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Original Article

Comparison of Clinical Outcomes of Unilateral Atrophic/Hypoplastic/Nephrectomized and Solitary Kidney

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ABSTRACT

Background and Aim: The congenital anomalies of the kidney and urinary tract (CAKUT) are the most common findings in the pediatric age group with congenital malformations. The aim of this study was to evaluate clinical characteristics and follow-up results of children with unilateral solitary kidney (SK)/hypoplasia/atrophy and nephrectomized kidney.

Methods: We retrospectively reviewed the medical records of patients with unilateral atrophic/hypoplastic/SK and nephrectomized kidney who presented to the pediatric nephrology clinic between January 2010 and January 2023. The review included demographic data, laboratory findings, imaging results, and the clinical course of these patients.

Results: Eighty-nine patients were included in the study (M/F=52/37). 42(47.2%) patients had SK, 29(32.6%) patients had atrophy, 6(6.7%) patients had hypoplasia, and 12(13.5%) patients had undergone nephrectomy. At the last examination, hypertension was present in a total of 8 patients (9%). Hypertension was observed in 16.7% of nephrectomized patients and 11.9% of SK patients. Proteinuria was detected in 15 patients (16.9%) at the last follow-up visit, with the highest frequency observed in nephrectomized patients (33.3%). The four groups exhibited notable variations in terms of serum creatinine and phosphorus levels, with the nephrectomized group showing a higher creatinine level (P=0.004) and a lower phosphorus level (P=0.027) compared to the SK group.

Conclusion: Nephrectomy patients exhibit relatively high rates of proteinuria, hypertension, and increased creatinine levels, indicating the need for close monitoring.

Keywords: Solitary kidney (SK), Renal atrophy, Renal hypoplasia, Nephrectomy

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common findings in the pediatric age group with congenital malformations [1]. In recent years, with the increasing prevalence of prenatal ultrasound, the frequency of CAKUT has been steadily rising [2]. These anomalies are the most common cause of end-stage renal disease in children [3]. Children with an insufficient number of nephrons are at a higher risk of developing hypertension, proteinuria, and chronic kidney disease (CKD) in later life [4]. Renal agenesis/hypoplasia and dysplasia constitute a significant portion of these anomalies [5]. Unilateral kidney agenesis (URA) is defined as a con-

genital unilateral condition characterized by the absence of kidney tissue, likely due to abnormal embryonic kidney development, excessive growth and/or malformation of the primary ureteric bud, as well as interactions with metanephric mesenchyme [6]. Renal hypoplasia is characterized by a normal progression of nephrogenesis but a reduced number of nephron numbers, leading to a smaller-sized kidney [7]. An atrophic kidney is one that has shrunk to an abnormal size with abnormal function [3]. Nephrectomy is a surgical procedure to remove a kidney due to a tumor or an untreatable infected kidney [8]. In children with such anomalies, there are only a few reports on the progression of renal function and related parameters, such as hypertension, proteinuria and serum creatinine. Currently, there are insufficient global and local statistics regarding the long-term outcomes of a "missing kidney structure" in the pediatric population. The aim of this study was to evaluate clinical characteristics and follow-up results of children with unilateral solitary kidney (SK)/hypoplasia/atrophy and nephrectomized kidney.

Material and Methods

We retrospectively reviewed the medical records regarding the demographic data, laboratory findings, imaging results, and clinical course of patients with unilateral atrophic/hypoplastic/SK and nephrectomized kidneys who presented to the pediatric nephrology clinic between January 2010 and January 2023.

The variables, including age, gender, blood pressure, urinary protein/creatinine ratio, serum creatinine level, serum urea level and complete blood count were recorded for each patient. The presence of vesicoureteral reflux (VUR) and dimercaptosuccinic acid (DMSA) was also recorded. Accompanying congenital anomalies, including cardiac and urologic anomalies, ophthalmologic pathologies, and blood groups, were analyzed. Following the examination of four anomalies, patients were categorized into two groups: Those with atrophy/hypoplasia and those with SK plus a nephrectomized kidney. These two groups were compared based on demographic and clinical variables.

Data were analyzed by SPSS software, version 16.0. Descriptive results were expressed as Mean±SD for continuous variables with a normal distribution and as median, minimum and maximum for variables with no normal distribution. Group comparisons were carried out using ANOVA, unpaired Student's t-test, non-parametric Kruskal–Wallis test, or Mann–Whitney test as appropriate. Categorical variables are described as percentages, and the chi-square test was used to evaluate distinctions between the groups, at the 0.05 significance level.

