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Long-term Outcomes in Patients with Very-Early Onset Autosomal Dominant Polycystic Kidney Disease

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Abstract

Background—Long-term clinical outcomes in children with very-early onset (VEO; diagnosis *in utero* or within the first 18 months of life) autosomal dominant polycystic kidney disease (ADPKD) are currently not well understood. We conducted a longitudinal retrospective cohort study to assess the association between VEO status and adverse clinical outcomes.

Methods—Seventy patients with VEO-ADPKD matched (by year of birth, sex, and race/ethnicity) to 70 patients with non-VEO-ADPKD who participated in research at the University of Colorado were studied. Kaplan-Meier survival analysis was performed. The predictor was VEO-status, and outcomes were progression to end-stage renal disease (ESRD), development of hypertension, progression to estimated glomerular filtration rate (eGFR) <90 mL/min/1.73m^2), glomerular hyperfiltration (eGFR≥140 mL/min/1.73m^2), and height-adjusted total kidney volume (htTKV) measured by magnetic resonance imaging ≥ 600 mL/m.

Results—Median follow-up was until 16.0 years of age. There were only 4 ESRD events during the follow-up period, all in the VEO group ($p<0.05$). VEO patients were more likely to develop hypertension (HR: 3.15 [1.86–5.34]; $p<0.0001$) and to progress to eGFR <90 mL/min/1.73m^2 (HR: 1.97 [1.01, 3.84]; $p<0.05$) than non-VEO patients. There was no difference between groups in the development of glomerular hyperfiltration (HR: 0.89 [0.56–1.42]; $p=0.62$). There were only 7 patients who progressed to htTKV ≥600 mL/m, 4 in the VEO group and 3 in the non-VEO group ($p<0.01$).

Conclusions—Several clinical outcomes are worse in patients with VEO-ADPKD compared to non-VEO ADPKD. Children with VEO-ADPKD represent a particularly high-risk group of ADPKD patients.

Keywords

ADPKD; children; epidemiology; glomerular filtration rate; hypertension; longitudinal; pediatrics; total kidney volume

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease, estimated to affect 1:500 to 1:1,000 live births [1,2]. Although often considered to be a disease of adults, complications of ADPKD begin in childhood [3], with diagnosis possible *in utero* [4]. Children diagnosed either *in utero* or within the first 18 months of life are considered to have very-early onset (VEO) disease [5].

A previous cross-sectional analysis found that after adjustment for age, children with VEO-ADPKD were more likely to have hypertension, lower estimated glomerular filtration rate (eGFR), and larger age-adjusted kidney volume by ultrasound when compared to non-VEO ADPKD children diagnosed between18 months and 18 years of age [5]. Other studies have followed VEO patients over time, but have only considered the prevalence of outcomes of interest (e.g. end-stage renal disease [ESRD], hypertension), with a relatively small number of patients [6–9]. To date, a longitudinal time-to-event analysis comparing children with VEO-ADPKD to matched patients with non-VEO-ADPKD has not been performed. Thus, long-term clinical outcomes in children with VEO-ADPKD are currently not well understood.

Clinical outcomes of interest in early ADPKD include development of hypertension, increase in total kidney volume (TKV), development of glomerular hyperfiltration, decline in estimated glomerular filtration rate (eGFR), and progression to ESRD. Hypertension in patients with ADPKD is associated with both larger TKV and progression to ESRD [10]. Height-adjusted TKV (htTKV) measured by magnetic resonance imaging (MRI) predicts both the decline in eGFR measured by iothalamate clearance and progression to ESRD [11,12]. Glomerular hyperfiltration has been shown to predict both increased kidney growth and a faster decline in renal function in children with ADPKD [13]. Both an early decline in eGFR and progression to ESRD are well appreciated, clinically relevant endpoints in ADPKD.

Accordingly, the aim of this study was to compare the development of clinically meaningful endpoints (hypertension, glomerular hyperfiltration, htTKV ≥ 600 mL/m, eGFR < 90 mL/min/1.73m^2, and ESRD) using time-to-event analysis in a cohort of VEO-ADPKD patients matched to non-VEO-ADPKD patients. We hypothesized that adverse clinical outcomes would occur at an earlier age in the VEO compared to non-VEO group.

