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Original Article

ORIGINAL ARTICLE

Autosomal dominant polycystic kidney disease in young adults

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ABSTRACT

Background. The clinical manifestations of autosomal dominant polycystic kidney disease (ADPKD) usually appear in adulthood, however pediatric series report a high morbidity. The objective of the study was to analyze the clinical characteristics of ADPKD in young adults.

Methods. Family history, hypertension, albuminuria, estimated glomerular filtration rate (eGFR) and imaging tests were examined in 346 young adults (18–30 years old) out of 2521 patients in the Spanish ADPKD registry (REPQRAD). A literature review searched for reports on hypertension in series with more than 50 young (age <30 years) ADPKD patients.

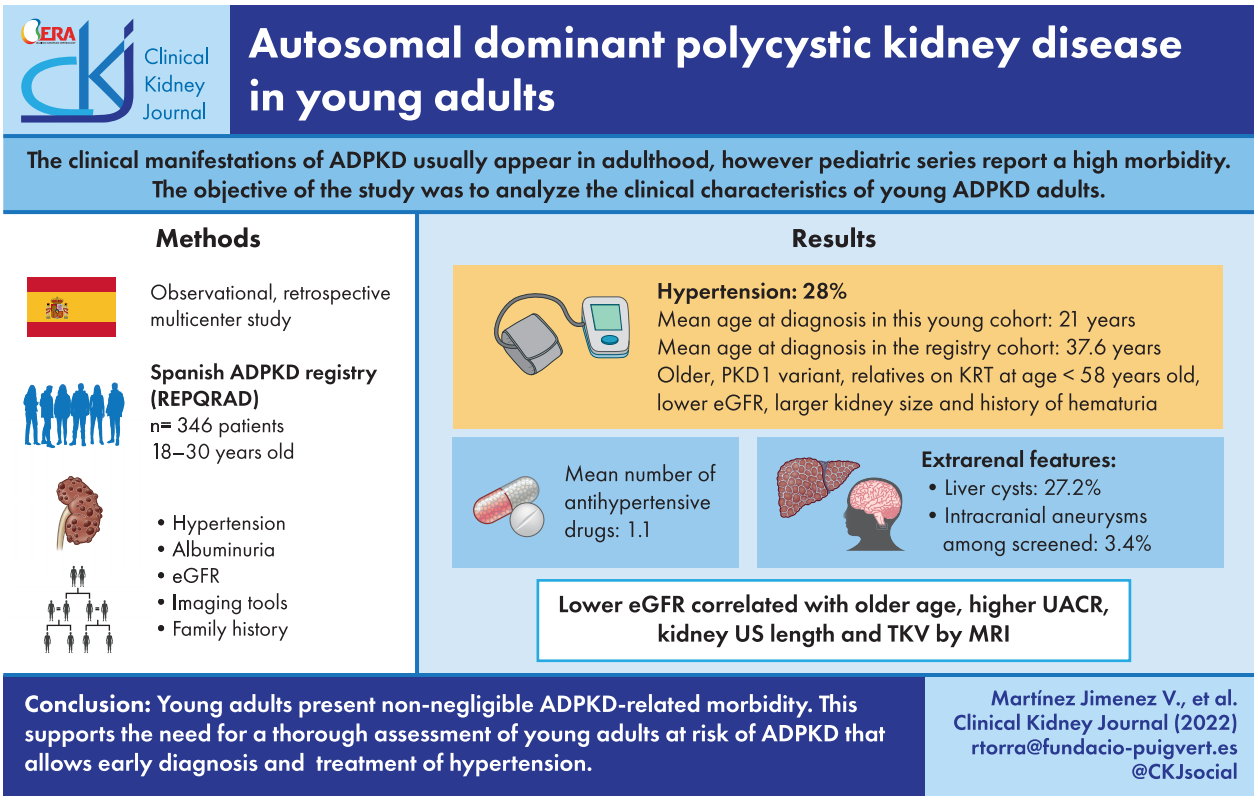
Results. The mean age of this young adult cohort was 25.24 (SD 3.72) years. The mean age at diagnosis of hypertension was 21.15 (SD 4.62) years, while in the overall REPQRAD population was aged 37.6 years. The prevalence of hypertension was 28.03% and increased with age (18–24 years, 16.8%; 25–30 years, 36.8%). Although prevalence was lower in women than in men, the age at onset of hypertension (21 years) was similar in both sexes. Mean eGFR was 108 (SD 21) mL/min/1.73 m^2, 38.0% had liver cysts and 3.45% of those studied had intracranial aneurysms. In multivariate analyses, hematuria episodes and kidney length were independent predictors of hypertension (area under the curve 0.75). The prevalence of hypertension in 22 pediatric cohorts was 20%–40%, but no literature reports on hypertension in young ADPKD adults were found.