Results

Eighty-nine patients were included in this study (M/F=52/37), of whom 42(47.2%) patients had SK, 29(32.6%) patients had atrophy, 6(6.7%) patients had hypoplasia, and 12(13.5%) patients had undergone nephrectomy (Figure 1). Among the patients with SK, 10 cases (23.8%) were diagnosed with multicystic dysplas-

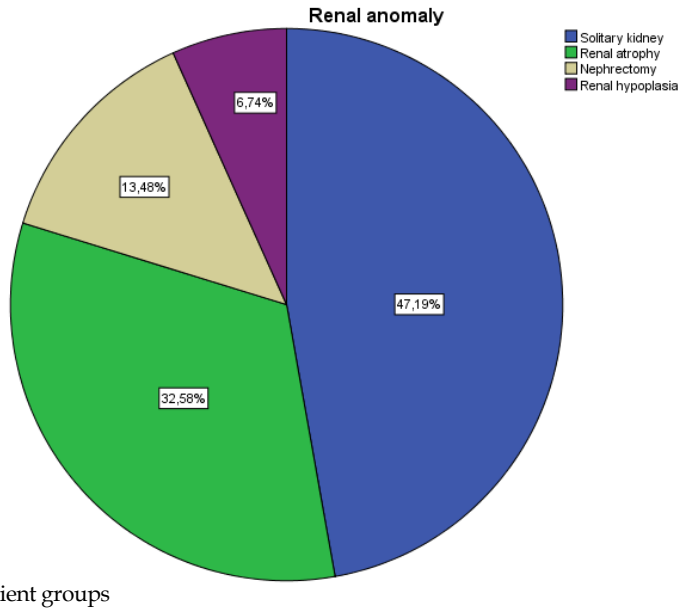

Figure 1. Distribution of patient groups

J Ped Nephrol
Journal of Pediatric Nephrology

tic kidney (MCDK) disease. In total, 54 patients (60.7%) had a single kidney. The median age of all patients at the time of participation in the study was 132 months (range 4-212 months), the median age at diagnosis was 48 months (range 1-182 months) and the median follow-up duration at our clinic was 36 months (range 3-122 months). Prenatal diagnosis was present in 25 patients (28.1%) and 54 patients (60.7%) had a history of previous urinary tract infections (UTIs). The indications for nephrectomy were as follows: 3(25%) for Wilms tumors, 3(25%) for reflux nephropathies, 2(16.7%) for advanced hydronephrosis-nonfunctional kidneys, 2(16.7%) for complicated pyelonephritides (abscess), 1(8.3%) for mesoblastic nephroma, and 1(8.3%) for nephrolithiasis. The mean renal uptake of DMSA in patients with atrophy/hypoplasia was 21.5±11.9%; in patients with renal atrophy, it was 21.6%±11.8% and the mean DMSA uptake in patients with renal hypoplasia was 21.2±14.6%. .

There was no significant difference in terms of gender and age between the four groups (P=0.115 and P=0.124, respectively) (Table 1). There was a significant difference between the groups in terms of age at diagnosis and follow-up time (P=0.009 and P<0.001, respectively). This difference was due to a younger age at diagnosis and a sorter follow-up time in the SK group compared to the atrophic group (P=0.046 and P=<0.001, respectively). The left side was dominant in all groups except the renal hypoplasia group (right/left=4/2). At the last examination, hypertension was present in 8 patients (9%). Specifically, 16.7% of nephrectomized patients and 11.9% of SK patients had hypertension. Proteinuria was detected in 15(16.9%) patients at the last follow-up visit, with the nephrectomized patients showing the highest frequency of proteinuria (33.3%). Three (20%) patients with proteinuria also had hypertension Additionally, two (25%) patients with hypertension had increased creatinine levels. Blood type A was significantly higher in the hypoplastic group (66.7%), and there were no patients with blood type AB in this group. A total of 15(16.9%) patients had a history of prematurity, with the hypoplastic group having the highest rate of premature birth (50%). A total of 20 patients (22.5%) had a family history of renal anomalies. VUR was detected in 23 patients (25.8%), of whom 18 patients were in the atrophic group. In terms of medical history of UTI, the atrophic group had the highest rate (72.4%). Nineteen (82.6%) patients with VUR had a history of UTI. There was a significant difference between the four groups in terms of serum creatinine and phosphorus levels. This difference was due to higher creatinine (P=0.004) and lower phosphorus (P=0.027) levels in the nephrectomized patient group compared to the SK group. Phosphorus levels were also lower in the atrophic kidney group than in the SK group (P=0.005). There was no significant difference regarding the mean levels of urea, uric acid, potassium, calcium and hemoglobin between the four groups (P<0.005).

