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The Clinical and Mutational Spectrum of 69 Turkish Children with Autosomal Recessive or Autosomal Dominant Polycystic Kidney Disease: A Multicenter Retrospective Cohort Study

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Keywords

Autosomal dominant polycystic kidney disease · Autosomal recessive polycystic kidney disease · Chronic kidney disease · *PKD1* · *PKD2* · *PKHD1* · Prognosis

Abstract

Introduction: Autosomal recessive polycystic kidney disease (ARPKD) is associated with pathogenic variants in the *PKHD1* gene. Autosomal dominant polycystic kidney disease (ADPKD) is mainly associated with pathogenic variants in *PKD1* or *PKD2*. The present study aimed to identify the clinical and genetic features of Turkish pediatric ARPKD and ADPKD patients. ***Methods:*** This multicenter, retrospective cohort study included 21 genetically confirmed ARPKD and 48 genetically confirmed ADPKD patients from 7 pediatric nephrology centers. Demographic features, clinical, and laboratory findings at presentation and during 12-month intervals were recorded. ***Results:*** The median age of the ARPKD patients at diagnosis was lower than the median age of ADPKD patients (10.5 months [range: 0–15 years] vs. 5.2 years [range: 0.1–16 years], respectively, [$p = 0.014$]). At the time of diagnosis, the median eGFR in the ARPKD patients was lower compared to that of ADPKD patients (81.6 [IQR: 28.7–110.5] mL/min/1.73 m^2 and 118 [IQR: 91.2–139.8] mL/min/1.73 m^2, respectively, [$p = 0.0001$]). In total, 11 (52.4%) ARPKD patients had malnutrition; 7 (33.3%) patients had growth retardation at presentation; and 4 (19%) patients had both malnutrition and growth retardation. At diagnosis, 8 (16.7%) of the ADPKD patients had malnutrition, and 5 (10.4%) patients had growth retardation. The malnutrition, growth retardation, and hypertension rates at diagnosis were higher in the ARPKD

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patients than the ADPKD patients ($p = 0.002$, $p = 0.02$, and $p = 0.0001$, respectively). ARPKD patients with malnutrition and growth retardation had worse renal survival compared to the patients without ($p = 0.03$ and $p = 0.01$). Similarly, ADPKD patients with malnutrition had worse renal survival compared to the patients without ($p = 0.002$). ARPKD patients with truncating variants had poorer 3- and 6-year renal outcome than those carrying non-truncating variants ($p = 0.017$). ***Conclusion:*** Based on renal survival analysis, type of genetic variant, growth retardation, and/or malnutrition at presentation were observed to be factors associated with progression to chronic kidney disease (CKD). Differentiation of ARPKD and ADPKD, and identification of the predictors of the development of CKD are vital for optimal management of patients with ARPKD or ADPKD.

Introduction

Polycystic kidney disease is a group of clinically and genetically heterogeneous inherited diseases characterized by the progressive development of cysts in both kidneys that lead to irreversible impairment of renal functions. Polycystic kidney disease is traditionally categorized into 2 groups according to the mode of inheritance: autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD), which are caused by pathogenic variants in the *PKHD1* gene that encodes fibrocystin/polyductin and mainly the *PKD1* gene encoding polycystin 1 (PC1) or *PKD2* encoding polycystin 2 (PC2), respectively [1].

ARPKD is a rare disease with an occurrence rate of 1 in 20,000 live Caucasian births that particularly affects the kidneys and liver. It is an important cause of morbidity and mortality in children and is characterized by nonobstructive fusiform dilatation of the renal collecting tubules and ductal developmental malformation resulting in congenital hepatic fibrosis [2]. Most cases of ARPKD are detected late in pregnancy or at birth. Affected fetuses exhibit the "Potter phenomenon," with enlarged kidneys, pulmonary hypoplasia, characteristic facial appearance, and limb anomalies [3].

ADPKD is the most common inherited kidney disease, with an incidence of 1 in 400–1,000 individuals, and accounts for 7%–10% of adult cases of end-stage renal disease (ESRD) [1]. It is usually asymptomatic until midlife; however, 2%–5% of ADPKD patients may present in prenatal or infancy period (very-early onset [VEO] ADPKD), which may be indistinguishable from ARPKD, with significant morbidity and mortality. In such cases, the two diseases can only be differentiated based on genetic analysis [4]. Differentiation is crucial for proper management and follow-up, as ARPKD presents a more severe clinical course than ADPKD. Studies on the genotype-phenotype correlation in ARPKD are limited in number, as the disease is rare. Burgmaier et al. [5] investigated genotype-phenotype correlation in 304 patients and showed that biallelic null variants were frequently associated with a severe phenotype. It has been reported that biallelic truncating mutations/null mutations are associated with an especially poor prognosis; however, it has been reported that some patients with 2 missense mutations might also be associated with a severe phenotype [5, 6]. To the best of our knowledge, the genotype-phenotype correlation in ARPKD has not been clearly established. The present study aimed to identify the clinical characteristics of Turkish children with genetically confirmed ARPKD and ADPKD in an effort to establish a genotype-phenotype correlation and to identify the factors that might be related to prognosis.

Methods

Study Design

This multicentric retrospective cohort study describes the clinical and genetic features of ARPKD and ADPKD in children. For the investigation of genotype-phenotype correlation, the study included 69 children with genetically confirmed ARPKD or ADPKD from 7 pediatric nephrology centers in Türkiye. The cohort included patients whose blood samples were sent to the Nephrogenetics Laboratory of Hacettepe University for genetic diagnosis (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000528258). Patient data were collected using a standard questionnaire. This questionnaire collected data regarding patient demographic features, date of diagnosis, parental consanguinity, family history of cystic kidney disease and chronic kidney disease (CKD), physical examination findings (including height and weight, and their percentiles for age), previous and current medication used, and laboratory findings (including serum biochemistry, and ultrasonographic findings of the urinary system, liver, and spleen). Anthropometric measurements were evaluated according to age and gender. Body weight, height, and body mass index (BMI) Z scores were calculated. Patients in whom height was <3rd percentile for age were considered to have growth retardation. Body weight <90% for height was considered as malnutrition [7]. The modified Schwartz formula was used to calculate the estimated glomerular filtration rate (eGFR) [8]. All data at the time of diagnosis were obtained retrospectively; follow-up data were collected at subsequent visits and were recorded annually in a database. Primary end point of the study was the analysis of the clinical characteristics of the patients including malnutrition, and growth retardation at the time of diagnosis and last visit. Secondary end point of the study was the

comparison of these parameters between ARPKD and ADPKD patients. Tertiary end point of the study was to determine the effects of genotype, growth retardation, and malnutrition on the kidney outcome. The study protocol was approved by the Board of the Hacettepe University Non-Interventional Clinical Research Ethics Committee (No. GO 18/329-14). Written informed consent was obtained from the patients when possible and/or their parents.