Conclusions. Young adults present non-negligible ADPKD-related morbidity. This supports the need for a thorough assessment of young adults at risk of ADPKD that allows early diagnosis and treatment of hypertension.

LAY SUMMARY

Impairment of renal function usually develops from the fourth decade of life in autosomal dominant polycystic kidney disease (ADPKD). However, hypertension precedes the onset of renal insufficiency. In published pediatric series, the prevalence of hypertension is 20%–40%. However, clinical information on young adults with ADPKD is scarce. We present the largest cohort of young adults (age 18–30 years) with ADPKD published to date. Prevalence of hypertension is 28% and increases with age, reaching 36.8% in the subgroup aged 25–30 years, despite normal glomerular filtration rate and albuminuria. The prevalence of hypertension is higher in males, but the mean age at diagnosis (21 years) was similar in both sexes. Young adults present non-negligible ADPKD-related morbidity. This supports the need for a thorough assessment that allows early diagnosis and treatment of hypertension, before decline of estimated glomerular filtration rate. Ambulatory blood pressure monitoring may be especially useful in this regard.

GRAPHICAL ABSTRACT



Keywords: ADKPD, children, glomerular filtration rate, hypertension, young adults

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by fluid-filled cyst development and causes progressive and irreversible deterioration of kidney function, leading to kidney failure [1, 2]. ADPKD is mainly caused by pathogenic variants in *PKD1* (78%) and *PKD2* (15%) and other minor genes: *GANAB*, *DNAJB11*, *ALG9*, *ALG5* and *IFT140* [3–5]. There are multiple publications on the pediatric population with ADPKD, however, very few articles analyze the characteristics of the disease in young adults [6, 7]. In both children and young adults, kidney function generally remains normal. However, some patients may show hypertension, increased total kidney volume (TKV), hematuria, albuminuria or defects of urinary concentration, which indicate progression of the disease [8, 9].

Children usually show no symptoms of ADPKD and extrarenal manifestations are extremely rare [10]. However, up to 2%–5% have a very-early onset disease (VEO), defined by diagnosis by intrauterine ultrasound or up to 18 months of age [11], which poses the differential diagnosis with autosomal recessive polycystic kidney disease. These patients show early hypertension, increased TKV and a progressive decrease of glomerular filtration rate (GFR), that may need kidney replacement therapy (KRT) in childhood [12, 13]. ADPKD-VEO is associated with pathogenic variants in other genes that cause cystic nephropathy (e.g. *HNF1B*, *PKDH1*, etc.) [14] or with biallelic hypomorphic variants in the *PKD* gene [15]. The KDIGO Controversies Conference provided no recommendation for presymptomatic screening for at-risk children [16, 17]. In most cases, these decisions on screening are made between the pediatrician and the parents [18].

The objective of this study is to analyze the clinical characteristics of the largest cohort to date of young adults (aged 18–30 years) with ADPKD belonging to the Spanish registry of autosomal dominant polycystic kidney disease (REPQRAD, https://www.bms-soft.com/registropqrad) and to compare this with pediatric data.

MATERIALS AND METHODS

Literature review of ADPKD pediatric series and young adult series

We reviewed all articles published in PUBMED and MEDLINE up to March 2022 that reported on the prevalence of hypertension in children and young adults under 30 years of age diagnosed with ADPKD. The search was performed using ('ADPKD') and ('Children' or 'Young Adult'). In each study, we analyzed: design, age, number of patients, diagnostic criteria for ADPKD, hypertension, estimated glomerular filtration rate (eGFR), proteinuria and kidney volume. We excluded series with fewer than 50 patients or those with no data on hypertension.

REPQRAD

REPQRAD is an observational, retrospective and multicenter study created in November 2016, in which data from 36 Spanish

hospitals are collected in an online platform. The Registry is open to centers from all Spanish regions.

The 2521 patients with ADPKD in REPQRAD were screened for patients aged between 18 and 30 years at the time of analysis. A focused data collection was aimed at completing most fields in the Registry for these patients.

Inclusion and exclusion criteria

We have analyzed 346 patients aged between 18 and 30 years at the time of analysis. All data collected in REPQRAD were studied until March 2022. The diagnosis of ADPKD was made by the ultrasound criteria of Pei *et al*. [19] with a positive family history or by compatible genetic study. All patients signed an informed consent. The REPQRAD protocol was approved by the ethics committee of the Fundació Puigvert as a reference Institutional Review Board.