Regarding comorbidities (Table 2), 5 patients (11.9%) in the SK group and 1 patient (8.3%) in the renal hypoplasia nephrectomy group had refractive errors in the eyes. Additionally, 7(16.7%) patients in the SK group, 1(3.4%) patient in the atrophy group and 1(16.7%) patient in the hypoplasia group had cardiac anomalies. One patient in the atrophy group also had Down syndrome, and 2 patients in the SK group were diagnosed with VACTERL syndrome (vertebral defects anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies and limb abnormalities). In total, 20 patients had additional urinary anomalies, including hydrocele, ureterocele, hypospadias, cryptorchidism, ectopic kidney, and ureteric pelvic obstruction, with their distribution among the groups presented in Table 2.

When comparing patients with a “missing kidney” to those without, female gender was significantly more common in the missing kidney group (57.1% vs 31.5%, P=0.016). The median age at diagnosis was significantly younger in patients with one kidney (P=0.001), and the follow-up duration was significantly longer (P≤0.001). There was no significant difference in left-sided dominance between the two groups (P=0.321). In the single kidney group, seven patients (13%) had hypertension at the last visit, compared to only one patient (2.9%) in the other group and this difference was statistically significant (P=0.001). Although the rate of proteinuria was higher in the single kidney group, this difference was not statistically significant (P=0.093) (Table 3). There was no significant difference between the two groups regarding a history of prematurity and a family history of kidney disease (P=0.558 and P=0.637, respectively). The incidence of VUR detected by cystogram was significantly higher in the non-single kidney group (54.3% vs 7.4%, P<0.001). There was no significant difference in terms of a history of urinary tract infection between the two groups (P=0.734). Laboratory parameters, such as urea, creatinine, uric acid, potassium, phosphorus and calcium levels showed no significant difference between the two groups (P>0.05).

Discussion

The kidney outcomes examined in children with different CAKUT forms include a range of standard outcome measurements, such as high blood pressure, proteinuria,

Table 1. The demographic and clinical laboratory characteristics of the patient groups

Variables	Solitary Kidney n=42	Renal Atrophy n=29	Nephrectomy n=12	Renal Hypoplasia n=6	P	Post Hoc analysis
Gender (female) No. (%)*	13(31)	17(58.6)	4(33.3)	3(50)	0.115	
Age median month (min-max)*	91(4-209)	150(13-210)	174.5(65-214)	144(40-204)	0.124	
Age of diagnosis-median month (min-max)**	1(1-181)	72(1-180)	42(1-96)	66(1-144)	0.009****	Between solitary kidney and atrophy: P=0.046
Following time-median month (min-maks)**	60(3-119)	17(4-80)	54(24-120)	22(12-100)	<0.001****	Between solitary kidney and atrophy: P<0.001
Effected side (right/left)	15/27	12/17	4/8	4/2		
Prenatal diagnosis No. (%)	20(47.6)	3(10.3)	2(16.7)	0(0)	<0.001****	Between solitary kidney and atrophy: P=0.002
Hypertension at last visit No. (%)	5(11.9)	1(3.4)	2(16.7)	0(0)		
Antihypertensive use No. (%)	3(7.1)	1(3.4)	2(16.7)	0(0)		
Proteinuria at last visit No. (%)	8(19)	3(10.3)	4(33.3)	0		
The most common blood group (%)	A(41.9)	A(42.1)	A(45.5)	A(66.7)		
The least common blood group (%)	AB(9.7)	AB(5.2)	AB(0.0)	AB(0.0)		
History of prematurity No. (%)	10(23.8)	2(6.9)	0	3(50)		
Familial history of renal anomaly No. (%)	10(23.8)	5(17.2)	3(25)	2(33.3)		
Positive VUR/Cystogram taken	1/5	18/25	3/5	1/3		
Past urinary tract infection	26 (61.9)	2 1(72.4)	6(50)	1(16.7)	0.067	
Urea** median (min-max) (mg/dL)	24 (6.4-72)	23.5(12-59)	25.5(16-31)	23.5(16-32)	0.989	
Creatinin** median (min-max) (mg/dL)	0.47 (0.20-1.45)	0.58 (0.33-1.08)	0.80 (0.39-1.04)	0.55(0.38-0.98)	0.002****	Between solitary kidney and nephrectomy=0.004
Uric acid ** median (min-max)(mg/dL)	4.1(1.5-6.6)	4.3(2.7-5.8)	4.6(2.6-7.6)	4.4(3.0-8.1)	0.305	
Potassium***(meq/L)	4.6±0.4	4.5±0.5	4.5±0.3	4.6±0.5	0.987	
Phosphor***(mg/dL)	4.7±0.8	4.1±0.9	3.8±0.7	4.5±0.9	0.002****	Between solitary kidney and atrophy P=0.027 Between solitary kidney and nephrectomy P=0,005
Calcium***(mg/dL)	9.9±0.4	9.8±0.6	9.8±0.2	9.7±0.6	0.328	
Hemoglobin***(g/dL)	13.1±1.5	13.6±1.4	14.1±1.8	14.0±1.4	0.158	

