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Pattern of clinical presentation of congenital anomalies of the kidney and urinary tract among infants and children

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SUMMARY AT A GLANCE

This paper describes the nature and pattern of congenital anomalies of the kidney and urinary tract (CAKUT) seen in a large centre in Cairo, Egypt.

ABSTRACT

Aim: **Congenital anomalies of the kidneys and urinary tract (CAKUT) comprise various entities of structural malformations that result from defects in morphogenesis of the kidney and/or urinary tract. These anomalies are the most commonly diagnosed malformations in the prenatal period and constitute the leading cause of end-+stage renal disease (ESRD) in children, worldwide. This prospective study was performed to report the patterns of clinical presentation and diagnosis of infants and children with such malformations.**

Methods: **Patients with suggestive features of CAKUT, presenting to Cairo University Children Hospital over one year duration were investigated and categorized based on underlying renal structural/functional malformation and associated extra-renal anomalies.**

Results: **One hundred and seven CAKUT children were enrolled in the study. Familial clustering was identified in 14% of the cohort and syndromic CAKUT accounted for 31.8% of cases. Different anomaly entities have been identified; posterior urethral valves (PUV) being the commonest detected abnormality (36.4%). Of note, 9.3% of cohort patients had ESRD at presentation, of which 60% had PUV as their primary renal disease. Obstructive cases were noted to present significantly earlier and attain advanced CKD stages rather than non-obstructive ones.**

Conclusion: **CAKUT is a clinically heterogeneous group of diseases with diverse clinical phenotypes. More efforts should be aimed at improving antenatal detection as well as classification with comprehensive reference to the clinical, genetic and molecular features of the diseases. The high frequency of familial and syndromic CAKUT among studied patients is seemingly a convincing reason to pursue the underlying genetic defect in future studies.**

Congenital anomalies of the kidney and urinary tract [CAKUT] comprise a wide range of structural malformations that result from defects in the morphogenesis of the kidney and/or the urinary tract.[1] This wide range of renal system structural and functional malformations that occur at the level of the kidney, collecting system, bladder, or urethra account for about 40–50% of children with chronic kidney disease (CKD), and are the most common cause of end-stage renal disease (ESRD) in children.[2,3] That being said, it is important to diagnose these anomalies early enough and initiate therapy to minimize renal damage, prevent or delay the onset of ESRD, and provide supportive care to avoid complications of ESRD.[4,5]

Although some forms of CAKUT are a part of a syndrome associated with extra-renal manifestations or have positive family history, most cases of renal system anomalies are sporadic and isolated to the urinary tract.[6,7] The majority of renal malformations are diagnosed antenatally, largely because of the widespread use and sensitivity of fetal ultrasonography.[8] The pathology of CAKUT is based on the

disturbance of normal nephronogenesis and can be due to genetic abnormalities in renal developmental genes that direct this process. Two main pathogenic theories are involved: (i) maldevelopment due to impaired budding hypothesis; and (ii) model of obstruction. Recently accumulating evidence suggests that the whole process is orchestrated by an interplay of a multitude of different disease-causing genes as well as environmental factors.[9]

To date, 23 monogenic CAKUT causing genes have been identified in patients with isolated, familial, or syndromic CAKUT, each gene representing a monogenic recessive or dominant cause of CAKUT. The malformation phenotypes vary from normally appearing kidneys with intact kidney function (i.e. incomplete penetrance) to severe hypodysplasia and ESRD.[10]

The aim of this work is to study the spectrum and pattern of clinical presentation of infants and children with CAKUT at both the Pediatric Nephrology and Pediatric Urology Units.

METHODS

Patients

A total of 107 patients from unrelated Egyptian families were enrolled in this study (median 25 months, range 0.59–156 months). They included patients presenting to Pediatric Nephrology and Pediatric Urology Units, Cairo University Children Hospital, through a period of one year starting from April 2010 to March 2011. Patients detected upon routine antenatal ultrasound scan; and later referred to either unit were also included.

In the current study, CAKUT patients were categorized into two main groups: (i) obstructive phenotype including posterior urethral valves (PUV), complete renal duplex, ureterocele, megaureter and pelvi-ureteric junction obstruction (PUJO); (ii) non-obstructive phenotype as primary vesico-ureteric reflux (VUR), multicystic dysplastic kidney (MCDK), renal agenesis (RA) and renal hypo-dysplasia.

