Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.63, No.2(2023). p.96-101; DOI: https://doi.org/10.14238/pi63.2.2023.96-101

Original Article

Predictive factors of advanced chronic kidney disease in children with congenital anomalies of kidney and urinary tract

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Abstract

Background Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease (CKD) in children. Delayed diagnosis of CAKUT due to lack of universal screening (such as prenatal ultrasound screening or postnatal ultrasound screening in neonates with risk of CAKUT) has led to more cases of advanced CKD in children. CKD has high morbidity and mortality, and early detection is required to prevent the progression of CKD.

Objective To determine the factors that predict the development of advanced CKD in children with CAKUT.

Methods This retrospective cohort study included children with CAKUT at Dr. Sardjito Hospital, Yogyakarta, Central Java, from January 2016 to February 2021. Patients who were diagnosed with CAKUT were followed up to 5 years or until the onset of advanced CKD. Advanced CKD was defined as a decreased estimated glomerular filtration rate (eGFR) of less than 30mL/min/1.73m^2 based on the revised Schwartz formula. CKD progression-free survival was determined with Kaplan-Meier and Cox regression analyses.

Results Among 62 subjects with CAKUT, 7 (11.3%) subjects progressed to advanced CKD. The mean time of advanced CKD progression was 52.2 (95%CI 46.9 to 57.5) months. The overall incidence rate was 22 per 1,000 person-years. Based on Kaplan-Meier analysis, children with eGFR <60 mL/min/1.73m^2 at the time of diagnosis had more rapid progression to advanced CKD than patients with eGFR ≥60 mL/min/1.73m^2 [40.2 (95%CI 33.4 to 46.6) months vs. 58.2 95%CI 46.9 to 57.5) months; P=0.02, respectively].

Conclusion Reduced eGFR at the time of diagnosis shows rapid progression to advanced CKD. **[Paediatr Indones. 2023;63:96-101; DOI: https://doi.org/10.14238/pi63.2.2023.96-101**].

Keywords: *CAKUT; advanced CKD; survival*

Congenital anomalies of the kidney and urinary tracts (CAKUT) are one of the most common congenital abnormalities in newborns, accounting for 25% of them all.[1,2] The CAKUT prevalence varies between 3-6 per 1,000 live births. CAKUT is linked to a number of morbidities, one of which is chronic kidney disease (CKD).1 CAKUT was the most frequently reported cause of CKD in children (49.3%).[3] According to data across the globe, 34-43% of children with CAKUT will develop end-stage renal disease. CAKUT leads to reduced number of nephrons at birth, results in renal scarring, and progresses to end-stage renal disease.[3]

Advanced CKD has a high risk of mortality and morbidity. Previous studies revealed that 4.5% of children with CKD can progress to end-stage renal disease (ESRD) in the 1st year, 10.3% in the 2nd year, and 23.9% in the 5th year.[4-7] Children with ESRD have a 30 times higher risk of death and higher likelihood

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.Submitted January 3, 2022. Accepted April 11, 2023.

of long-term renal replacement therapy, which will have a psychosocial, emotional, and financial impacts on these patients and their families.[8,9]

Several studies have found that the urine protein/creatinine ratio, systolic blood pressure, CAKUT type, and urinary neutrophil gelatinase-associated lipocalin (NGAL) levels are all factors that influence ESRD progression.[10-13] To prevent the progression of CKD, early detection, treatment, and modification of predictor factors are critical. This study was conducted to determine the predictors of advanced CKD and renal survival time in children with CAKUT. Renal survival time defined as the time from onset of the cause to confirmed advanced CKD.

Methods

We conducted a retrospective cohort study in clinic outpatients and pediatric ward inpatients at Dr. Sardjito Hospital, Yogyakarta, Central Java, from January 2016 to February 2021. Children less than 18 years of age, diagnosed with CAKUT, and with CKD stage 1-3 (eGFR ≥30mL/min/1.73m^2) when diagnosed. To ensure the validity of the index date, patients were monitored for at least 6 months and those with incomplete observation were not included in this study.

