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Risk factors for progression of chronic kidney disease: An investigation in prepubertal children

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Abstract

Aim: Previous studies on progression of chronic kidney disease (CKD) in children have included older post-pubertal subjects. This study attempted to evaluate risk factors for progression of CKD in pre-pubertal children.

Methods: An observational study of children aged 2–10 years with an eGFR within the limits of >30 and <75 mL/min/1.73 m^2 was performed. Presenting clinical and biochemical risk factors, as well as diagnosis, were analysed for their association with progression to kidney failure, time to kidney failure and for the rate of decline of kidney function.

Results: One hundred and twenty-five children were studied of whom 42 (34%) had progressed to CKD stage 5 during the median period of follow up of 3.1 (IQR = 1.8–6) years. Hypertension, anaemia and acidosis at entry were associated with progression but they did not predict reaching the end point. Only glomerular disease, proteinuria and stage 4 kidney disease were independent predictors of kidney failure and the time to kidney failure. The rate of kidney function decline was greater in patients with glomerular than non-glomerular disease.

Conclusions: Common modifiable risk factors, when present at initial evaluation, were not independently associated with CKD progression to kidney failure in prepubertal children. Only non-modifiable risk factors and proteinuria predicted eventual stage 5 disease. The physiological changes of puberty may be the major precipitator of kidney failure during adolescence.

KEYWORDS
chronic kidney disease, kidney, paediatric, puberty, risk factors

Summary at a glance

We investigated risk factors at presentation for progression of chronic kidney disease in a cohort of prepubertal children. Common modifiable clinical factors hypertension, anaemia and acidosis did not predict kidney failure. Proteinuria, stage 4 CKD and glomerular disease were associated with progression and a shorter time to failure.

1 | INTRODUCTION

Chronic kidney disease (CKD) is an uncommon but important cause of illness in children. Emotional and physical consequences are significant burdens on the carers, and metabolic, cardiovascular, and physical effects of CKD are devastating to the child.[1] The societal imperative to treat children is strong and the costs high. In the United States, the life expectancy of a child less than 15 years of age with CKD is 30 years.[2] There is little data on paediatric CKD in Africa[3] where the prognosis is likely to be poorer because of deficient treatment and more rapid progression.[4]

Progression occurs commonly in CKD. The rate of decline of kidney function is variable and influenced by both modifiable and non-modifiable factors.[5] Paediatric nephrologists aim to retard this progression, in order to postpone reaching a deficit of functioning nephrons and consequent CKD stage 5. It is important to identify modifiable factors that contribute to progression of CKD.[6–8] Hypertension[9,10] and proteinuria[11,12] have been shown to be particular predictors of progression of CKD. However, some paediatric studies have included adults, and the age range of subjects included in paediatric studies varies substantially. Nephrologists recognize that puberty is accompanied by deterioration in kidney function and may precipitate initiation of kidney replacement therapy (KRT) in children with CKD.[13,14] This may be due to the stress on kidney function brought about by the growth spurt associated with puberty, and resultant glomerular hypertension and hyperfiltration. Studies on the progression of CKD in children are therefore clouded by this major physiological event. The causes of CKD in children are mostly congenital abnormalities of the kidney and urinary tract (CAKUT), in contrast to those in adults, in whom diabetes and hypertension predominate.[15] Consequently, risk factors for progression of CKD in prepubertal children, are likely to be different from those in older children and adults.

There is scant literature on risk factors for progression of CKD in low- and middle- income countries (LMICs)[16] and none on factors in prepubertal children.

The hypothesis for this study was that the risk factors for progression of CKD in pre-pubertal children would not be identical to those in older children and adults. The aim of the study was to determine the association of clinical and biochemical parameters at presentation of pre-pubertal children with CKD, with progression of kidney dysfunction to CKD stage 5. Puberty itself being a risk factor, this study did not address the physiological effects of puberty on progression of CKD, or any risk factors after puberty.