Genetic Analysis

All genetic analyses were performed at the Nephrogenetics Laboratory of Hacettepe University Pediatric Nephrology Unit. Briefly, DNA was extracted from peripheral blood using a commercial kit (Invitrogen PureLink Genomic DNA Mini Kit) according to the manufacturer's instructions. In all patients, a gene panel containing relevant genes (i.e., *PKD1*, *PKD2*, and *PKHD1*) was run using the next-generation sequencing method and an Ion S5 System® (ThermoFisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. The genomic region encompassing exons 1–33 of the *PKD1* shares 90%–99% sequence homology with 6 known pseudogenes on chromosome 16 making this region very difficult to resolve using traditional next-generation sequencing methods and resulting in reduced sensitivity to detect disease-causing variants. To increase sensitivity, we applied somatic mutation analysis (about 10%) on *PKD1* apart from "germline mutation analysis" method for the rest of the genes in our panel. In addition, we also used relatively longer amplicons (about 375bp) in comparison with other systems and workflows to empower specific reference data alignment. Data were analyzed using Ingenuity® Variant Analysis™ software (Qiagen, Redwood City, CA, USA). All relevant variants were confirmed via direct sequencing, using BigDye v.3.1 chemistry and an ABI3130 genetic analyzer (Applied Biosystems, Foster City, CA, USA). Parents and other affected individuals in the families of the index cases were also screened for the same variant identified in the index case via Sanger sequencing, when possible. Only variations that were considered to be responsible for the phenotype were included in the study. These were searched in established databases (i.e., Aachen database for ARPKD and Mayo database for ADPKD). Novel missense variants were tested with at least one of the following in silico analysis methods: Mutation Taster (http://www.mutationtaster.org), Sorting Tolerant From Intolerant (http://sift.jcvi.org), Polymorphism Phenotyping v2 (http://genetics.bwh.harvard.edu/pph2/index.shtml), and novel splice site variants with Human Splicing Finder (http://www.umd.be/HSF3/index.html) and all variants, when available, were searched for their minor allele frequencies in the healthy populations in the Genome Aggregation Database (https://gnomad.broadinstitute.org). Variations were considered to be responsible for the phenotype according to the following criteria: (1) they should be predicted as pathogenic in at least 1 in silico analysis method, and/or (2) if reported in the Genome Aggregation Database, their minor allele frequencies should be less than 0.01 in the healthy population for *PKHD1* and 0 for *PKD1* and *PKD2* genes, and/or (3) they should be previously reported as "pathogenic" in other studies, and/or (4) they should be predicted as pathogenic/likely pathogenic in established databases, and/or (5) they should be co-segregated with the disease within families. All variations causing frameshift were predicted as pathogenic as they give rise to a truncated protein.

Statistical Analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, USA) software. Descriptive statistics are presented as mean ± SD, median (IQR), frequency distribution, and percentage. Frequency tables were used to evaluate categorical variables. The relationship between qualitative variables was examined using the χ^2 test or Fisher's exact test. When comparing the groups, the significance test of the difference between 2 means (independent Student's *t* test) was used for normally distributed data, and the Mann-Whitney U test was used for data not normally distributed. To determine the correlation between 2 numerical variables, Pearson's and Spearman's correlation tests were used for parametric and nonparametric analyses, respectively. Survival curves for the entire patient cohort, as well as the ADPKD and ARPKD groups, were obtained using the Kaplan-Meier method. Standard errors of the survival rates were symmetrical around the point estimate. The level of statistical significance was set at $p < 0.05$.

Results

The study included 69 patients (38 female and 31 male). In all, 21 (30.4%) of the patients (10 female and 11 male) had biallelic *PKHD1* variants and were classified as ARPKD, whereas 46 (66.6%) of the patients (26 female 20 male) had either *PKD1* ($n = 40$) or *PKD2* monoallelic variants ($n = 6$) and were classified as ADPKD. Two female patients (3%) had biallelic variants in *PKD1* (Table 1).

Characteristics of the ARPKD Patients

Demographic, clinical, and laboratory findings, and genetic results are presented for each of the ARPKD patients in online supplementary Tables 1 and 2, respectively. All of the patients' parents did not have renal cyst based on ultrasonographic examination. The median age at diagnosis was 10.5 months (range: 0–15 years). Parental consanguinity was noted in 11 (52.4%) of the patients. The siblings of 4 (19%) patients had cystic kidney disease. Family history of cystic kidney disease was positive in 7 (33.3%) patients, and family history of CKD was positive in 5 (23.8%) patients. Homozygous variants were detected in 6 (28.6%) patients, and compound heterozygous variants were identified in 15 (71.4%) patients (Table 1, online suppl. Table 2).

In total, 11 (52.4%) patients had malnutrition; 7 (33.3%) patients had growth retardation at presentation; and 4 (19%) patients had both malnutrition and growth retardation. At the time of diagnosis, the median weight Z score was −1.79 SD (IQR: −3.15–0.3), the median height Z score was −1.05 SD (IQR: −2.7-[−0.09]), and the median BMI Z score was −1.1 SD (IQR: −2.59–0.99). Height

Table 1. Comparison of demographic and clinical features according to the genes

	PKHD1 (*n* = 21)	*PKD1* (*n* = 42)	*PKD2* (*n* = 6)	*p* value
Age at diagnosis	10.5 months (IQR 0.75 months–4.9 years)	4.6 years (IQR 8 months–7.6 years)	9.3 years (IQR 4.7–15 years)	**0.009**
Gender				
Female, *n* (%)	10 (47.6)	23 (54.8)	5 (83.3)	0.30
Male, *n* (%)	11 (52.4)	19 (45.2)	1 (16.7)	
Consanguinity between parents, *n* (%)	11 (52.4)	10 (23.8)	0 (0)	**0.017**
Cystic kidney disease in parents, *n* (%)	0 (0)	26 (61.9)	4 (66.7)	**0.0001**
Cystic kidney disease in siblings, *n* (%)	4 (19)	12 (28.6)	3 (50)	0.32
Family CKD history, *n* (%)	5 (23.8)	19 (45.2)	1 (16.7)	0.14

in 7 (33.3%) patients, body weight in 10 (47.6%) patients, and BMI in 7 (33.3%) patients were below −2 SD according to age. In all, 7 (33.3%) patients had abdominal distension; 13 (61.9%) patients had hypertension. The median age at diagnosis of 8 patients without hypertension was 11.5 months (IQR: 6 months-8.5 years). Of them, 3 were over 5 years old at diagnosis. In the cohort, 2 (9.5%) had polyuria and polydipsia, and 3 (14.3%) had recurrent urinary tract infection. Two patients (9.5%) had collateral blood flow (i.e., esophageal varices, hemorrhoids, and venous formations such as paraumbilical veins) and hematemesis, and 1 (4.8%) patient had melena (Table 2).

Median eGFR at diagnosis was 81.6 (IQR: 28.7–110.5) mL/min/1.73 m^2. In total, 14 (66.7%) of the patients had an eGFR <90 mL/min/1.73 m^2. Increased echogenicity and renal cysts were the most common ultrasound findings and were observed in 17 (81%) and 21 (100%) of the patients, respectively (online suppl. Table 1).