Demographic variables, genotype and family history

Demographic variables were recorded. The description of the genotype includes the causative gene: *PKD1* or *PKD2*, and for *PKD1* whether the pathogenic variant is truncating or non-truncating.

Regarding the family history, the paternal or maternal origin was reported. Patients without affected parents were considered *de novo* cases. The existence of relatives on KRT and with an early (before 58 years of age) start of KRT was collected.

Laboratory tests and urological events

The GFR was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation in adults and by the new modified Schwartz formula from 2009 in children. The albumin/creatinine ratio (UACR in mg/g) was assessed in the first morning urine and data presented for the last follow-up. The number of episodes of hematuria and the age of the first episode were recorded, as well as history of low back pain.

Hypertension

Hypertension was considered when patients were under antihypertensive treatment. The number and type of antihypertensive drugs and the age of onset of hypertension were recorded. If available, the last measurement of the systolic blood pressure and diastolic blood pressure figures from the ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM) were analyzed.

Imaging

In REPQRAD, the following imaging tests performed are collected: ultrasound, abdominal magnetic resonance imaging (MRI) and cerebral angio-MRI. TKV was determined by both ultrasound and MRI in milliliters according to the ellipsoid formula. In addition, abdominal ultrasound measured the length in centimeters of both kidneys. The presence or absence of intracranial aneurysms was only analyzed in patients in whom a cerebral angio-MRI had been performed. Liver cysts were defined as present or absent by ultrasound and massive polycystic liver disease was defined as hepatomegaly with countless cysts.

Imaging data was retrieved from the last imaging procedure.

Statistical study

Descriptive statistics are expressed as mean and standard deviation (SD) or as median and interquartile range (IQR) for quantitative variables, and as frequencies (*n*) and percentages (%) for categorical data.

Student's *t*-test was used to compare quantitative variables from two groups. Chi-squared was used to compare categorical variables and Pearson correlation coefficients between quantitative variables were calculated. The corresponding non-parametric test was used when the variables did not follow a normal distribution. Statistics were calculated using SPSS 23.0. The level of statistical significance was considered with $P < .05$ (bilateral).

Logistic regression was used for multivariate analysis. We first selected the 163 patients who had complete data for variables shown in Supplementary data, Table S1, and applied a step-by-step procedure. As sensitivity analyses, we repeated the analysis in the 220 patients who had complete data for the variables shown in Supplementary data, Table S1. A second sensitivity analysis used multiple data imputation in the full cohort of 346 patients using multivariate imputation by chaine equations (mice), implemented in a library in R.

RESULTS

Hypertension in children and young adults in the literature

A total of 768 articles were identified with the search ('ADPKD') and ('Children' or 'Young Adult'). Of these, 22 reported data on hypertension on more than 50 patients. All studies reporting on hypertension were pediatric studies, having a mean age ranging from 8.2 to 16.3 years or having an upper age limit of 18–21 years (Supplementary data, Table S2) [20–38]. Thus, we found no article that analyzed the prevalence of hypertension only in young adults with ADPKD. In children the prevalence of hypertension ranged from 7.7% to 45% (Fig. 1), with an overall prevalence of 620/2197 (28.2%), excluding the meta-analysis. However, the studies were heterogenous in several aspects, including the criteria and methods used to define hypertension.

General population of REPQRAD

In REPQRAD, 2521 patients with ADPKD were registered from November 2016 to March 2022; there were 1185 males and 1336 females. The mean age was 50.5 (SD 18.2) years. Some 272 (10.5%) patients were on KRT. The mean eGFR for patients with data available and not on KRT ($n = 1121$) was 85.7 (SD 32.9) mL/min/1.73 m^2, and median (IQR) UACR ($n = 560$) 14 (5, 33.2) mg/g. Hypertension was present in 1184 patients (45.9%): in 610/1185 (51.5%) of men and in 574/1336 (43%) of women ($P < .000$). The mean age at detection of hypertension ($n = 888$) was 37.6 years (SD 14.8): 37.0 (SD 12.1) years for men and 38.8 (SD 11.9) years for women ($P = .03$).

Pediatric ADPKD patients

The 72 pediatric patients (<18 years) included 35 males and 37 females with a mean age of 12.6 (SD 3.7) years. Hypertension was detected in five patients (6.9%): three boys and two girls. The mean age at detection of hypertension was 11.5 (SD 1.7) years. The eGFR was 113.9 (SD 26) mL/min and median (IQR) UACR 9 (5, 22.5) mg/g.