2 | METHODS

A cohort study of patients attending the paediatric nephrology units at Steve Biko Academic Hospital and Morningside Children's Kidney Treatment Centre was undertaken. Both these clinics are affiliated to the University of Pretoria Medical School. Prepubertal children aged 2 to 10 years with CKD and an eGFR of >30 but <75 mL/min/1.73 m^2 were selected from the databases of the two clinics. Data of these patients was recorded retro- and prospectively. New patients meeting the GFR criteria were included as they presented, and their data recorded prospectively. Patients were followed until they reached the endpoint of CKD stage 5 or the termination date of the study. Patients were excluded from analysis if they reached the age of 13 years or developed beyond Tanner stage 2, received a pre-emptive kidney transplant, or died before reaching the endpoint.

While comprehensive data including sociodemographic factors were collected, variables for the assessment of progression of kidney function decline, were selected clinical and biochemical characteristics of the patients at the time they were included in the study and not at diagnosis of CKD. Serum albumin was excluded from all analyses because of its close inverse relationship, seen in these patients, with the urinary protein: creatinine ratio (UPCR). Categorical data which were recorded were age, sex, height-for-age Z score (stunted: below 10th percentile, severely stunted: below 5th percentile), CKD stage and aetiology of CKD. The cut-off values chosen for variables are defined in the tables. Data of possible risk factor covariates of patients who had reached the eGFR endpoint by termination of the study in March 2021 were analysed. Estimated GFR was calculated using the modified bedside Schwartz formula, with a k-constant of 40 in all children.

Patients were under the care and supervision of two paediatric nephrologists. They were managed according to KDIGO clinical practice guidelines and were followed up at 3–6 monthly intervals. At each visit clinical and biochemical evaluations were repeated.

Anaemia was defined as a haemoglobin of <11 g/dL for children younger than 7 years of age and <11.5 g/dL for those older than 7 years. No blood transfusions were administered. Metabolic acidosis was defined as sHCO3 of less than 22 mmol/L. These children were treated with oral alkaline solutions.

Hypertension was diagnosed at presentation to the nephrologist and included some patients who were already on antihypertensive treatment. This was changed according to KDIGO guidelines where necessary. The definition used for treatment-naïve patients was a systolic and/or diastolic blood pressure ≥ 95th percentile for blood pressure for age, sex and height percentile according to the 4th Report of the National High Blood Pressure Education Program working Group on High Blood Pressure in Children and Adolescents.[17] Blood pressure was measured with an oscillometric machine with the child in a seated position. The mean of three readings was recorded and rechecked by the nephrologist. While angiotensin-converting enzyme inhibitors (ACEi) are possibly less effective in treating hypertension in ethnic Africans, they were prescribed as first line treatment for hypertension and/or proteinuria in patients with glomerular disorders. Calcium channel blockers (CCB) were prescribed in children with non-glomerular disorders who had hypertension but no, or negligible, proteinuria, or an ACEi if they had proteinuria. ACEi treatment was discontinued if necessitated by side effects, or when judged necessary in an individual patient if eGFR declined to <30 mL/min/1.73 m^2, such as if a child was likely to miss an appointment.

Patients were evaluated for three outcome variables: progression to an endpoint of an eGFR of <15 mL/min/1.73 m^2, time to reach this endpoint and the rate of kidney function decline. The time-to-event analysis was calculated using the median time of survival of kidney

function in years for 50% of patients for each risk factor. The rate of kidney function deterioration was categorized in decrements in GFR of <1, 1–3, 3–5 and >5 mL/min/1.73 m^2/year.

Written informed consent for inclusion in the study was obtained from the parents or guardians of all the patients. The study protocol was approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria (Study 92/2013). The authors certify that the study was performed in accordance with the ethical standards laid down by the 1964 Declaration of Helsinki.