The median duration of follow-up in the ARPKD patients was 28 months (IQR: 6.5–86.5 months). At the end of follow-up, the median weight Z score was −1.5 SD (IQR: −2.15–0.2), the median height Z score was −1.69 SD (IQR: −3.1-[−0.1]), and the median BMI Z score was 0.12 SD (IQR: −1.4–1.05). During the follow-up period, there was improvement in the body weight Z score in 12 (57.1%) patients, height Z score in 10 (47.6%) patients, and BMI Z scores in 7 (33.3%) patients. Renal replacement therapy was initiated in 6 patients with a median eGFR of 18.8 (IQR: 12.5–30) mL/min/1.73 m^2 at diagnosis and median follow-up of 9.5 months (IQR: 0–61.2 months). Among these 6 patients, 3 died (1 patient due to sepsis, 2 patients due to respiratory distress associated with prematurity), 2 underwent successful renal transplantation (1 cadaveric and 1 living related), and 1 was being prepared for renal transplantation at the time this manuscript was written. Among the remaining 15 ARPKD patients, the median eGFR at diagnosis was 86.5 (IQR: 75.8–119.8) mL/min/1.73 m^2. After a median of 62 months (IQR: 18–87 months) of follow-up, the median eGFR was 74 (IQR: 43.6–96.8) mL/min/1.73 m^2, which did not differ significantly from the eGFR at diagnosis (p = 0.18).

The ARPKD patients were divided into 2 subgroups according to age at diagnosis: those diagnosed at age <1 year (n = 13) (early diagnosis) and those diagnosed at age ≥1 year (n = 8) (late diagnosis) (Table 3). The median duration of follow-up in the early diagnosis subgroup was 19.5 months (IQR: 0.5–53.5 months) versus 86 months (IQR: 39.5–103.5 months) in the late diagnosis subgroup (p = 0.02). Kidney transplantation was performed in 2 patients in the early diagnosis subgroup. The eGFR at the end of the follow-up period did not differ significantly between the early and late diagnosis subgroups (Table 3). Patients with malnutrition and growth retardation tended to have a lower eGFR both at diagnosis and at the end of the follow-up period, as compared to those without, but only growth retardation at diagnosis was differed significantly (p = 0.007) (Table 4).

Characteristics of the ADPKD Patients

Demographic, clinical, and laboratory findings, and genetic results are presented for each of the ADPKD patients in online supplementary Tables 3 and 4, respectively. All patients had a heterozygous variant in *PKD1* or *PKD2*, except for 2 patients with a homozygous variant in *PKD1* (online suppl. Table 4). The median age at diagnosis was 5.2 years (range: 0.1–16 years). A total of 13 patients (27.1%) were diagnosed less than 18 months of age (VEO ADPKD). In total, 15 (31.3%) of the patients had a sibling with cystic kidney disease, and 30 (62.5%) of the patients had a parent with cystic kidney disease. In all, 30 of the patients had a family history of cystic kidney disease, and 20 had a family history of CKD (Table 1 and online suppl. Table 3).

Table 2. Comparison of clinical, laboratory, and ultrasonographic findings of patients with ARPKD and ADPKD

	ARPKD (n = 21)	ADPKD (n = 48)	p value
Findings at diagnosis			
Malnutrition	11 (52.4)	8 (16.7)	**0.002**[a]
Growth retardation	7 (33.3)	5 (10.4)	**0.02**[b]
Hypertension	13 (61.9)	9 (18.8)	**0.0001**[a]
Abdominal distention	7 (33.3)	5 (10.4)	**0.03**[b]
Polyuria/polydipsia	2 (9.5)	1 (2.1)	0.21[b]
Recurrent UTIs	3 (14.3)	10 (20.8)	0.74[b]
Collateral blood flow	2 (9.5)	0 (0)	0.09[b]
Laboratory at diagnosis			
Na^+, mEq/L	137.4±3.8	138.6±1.6	0.17
K^+, mEq/L	4.5±0.6	4.4±0.3	0.76
Blood urea nitrogen, mg/dL	17.1±9.9	13.6±11.5	0.06
Uric acid, mg/dL	4.5±2.1	3.9±1	0.24
Creatinine, mg/dL	0.58 (IQR 0.37–0.83)	0.38 (IQR 0.3–0.52)	0.058
eGFR, mL/min/1.73 m^2	70.8±43	114.2±35.5	**0.0001**
Urine specific gravity	1,008±5	1,016±8	**0.0001**
Spot urine protein/creatinine ratio, mg/mg	0.3 (IQR 0.2–2)	0.15 (IQR 0.1–0.24)	**0.005**
Renal USG at diagnosis			
Echogenicity increase	17 (81)	12 (25)	**0.0001**[a]
CMD disappearance	9 (42.9)	7 (14.6)	**0.017**[a]
Cyst placements			
Cortical	2 (9.5)	13 (27.1)	
Medullary	3 (14.3)	3 (6.3)	0.22
Corticomedullary	10 (47.6)	20 (41.7)	
Abdominal USG at diagnosis			
Liver cyst	5 (23.8)	2 (4.2)	**0.03**[b]
PF	6 (28.6)	1 (2.1)	**0.005**[b]
Ascites	1 (4.8)	1 (2.1)	1.00[b]
Dilatation in the bile ducts	3 (14.3)	2 (4.2)	0.31[b]
Splenomegaly	1 (4.8)	2 (4.2)	1.00[b]
Follow-up creatinine, mg/dL	0.78 (IQR 0.51–1.3)	0.46 (IQR 0.37–0.59)	**0.009**
Follow-up eGFR, mL/min/1.73 m^2	74 (IQR 43.6–96.8)	114 (IQR 98.2–135.7)	**0.0001**
Delta eGFR (last eGFR-first eGFR)	0 (IQR -16.5–12.5)	0 (IQR -17 – 34)	0.59
Follow-up period, months	28 (IQR 6.5–86.5)	25.5 (IQR 9.5–48.2)	0.36
RRT	6 (28.6)	1 (2.1)	**0.03**[b]
Renal transplantation	2 (9.5)	1 (2.1)	0.21[b]

CMD, cortico-medullary differentiation; eGFR, estimated glomerular filtration rate; PF, portal fibrosis; RRT, renal replacement therapy; USG, ultrasonography; UTI, urinary tract infection. [a] Pearson χ^2 was used. [b] Fisher's exact test was used.

At diagnosis, 8 (16.7%) of the patients had malnutrition and 5 (10.4%) of the patients had growth retardation (Table 2). Two patients had both malnutrition and growth retardation. Among patients with malnutrition or growth retardation, 4 were in VEO group and 3 of them had an eGFR less than 90 mL/min/1.73 m^2 at the time of diagnosis. An additional 3 patients with malnutrition or growth retardation were not in VEO group but had an eGFR less than 90 mL/min/1.73 m^2 at the time of diagnosis. The median weight Z score at the time of diagnosis was 0.08 SD (IQR: −0.7–0.78), the median height Z score was −0.18 SD (IQR: −0.68–0.9), and the median BMI Z score was −0.13 SD (IQR: −0.88–0.93). Height in 4 (8.3%) patients, body weight in 6 (12.5%) patients, and BMI in 3 (6.25%) patients were below −2 SD according to age. In all, 5 (10.4%) patients had abdominal distension and 9 (18.8%) had hypertension. Among the patients, 10 (20.8%) had a history of recurrent urinary tract infection. Polyuria was not noted in any of the patients; however, 1 patient had polydipsia (Table 2).