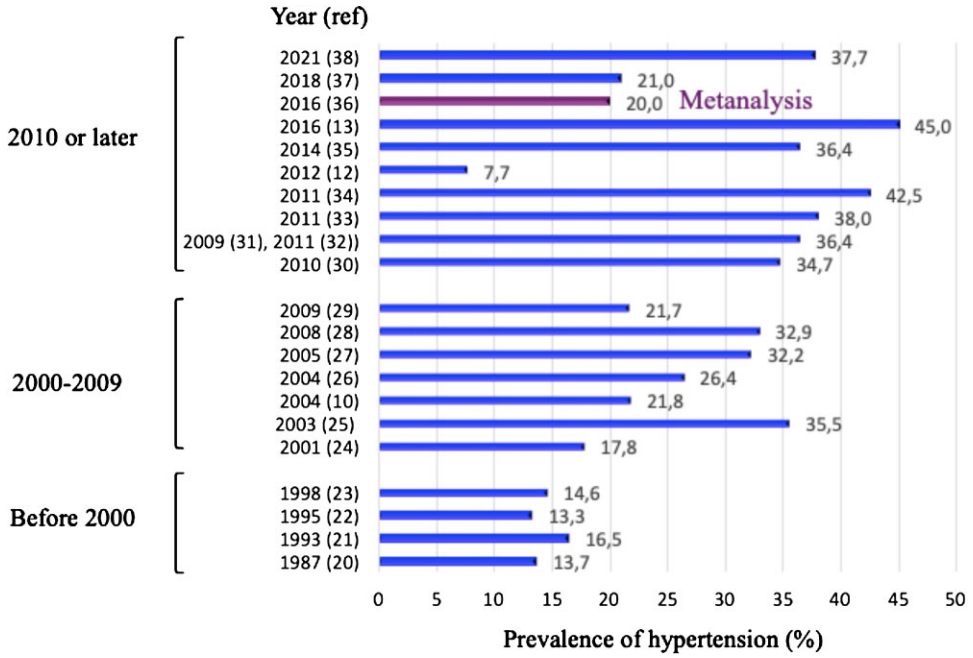


Figure 1: Prevalence of hypertension in 22 studies from the literature reporting the prevalence of hypertension in >50 young ADPKD patients. A metanalysis or 14 prior studies is indicated. Details of the 22 studies are shown in Supplementary data, Table S2. Note that most reports refer to children or very young adults (≤21 years old).

Young adults with ADPKD

In REPQRAD, there were 346 participants aged between 18 and 30 years (Table 1). Hypertension, imaging and laboratory tests were analyzed in detail, as follows.

Hypertension

Hypertension was observed in 28%: 34.1% men and 22.2% women ($P = .01$). The mean age at documentation of hypertension was 21.1 (SD 4.6) years in both men and women (Table 1) and the mean number of anti-hypertensive drugs prescribed was 1.1 (SD 0.4): 87 (89.7%) patients were on renin–angiotensin–aldosterone system (RAAS) blockade monotherapy while the remaining 10 (10.3%) patients were also taking a second drug: beta-blocker (4 patients), combination of two RAAS blockers (2 patients), thiazide (2 patients) and calcium antagonist (2 patients).

The prevalence of hypertension increased with age (Fig. 2). In the general REPQRAD population, it reached a plateau of around 80% at age 51–70 years while in young adults it was higher in patients aged 25–30 years (36.8%) than in those aged 18–24 years (16.8%), ($P < .001$).

Table 2 describes the relationship between the presence of hypertension and other variables. Young adults with hypertension were older, more often male, with a *PKD1* gene variant, had more frequently relatives starting KRT <58 years old, had lower eGFR, larger kidney size and had more frequently a history of hematuria. However, the clinical characteristics of men and women with hypertension were similar (Supplementary data, Table S3).

In the main multivariate analysis, kidney length, as assessed by ultrasound, and a history of hematuria were significant independent predictors of hypertension with an area under the receiver operating characteristic curve (AUC ROC) of 0.75 (Hosmer–Lemeshow test: $P = .856$) (Table 3). Sensitivity analyses, in which kidney length was not considered, confirmed that hematuria is independent predictor of hypertension. Additionally, in the absence of kidney length data, a history of relatives starting KRT <58 years was associated with hypertension, while a higher eGFR and a family history were associated with a decreased risk of hypertension. A second sensitivity analysis, using data imputation in the full cohort of 346 patients, confirmed these findings and additionally identified female sex as associated with a decreased risk of hypertension. Finally, further sensitivity analyses adding patient age to the models did not change the results (Supplementary data, Table S4).