Based on the definition of obstruction, and whether it is used to describe the presence of a physical blockage to urine flow or the failure of urine transport from the kidney to the ureter in the absence of physical blockage, obstructive cases were further subdivided into anatomical (PUV, ureterocele and complete duplex collecting system) and functional obstruction (PUJO and megaureter).

Patients with neurogenic bladder, bladder exstrophy, metabolic diseases, and polycystic kidney diseases were excluded from the study.

METHODS

Clinical data were collected including: (i) detailed history with special emphasis on the age of onset, diagnosis and sex; (ii) presenting symptoms (fever, failure to thrive, acute renal failure, abdominal mass, hypertension, urinary tract infection and voiding disorder); (iii) three generations family pedigree; (iv) laboratory investigations (kidney functions, urinalysis and urine culture); and (v) imaging (abdominal ultrasonography, voiding cystourethrography, diuretic-loaded diethylene-triaminepenta acetic acid [DTPA] renography and dimecaptosuccinic acid [DMSA] renal scintigraphy as indicated by clinical findings.

Voiding cystourethrography (VCUG) was performed in suspected cases of VUR for delineation of bladder and urethra anatomy, and to rule out urinary tract obstruction as an aetiology of the VUR. The detection of dilated elongated posterior urethra, thin linear defect during the voiding phase, pre-stenotic dilatation of the prostatic urethra, trabeculated and sacculated bladder were indicative of PUV, hence VUR was categorized in such cases as secondary VUR.

Statistical analysis

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 17. Numerical data were summarized using means and standard deviations or medians and ranges. Categorical data were summarized as percentages. Comparisons between two groups, with respect to numerical data, were done using the Mann–Witney test. The χ^2 test was used to compare between the groups with respect to categorical data. To measure the strength of the association between numerical data, which is not normally distributed, the Spearman's correlation coefficient was performed. All *P*-values are two-sided. *P*-values < 0.05 were considered significant.[11]

RESULTS

A total of 107 CAKUT patients (67% obstructive) were identified in the course of the current study, which revealed that 50.5% of the studied CAKUT patients in our hospital were the product of consanguineous marriage, relatively higher than the figure of almost 37% in the general Egyptian population. Moreover, in 14% of study patients, CAKUT was familial, as diagnosis was confirmed in at least one symptomatic family member. Interestingly, 46.7% of familial CAKUT patients were the products of consanguineous marriages. Male predominance was noted ($n = 75$, 70.09%) with an approximate male to female ratio 2.3:1. This is presumably due to the high frequency of PUV cases. Table 1 shows different CAKUT entities and their sex distribution.

Forty three cases (40.2%) (23 obstructive, 20 non-obstructive) were recruited from Pediatric Nephrology Unit, whereas 64 cases (59.8%) (49 obstructive, 15 non-obstructive) were recruited from Pediatric Urology Unit. Clinical assessment revealed a broad spectrum of presenting symptoms in identified CAKUT cases. Figure 1 shows the symptoms of all patients after enrolment in the study whether discovered antenatally or postnatally. Different CAKUT entities have been identified of which posterior urethral valve (PUV) was the commonest abnormality [$n = 39$, 36.4%].

Notably, more than one anomaly coexisted in 12 patients, of whom six had both the obstructive and non-obstructive components, hence excluded from statistical analysis to avoid fallacies. With exclusion of combined anomalies, obstructive cases comprised 65.3% ($n = 66$), and non-obstructive ones 34.7% ($n = 35$) of the cohort. Interestingly,

Table 1 Frequency and percentages of identified congenital anomalies of the kidneys and urinary tract (CAKUT) anomalies and their sex distribution among the studied cohort

Anomaly	Frequency	%	Gender M/F
PUV	39	36.4	39/0
MCDK	17	15.9	10/7
Unilateral ureterocele	4	3.7	0/4
Unilateral duplex	5	4.7	0/5
Unilateral PUJO	17	15.9	13/4
Bilateral PUJO	3	2.8	2/1
Unilateral megaureter	2	1.9	2/0
PBS	2	1.9	2/0
Unilateral VUR	15	14	7/8
Bilateral VUR	6	5.6	2/4
Unilateral RA	9	8.4	6/3
Unilateral renal hypoplasia	2	1.85	0/2
Bilateral renal hypoplasia	2	1.85	2/0
Unilateral ectopic kidney	1	0.9	1/0
Unilateral ectopic ureter	1	0.9	0/1

MCDK, multi-cystic dysplastic kidney; PBS, prune belly syndrome; PUJO, pelvi-ureteric junction obstruction; PUV, posterior urethral valves; RA, renal agenesis; VUR, vesico-ureteric reflux.