2.1 | Statistical analysis

The endpoint outcome variable was defined as the attainment of an eGFR of <15 mL/min/1.73 m^2 (CKD stage 5). Demographic and clinical characteristics were summarized for all patients by CKD diagnosis (glomerular and non-glomerular disorders) using mean and standard deviation (SD) for continuous variables, and percentages for categorical variables. Differences by diagnosis were tested using Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical variables. For each of the potential risk factors, univariate logistic regression was fitted, after which risk factors that were significant at the .15 level of significance were considered in a multivariable Cox regression analysis. Non-significant ($p \geq .05$) risk factors were then manually removed one at a time, and when necessary re-inserted. After each removal/insertion the Cox regression was fitted and assessed with a binary outcome for eGFR (> or <15 mL/min/1.73 m^2). Kidney survival was defined, using the survivor function, as retention of function in 50% of patients. This is presented using the Kaplan–Meier method. Testing was done at the .05 level of significance.

3 | RESULTS

One hundred and twenty-five children were included in the study. Patient characteristics are shown in Table 1 and differentiated into patients having either glomerular or non-glomerular disease. The majority of the patients (90, 72%) were black Africans, and most were under 7 years of age at the time of inclusion. Almost twice as many non-glomerular (81) as glomerular (44) disorders were diagnosed. Children with non-glomerular disorders were younger, the majority were male, and they were more likely to have severely stunted growth. Hypertension had been treated with various combinations of CCB, beta-blocker and ACEis. At entry 40 patients (32%) received an ACEi and at exit 18 patients (14%). None of the patients had reached the pubertal growth spurt during the study period and only a few had attained Tanner stage 2 development. None had progressed beyond stage 2, irrespective of age. Patients were followed up for a median period of 3.1 (IQR = 1.8–6) years.

Incomplete data were obtained for acidosis (*n* 3) and proteinuria (*n* 4). (Tables 1 and 2). This constitutes 0.93% of clinical and biochemical data sets.

Almost a third (31%) of patients were from rural areas and 14% from impoverished peri-urban settlements. The family had no stable income in 18% of cases. A substantial proportion of families were dependent on social grants. Travel time to the nephrology clinic was more than 4 h for 35% of the patients. Only 37% of patients were brought to the clinic in private transport. These factors were responsible for some problems of follow up and treatment compliance.

TABLE 1 Patient characteristics (*N* 125)

	Glomerular disease (*N* 44; *n* %)	Non-glomerular disease (*N* 81; *n* %)
Age[a] (yrs)		
Mean 4.83 (SD 2.53)	6.1	4.1
Sex: Male (*n* 91)	22	69
Female (*n* 34)	22	12
Hypertension[b] (*n* 69)	13 (30)	20 (25)
Anaemia[c]	32 (73)	30 (37)
Acidosis[d]	14 (32)	22 (29)
Growth (height *Z* score)		
Stunted (*n* 34)	9 (20)	25 (31)
Severely stunted (*n* 30)	15 (34)	15 (19)
Kidney failure		
Stage 2	15 (34)	15 (19)
Stage 3	27 (61)	48 (59)
Stage 4	2 (5)	18 (22)
Mean GFR, mL/min/1.73 m^2 (SD)	52 (12)	43 (16)

[a]Mean age at exit 8.78 (SD 3.17) years.
[b]Systolic and/or diastolic BP ≥95th percentile.
[c]Hb <11 g/dL <7 years, <11.5 g/dL ≥7 years.
[d]sHCO3 < 22 mmol/L (Data for 122 patients).

At the time of termination of the study 42 (34%) of the patients had progressed to CKD stage 5. Clinical and laboratory data and their association with progression to CKD stage 5 are depicted in Table 2. This depicts the proportions of patients with each risk factor who progressed to kidney failure. Univariate analysis showed proteinuria and glomerular disease to be significantly, and stage 4 disease marginally, associated with progression. Of the modifiable clinical consequences of CKD, anaemia, acidosis and hypertension did not reach statistical significance as risk factors for progression whereas proteinuria did. Metabolic acidosis was present at entry in 13 of 15 children with non-glomerular disease who reached the endpoint, but this also failed to reach statistical significance (p .2). A sub-analysis of patient sex revealed that girls had reached the endpoint statistically sooner than boys.