Imaging

TKV also increased with age, from 461.8 (SD 189) mL in those aged 18–24 years to 708.4 (SD 400.9) mL in those aged 25–30 years ($P = .001$) as assessed by ultrasound, and from 699.9 (SD 487.3) mL to 1157.8 (SD 1156) mL ($P = .03$) as assessed by MRI.

In 21 patients there were TKV data from both ultrasound and MRI, but in most patients kidney volume was only available for one of the two imaging techniques. The larger volume by MRI is likely explained by the use of MRI in patients with larger kidneys in which ultrasound may no longer be informative.

In the 145 cerebral angio-MRI performed, 5 (3.4%) patients had cerebral aneurysms with mean age at diagnosis of 24 (SD 2.8) years. All aneurysms were less than 2 mm without requiring interventions, only follow-up, and there were no cases of rupture.

Laboratory tests

The eGFR decreased with age and was higher in patients aged 18–24 years [113.2 mL/min (SD 22.8)] than in those aged 25–30 years [105.5 mL/min (SD 18.9)] ($P = .002$). Lower eGFR correlated with older age ($r = -0.22$; $P < .001$), higher UACR ($r = -0.21$; $P < .001$), kidney size [ultrasound length of the right ($r = -0.27$; $P < .001$) and left ($r = -0.25$; $P < .001$) kidneys] and TKV by MRI

Table 1: Clinical features in ADPKD patients aged 18–30 years in overall population and male versus female.

Clinical features	Overall	Males	Females	P
N (%)	346 (100)	169 (48.8)	177 (51.2)	
Age, years	25.2 (3.7)	25.5 (3.6)	25.1 (3.8)	0.3
Genotype, *N*	98	47	51	
PKD1-truncating, *n/N* (%)	29 (29.6)	*PKD1*: 39 (83.0)	*PKD1*: 42 (82.4)	
PKD1-non-truncating, *n/N* (%)	52 (53.1)			0.94
PKD2, *n/N* (%)	17 (17.3)	*PKD2*: 8 (17.0)	*PKD2*: 9 (17.6)	
Family history, *N*	326	157	169	
Paternal line, *n/N* (%)	155 (47.6)	80 (51.0)	75 (44.4)	0.49
Maternal line, *n/N* (%)	153 (46.9)	70 (44.6)	83 (49.1)	
De novo, *n/N* (%)	18 (5.5)	7 (4.4)	11 (6.5)	
Relatives in KRT <58 years, *n/N* (%)	126/311 (40.5)	57/151 (37.7)	67/160 (43.1)	0.34
Age at KRT, years	47 (6.1)	47 (6.0)	47 (6.1)	0.97
eGFR, *N*	307	152	155	
Mean (SD), mL/min/1.73 m^2	108.4 (20.8)	106 (21.4)	110.9 (19.9)	0.04
UACR, *N*	273	135	138	
Median (IQR), mg/g	8.3 (3.5, 19.5)	6.7 (3.5, 21.4)	9.3 (4.0, 18.2)	0.44
Patients with hypertension, *n/N (%)*	97/346 (28)	58/170 (34.1)	39/176 (22.2)	0.01
Age of hypertension detection years	21.1 (4.6)	21.2 (4.5)	21.1 (4.8)	0.91
Number of antihypertensive drugs	1.1 (0.4)	1.07 (0.3)	1.1 (0.4)	0.33
ABPM, *N*	49	27	22	
sBP, mmHg	124.2 (14.3)	125.9 (13.1)	122.1 (15.7)	0.36
dBP, mmHg	74.5 (11.3)	73.3 (8.7)	76.1 (13.9)	0.38
HBPM, *N*	106	55	51	
sBP, mmHg	122 (12.2)	125.6 (11.5)	118.2 (12.0)	0.02
dBP, mmHg	75.1 (9.4)	76.7 (8.6)	73.4 (9.9)	0.07
Renal ultrasound	216	106	110	
Length RK, cm	12.7 (2.1)	13.0 (2.2)	12.4 (1.9)	0.03
Length LK, cm	13.2 (2.4)	13.3 (2.4)	13.1 (2.3)	0.48
TKV, mL	575.6 (327.7)	613.5 (312.9)	541.4 (340.7)	0.34
Renal MRI, mL, *N*	110	52	58	
TKV, mL	1020.5 (1022.7)	1246.7 (1368.2)	817.7 (486.4)	0.03
Episode of hematuria, *n/N* (%)	38/308 (12.3)	18/150 (12.0)	16/158 (10.1)	0.63
Age first episode, years	19.2 (6.7)	19.1 (8.0)	19.4 (5.4)	0.89
Low back pain, *n/N* (%)	17/213 (8.0)	10/106 (9.4)	7/107 (6.5)	0.7
Liver cysts, *n/N* (%)	80/294 (27.2)	37/150 (24.7)	43/144 (29.9)	0.37
Hepatomegaly, *n/N* (%)	1/294 (0.3)	1/150 (0.7)	0/144 (0)	0.56
Intracranial aneurysms[a], *n/N* (%)	5/145 (3.4)	1/61 (1.6)	4/84 (4.8)	0.31