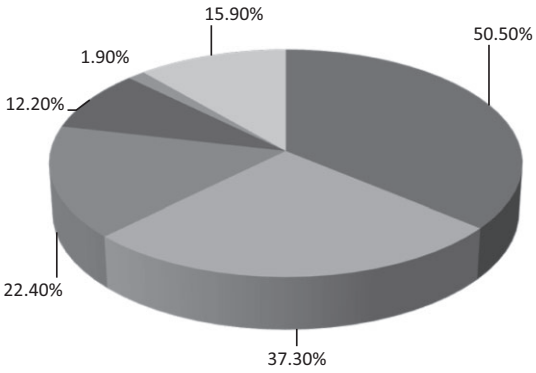

Fig. 1 Presenting symptoms of the study cases. Urinary symptoms: oliguria, dribbling, frequency, polyuria, and/or urinary tract infection; Abdominal symptoms: abdominal mass, distention, pain, and/or diarrhoea; Other symptoms: polydipsia, oedema, hypertension, vomiting and dehydration. ■, Abdominal symptoms; ■, Urinary symptoms; ■, Fever; ■, Acute kidney injury; ■, Failure to thrive; ■, Other symptoms.

all renal duplex cases were of the complete type; with one moiety obstructed (ureterocele or PUJO).

When comparing obstructive and non-obstructive cases, there was no statistically significant difference in the age of onset and diagnosis as well as the frequency of antenatal diagnosis, UTI, renal echogenicity, or ESRD.

Obstructive group patients, however, had advanced CKD stages (I: 45.5%, II–III: 22.7%, IV–V: 31.8%) in comparison to the non-obstructive group (I: 62.9%, II–III: 31.4%, IV–V: 5.7%) ($P = 0.021$) with significantly lower mean estimated glomerular filtration rate (e-GFR) ($P < 0.001$). Similarly, the

Table 2 Comparison between obstructive and non-obstructive cases

		Non-obstructive	Obstructive	Total	*P*-value
Gender	Female	17	14	31	
		48.6%	19.7%	30.4%	
	Male	18	53	71	
		51.4%	80.3%	69.6%	0.003
Antenatal diagnosis		10	27	37	
		28.6%	40.9%	36.6%	0.221
CKD stages	I	22	30	52	
		62.9%	45.5%	51.5%	
	II – III	11	15	26	
		31.4%	22.7%	25.7%	
	IV – V	2	21	23	
		5.7%	31.8%	22.8%	0.021
ESRD		2	7	9	
		5.7%	10.6%	8.9%	0.491
UTI		26	51	77	
		74.3%	77.3%	76.2%	0.737
Echogenicity		18	37	55	
		51.4%	56.1%	54.5%	0.656
Dilated system		14	66	79	
		40.0%	100%	78.2%	<0.001
Total		35	66	101	
		100.0%	100.0%	100.0%	

CKD, chronic kidney disease; ESRD, end-stage renal disease; UTI, urinary tract infection.

dilated system with subsequent atrophic changes, were significantly higher in the obstructive group ($P < 0.001$). Notably, the obstructive phenotype was higher among males (79.2% as compared to females (20.8%), presumably due to high prevalence of PUV. (Table 2).

The obstructive group was further subdivided into anatomical ($n = 45$) and functional ($n = 21$) obstruction. There was no significant difference between anatomical and functional obstruction regarding age of presentation. However, e-GFR was significantly lower in patients with anatomical obstruction compared to those showing functional obstruction ($P = 0.01$). Therefore, patients with anatomical obstruction had significantly advanced CKD as compared to patients suffering functional obstruction ($P = 0.005$).

