(8.6,9.8)	9.3(8.8,9.5)	9.1(8.2,9.5)	0.55
Phosphate	4.9(4.5,5.8)	4.8(4.5,5.2)	5.1(4.35,5.9)	0.51
Vitamin D	11.89(7.27,17.97)	15.67(10.15,18.7)	13.44(8.57,18.97)	0.77
***Parathormone**	62.3(26.27,107.7)	84.8(57.7,206.6)	225.25(97.69,375.47)	**0.003**

Table 5: Quality of life scores

Score	**Child (n= 45)**	**Parent(n= 47)**
Physical score	76.56(62.37,82.81)	75(42.18,89.05)
Psychosocial score	71.66(64.16,78.74)	75(55.8, 86.6)
Total score	72.26(60.17, 82.05)	70.47 (50.6, 83.36)

Figures:

Figure 1: Algorithm depicting recruitment and follow up with demographic details

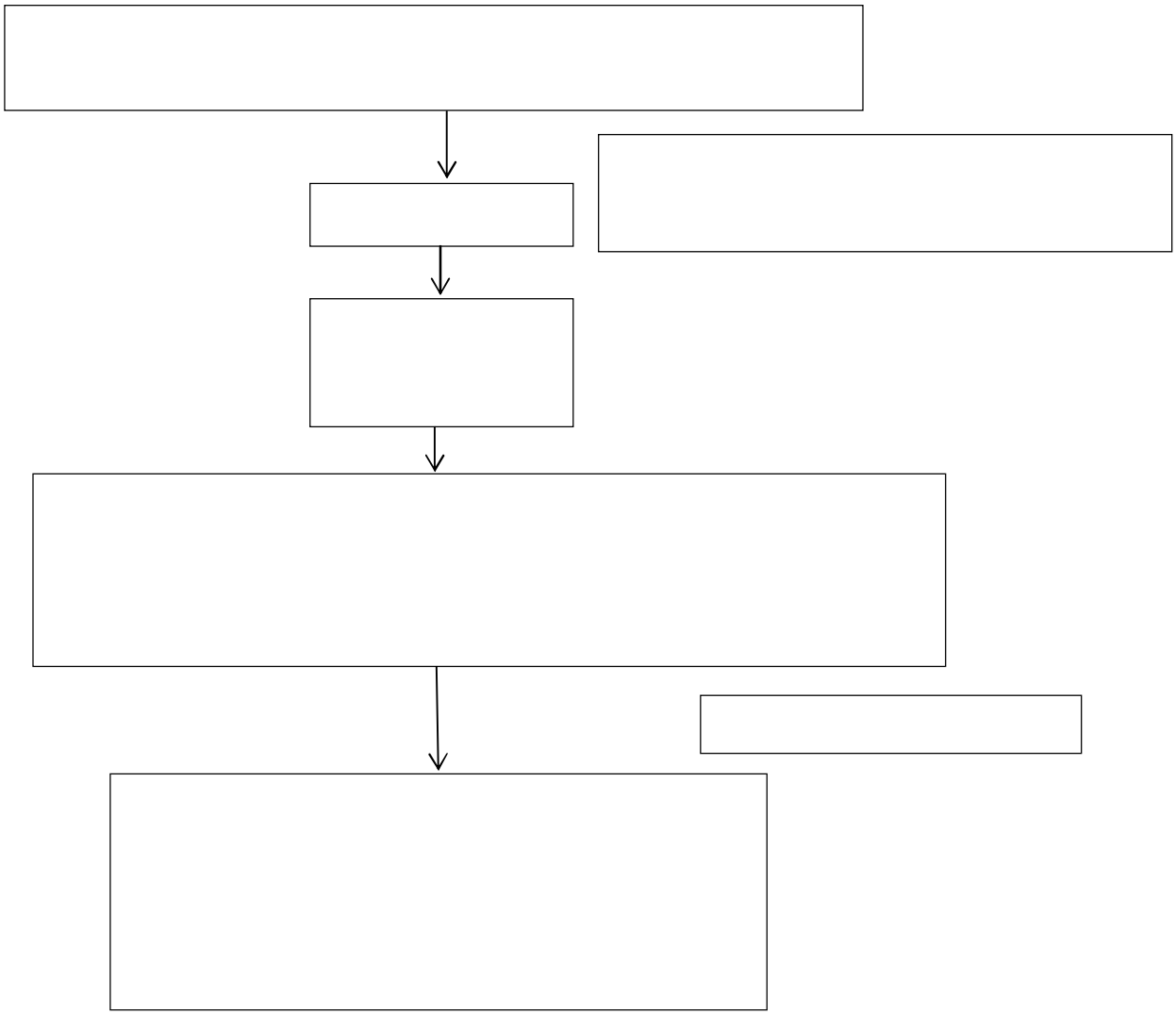


Figure 2: The survival analysis graph which shows the survival time of the chort (n=65)

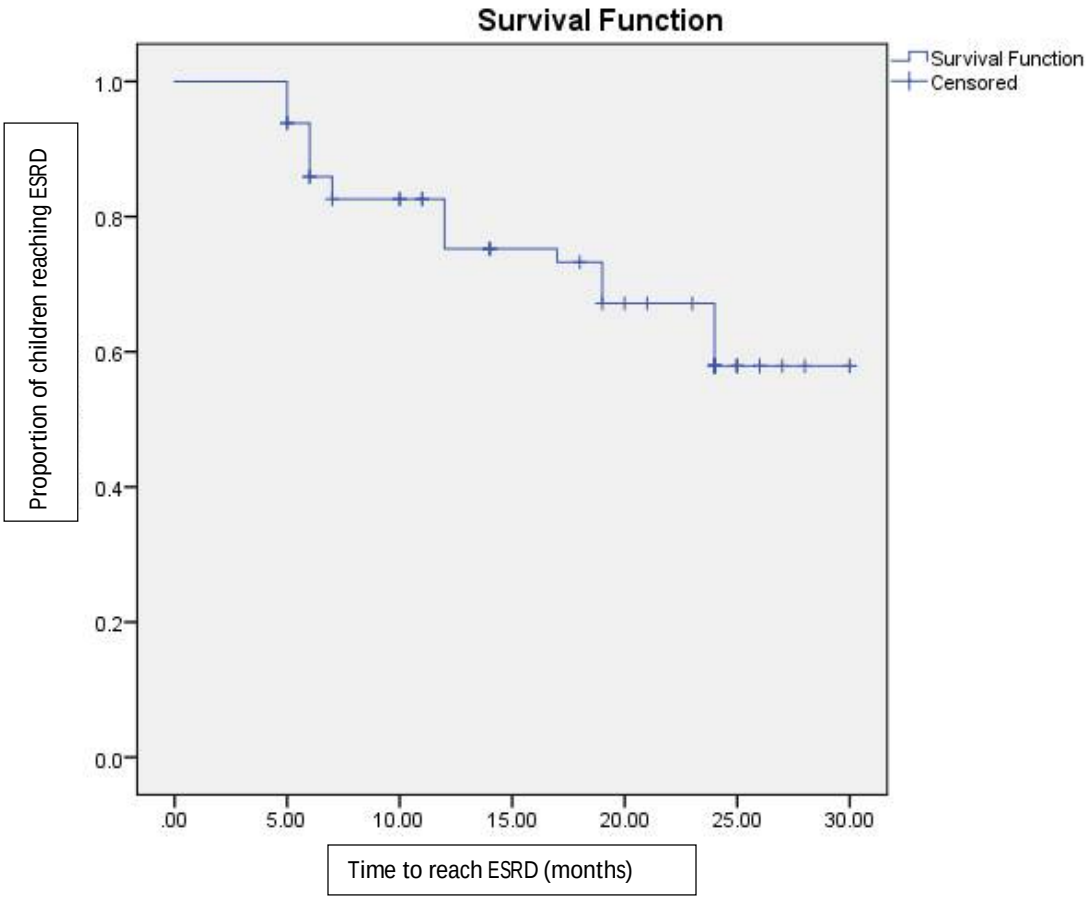
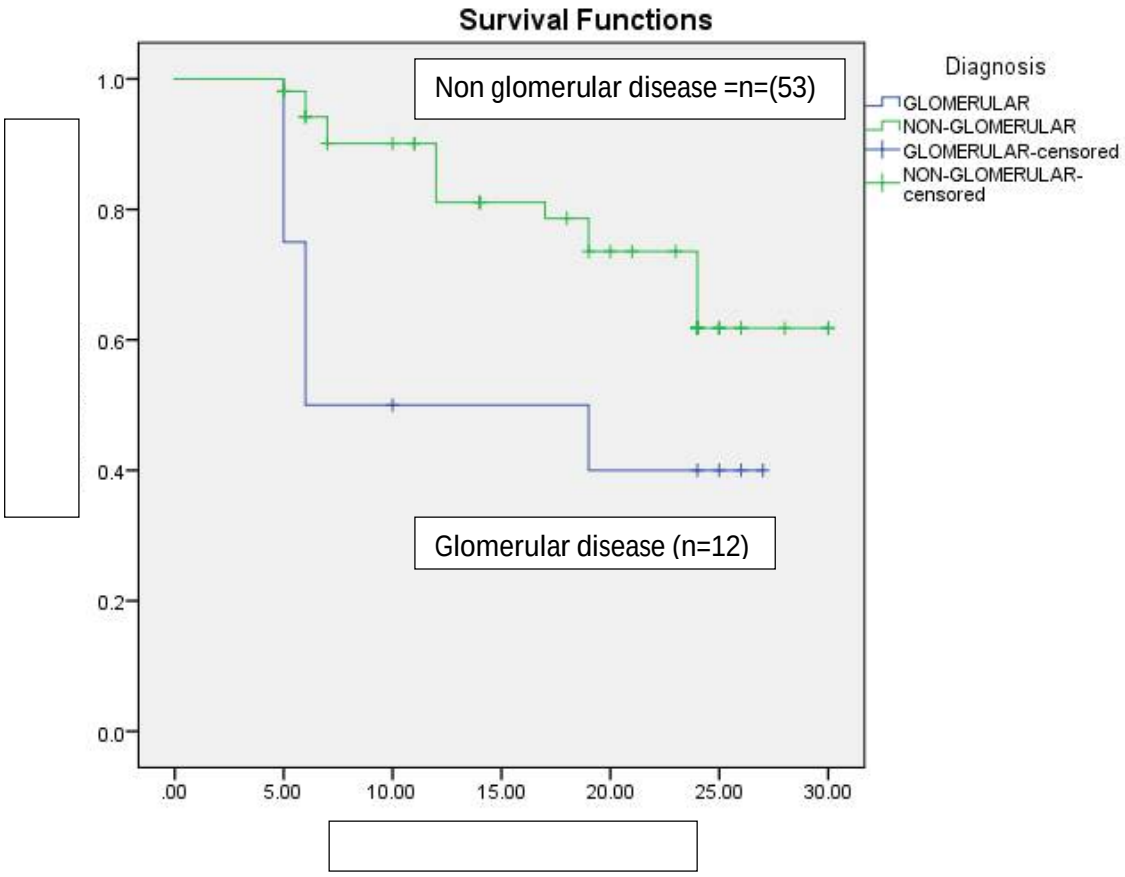