N after each variable means the number of patients with available data for that variable. If there is no other indication, continuous data are expressed as a mean (standard deviation).
[a]For 160 patients the status was 'unknown', because cranial MRI angiography was not performed.
sBP: systolic blood pressure; dBP: diastolic blood pressure; RK: right kidney; LK: left kidney.

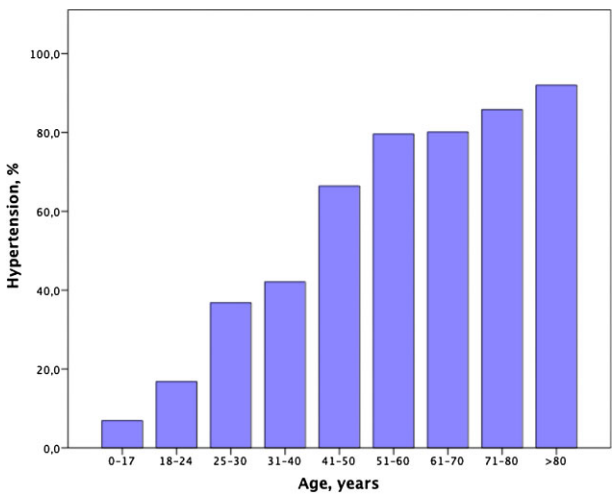


Figure 2: Prevalence of hypertension in ADPKD patients by age group in REPQRAD.

($r = -0.52$; $P < .001$). Additionally, eGFR was lower in patients with hypertension (Table 4).

Median albuminuria values were low and there were no statistically significant differences in UACR between those aged 18–24 years and 25–30 years [median IQR 6.5 (4, 21.8) *vs* 10 (3, 20) mg/g] or between men and women (Table 1). Data used to write this article may be shared upon request to the Spanish Society of Nephrology.

DISCUSSION

To our knowledge, this is the first comprehensive report of ADPKD manifestations in young adults based on data from a national ADPKD registry that characterizes the onset and risk factors for hypertension and other comorbidities. The main findings of the present report are that young adults with ADPKD may already suffer from clinical manifestations that may be potentially severe and/or susceptible to early intervention to prevent CKD progression and severe cardiovascular disease.

Table 2: Relationship of hypertension with other variables in 18- to 30-year-old patients from REPQAD.

	Hypertension				
Clinical features	Yes	*n*	No	*n*	*P*
Age (years)	26.3 (3.0)	97	24.8 (3.9)	243	<.001
Sex (male), %	59.8	97	44.4	243	.01
Genotype (*PKD1*), %	96.3	27	77.5	71	.03
Relatives on KRT <58 years old, %	64.6	53	31.8	70	<.001
eGFR (mL/min/1.73 m^2)	99 (24.9)	96	112.6 (17.1)	209	<.001
UACR, median (IQR), mg/g	19.4 (7.0, 36)	86	8,5 (4.2, 16)	185	.54
RK length by US (cm)	14.2 (2.3)	58	12.2 (1.7)	156	<.001
LK length by US (cm)	14.8 (2.7)	57	12.6 (1.9)	156	<.001
TKV by US (mL)	830.6 (422.6)	22	475.4 (214.3)	56	.001
TKV by MRI (mL)	1436.4 (1351.3)	51	666.2 (328.7)	58	<.001
Hematuria, %	18.6	97	6.2	243	<.001
Liver cysts, %	34.9	86	24.6	203	.07

If there is no other indication the continuous data are expressed as mean (standard deviation)
RK: right kidney; LK: left kidney; US: ultrasound.

Table 3: Multivariate analysis of predictors of hypertension in 18- to 30-year-old patients in REPQAD.