In our cohort, secondary reflux was significantly associated with anatomical obstruction rather than functional obstruction ($P < 0.001$). Dilated systems, however, were detected in all patients with anatomical ($n = 47$) and functional obstruction ($n = 24$). Gender, antenatal diagnosis, UTI, renal echogenicity and ESRD were not significantly helpful to differentiate between types of obstructive anomalies.

Notably, in 34 out of the 107 CAKUT study patients (31.8%), CAKUT lesions were not the sole abnormalities found since a number of extra-renal manifestations were reported, hence categorized as syndromic CAKUT. Within this category, three patients had CAKUT in well identified syndromes; Turner syndrome ($n = 2$), Rotor syndrome ($n = 1$). However, the other 31 cases were associated with a range of anomalies, but not in the context of previously

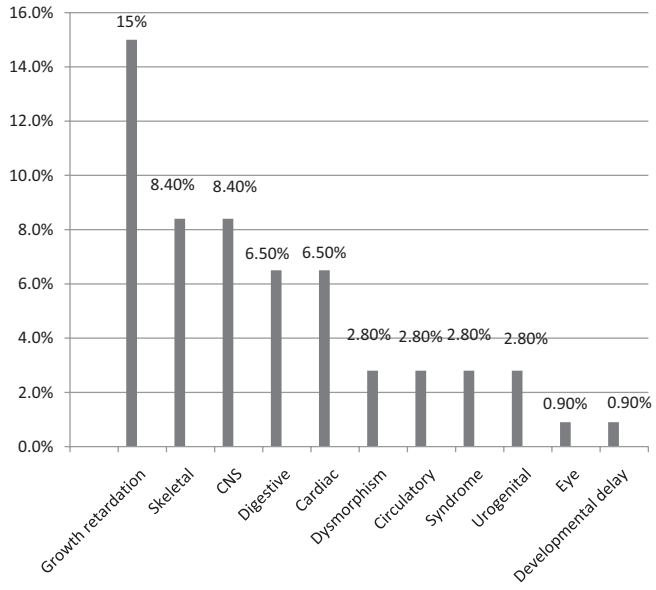

Fig. 2 Frequency of extra-renal features in congenital anomalies of the kidneys and urinary tract (CAKUT) patients. CNS, central nervous system.

reported syndromes. Extrarenal involvement in these children included: cloaca with occult myelomeningocele and bilateral talipes equino varus, spina bifida, aortic coarctation with brain infarction and syndactyly, inflammatory bowel disease, intracranial haemorrhage and deep venous thrombosis, retinal dysplasia and blindness, pulmonary hypertension, patent ductus arteriosus, pulmonary artery stenosis, patent foramen oval, brain atrophy, mental retardation, hypospadias, hydrocele, dysmorphism and growth retardation.

Identified extrarenal features in study patients were classified as: malformation syndromes ($n = 3$, 2.8%), growth retardation ($n = 16$, 15%), urogenital ($n = 3$, 2.8%), digestive ($n = 7$, 6.5%), circulatory ($n = 3$, 2.8%), cardiac ($n = 7$, 6.5%), skeletal ($n = 9$, 8.4%), central nervous system (CNS) ($n = 9$, 8.4%), developmental delay ($n = 1$, 0.9%), eye ($n = 1$, 0.9%) and dysmorphism ($n = 3$, 2.8%) (Fig. 2).

DISCUSSION

Congenital malformations of the kidney and urinary tract represent 23% of all birth defects. These malformations account for 40–50% of paediatric and 7% of adult end-stage renal disease worldwide. Among these malformations, renal aplasia, agenesis, hypoplasia, and dysplasia represent severe forms of disease with a profound impact on long-term renal survival.[3,6,12]

In this cohort of CAKUT patients, male predominance (70.09%) was evident with an approximate male/female ratio 2.3:1, compared to 9:1 as reported by Saha *et al*., 2009[13] and Ahmadzadeh *et al*., 2009.[14] Given the aetiological list in our cohort, it seems reasonable to ascribe this male predominance to the high frequency of PUV cases. Nevertheless, in a recent study including 213 index patients from unrelated Turkish families, there was no male predilection (male to female ratio 1:1.13) and VUR was the commonest anomaly (42.7%), followed by PUJO (15.1%), hypo-dysplasia (8.7%), PUV (6%), ectopic kidney (6%), MCDK (5%), RA (4.6%), horse-shoe kidney (4.6%), vesico-ureteric junction obstruction [VUJO] (4.1%), and the least reported anomaly of double collecting system (3.2%).[15] A Canadian CKD study suggested that male sex might be a general risk factor for CKD progression.[16] Also a single-centre CAKUT study from Italy showed that male sex predicted a shorter renal survival.[7]