Multivariate regression analysis showed proteinuria, CKD stage 4 and glomerular disease to be independent predictors of progression to kidney failure (Table 3).

The median survival time of survival of kidney function for all patients was 10.8 years. Kidney function survival times and hazard ratios for each risk factor are shown in Table 4. This depicts median

TABLE 2 Risk factors for progression to CKD 5 (N125)

Characteristic	CKD 5	Odds ratio	95% CI	*p*
UPCR[a] >0.2 g/mmol (*n* 56)	32	8.30	3.07–22.41	<.001
CKD stage 4 (*n* 20)	10	2.28	0.85–6.11	.092
Glomerular disease (*n* 44)	27	6.99	2.78–17.54	<.001
Anaemia[b] (*n* 62)	25	1.83	0.85–3.92	.116
Acidosis[c] (*n* 86)	30	1.22	0.53–2.82	.646
Hypertensiond[d] (*n* 69)	20	0.63	0.30–1.34	.227
Sex: girls (*n* 34)	22	2.64	0.14–6.10	.018

[a]Urine protein: creatinine ratio.
[b]Hb <11 g/dL <7 years, <11.5 g/dL >7 years.
[c]sHC03 < 22 mmol/L.
[d]Systolic and/or diastolic blood pressure ≥95th percentile.

TABLE 3 Multivariate Cox regression of risk factors for progression to CKD 5

	Odds ratio	Standard error	95% CI	*p*
UPCR >0.2 g/mmol	3.37	1.93	1.10–10.33	.034
CKD Stage 4	6.95	4.55	1.93–25.07	.003
Glomerular disease	6.40	3.99	1.89–21.73	.003

TABLE 4 Risk factors for time to endpoint (CKD 5) (N125)

Characteristic	Time (years)	Hazard ratio	95% CI	*p*
Overall	10.8			
UPCR[a] >0.2 g/mmol (*n* 56)	2.5	10.59	4.54–24.70	<.001
CKD stage 4 (*n* 20)	4.3	1.81	0.88–3.71	.12
Glomerular disease (*n* 44)	2.3	9.31	4.57–18.97	<.001
Anaemia[b] (*n* 62)	7.7	1.88	1.01–3.50	.04
Acidosis[c] (*n* 86)	9.1	1.38	0.69–2.76	.36
Hypertension[d] (*n* 69)	10.8	0.63	0.34–1.17	.14
Sex: girls (*n* 34)	2.7	2.90	1.55–5.44	.001

[a]Urine protein: creatinine ratio.
[b]Hb <11 g/dL <7 years, <11.5 g/dL >7 years.
[c]sHC03 < 22 mmol/L.
[d]Systolic and/or diastolic blood pressure ≥95th percentile.

survival time for each risk category. In this analysis also, glomerular disease, proteinuria and female sex were significant, and anaemia marginal, predictors of shorter kidney survival time. This is depicted for three factors by Kaplan–Meier curves in Figure 1. Acidosis and hypertension were not significantly associated with the time to kidney failure. Multivariate regression showed proteinuria, CKD stage 4 and glomerular disease to be independent predictors of earlier kidney failure. Female sex was marginally predictive (Table 5).

The rate of decline in GFR of all patients during the total follow up was calculated as annualized decrements for glomerular and non-glomerular disease. Decline of more than 5 mL/min/1.73 m^2/year occurred in 82% of patients with glomerular compared with 5% with non-glomerular disorders. Forty-eight (38%) of the patients had a decline in GFR of <1 mL/min/1.73m^2/year over the study period, mostly children with non-glomerular disorders. The median GFR decline was more pronounced in patients with glomerular disorders (16.8 [IQR = 9.5–26.2]) than in patients with non-glomerular disorders (1.32 [IQR = −3.43-3.86] mL/min/1.73 m^2/year). The excessive decline in patients with glomerular disease may, however, be due to skewed distribution, with a data skewness coefficient of −1.27.