Variable	OR	95% CI	*P*
Main multivariate analysis ($n = 163$)			
Kidney length (ultrasound)	1.66	1.37, 2.07	<.001
Hematuria	3.72	1.36, 10.4	.011
AUC = 0.75			
Hosmer–Lemeshow test: $P = 0.856$			
Sensitivity multivariate analysis ($n = 220$)			
Relatives starting KRT <58 years	3.46	1.85, 6.63	<.001
eGFR	0.97	0.96, 0.99	.001
Family history	0.20	0.05, 0.83	.023
Hematuria	2.57	1.09, 6.13	.030
AUC = 0.71			
Hosmer–Lemeshow test: $P = .075$			
Sensitivity multivariate analysis 3 ($n = 345$), data imputation			
Relatives starting KRT <58 years	3.95	2.24, 6.97	<.001
eGFR	0.97	0.96, 0.98	<.001
Family history	0.26	0.09, 0.81	.020
Hematuria	3.44	1.59, 7.44	.002
Female	0.47	0.27, 0.81	.007
AUC = 0.76			
Hosmer–Lemeshow test: $P = .051$			

In ADPKD patients, symptoms and impaired kidney function usually develop in the fourth to fifth decade of life. For example, hypertension precedes the decrease in eGFR in up to 60% of patients [39]. In the full REPQRAD cohort, the mean age at diagnosis of hypertension was 37.6 years, and almost 2 years earlier in males compared with females. However, in the 18–30 years old cohort, the mean age at diagnosis of hypertension was 21 years for both sexes. This is explained by the fact that these young hypertensive patients probably represent a subgroup of severely affected or rapid progressor patients with earlier onset of hypertension. While it may be argued that young patients under nephrology care may represent a population biased for severity, national guidelines since 2014 recommend screening of family members [40] and the most recent 2020 national ADPKD guidelines emphasize the recommendation to study the offspring of parents with ADPKD from the age of 18 years [41]. Thus, selection bias is expected to be significantly reduced due to the national ADPKD recommendations, supporting an interpretation that the older age at diagnosis of hypertension in the full cohort may partially represent lack of nephrological assessment at earlier age in the past, given that until recently, there was no specific therapy for ADPKD and this negatively influenced the care-seeking behavior of patients and any proactive attitude by physicians.

Young ADPKD adults aged 18–30 years are understudied, unlike the large number of papers published on children [42] (Supplementary data, Table S2). A literature review of pediatric series disclosed a significant prevalence of clinical manifestations in ADPKD children, the prevalence of hypertension being around 20% [36]. However, pediatric series likely suffer from several selection biases that overall tend to increase the reported severity of disease: (i) lack of mildly affected children [20, 23]; (ii) predominance of VEO-ADPKD [12, 13], characterized by severe symptoms at early ages [10, 12, 13, 27]; (iii) reports representing

Table 4: eGFR values according to the presence (yes) or absence (no) of qualitative variables in 18- to 30-year-old patients from REPQRAD.

	eGFR (mL/min/1.73 m^2)				
Clinical features	Yes	*n*	No	*n*	*P*
Sex (males)	106 (21.4)	152	110.9 (19.9)	155	.04
Genotype (*PKD1*)	108.9 (19.9)	71	118.3 (11.6)	17	.1
Relatives on KRT <58 years old, %	107.5 (19.2)	117	110.8 (19.7)	158	.12
Patients with hypertension	99 (24.9)	96	112.6 (17.1)	209	<.001
Episode of hematuria <30 years	108.6 (18.2)	32	108.4 (21.1)	275	.97
Liver cysts	106.5 (19.8)	76	109.3 (22.4)	186	.33

If there is no other indication, continuous data are expressed as mean (standard deviation).

reference centers, which probably care for the most severe cases [23]; (iv) parents from families with more severe ADPKD may be more likely to study their children than those with mild ADPKD. Additionally, in only seven reports was the mean age above 11 years, emphasizing the paucity of data in young adults and older children. In this regard, based on data from pediatric series, the prevalence of hypertension in young adults would be expected to be much higher than the 16.8% observed in those aged 18–24 years and 28% overall in young adults in REPQRAD.

ABPM is the test of choice in the diagnosis of hypertension in children, being more accurate and reproducible than HBPM or office blood pressure [43]. In a recent study of 310 children with early-stage ADPKD, with a mean age of 11.5 years, the prevalence of hypertension was 31%, 42% and 35% during daytime, nighttime or the entire 24-h cycle, respectively. In addition, 52% of participants lacked a physiologic nocturnal BP dipping, and 18% had isolated nocturnal hypertension [37]. Similar studies are needed for young ADPKD adults. In this regard, data from the present REPQRAD report a low uptake of ABPM in young adults with ADPKD.