Figure 3: Comparison of survival between children with glomerular (n=12) and non glomerular disease (n=53)



Abbreviations:

ABPM- ambulatory blood pressure monitoring
ACEi – Angiotensin converting enzyme inhibitor
BMI- body mass index
BP- blood pressure
CDC- Centre for disease control
CIMT- carotid intimal medial thickness
CKD- Chronic kidney disease
eGFR- estimated glomerular filtration rate
ESRD – End stage renal disease
FGF23- Fibroblast growth factor 23
GFR- glomerular filtration rate
HRQoL- Health related quality of life
KDIGO – Kidney Disease Improving Global Outcomes
KDOQI- Kidney Disease Outcome Quality Initiative
LVH- Left ventricular hypertrophy
LVMI- left ventricular mass index
NAPRTCS – North American Pediatric Renal Trials and Collaborative Studies
PedsQL – Pediatric Quality of Life Score
PTH- parathormone
QoL- Quality of life
UPCr- urine protein creatinine ratio

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Conflict of interest: None

Statement that the study is conducted in the southern states of India: This is to certify that this study has been conducted at St John's Medical College Hospital, Bangalore, Karnataka.

ISNSC membership details: This is to certify that DrNivedita Kamath, the Principal Investigator and Presenting Author is a member of ISNSC.