*Chı-square test

**Mann Whitney U test

***Unpaired Student's t-test :Mean±SD

****P<0.05

J Ped Nephrol
Journal of Pediatric Nephrology

Table 2. Accompanied findings and anomalies of patient groups

Variables		No. (%)			
		Solitary Kidney (n=42)	Renal Atrophy (n=29)	Nephrectomy (n=12)	Renal Hypoplasia (n=6)
Eye finding	Refractory error	5(11.9)	0(0)	1(8.3)	1(16.7)
	Retinopathy	1(2.4)	0 (0)	0(0)	0(0)
Cardiac anomaly	ASD	7(16.7)	1(3.4)	0(0)	1(16.7)
	VSD	3(7.1)	0(0)	0(0)	1(16.7)
	MVP	2(4.8)	0(0)	0(0)	0(0)
	PDA	0(0)	1(3.4)	0(0)	0(0)
		2(4.8)	0(0)	0(0)	0(0)
Down syndrome	VACTER-L	0(0)	1(3.4)	0(0)	0(0)
		2(4.8)	0(0)	0(0)	0(0)
Other urinary anomalies other than VUR	(Hydrocele, ureterocel, hypospadias, cryptorchidism, ectopic kidney, ureteric pelvic obstruction)	6(14.3)	8(27.6)	4(33.3)	2(33.3)

ASD: Atrial septal defect, VSD: Ventricular septal defect; MVP: Mitral valve prolapsus; PDA: Patent ductus arteriosus (PDA); VACTER-L: Vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities; VUR: Vesicoureteral reflux.

and a decrease in kidney function. This study investigated the mid-term prognosis of children with solitary, hypoplastic, atrophic kidneys, and those who had undergone nephrectomy, focusing on their clinical features, including creatinine levels, hypertension, and proteinuria.

The predominant group in our population was SK. In line with our results, prior studies have shown a higher prevalence among males and a left-side predominance in cases of kidney agenesis [9, 10]. Urinary tract abnormalities may coexist with SK in 10-50% of cases, underscoring the importance of imaging the opposite side [11, 12]. In our study, the incidence of associated urological anomalies varied between 14.3% and 33.3%. A prenatal diagnosis was established in 25 patients (28.1%), predominantly in SK cases with 20 patients diagnosed prenatally. Similarly, Plaud Gonzalez et al. found a similar rate (24.9%). The widespread use of ultrasound, especially in cases of URA, makes prenatal diagnosis possible [13]. Studies have reported that 10% to 50% of children with CAKUT have a family history of kidney abnormalities or urinary tract conditions [14, 15]. In our study cohorts, the prevalence of family history for SK, hypoplasia, and atrophy ranged from 17.2% to 33.3%. Hence, screening with ultrasound is advised for the first-degree relatives of these individuals [16].