4 | DISCUSSION

In this study, the association of variables related to progression of CKD was investigated in prepubertal children because of the hypothesis that variables may be affected by the physiological effects of puberty. Deterioration of kidney function during adolescence is a phenomenon familiar to paediatric nephrologists. The reasons are uncertain and not well studied.[13,14] The rational explanation of progression is the additional workload imposed by the increasing physical bulk of puberty, including muscle mass, on the limited number of remaining functioning nephrons. For these reasons, it was thought useful to

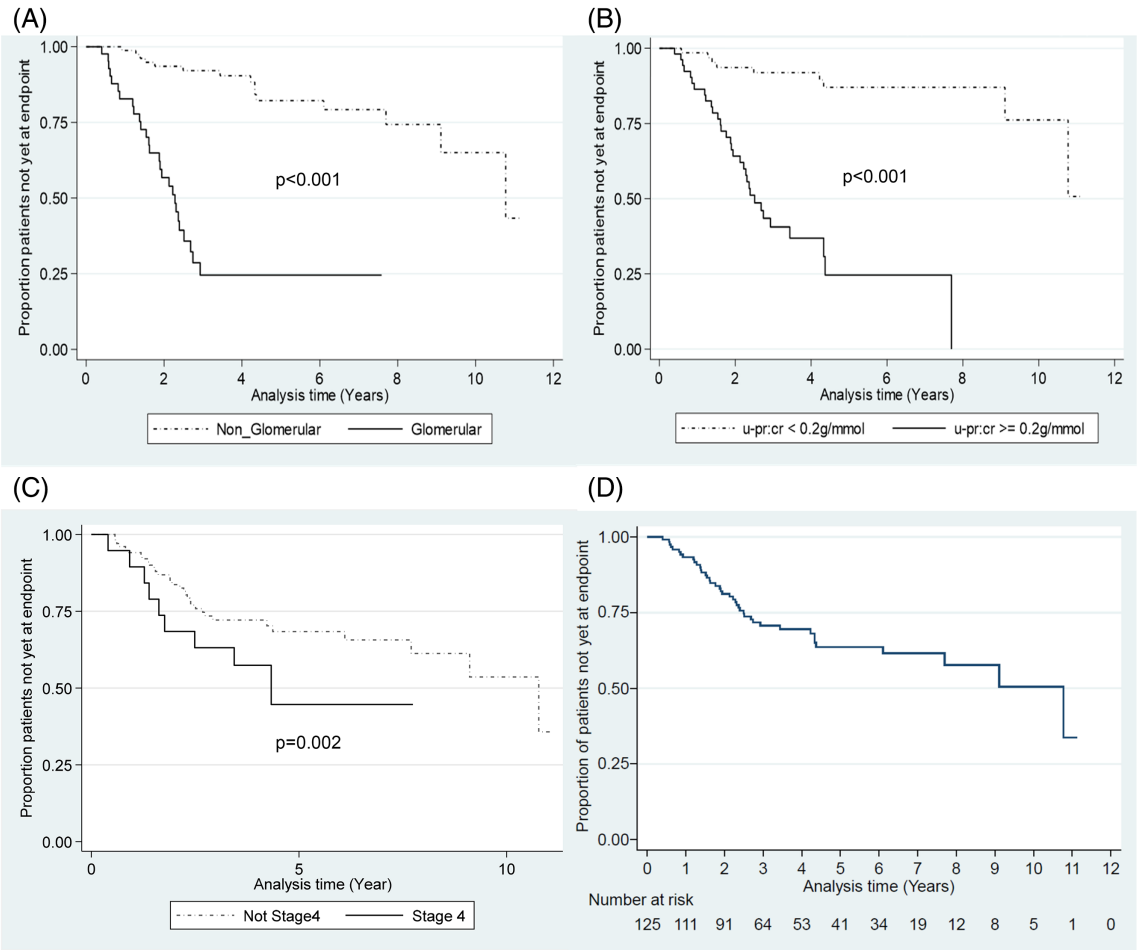

FIGURE 1 Kaplan–Meier curves of renal survival comparing glomerular and non-glomerular disease in A, showing the effects of proteinuria in B and CKD stage 4 in C, and for all patients in D