Table 3. Comparison of clinical and laboratory findings of patients with ARPKD according to the age at diagnosis

	Age at diagnosis <1 year (*n* = 13)	Age at diagnosis ≥1 year (*n* = 8)	*p* value
Age at diagnosis (median, IQR), months	4 (0–8.8)	92 (30–156)	<0.001
Gender			
Female, *n*(%)	6 (46.1)	4 (50)	1.0[a]
Male, *n*(%)	7 (53.9)	4 (50)	
Growth retardation, *n* (%)	5 (38.4)	2 (25)	0.65[a]
Malnutrition, *n* (%)	8 (61.5)	3 (37.5)	0.38[a]
Creatinine at diagnosis, mg/dL	0.52 (IQR 0.24–0.75)	0.63 (IQR 0.45–0.87)	0.71
eGFR at diagnosis, mL/min/1.73 m^2	58.1±40.6	91.5±40.9	0.07
Creatinine at last visit, mg/dL	0.53 (IQR 0.3–0.95)	0.9 (IQR 0.55–1.25)	0.19
eGFR at last visit[b], mL/min/1.73 m^2	80.3±34.3	52.9±39.9	0.19
Follow-up period, months	19.5 (IQR 0,5–53,5)	86 (IQR 39.5–103.5)	**0.02**

IQR, interquartile range; eGFR, estimated glomerular filtration rate. [a] Fisher's exact test was used. [b] Two transplanted patients were excluded from the calculation of last visit eGFR.

Table 4. Comparison of the eGFR values at diagnosis and at the end of the follow-up period according to the presence of malnutrition and growth retardation in ARPKD

	eGFR at diagnosis, mL/min/1.73 m^2	*p* value	eGFR at last visit, mL/min/1.73 m^2	*p* value
Malnutrition				
Yes	63.2±42	0.41	60.3±50.4	0.11
No	79.2±38.8		104.4±68.8	
Growth retardation				
Yes	37±29.5	**0.007**	59.4±56	0.27
No	87.8±39		92.3±65.8	

eGFR, estimated glomerular filtration rate.

Table 5. Comparison of ADPKD patients according to the age at diagnosis with clinical and laboratory findings

	Age at diagnosis <2 year (*n* = 13)	Age at diagnosis ≥2 year (*n* = 35)	*p* value
Age at diagnosis (median, IQR), months	4.0 (2.3–8)	72 (55–121)	<0.001
Gender, *n* (%)			
Female	9 (69.2)	19 (54.3)	0.51[b]
Male	4 (30.8)	16 (45.7)	
Growth retardation, *n* (%)	3 (13)	2 (8)	1.0[a]
Malnutrition, *n* (%)	2 (15.4)	6 (17.1)	1.0[a]
Creatinine at diagnosis, mg/dL	0.38 (IQR 0.24–0.54)	0.40 (IQR 0.32–0.53)	0.40
eGFR at diagnosis, mL/min/1.73 m^2	81.6±33.8	128.6±38.7	**0.04**
End of follow-up creatinine, mg/dL	0.42±0.18	0.51±0.15	0.26
End of follow-up eGFR, mL/min/1.73 m^2	102 (IQR 85.5–125.3)	122 (IQR: 99–139.2)	0.31
Follow-up period, months	20 (IQR 12–41.5)	26 (IQR: 8.5–46)	0.77

IQR, interquartile range; eGFR, estimated glomerular filtration rate. [a] Fisher's exact test was used. [b] Pearson χ^2 test was used.

Table 6. Comparison of the eGFR values at diagnosis and at the end of the follow-up according to the presence of malnutrition and growth retardation in ADPKD

	eGFR at diagnosis, mL/min/1.73 m^2	*p* value	eGFR at last visit, mL/min/1.73 m^2	*p* value
Malnutrition				
Yes	105.5±72.6	0.45	121.4±47.5	0.93
No	117.9±34.9		125±32.5	
Growth retardation				
Yes	66±36.9	0.005	105.1±26.7	0.30
No	121.6±39.7		122.2±31.3	

eGFR, estimated glomerular filtration rate.

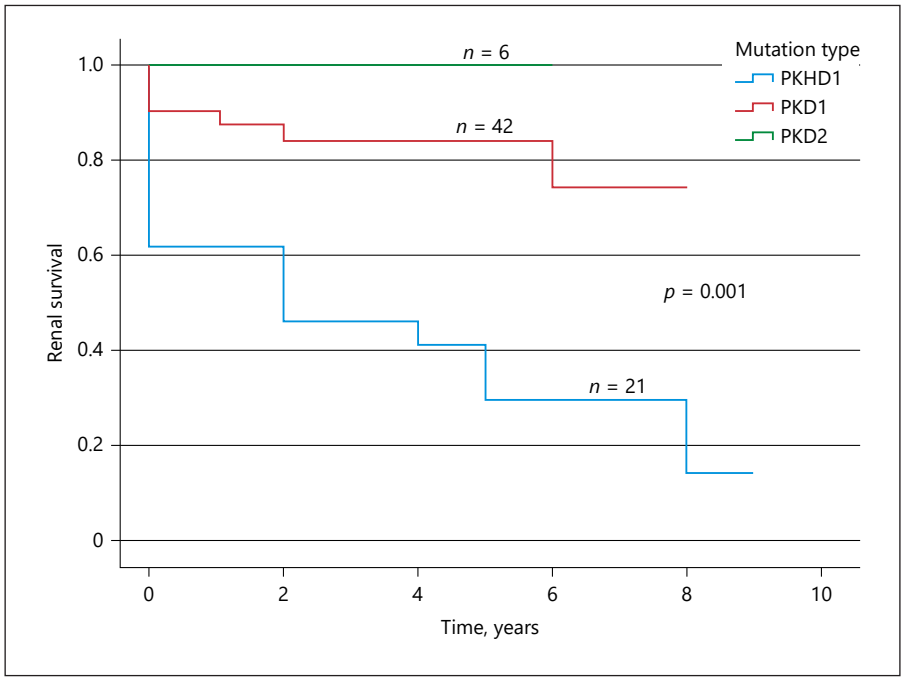

Fig. 1. RS according to mutation types (eGFR <90 mL/min/1.73 m^2).

Renal ultrasonography (USG) at diagnosis showed that 12 (25%) patients had increased echogenicity in both kidneys and 7 (14.5%) patients lacked cortex-medulla differentiation in the kidneys. Cyst rupture was noted in 2 patients, and 4 patients had signs of nephrocalcinosis. Cyst location was cortical in 13 patients, medullary in 3 patients, and corticomedullary in 20 patients. USG of the liver showed that 2 patients had liver cysts, and one of them (individual PN1608-II1 in the online suppl. Table 3) had periportal fibrosis and dilated bile ducts (Table 2). Some USG findings that were not observed at diagnosis were noted during follow-up. All USG data, both at diagnosis and during follow-up, are presented in online suppl. Table 3.