The high rate of VUR in the atrophy group is an expected finding due to a cause-and-effect relationship. Moreover, the most prevalent UTI was identified in the atrophy group, leading to a higher occurrence of VUR within the same group; hence, 82.6% of those with VUR had a history of UTI. The most important indication for performing a VCUG (voiding cystourethrogram) is to assess the presence or absence of VUR [17]. Reflux nephropathy (kidney scarring) is characterized by atrophy, tubular damage, and interstitial fibrosis. Reflux nephropathy (kidney scarring) is characterized by atrophy, tubular damage, and interstitial fibrosis. Therefore, in patients displaying atrophy alongside hydronephrosis and a history of urinary tract infection, a voiding cystourethrogram should be carried out. Given the low rate of VUR in agenetic patients, a routine cystogram is unnecessary.

CAKUT is often associated with malformations of the reproductive system on the same side (ipsilateral) and various other malformation syndromes. The genetic causes for most cases remain unknown. In individuals with CAKUT, around one-third to half of them present one or more associated anomalies in other organ systems. These can involve cardiovascular, gastrointestinal, central nervous, skeletal, genitourinary, pulmonary, and renal systems, along with facial anomalies, chromosomal abnormalities, and multiple congenital anomaly syndromes [18]. According to the results of a meta-analysis conducted by Westland et al. additional CAKUT and extrarenal anomalies were observed in 32% and 31% of the cases, respectively [19]. Recognizing this relationship is important, especially when the anomaly is not evident

Table 3. Comparison of groups in mean of presence of kidney in the affected side

Variables	Group A* (n=54)	Group B* (n=35)	P
Gender (female) No. (%)**	17(31.5)	20(57.1)	0.016**
Age –median month (min-max)***	102(4-214)	150(13-210)	0.296
Age of diagnosis-median month (min-max)***	7(1-182)	72(1-180)	0.001**
Following time-median month (min-maks)***	60(3-122)	19(4-100)	<0.001
Effected side (right/left)**	19/35	16/19	0.321
Hypertension at last visit No. (%)**	7(13)	1(2,9)	0.001**
Antihypertensive use No. (%)**	5(9.3)	1(2,9)	0.239
Proteinuria at last visit No. (%)	12(22.2)	3(8.6)	0.093
History of prematurity No. (%)**	10(18,5)	5(14.3)	0.558
Familial history of renal anomaly No. (%)**	13(24.1)	7(20)	0.637
Positive VUR/Cystogram taken**	4(7.4)	19(54.3)	<0.001**
Past urinary tract infection**	32(59.3)	22(62.9)	0.734
Urea** median (min-max) (mg/dL)	24(6.4-72)	23(12-59)	0.946
Creatinin*** median (min-max) (mg/dL)	0.55(0.2-1.45)	0.58(0.33-1.08)	0.212
Uric acid *** median (min-max)(md/dL)	4.2(1.5-7.6)	4.35(2.7-8.1)	0.640
Potassium****(meq/l)	4.4 ±1.3	4.5±1.0	0.688
Phosphor****(mg/dL)	4.6 ±0.4	4.5 ±0.5	0.775
Calcium****(mg/dL)	4.5± 0.9	4.2±0.9	0.095
Hemoglobin****(g/dL)	9.9±0.4	9.8±0.6	0.134

*Group A: Soliter+ Nephrectomized, Group B: Atrophy+ Hypoplesia

**Chı-Square Test

***Mann Whitney U test

**** Unpaired Student's t-test :Mean±SD.

during routine physical examination [20]. In the present study, seven patients had congenital heart diseases (5.8%). Among the SK patients, two cases were syndromic (VACTER-L syndrome) and within the atrophy group, one patient had Down syndrome. Hence, we suggest that an echocardiogram be conducted, particularly in SK patients. Patients with URA should be evaluated from a distinct perspective regarding the potential presence of the syndrome.

Brenner et al. [4] states that a decrease in the number of nephrons can lead to glomerular hypertension, hypertrophy, and injury, which, in turn, results in systemic hypertension, albuminuria, and ultimately, glomerulosclerosis. Factors, such as an earlier gestational age, smaller kidney size at diagnosis, a decreased estimated glomerular filtration rate (eGFR), proteinuria and elevated blood pressure have been linked to the onset of CKD [21]. In our study group, proteinuria was predominantly observed in the nephrectomized group (33.3%), followed by SK (19%). Similarly, hypertension was more prevalent in nephrectomized patients compared to the SK group (16.7% and 16.9%, respectively). Similarly, Westland et al. found a similar hypertension rate in URA [19]. The crucial point to note is that the prognosis for nephrectomized patients was poorer than the other three groups concerning mean proteinuria and hypertension