TABLE 5 Multivariate Cox regression for time to CKD 5

	Hazard ratio	Standard error	95% CI	*p*
UPCR >0.2 g/mmol	4.71	2.35	1.77–12.54	.002
CKD Stage 4	6.25	3.00	2.44–16.0	<.001
Glomerular disease	8.07	4.22	2.90–22.47	<.001
Female	1.87	0.62	0.98–3.57	.057

examine factors associated with CKD progression unrelated to the deleterious effects of puberty.

Studies on CKD progression in children invariably include adolescent and post-adolescent subjects, whereas none of the children in this study had reached puberty during the follow-up period. Some of the predictors of progression in this study were similar to those in other paediatric studies. Proteinuria and glomerular disease are consistently reported to be strong predictors in all studies,[18] and this was corroborated in the prepubertal children studied here. Some progression variables reported as significant in other studies were, however, absent in our subjects. Hypertension has been reported to be a significant predictor of progression in several paediatric studies. The ESCAPE trial, which included children up to 18 years of age, demonstrated that tight blood pressure control was beneficial in retarding progression of CKD in children.[9] The report by Warady et al. also demonstrated this: hypertension was associated with a 67% reduction of time to a composite kidney function endpoint.[8] However, this study included children up to 16 years of age, with a mean age of 11 years in children with non-glomerular disease, and 15 years with glomerular disease. In a report from the North American Paediatric Renal Transplant Cooperative Study (NAPRTCS) registry, children with hypertension progressed to CKD stage 5 two years sooner than non-hypertensive children.[10] In these trials, prepubertal children were not categorized or analysed separately. In the current study, 69 children (55%) were hypertensive at presentation, but this was not significantly associated with progression of CKD to the endpoint.

Anaemia is a common consequence of CKD. It has been reported in numerous studies to be associated with progression.[7,8,18] Management of anaemia in non-dialysis CKD children is difficult and less than satisfactory. However, there was little change in the occurrence of anaemia during the course of this study. Sixty-two (49.6%) of our patients were anaemic at entry and 59 (47.2%) at termination. Anaemia was not significantly associated with progression to the endpoint.

Presentation of patients with advanced disease was predictably associated with progression. This has been demonstrated in other studies.[1,7,10,14] It was corroborated in this study, where patients with stage 4 CKD at entry had an odds ratio of 6.95 for reaching the endpoint.

Proteinuria has consistently been demonstrated to be a significant predictor of CKD progression in adult as well as paediatric studies,[11,12,18] particularly in patients with glomerular disorders who are also more at risk of developing hypertension. From the CKiD cohort, Wong et al reported that patients with glomerular disorders causing CKD had UPCR levels that were on average 140% higher than in patients with non-glomerular aetiology.[11] The underlying causes of CKD may therefore be associated with different levels of proteinuria and rates of progression. Rapid progression occurs typically in the adolescent group in which there is also a higher incidence of glomerulonephritis. Proteinuria and glomerular disorders as predictors of CKD progression are corroborated in this study of prepubertal children. These two factors therefore seem to affect progression of kidney dysfunction independently of the effects of puberty.

Metabolic acidosis is reported to be associated with CKD progression.[8,19] Harambat et al classified acidosis into three levels in a large group of children. Bicarbonate levels of <18 mmol/L were associated with a significantly greater risk of progression than levels of <22 mmol/L.[20] The study population subjects had a median age of 12.3 years, unlike the prepubertal children in the current study.