The mean eGFR at diagnosis was 114 ± 35.5 mL/min/1.73 m^2. At diagnosis, 11 (22.9%) had an eGFR <90 mL/min/1.73 m^2 (Table 2). After a median follow-up of 25.5 (IQR: 9.5–48.2) months, the median eGFR was found to be 114 (IQR: 98.2–135.7) mL/min/1.73 m^2. At the end of the follow-up period, the median weight Z score was −0.17 SD (IQR: −0.7–0.89), the median height Z score was −0.15 SD (IQR: −0.63–0.92), and the median BMI Z score was −0.09 SD (IQR: −0.63–0.85). During the follow-up period, there was improvement in the body weight Z scores in 22 (45.8%) patients, and height and BMI Z scores in 19 (39.6%) patients. Among the patients, 1 underwent cadaveric kidney transplantation during follow-up. None of the patients received renal replacement therapy (i.e., dialysis). In all, 1 patient with a *PKD2* mutation was also diagnosed with vesicoureteral reflux and neurogenic bladder. None of the ADPKD patients died during follow-up (Table 2).

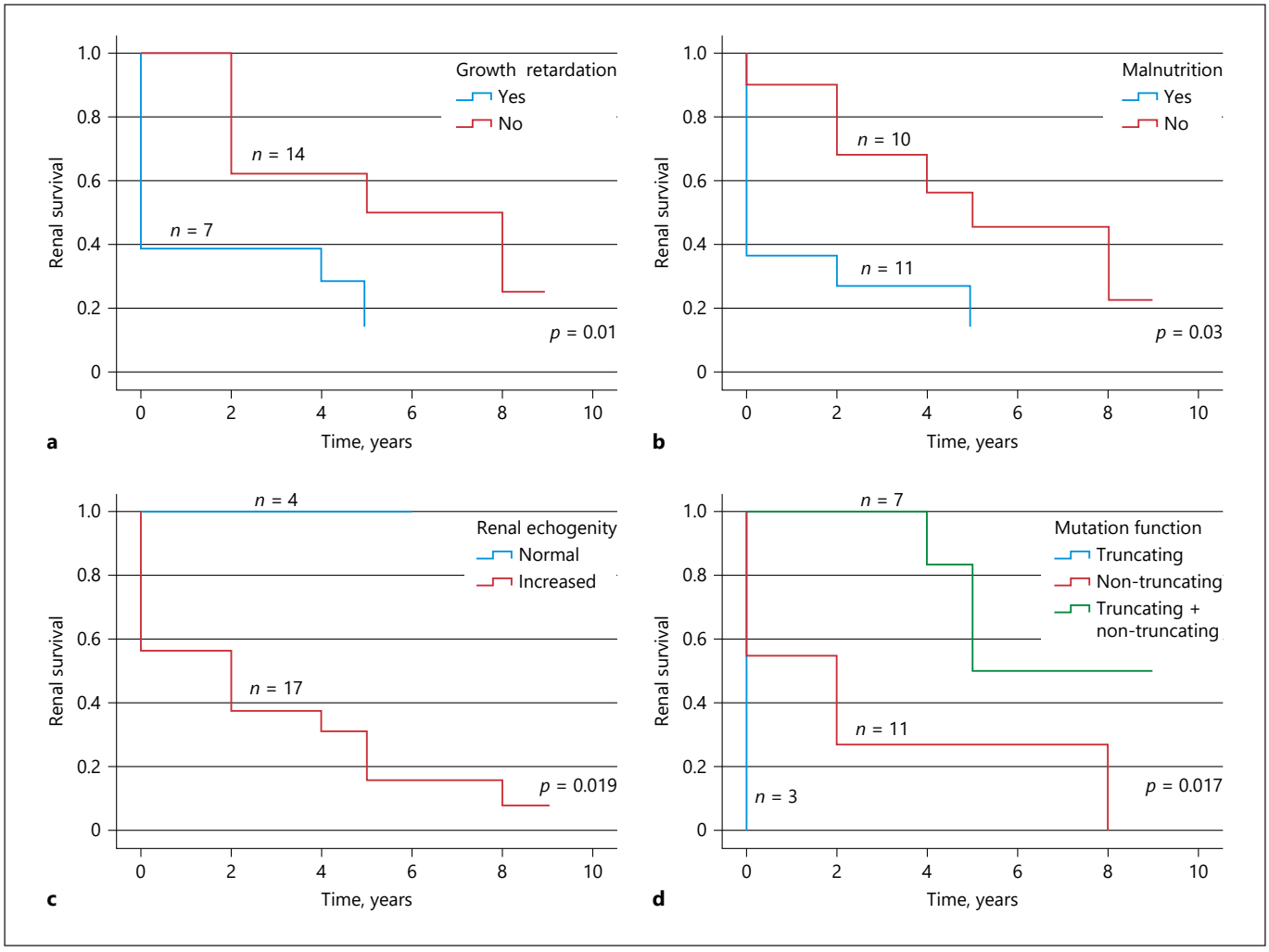

Fig. 2. RS of patients with ARPKD according to growth retardation, malnutrition, renal echogenicity in ultrasound, and mutation type (eGFR <90 mL/min/1.73 m^2).

The ADPKD patients were divided into 2 subgroups according to age at diagnosis: those diagnosed at age <2 years (n = 13) (early diagnosis) and those diagnosed at age ≥2 years (n = 35) (late diagnosis) (Table 5). There were not any significant differences in growth retardation or malnutrition at diagnosis or during follow-up between the early and late diagnosis subgroups (Table 5). The mean eGFR at diagnosis was 81.6 ± 33.8 mL/min/1.73 m^2 in the early diagnosis subgroup versus 128.6 ± 38.7 mL/min/1.73 m^2 in the late diagnosis subgroup (p = 0.04). There was not a significant difference in the eGFR at the end of the follow-up between these subgroups (p = 0.31) (Table 5). While there was a significant difference in the eGFR at diagnosis and at the end of the follow-up period in the early diagnosis group (p = 0.02), the difference was not statistically significant in the late diagnosis subgroup (p = 0.47). Patients with malnutrition or growth retardation had a lower eGFR at both diagnosis and at the end of the follow-up period, as compared to those without (Table 6).

Clinical Comparison of the ARPKD and ADPKD Patients

Among patients with *PKHD1*, *PKD1*, or *PKD2* variants, mean age at diagnosis was significantly lower in the patients with *PKHD1* mutations (p = 0.009) (Table 1). Malnutrition, growth retardation, hypertension, and abdominal distention at diagnosis were significantly more common in the ARPKD patients than in the ADPKD patients (p = 0.002, p = 0.02, p = 0.0001, and p = 0.03, respectively) (Table 2).