Of note, consanguinity was recorded in 50.5% of study patients and in 46.7% of familial CAKUT (confirmed diagnosis in at least one symptomatic family member) that comprised 14% of study patients. Even though the percentage of familial CAKUT seems relatively high, yet is believed to be an underestimate that could have gone up with screening of asymptomatic family members, which was out of the scope of this work. Moreover, familial clustering of CAKUT strongly suggests a genetic predisposition as aforementioned in the literature. Weber and colleagues, 2006,[17] studied 100 cases with renal hypodysplasia and renal insufficiency revealing an underlying disease causing genetic mutation in 16%. Likewise, increased recurrence risk of CAKUT among first-degree relatives was reported.[15]

Variable extrarenal features (31.8%) were identified (growth retardation, CNS, cardiac, circulatory, digestive, skeletal, urinary and eye symptoms, developmental delay, syndrome and dysmorphism) with known syndromes (Turner and Rotor syndromes) reported in three patients. Growth delay was the eminent feature accounting for 15%, denoting the importance of medical follow up, not only for the primary disease but also for the ensuing complications requiring electrolyte replacement therapy and supportive measures. Growth retardation seems not to be related to CKD as it was reported in patients maintaining normal renal functions (CKD I).

Complex renal anomalies were noted in 10.3% of our study patients, while the remaining were isolated lesions. Additionally, kidney abnormalities (renal hypoplasia, RA and MCDK) had been reported in 17.8% of patients, whereas in the majority (82.2%) it was confined to the urinary tract (PUV, PUJO, ureterocele, megaureter, complete duplex, VUR). Interestingly, the frequencies in the current study with respect to sporadic versus familial and isolated versus syndromic CAKUT are consistent with earlier literature reports that although some forms of CAKUT are part of a syndrome or are associated with familial aggregation, yet most cases of renal system anomalies are sporadic and isolated to the urinary tract.[4]

In our study, different CAKUT entities have been identified of which PUV was the commonest abnormality (36.4%),

followed by VUR (19.6%), then PUJO (18.7%), MCDK (15.9%), RA (8.4%), complete duplex (4.7%), renal hypoplasia and ureteroceles (3.7% each), megaureter (1.9%) and ectopic kidney (0.9%). In contrast, Aksu *et al.* (2005),[18] reported PUJO in 62.7% and VUR in 16.6%. Other investigators identified the commonest CAKUT anomaly in their cohort as PUJO in 62.7%,[19] VUR in (40.2%),[14] and again VUR in 42.7%.[15]

Not surprisingly, obstructive cases presented earlier with significantly dilated system causing back pressure, renal parenchymal changes and consequently significant impairment of e-GFR as compared to the non-obstructive group. Also, obstructive group patients had advanced CKD stages (I: 45.5%, II–III: 22.7%, IV–V: 31.8%) in comparison to the non-obstructive one (I: 62.9%, II–III: 31.4%, IV–V: 5.7%). Ten of our CAKUT patients developed ESRD necessitating renal replacement therapy, of which eight suffered obstructive anomalies. Also, obstructive patients diagnosed by antenatal ultrasonography were higher ($n = 27$) than those of the non-obstructive type ($n = 10$), denoting the effectiveness of ultrasonography in early detection of urinary tract anomalies as well as kidney anomalies.

In an earlier study, ultrasound mass screening for kidney and urinary tract abnormalities in infants at 2 months of age in Italy involved a total of 17 783 infants between January 1992 and December 2010, authors reported that the frequency of CAKUT was 0.96% and none of their 171 patients with CAKUT has started dialysis. Two cases had chronic renal failure and three patients had proteinuria.[19] This again emphasizes the importance of early screening for CAKUT. The higher percentage of ESRD among our studied patients may be due to delayed diagnosis where 13 out of the 107 patients had acute renal failure (ARF) as their first presentation of which five progressed to ESRD. Arguably other hereditary, environmental and socioeconomic factors could be involved as further contributing factors.