The comparative analysis of kidney survival in boys and girls was performed because of the apparently slower progression of CKD in women.[21] In the CKiD study of children of all ages, CKD progressed more rapidly in boys than in girls.[8] In our cohort, however, girls were more likely to reach CKD stage 5 than boys were. This suggests that physiological changes during and after puberty affect progression of CKD in boys and girls differently.

To the best of our knowledge, no study on progression of CKD in prepubertal children exclusively has been published. Some studies have alluded to progression in this group of children.[13,14] Mitsnefes et al compared certain age groups of children with CKD and found that children aged 6–12 years and 13–17 years progressed significantly more rapidly than those aged 2–5 years.[10] A report from the NAPRTCS found that children aged 2–5 years and children aged 6–12 years had a hazard ratio of less than 1 for progression of CKD.[7] These results suggest that CKD in younger children progresses more slowly than in pubertal and older children. However, the structure of the current study was different to those quoted in that we entered only prepubertal children and statistical analysis was focused on this group alone. It would seem that some common risk factors for progression of CKD reported in studies including older children, are absent in prepubertal children.

The absence of hypertension and anaemia as risk factors for progression to the end point in our subjects is surprising. There may be physiological explanations as in the nature of arteries and erythropoiesis at this age. In addition, the children were younger and therefore exposed to the effects of CKD for a shorter period of time. The possible longer term cardiovascular consequences of anaemia and hypertension had not yet developed.

Of the variables that affected progression of CKD in this study, glomerular disorders and presentation with advanced disease are non-modifiable. Proteinuria, which is modifiable, was treated with ACEi. While the effect of ACEis on proteinuria specifically in African children is unknown, proteinuria was nevertheless a significant predictor of progression in this study. Confirmation of this modifiable condition as a risk factor for progression could be because the beneficial effect of ACEis on proteinuria may be evanescent.[22]

This study has limitations. The children were not followed through puberty to observe the effects on progression of CKD. The study also did not include a comparator group of post-pubertal children.

As with all data base studies some data was missing, although this was minimal in this study (<1%). A decided strength of this study is that all patient care and data recording were under the direct care of two paediatric nephrologists at all times.

The study was performed in a developing country and therefore some logistic challenges were experienced. Because of great travel distances, patients sometimes missed appointments and urine specimens were not always from early morning voiding collections. Prescribed drugs were, at times, not available. These factors may have contributed to the rate of progression of CKD in this cohort.

This study evaluated only variables that were present at the time of recruitment, and therefore did not consider the effect of subsequent management such as that of hypertension. We feel however that our findings are tenable because the patients were managed according to the KDIGO guidelines. Several of the quoted studies used a similar design.[7,8,16]

As with many clinical studies of this nature, ours suffers from the use of estimated GFR based on the bedside Schwartz formula only, rather than CKidU25. This was done in the interest of uniformity and because Cystatin C is not available in state laboratories in South Africa. In addition, serum creatinine measurements may be inconsistent between laboratories. However, some uniformity is present in this study as only two laboratories were responsible for laboratory investigations.

5 | CONCLUSION

Progression of CKD to kidney failure may differ between adults, adolescents and young children. This study evaluated risk factors for progression in prepubertal children. The presence of common modifiable indicators of CKD progression such as hypertension, anaemia and acidosis at initial evaluation, were not predictive of progression to ESKD in children who had not yet reached puberty. Only glomerular disease,

proteinuria and stage 4 CKD were independent predictors in this cohort. The absence of effect of modifiable factors on progression of CKD in this study suggests that more research on the underlying pathological processes in prepubertal children may reveal targets more amenable to treatment.

AUTHOR CONTRIBUTIONS

Conceptualisation: Gertruida van Biljon, Victor O L Karusseit, and Piet J Becker; data collection: Gertruida van Biljon, and Cornelius J Meintjes; data analysis: Piet J Becker, and Cornelius J Meintjes; manuscript preparation and editing: Gertruida van Biljon, and Victor OL Karusseit; Final approval of manuscript: Gertruida van Biljon, Victor OL Karusseit, Piet J Becker, and Cornelius J Meintjes.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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