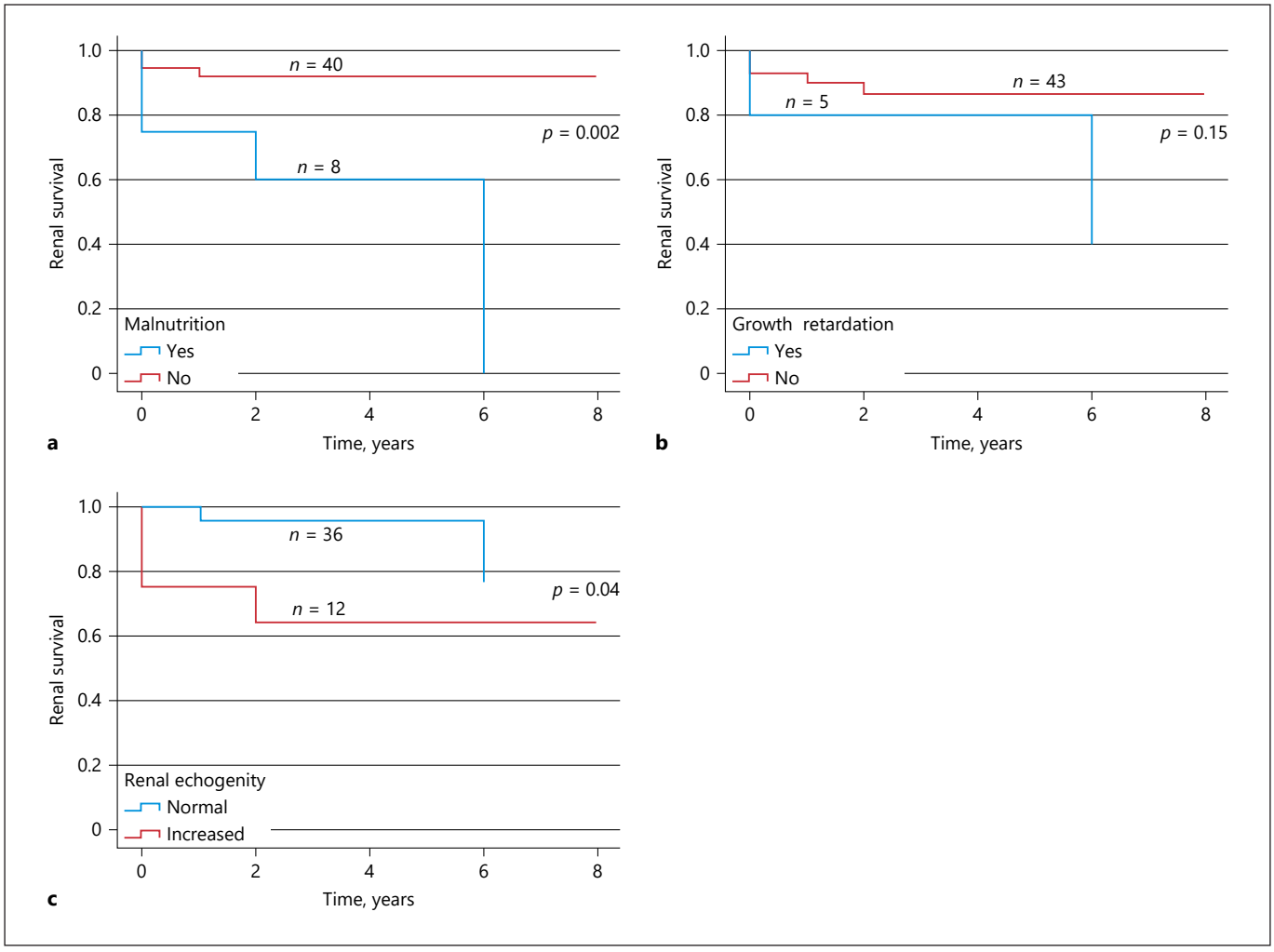

Fig. 3. RS of patients with ADPKD according to malnutrition, growth retardation, and renal echogenicity in ultrasound (eGFR <90 mL/min/1.73 m^2).

The eGFR and urine specific gravity at diagnosis were lower in the ARPKD patients ($p = 0.0001$ and $p = 0.0001$, respectively). Increased renal echogenicity, liver cysts, and periportal fibrosis were more common in the ARPKD patients than in the ADPKD patients ($p = 0.0001$, $p = 0.03$, and $p = 0.005$, respectively) (Table 2). A significant increase in the eGFR was observed in all patients with improvement in the height Z score ($p = 0.02$); however, no such correlation was noted for the body weight or BMI Z scores ($p = 0.31$ and $p = 0.64$, respectively).

Renal Survival Analysis and Genotype-Phenotype Correlations

In patients with biallelic *PKHD1* variants, 3- and 6-year renal survival (RS) was 51.6% and 32.8%, respectively, whereas 3- and 6-year RS in the patients with *PKD1* variants were 83.8% and 74.5%, respectively, both were 100% in the those with *PKD2* variants ($p = 0.001$) (Fig. 1 and online suppl. Table 5).

RS analysis showed that growth retardation at diagnosis was associated with poor prognosis among all the patients. In patients with growth retardation ($n = 12$), 3- and 6-year RS were 50% and 16.7%, respectively versus 80.4% and 71.5%, respectively, in those without growth retardation ($n = 57$) ($p = 0.001$) (online suppl. Table 5). In patients with malnutrition ($n = 19$), 3- and 6-year RS were 40.9% and 0%, respectively, versus 88.8% and 79.4%, respectively, in those without malnutrition ($n = 50$) ($p = 0.0001$) (online suppl. Table 5). Hypertension and increased renal echogenicity based on USG at

diagnosis were also associated with poor prognosis based on 3- and 6-year RS (online suppl. Table 5). When separately analyzed, the negative effects of malnutrition, growth retardation, and increased renal echogenicity were observed in both the ARPKD and ADPKD patients (Fig. 2 and online suppl. Table 6 and Fig. 3 and online suppl. Table 7, respectively).

Renal outcome in the ARPKD patients was evaluated according to genetic variation type. Patients with homozygous variants (n = 6) had much poorer renal function at diagnosis than those with a compound heterozygous variants (n = 15) (p = 0.0001) (online suppl. Table 6). Genetic variants were grouped according to exons, but there were not any significant differences based on RS analysis. Variants were then grouped as truncating (i.e., splice site, nonsense, and frameshift) (n = 3) and non-truncating (i.e., missense) (n = 11). In all, 7 patients carrying 1 truncating and 1 non-truncating variant were grouped separately. Among the ARPKD patients, those with biallelic truncating variants had a lower eGFR than those with biallelic non-truncating or compound heterozygous comprised 1 truncating and 1 non-truncating variant, both at the time of diagnosis and at the end of follow-up (p = 0.055 and p = 0.02, respectively) (online suppl. Table 8). Patients with truncating variants had poorer 3- and 6-year renal outcome than those carrying non-truncating variants (p = 0.017) (Fig. 2d, online suppl. Table 6). All patients with truncating variants presented at age <1 year. Although not significant (most likely due to the small numbers of patients), malnutrition and growth retardation were more common in the patients with truncating variants than in those with non-truncating variants (100% and 66.7% vs. 54.5% and 27.3%, respectively) (p = 0.11 and p = 0.41, respectively). In patients with compound heterozygous variants, both malnutrition and growth retardation were noted in 28.6% of the patients (online suppl. Table 8).

As were *PKHD1* variants, *PKD1* and *PKD2* variants were grouped according to exon, and as truncating and non-truncating, and their effects on prognosis were investigated. There was not any significant difference in age at diagnosis (<2 years vs. ≥2 years) or growth retardation (presence vs. absence) according to the exons. The 3- and 6-year RS of the early diagnosis group was less than the late diagnosis group in ADPKD patients (p = 0.04) (online suppl. Table 7). The eGFR at diagnosis was lower in the patients without truncating variants, but there was not a significant difference between the eGFR at the time of diagnosis and during follow-up.