J Ped Nephrol
Journal of Pediatric Nephrology

rates. We observed higher rates of hypertension, proteinuria, and creatinine elevation in nephrectomized patients compared to SK patients. Jaoudé et al. suggested that the compensation of the remaining kidney for renal metabolism may be of greater significance. This could pose challenges in cases of nephrectomy following trauma [22], potentially explaining the development of additional hypertension. Furthermore, another contributing factor is that upon examining the reasons for nephrectomy, four of these patients had malignancies and underwent chemotherapy. We speculate that the contralateral kidney may have been affected as a consequence of that treatment. In addition, cancer can have direct effects on kidney function through multiple factors, such as tumor lysis and hypercalcemia [23]. Conversely, Catalina et al. noted that individuals with an oncological condition exhibited a delayed decline in GFR compared to those with a non-oncological condition, specifically 63.5 months versus 41.3 months [24]. However, we advocate for the prompt implementation of adequate renal protective therapy and blood pressure management, particularly in these nephrectomized pediatric patients. In cases where the contralateral kidney remains unaffected, the long-term renal functional prognosis is typically favorable. However, in children with persistent urinary tract anomalies, the risk of adverse outcomes increases, with the average duration until CKD being 14.8 years [19, 25].

Upon comparing the single-kidney patient group with the group possessing kidney tissue, it was noted that the prevalence of hypertension was significantly higher in single-kidney patients. Although proteinuria was elevated, the statistical significance was not established. The renin-angiotensin system stands out as the most potent mechanism for maintaining sodium balance in reaction to alterations in sodium intake and/or excretion. It plays a crucial role in protecting against decreases in blood pressure due to a decrease in extracellular fluid volume [26, 27]. Even the presence of an extra glomerule might offer protection against hypertension.

In the present study, the median follow-up time was longer in the SK group and shorter in the atrophy group. The diagnosis of SK can be made antenatally; however, atrophy will be diagnosed during the evaluation of urinary tract anomalies, or it can also be incidentally diagnosed, which leads to delayed diagnosis.

In a study conducted on over 7,000 individuals in Turkey, the blood group distribution was as follows: A blood group 39.9%, B blood group 17%, AB blood group 14.6% and O blood group 28.2% [28]. A striking point in our study is the relatively high prevalence of blood group A in the hypoplastic group, while blood group AB was not found in this group. The *ABO* gene is located near the *NOTCH1* and *EHMT1* genes on chromosome 9q34, which play a significant role in cardiovascular development [29]. Despite the prevalence of cardiovascular malformations in the solitary group within our study, this factor alone does not account for our findings. Our current understanding of CAKUT genetics primarily stems from syndromic human developmental disorders, which are more accessible for study and have led to the identification of numerous candidate CAKUT genes, largely based on insights from mouse models [30]. The hypothesis that CAKUT could arise from single-gene mutations is supported by observations that certain monogenic mouse models can display CAKUT phenotypes and that monogenic human syndromes may encompass CAKUT phenotypes [31].

Among the most crucial genes identified to influence kidney development in both humans and mice are *RET* and *WNT11* (located on chromosomes 10 and 11, respectively), *GDNF*, *WT1*, *EYA1* (on chromosomes 5, 11 and 8, respectively) and *PAX2* (on chromosome 10). As such, there appears to be no direct association with the blood type gene on chromosome 9 [32, 33]. We anticipate that forthcoming genetic studies will shed light on the rationale behind our findings.

The present study has several limitations, including its retrospective nature, the lack of kidney function assessment using a standard method like creatinine clearance, and the inconsistent measurement of microalbumin levels across all patients. Furthermore, another constraint is that most statistical tests commonly employed to compare data categorized into groups (particularly those indicated by P) may not be as reliable when there is a comparison group consisting of <10 individuals (renal hypoplasia, n=6).

Conclusion

Given the notably elevated rates of proteinuria, hypertension, and increased creatinine levels in nephrectomy patients, close monitoring is imperative. The follow-up of children with a single kidney requires long-term and vigilant monitoring, actively investigating conditions, such as proteinuria and hypertension. Additionally, echocardiographic assessments should be conducted, particularly in URA patients.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of Kırıkkale University (Code: 2022.01.09; date: 11.1.2022).

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Authors' contributions

All authors equally contributed to the preparation of this article.

Conflict of interest

The authors declared no conflicts of interests.

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J Ped Nephrol
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