Cases with anatomical obstruction were found to be significantly associated with secondary reflux rather than the functionally obstructive group. Also, anatomical obstructive cases exhibited significantly lower e-GFR and as a consequence, the latter group significantly acquired higher CKD grades.

Posterior uretheral valves

Regarding PUV, cases were characterized by consanguinity in 48.7%, early presentation, impaired renal functions and decreased e-GFR. PUV was the primary anomaly in majority (60%) of our CAKUT end-stage renal disease (ESRD) patients. This is strikingly consistent with the progressive nature of PUV and earlier reports that one-third of PUV cases develop significant CKD and 15% to 20% eventually progress to ESRD.[20]

Vesico ureteric reflux

In the present study, we observed that VUR patients had delayed presentation with less impairment of renal functions where CKD staging was I–II in all except for a single patient with CKD III. Moreover, consanguinity was evidenced in 71.4% of VUR cases. This finding might be a clue for genetic predisposition. Nevertheless, earlier studies report that reflux was detected in two-thirds of children whose parents had VUR, suggesting an autosomal dominant rather than autosomal recessive inheritance.[21]

We demonstrated mild to moderate grading of VUR in 11 out of the total 21 VUR patients (52.4%; grade I–III). A previous study of 43 infants with VUR graded reflux as low grade (grade I to III) in 32 (74%) of patients.[22]

Pelvi-ureteric junction obstruction

Pelvi-ureteric junction obstruction (PUJO) in study patients demonstrated male predominance (3:1). In unilateral PUJO there was predilection for the left kidney as compared to the right kidney (13:4); whereas bilateral involvement was elicited in 15% of total PUJO patients. Such results are consistent with previous literature reports documenting male predominance, left kidney predilection, and bilateral involvement in 10 to 40% of PUJO patients.[23] Interestingly, 25% of PUJO study patients demonstrated associated urinary tract anomalies as MCDK ($n = 2$), RA ($n = 2$), renal ectopia ($n = 1$). Age at diagnosis of PUJO cases was variable ranging from antenatal detection by ultrasound with postnatal confirmation (40%) to 8 years old. Fifty-five percent of PUJO patients had CKD I, 35% had CKD II–III and 10% had CKD IV–V. Of note, advanced CKD stages were observed in patients with contralateral MCDK.

Multicystic dysplastic kidney

In MCDK cases ($n = 17$), cases were characterized by early onset, where most cases (82.4%) were prenatally diagnosed, and variable CKD stages ranging from CKD I–V, however, most degrees were from CKD I–III. It has to be mentioned that one of the cases with PUJO on one side and MCDK on the contralateral side-developed ESRD and died one month after surgery. All of the cases were unilateral, more on the right side (58.8%). The contralateral side of the urinary tract was affected in five cases only (29.4%), of which three had VUR and the other two had PUJO. Our findings were partly consistent with earlier reports that most cases are unilateral and the contralateral urinary tract may be normal or it may be associated with a variety of other defects, including VUR (most common), rotational or positional anomalies, hypoplasia, areas of dysplasia, PUJO, ureterocoele or genital abnormalities.[24–26]

In 74 of the total cohort patients, surgical intervention was indicated within the postnatal management plan according

to their diagnoses. This ranged from minor endoscopic procedures (valve fulgration in PUV) to more complex interventions (pyeloplasty in PUJO; heminephrectomy in refluxing duplex moiety) according to standard protocols. Medically, patients in CKD stages 1–4 were managed conservatively, while ESRD patients joined the renal replacement program.

One limitation of the current study is being a hospital-based study carried in a tertiary centre with mostly referred complicated cases. Therefore, it does not necessarily reflect actual CAKUT prevalence in the community. Additionally, this study was time-limited over one year, which does not allow long-term follow up after medical and/or surgical treatment.

The pattern of clinical presentation of CAKUT in infants and children is extremely heterogeneous. Therefore, timely and precise clinical characterization of CAKUT both structurally and functionally is of utmost importance.

Frequent familial and syndromic CAKUT among study patients indicates the crucial need for detailed family history and thorough clinical examination for proper clinical phenotyping of all CAKUT patients. It also emphasizes the need to look for underlying genetic defects in future studies. Long-term studies are warranted to follow up these patients in terms of both renal and patient survival.

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