Discussion

ADPKD and ARPKD are both clinically and genetically heterogenous diseases. In contrast to the belief that ADPKD is almost always seen in adult patients and ARPKD in pediatric patients, both diseases can be seen in young children, and in such cases, it may not be possible to clinically differentiate them. In pediatric patients, many symptoms of both diseases may overlap. Several studies evaluated the clinical and genetic features of ARPKD and ADPKD. To the best of our knowledge, the present study is the first multicenter cohort study to evaluate nutrition status/growth, genetic characteristics, and long-term follow-up and to compare them in pediatric patients with ARPKD and ADPKD. An especially important finding of the present study is the observation that malnutrition and growth retardation are the factors associated with poor prognosis. They were significantly more common in the ARPKD patients than in the ADPKD patients. Growth retardation and malnutrition commonly occur in many CKD patients. Factors that contribute to malnutrition and growth retardation in CKD patients are decreased nutritional intake, alteration of regulatory hormones and the growth hormone/insulin-like growth factor axis, orexigenic and anorexigenic hormone imbalance, the effect of peritoneal dialysis on abdominal distention, increased loss of nutrients, metabolic problems caused by the disease (i.e., chronic acidosis, electrolyte imbalance, hyperparathyroidism, and renal osteodystrophy), hospitalizations, and frequent infections [9, 10]. The reported prevalence of growth retardation in ARPKD patients is 25% [11, 12]. One study compared the frequency of growth retardation in ARPKD patients and patients with CKD, due to other congenital causes (i.e., renal aplasia, hypoplasia, dysplasia, and obstructive uropathy) [13], reporting that there is not a disease-specific effect of ARPKD on linear growth [12]. Growth retardation in ARPKD patients could be attributed to the early onset of the disease with impaired renal function, premature birth or low birth weight, the need for intensive care unit hospitalization, malnutrition, and other comorbid conditions. It was reported that feeding intolerance in ARPKD patients can negatively affect growth due to liver and lung problems and very enlarged kidneys [14].

In the present study, the growth retardation and malnutrition rates did not differ significantly between the ARPKD patients in the early and late diagnosis subgroups. The mean eGFR at diagnosis was significantly lower in the ARPKD patients with growth retardation than in those without (p = 0.007). At the end of the follow-up period,

the eGFR did not differ significantly than at the time of diagnosis ($p = 0.19$), whereas RS analysis showed that renal outcome was worse in the patients with growth retardation. Malnutrition or growth retardation is expected findings in ARPKD patients due to the massive kidneys, early deterioration of kidney functions, and intrauterine growth retardation. However, it is not common in ADPKD patients. In our ADPKD cohort, approximately one-third of the patients were in VEO group and additional one-third of the patients had CKD at the time of diagnosis. Each of these factors may be contributory to the development of malnutrition and/or growth retardation in ADPKD patients. The present findings also suggest that there might be factors other than renal function that affect growth by means of eGFR itself in patients with *PKHD1* mutation. Indeed, it has been shown that intraflagellar transport (IFT) and primary cilia play a role in skeletal development [15]. Primary cilia are nonmotile microtubules extending from the surface of almost all cells. The process of IFT is responsible for building and maintaining the structure and function of primary cilia. Disruption of Kif3α, a component of the kinesin-II motor complex, disables anterograde IFT and leads to failure of cilia formation and maintenance. Deletion of Kif3α or IFT88 in Prx1-expressing cells results in defective embryonic endochondral bone formation, including a dramatic reduction in bone length. As fibrocystin/polyductin encoded by *PKHD1* is found on the primary cilia, this would be relevant to skeletal growth; therefore, we speculate that *PKHD1* mutation itself may have played a role in the impaired growth observed in the present study's ARPKD patients, independent of the eGFR.

A study that included 10 neonatal ARPKD patients that underwent bilateral nephrectomy, reported 9 of the patients subsequently underwent kidney transplantation [16]. Nephrectomy was performed due to massive kidneys that resulted in suboptimal nutrition and respiratory compromise. All the patients received assisted enteral nutrition, with a significant increase in mean number of tolerated feedings following nephrectomy and an increase in mean weight and height. It was reported that in patients with massive kidneys due to ARPKD, preemptive bilateral nephrectomy, supportive peritoneal dialysis, and early aggressive nutritional support can reduce infant mortality and facilitate subsequent kidney transplantation with excellent patient and graft survival, highlighting the importance of measures that prevent the development of malnutrition and its negative effects on long-term survival. The present findings clearly show that growth retardation and malnutrition are associated with poor 3- and 6-year RS. In addition, ARPKD patients with malnutrition in both the early and late diagnosis subgroups had a poorer prognosis than those without malnutrition. Another interesting finding of the present study is that there is a positive correlation between the eGFR and the height Z score. It remains unclear if improvement in kidney function resulted in better growth performance or if better growth led to improvement in the eGFR; these causal relationships require further research.

A few studies have investigated the genotype-phenotype relationship in ARPKD patients [5, 6]. Recently, Burgmaier et al. [5] investigated the genotype-phenotype relationship in 304 ARPKD patients, reporting that patients with biallelic null mutations exhibited a severe phenotype. They also reported that the affected region of *PKHD1* played an important role in determining the phenotype. Patients with 2 missense or 1 missense and 1 null mutation affecting fibrocystin amino acids 709–1,837 less frequently developed CKD, and patients with missense mutations affecting amino acids 1,838–2,624 exhibited a better hepatic phenotype. Mutations affecting fibrocystin amino acids 2,625–4,074 were associated with poor hepatic outcome. In the present study, when variants were grouped according to exon, there was not a significant difference based on RS analysis, which might have been due to the small number of patients. On the other hand, it was observed that 3- and 6-year RS in the patients with a homozygous variant were significantly worse than the patients with a compound heterozygous variant. The present study also investigated the effects of variants on RS by dividing them into truncating and non-truncating variants. Patients with homozygous truncating variants had worse RS than those with non-truncating variants. Denamur et al. [6] reported that the presence of 2 truncating *PKHD1* mutations is associated with the most severe renal forms in neonates; however, the absence of truncating mutations does not guarantee neonatal survival. Similarly, Hamo et al. [17] reported that ARPKD patients with two truncating mutations in *PKHD1* had the most severe phenotype. In the present study, patients with homozygous truncating variants had the worst prognosis, whereas patients with 1 truncating and 1 non-truncating variant had a better prognosis. Thusly, the present study expands the spectrum of the genotype-phenotype relationship.

The literature includes some studies on how nutrition affects disease progression in ADPKD patients; however, they are all adult and animal studies [18–21]. To the best of our knowledge, the present study is the first to report the effects of malnutrition on RS in the pediatric population.

In the present study, RS analysis of the ADPKD patients showed that 3- and 6-year RS were 60% and 0% in those with malnutrition, respectively, versus 92% and 92%, respectively, in those without malnutrition ($p = 0.002$). In addition, 3-year survival in those with growth retardation was 80% versus 86% in those without ($p > 0.05$); however, in terms of 6-year RS, patients with growth retardation had a worse outcome than those without (40% and 86%, respectively) ($p = 0.15$), and although the difference was not significant most likely due to the small number of patients with growth retardation, we think that this finding is still important and should be investigated further in larger cohorts.