In the present series, hypertension was related to several factors generally associated with more severe disease, such as age, *PKD1* genotype, male sex, relatives who needed KRT before age 58 years, eGFR, TKV or hematuria. However, multivariate analysis identified kidney length by ultrasound and episodes of hematuria as the key predictors of hypertension, with an AUC ROC of 0.75. In the absence of kidney length data, hematuria was confirmed as an independent predictor of hypertension, while a history of relatives starting KRT <58 years was associated with hypertension, and higher eGFR and a family history were associated with a decreased risk of hypertension. Kidney length by ultrasound should be considered a surrogate for kidney size. Ultrasound is more widely available than MRI and at this young age, most kidneys had a length that could be measured by sonography. It is likely that if more data were available for TKV assessed by MRI, this assessment would have also predicted hypertension.

The prevalence of hypertension was higher in males than in females, as was the case for other features of more severe disease (e.g. eGFR was lower and kidney size higher in males), which is in line with the literature. However, in young ADPKD women with hypertension, both the age at onset of hypertension and the overall severity of ADPKD was similar to in males. Thus, emphasis should be made on assessing blood pressure also in young ADPKD women.

Our findings in young adults were generally aligned with those in children, as hypertension was also associated with increased TKV [25, 32]. However, the independent predictive value of hematuria is a novel finding. Activation of the RAAS has been invoked as the main mechanism involved in the pathogenesis of ADPKD-related hypertension [33] and RAAS blockade is the treatment of choice [41]. In children, 2.8 antihypertensives were needed to control hypertension [31], which contrasts with the 1.1 drugs in young adults in REPQRAD data and further raises the possibility that current pediatric reports may be biased towards the most severely affected children. The majority of young patients in REPQRAD were on RAAS blocker monotherapy, confirming that monotherapy is usually enough at this age.

ADPKD is not usually considered an albuminuric disease and in the present cohort median albuminuria remained within the normal range. In the published literature, the high prevalence of proteinuria in children stands out [44], although in no article was orthostatic proteinuria ruled out. Also, in the small pediatric cohort of our Registry albuminuria was higher than in young adults. There are several potential explanations, including a bias towards diagnosing ADPKD in childhood only in the most severe cases.

Intracranial aneurysms were found in 3.4% of the cases studied in the present series. This percentage is not negligible and may be biased by having performed MR angiography in patients with a family history of intracranial aneurysms. Based on this observation, and according to the literature, the presence of aneurysms is not correlated with the severity of kidney disease. This raises the need for early cranial MR angiography in young adults from at-risk families [16]. In this regard, rupture of brain aneurysms has been described in childhood, although it is extremely rare [45].

The prevalence of hepatic cysts in this series was 23%, without differences between sexes, with only 1 case of massive cystic hepatomegaly (interestingly in a male). This is in line with prior reports in young ADPKD patients [46]. The prevalence of hepatic cysts increases with age and does not cause comorbidity in the early stages of the disease; however, all young women with ADPKD considering contraceptive therapy should receive counselling on potential aggravation of polycystic liver disease with exogenous estrogen exposure [17].

Certain limitations should be acknowledged that are inherent to registry studies. These include the retrospective nature and missing data, especially for certain variables, such as TKV by MRI, for which there might be limitations to access or may not be clinically indicated at the age of the study, as not all fields in the Registry were mandatory to fill. Mayo classification could not be calculated either due to lack of data on height. Furthermore, there were scarce ABPM data due to unrecorded reasons. However, this reflects routine clinical practice and the detection of this low uptake of ABPM in real-world data which reflects practice across many centers in different regions should be considered a strength of the manuscript. Finally, the precise method to diagnose hypertension in individual patients (ABPM, HBPM or office blood pressure) was not recorded.

CONCLUSIONS

In conclusion, in the largest cohort of young ADPKD adults to date, the prevalence of hypertension was 28% overall and 37% in those aged 25–30 years, and cerebral aneurysms were found in over 3%. Bearing in mind the positive effect of strict blood pressure control on end organ damage, including cerebral hemorrhage [47] and on kidney outcomes [48], awareness should be raised among nephrologists and primary care physicians alike of this high prevalence of hypertension in young ADPKD patients, both male and female. Thus, ADPKD patients may benefit from intervention even before they may be candidates for disease-modifying therapy. In this regard, wider use of ABPM early in the disease course should be encouraged. Additionally, these data suggest that current information from pediatric series may have overestimated the prevalence of hypertension in childhood, although this should be confirmed by prospective evaluation of ABPM in patients with or at high risk of ADPKD from age 18 years onwards.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

DATA AVAILABILTY STATEMENT

Data is the property of the Spanish Society of Nephrology and available upon reasonable request.

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CONFLICT OF INTEREST STATEMENT

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APPENDIX

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(See related article by Cadnapaphornchai and Ong. Hypertension in young adults with autosomal dominant polycystic kidney disease: a case for early screening?. *Clin Kidney J* (2023) 16: 901–904.)

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