From subjects' medical records, we recorded the type of CAKUT, eGFR, and proteinuria at the time of diagnosis. Patients were categorized based on type of CAKUT, obstructive or non-obstructive, based on imaging results (USG or voiding cystourethrogram/VCUG or intravenous pyelography/IVP or retrograde pyelogram/RPG and/or CT scan of the abdomen). The obstructive type consisted of ureteropelvic junction (UPJ) obstruction, vesicoureteric junction (VUJ) obstruction, posterior urethral valves (PUV), and ureterocele. The non-obstructive type consisted of primary vesicoureteral reflux (VUR), multicystic dysplastic kidney (MCDK), horseshoe kidney, renal agenesis, renal ectopia, renal dysplasia/hypoplasia, non-obstructive hydronephrosis, and complete duplex collecting system. Proteinuria was defined as urine protein ≥2+, based on a dipstick examination (semi-quantitative). Subjects' eGFRs were recorded every 3 months, for 5 years or until the onset of advanced CKD. Advanced CKD was defined as decreased eGFR <30ml/min/1.73m^2 based on the revised Schwartz formula.[14]

We performed Kaplan-Meier and log-rank tests to determine CKD progression survival, and Cox regression analysis to determine potential relationships between variables and advanced CKD. Variables with $P<0.25$ in univariate analysis were included in a multivariate analysis. This study was conducted after obtaining study approval from the Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta, Indonesia.

Results

During the study period, 19 patients presented with advanced CKD at the time of diagnosis. From 84 patients remaining, only 62 patients were followed-up until progression to advanced CKD or until 5 years from the time of diagnosis. The basic characteristics of subjects are shown in **Table 1**.

Table 1. Basic characteristics of CAKUT subjects

Characteristics	(N= 62)
Female, n (%)	32 (51.6)
Median age (IQR), months	7 (0.7-72)
CAKUT type, n (%)	
Obstructive	22 (35.5)
UPJ obstruction	12 (19.4)
VUJ obstruction	10 (16.1)
PUV	0
Ureterocele	0
Non-obstructive	40 (64.5)
Renal agenesis and hypoplasia	10 (16.1)
Renal cyst	9 (14.5)
VUR	7 (11.3)
Double collecting system	10 (16.1)
Other	4 (6.5)
Median eGFR at diagnosis (IQR), mL/min/1.73/m^2	72.8 (37.6-94)
Initial eGFR, n (%)	
<60 mL/min/1.73/m^2	25 (40.3)
≥60 mL/min/1.73/m^2	37 (59.7)
Proteinuria at diagnosis, n (%)	24 (38.7)
Definitive surgery, n (%)	29 (46.8)

CAKUT=congenital anomalies of the kidney and urinary tracts; UTI=urinary tract infection; IQR=interquartile range; eGFR=estimated glomerular filtration rate; UPJ=ureteropelvic junction; VUJ=vesicoureteral junction; PUV=posterior urethral valve; VUR=vesicoureteral reflux

Among 62 patients with CAKUT, 7 (11.3%) patients progressed to advanced CKD and 3.2% progressed to end-stage renal disease (ESRD). Slightly more than half of CAKUT subjects were female, but males comprised 57.1% of those who progressed to advanced CKD. The median age at CAKUT diagnosis was 7 (IQR0.7-72) months. The incidence of non-obstructive type was higher than that of the obstructive type (64.5% *vs.* 35.5%, respectively). Ureteropelvic junction obstruction was the most common (19.4%), followed by VUJ obstruction (16.1%), double collecting system (16.1%), and renal agenesis or renal hypoplasia (16.1%). The majority of CAKUT patients in this study did not undergo definitive surgery (53.2%). The incidence of advanced CKD was 20% higher in children over the age of ten years. In terms of frequency, the non-obstructive type was 12.5% more likely to progress to advanced CKD than the obstructive type.

The Kaplan-Meier curve in **Figure 1A** shows that the overall CKD progression-free survival was 82.4%. The overall incidence rate was 22 per 1,000 people annually. The mean time of advanced CKD progression was 52.2 months. Among 25 patients with eGFR <60 mL/min/1.73/m^2 at the time of diagnosis, 6 patients (24%) progressed to advanced CKD. Subjects with eGFR <60 mL/min/1.73/m^2 at the time of diagnosis had a lower CKD progression-free survival compared to those with eGFR ≥60 mL/min/1.73/m^2 (66.4% *vs.* 96.3%, respectively). The mean time of advanced CKD progression was significantly more rapid in this group (40.7 *vs.* 58.2 months, respectively, P=0.020) (**Figure 1B**). CKD progression-free survival began to decline within the first year for group with eGFR <60mL/min/1.73/m^2 (**Figure 1C**).