Earlier adult and animal studies investigated the effects of fluid intake, salt consumption, and protein and sodium restrictions on cyst development [19, 22, 23]. In the present study, patients with malnutrition and/or growth retardation had a poorer renal prognosis than those without. A study that included 288 adult patients reported 7.3% of the patients had mild to moderate malnutrition and 21.7% of the patients were at risk of malnutrition [24]. This study also showed that patients with a calculated total kidney volume >2,340 mL m^{-2} had a 7-fold higher risk of malnutrition. Aukema et al. [25] experimentally showed a 46% reduction in cystic volume in mice fed a low protein diet, as compared to mice with normal protein intake, or casein, and sunflower seed oil and fish oil. Evenepoel et al. [26] investigated bone phenotypes in 518 adult ESRD patients, of which 99 had a diagnosis of ADPKD. They reported that patients with ADPKD presented with a different bone and mineral phenotype characterized by suppressed bone turnover, better preserved cortical bone mineral density, and a high sclerostin level. An animal study showed that PC1 plays a role in regulation of intracellular calcium-dependent signaling in osteoblasts [27]. Thus, the present findings, in light of the literature, suggest that ADPKD patients need special care for nutrition, bone development, and growth. Children with ADPKD should undergo detailed evaluation of anthropometric measurements at the time of diagnosis and must be regularly monitored for growth parameters. Necessary precautions should be taken in terms of nutritional status to achieve a good outcome.

All the present study of ADPKD patients had monoallelic *PKD1* or *PKD2* variants, except for 2 ADPKD patients who had biallelic *PKD1* variants. There was not a significance in 3- and 6-year RS between the ADPKD patients with *PKD1* and *PKD2* variants, which might be due to the small number of patients with *PKD2* variants. Nonetheless, an adult ADPKD study reported that patients with *PKD2* mutation have a better prognosis than patients with *PKD1* mutations [28]. This study also observed that the risk of developing ESRD among patients with truncating mutations group was 2.74-fold greater in those with *PKD1* mutations.

As did earlier studies, the present study compared renal prognosis by considering *PKD1* and *PKD2* variants as truncating and non-truncating. Among the patients with *PKD1* variants, those with truncating variants had better RS. The mean eGFR in the patients with non-truncating variants at diagnosis was 95 ± 47 mL/min/1.73 m^2 versus 131 ± 35.4 mL/min/1.73 m^2 in those with truncating variants ($p = 0.008$). This finding remains unexplained and requires further research by means of in vitro and in vivo protein function experiments. In addition to genetics, it should be kept in mind that many environmental and epigenetic factors can affect disease progression and overall prognosis. Phenotype of genetic disease depends on many factors including genetic mosaicism and pathogenic variations in disease-modifying genes [29–33]. It has been reported that such environmental factors as obesity, diabetes, vascular disease, smoking, acute kidney injury, adequate water intake, and diet, are also effective in ADPKD patients [34, 35].

A study from Saudi Arabia described early onset ADPKD patients with biallelic *PKD1* mutations from 4 families [36]. The researchers reported that the patients had a severe phenotype that mimics autosomal recessive ciliopathy syndromes. It was suggested that biallelic *PKD1* mutations should be kept in mind, especially in countries with a high rate of parental consanguinity. In the present study, 2 patients had a homozygous *PKD1* variant. In the family of a patient in the present study, p.Arg3345Trp variant was homozygous in 1 individual (individual PN1590-II1 in the online suppl. Table 3) and heterozygous in the sibling (individual PN1590-II2 in the online suppl. Table 3), and the family had a positive history of PKD. The patient with a homozygous variant was diagnosed at 1.5 months of age with an eGFR of 27.5 mL/min/1.73 m^2. Interestingly, the sibling with a heterozygous variant was diagnosed at 10 years of age with an eGFR of 113 mL/min/1.73 m^2. In the present study, differences in the phenotypic expression of homozygosity and heterozygosity of the same variant were clearly observed in the siblings in this family. Another child of consanguineous parents that had a homozygous p.Val2618Met variant (individual PN1991 in the online suppl. Table 3) was diagnosed at 2 months of age with an eGFR of 117 mL/min/1.73 m^2 and resembled ARPKD both clinically and in terms of age of disease onset.

Similar to the siblings with homozygous and heterozygous *PKD1* variants, we also observed phenotypic variation between 2 siblings with ARPKD (individuals PN1540-II1 and PN1540-II2 in the online suppl. Table 1). Both siblings had p.Arg1624Trp variant in 1 allele and p.Asn3063Lys in the other allele of *PKHD1*. PN1540-II1 was 14 years of age at the time of diagnosis versus 2 years of age for the sibling. The younger sibling's eGFR was 39 mL/min/1.73 m^2, when growth retardation and liver cysts were detected via USG; however, the older sibling had only hypertension at diagnosis, with an eGFR was 95 mL/min/1.73 m^2.

The present multicenter study has some limitations. As the study included patients once diagnosed during the study period, follow-up periods were not homogenous and quantitative assessment of nutrition could not be performed. In addition, the number of ARPKD and ADPKD patients was not comparable. In our study, estimated GFR values were used for the evaluation of kidney functions, and this may have some limitations, especially in very young patients with polycystic kidneys; they may not entirely reflect the renal functions. Besides, a significant number of ARPKD neonates may not have diagnosed during the neonatal period because they may not have nephrological care due to their poor prognosis and necessity of immediate intensive care.

In conclusion, our findings highlight the importance of detailed evaluation of anthropometric parameters and of providing adequate nutritional support immediately following diagnosis in patients with ARPKD or ADPKD. Further research is required to more clearly determine the mechanisms other than CKD itself, which are effective on growth in ARPKD and ADPKD and if taking measures to prevent growth retardation and malnutrition can improve RS in ARPKD and ADPKD patients. Differentiation of ARPKD and ADPKD, and identification of the predictors of the development of CKD are vital for optimal management of patients with ARPKD or ADPKD.

Statement of Ethics

The study protocol was approved by the Board of the Hacettepe University Non-Interventional Clinical Research Ethics Committee (No. GO 18/329-14). Written informed consent was obtained from the patients when possible and/or their parents.

Conflict of Interest Statement

None.

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Author Contributions

Ozum Tutal, Bora Gulhan, Selcuk Yuksel, Z. Birsin Ozcakar, Oguz Soylemezoglu, Seha Saygili, Salim Caliskan, Mihriban Inozu, Esra Baskin, Ali Duzova, and Fatih Ozaltin contributed to the study conception, design, and patient recruitment. Material preparation, data collection, and analysis were performed by Ozum Tutal, Bora Gulhan, Emine Atayar, Fatih Ozaltin, Mutlu Hayran, and Rezan Topaloglu. The first draft of the manuscript was written by Ozum Tutal, Bora Gulhan, and Fatih Ozaltin. Emine Atayar, Selcuk Yuksel, Z. Birsin Ozcakar, Oguz Soylemezoglu, Seha Saygili, Salim Caliskan, Mihriban Inozu, Esra Baskin, Ali Duzova, Mutlu Hayran, and Rezan Topaloglu commented on this draft and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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