The Kaplan-Meier curve revealed no significant difference between type of CAKUT and proteinuria at diagnosis (log rank >0.05) (**Figure 1D**). According to the univariate analysis in **Table 2**, eGFR <60 mL/min/1.73/m^2, was predicting 8.18 times more progressive advanced CKD than was eGFR ≥60 mL/min/1.73/m^2 at the time of diagnosis (HR 8.18; 95%CI 0.98 to 68.00; P= 0.052), but the difference was not statistically significant.

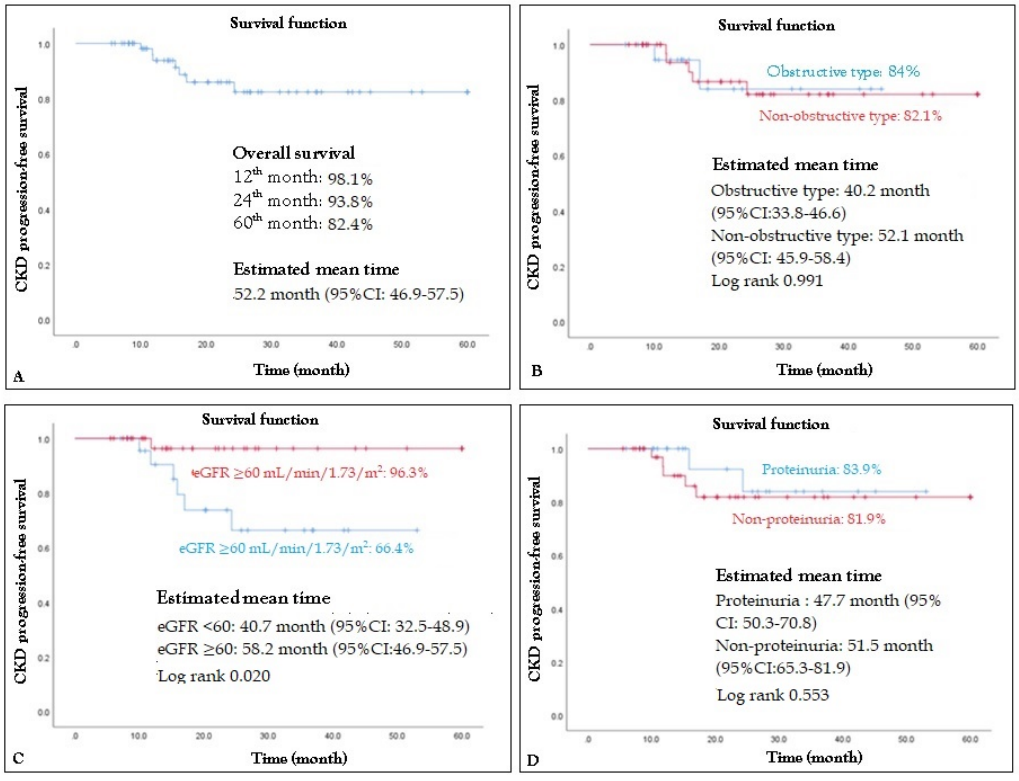

Figure 1. CKD progression-free survival based on Kaplan-Meier curve in CAKUT (A. CAKUT overall; B. CAKUT type; C. eGFR at diagnosis; D. proteinuria at diagnosis)

Table 2. Univariate analysis (Cox regression) of CAKUT characteristics and the incidence of advanced CKD

Variables	Univariate		
	HR	95%CI	P value
Type of disorder Obstructive Non-obstructive	0.99	0.19 to 5.15	0.991
Proteinuria at diagnosis\ Yes No	0.61	0.11 to 3.15	0.557
eGFR at diagnosis <60 mL/min/1.73/m^2 ≥60 mL/min/1.73/m^2	8.18	0.98 to 68.00	0.052

HR=hazard ratio; CI=confidence interval; eGFR=-estimated glomerular filtration rate

Discussion

CAKUT are primary kidney disorders that frequently result in end-stage renal disease. The pathogenesis of CKD occurs through three mechanisms, consisting of tubulointerstitial scarring, glomerulosclerosis, and vascular sclerosis. Reflux nephropathy, obstructive uropathy, and parenchymal abnormalities will lead to end-stage renal disease in CAKUT.[14] In our study, the incidence of advanced CKD in CAKUT was lower than in previous studies. According to a previous study, the majority of CAKUT phenotypes are PUV, which PUV progresses to advanced CKD more rapidly than other phenotypes. In our study, the majority of the phenotypes were UPJ obstruction. Furthermore, the median age at diagnosis was 7 months, with half of patients age diagnosed early below one year old (50.0%) and 49.1% of children received definitive intervention before the age of one year, resulting in a lower incidence of advanced CKD in our study.

Our CAKUT patients had a higher survival rate (82.4%). The median time of progression to advanced CKD could not be assessed because the incidence of advanced CKD was less than 50% of subjects. One of the predictors of advanced CKD is eGFR at the time of diagnosis. Decreased glomerular blood flow due to increased intratubular pressure causes eGFR to decrease rapidly and eventually progress to ESRD. In contrast, a study found a median ESRD survival of 57.13 months (95%CI 11.18 to 103.09).[15] Moreover, another study revealed that CKD doubles the risk of end-stage kidney disease compared to the incidence of ESRD in the general population (HR 2.0; 95%CI 1.64 to 2.42; P<0.0001).[16]

Compared to glomerular disorders, the progression of advanced CKD in CAKUT was slow. Progression to end-stage renal disease occurs in CKD stages 2-4 within 5 years on average, at puberty or in the second decade of life.[3,16,17] In our study, patients diagnosed with eGFR <60 mL/min/1.73/m^2 had multifactorial aggravating conditions such as syndromic, bilateral renal and urinary tract disorders, and spina bifida, resulting in faster progression.

In the progression of advanced CKD, there were no significant differences in type of CAKUT or proteinuria at the time of diagnosis. In contrast to previous studies, the non-obstructive group in these studies had a higher frequency of advanced CKD than obstructive group.[3,13,18] This finding was likely due to majority of the obstructive type (82.3%) having been treated with definitive intervention. Definitive interventions carried out before the age of one year can improve renal function, slowing the progression to end-stage renal disease. The non-obstructive type is often late to be diagnosed due to asymptomatic conditions. Symptoms appeared when the degree of reflux nephropathy was severe or when it progressed to CKD.[3,13,18]

Mechanisms of proteinuria can be classified as glomerular, tubular, secretory, or overflow. Tubulointerstitial disease is a less common cause of proteinuria than glomerular disease. Tubular proteinuria occurs when there is an increased excretion of normally filtered low-molecular-weight proteins because of impaired reabsorption by the proximal tubules. In CAKUT, the most common cause of proteinuria is tubulointerstitial and is generally mild. Tubular proteinuria rarely presents a

diagnostic dilemma because the underlying disease is usually detected before the proteinuria. As such, proteinuria had no significant association in our study. Kamath *et al.*[19] however, showed a significant relationship between proteinuria and the incidence of end-stage renal disease. They defined proteinuria as urine protein-to-creatinine ratio (UPCr) of >2, a quantitative examination. The protein-creatinine ratio had a higher sensitivity for measuring proteinuria than urine dipstick (75.6% *vs.* 45%, respectively).[19,20] We used the semi-quantitative method of dipstick examination. This examination was useful, but it can be influenced by variations in urine specimens.

In our study, we found that lower eGFR at the time of diagnosis showed rapid progression of the advanced CKD in children with CAKUT. We found that type of CAKUT, eGFR, and proteinuria at the time of diagnosis were not predictive factors of advanced CKD. Ramayani *et al.*[3] showed the median renal survival for obstructive type was 14.50 (range 8.09-20.90) years and for non-obstructive type 15.00 (range 6.92-23.07) years. Their study had several limitations which may have influenced the results. The limitation of their study was the short term of follow up and the multivariate Cox regression analysis did not perform to find out which variables were most significant to the progressivity of advanced CKD. As our study was based in a tertiary referral hospital, the majority of participants presented with advanced CKD. Further study is needed to determine other factors that influence advanced CKD in CAKUT patients (such as hypertension, social-economy, protein/creatinin ratio urine) with a larger sample size and by using a prospective cohort study design. Universal screening, early diagnosis and intervention, as well as long-term follow-up, are very important to reduce the progression to CKD in CAKUT patients.

Conflict of interest

None declared.

Acknowledgments

The authors received no specific grants from any funding agency in the public, commercial, or non-profit sectors.

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