Subjects and Methods

Study Design

Since 1985, the University of Colorado has maintained a registry of patients with ADPKD. Of the 2,126 patients currently in the registry who had data available on at least one of the outcomes of interest and age/year of diagnosis, we identified 70 ADPKD patients (3.3%) as VEO (i.e. diagnosis *in utero* or within the first 18 months of life) (Supplemental Figure 1). In total, 534 (25.1%) of these 2,126 patients were diagnosed with ADPKD prenatally or in childhood. The 70 patients identified as VEO participated in a longitudinal natural history study of ADPKD [3] (n=43) and/or completed or ongoing randomized placebo-controlled trials/genetic modifier study (n= 24 total; angiotensin converting enzyme inhibitor (ACEI) study in children/young adults [14], n=19; statin study in children/young adults [15], n=14;

mineralcorticoid antagonism study (NCT01853553), n=3; genetic modifier study (U01DK079856), n=3), or completed only survey data by questionnaire (n=20). We also identified 70 ADPKD patients who were diagnosed after 18 months of age, matched to controls for age (year of birth ± 3 years), sex, and when possible, race and ethnicity. These patients were also matched as closely as possible for study participation (longitudinal natural history study, n =28; randomized placebo-controlled trials/genetic modifier study, n= 32 total (ACEI study, n=17; statin study, n=21; mineralcorticoid antagonism study, n=1; genetic modifier study, n=2); questionnaire only (n=20). Follow-up visits for those who participated in intervention trials were only included in analysis if they were in the placebo group. All analysis was retrospective, and participants did not return specifically for this study.

The study was approved by the Colorado Multiple Institutional Review Board and conform with the *Declaration of Helsinki*. The nature, benefits and risks of the study were explained to all participants and participant or parental written informed consent was obtained prior to participation. Participants consented to storage of data for future analyses at the time of consent to study participation. Children over 7 and under 18 years of age provided an assent.

Study Variables

Predictor—Patients with VEO ADPKD were identified as being diagnosed either *in utero* or within the first 18 months of life [5]. Matched patients with non-VEO ADPKD were identified as non-VEO based on diagnosis of ADPKD at >18 months of age. Diagnosis of ADPKD in children was based upon the presence of bilateral renal cysts by ultrasonography with a positive family history [5,16]. Importantly, any prenatal ultrasound was routine, mothers of VEO ADPKD patients were as equally likely to have received prenatal ultrasound, and patients were matched as closely as possible for year of birth, thus accounting for changes in sensitivity of ultrasound over time.

Outcomes—Outcomes of interest, defined *a priori*, were development of hypertension, height-adjusted htTKV ≥ 600 mL/m, glomerular hyperfiltration, eGFR < 90 mL/min/ $1.73m^2$, and. progression to ESRD. htTKV ≥ 600 mL/m was selected because this threshold was shown to predict the risk of developing stage 3 CKD within 8 years in adults with ADPKD [11].

Progression to ESRD (all participants) and hypertension status (n=69 VEO and n=69 non-VEO) were evaluated by questionnaire asking whether the outcomes had occurred, and if so, in what year [17,18]. For participants in the natural history study or randomized controlled trials, multiple blood pressures automatic blood pressues (Dinamap) were also taken in the seated position with an appropriately sized cuff based on arm circumference for evaluation of hypertension status (n=49 VEO and n=49 non-VEO) [5,14,15,19]. In the natural history study, a mean of 16 measurements was calculated in adults [19] and on average 14 automatic measurements were taken and averaged in children [5]. In the randomized controlled trials, 12 blood pressures were averaged [14,15]. Hypertension was defined as mean systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg in adults and as SBP ≥ 95^{th} percentile for age, sex, and height for children [20].

htTKV by abdominal magnetic resonance imaging (MRI) was determined using the stereology method, as described in detail previously (n=24 VEO and n=33 non-VEO) [15,21]. Only baseline data were included for participants in the statin study who were randomized to the active group, as pravastatin slowed the growth of height-adjusted TKV [15]. In addition to htTKV ≥ 600 mL/m, we evaluated time to htTKV ≥ 300 mL/m as a supplementary analysis.

eGFR was calculated in adults using the 4-variable Modified Diet Renal Disease [MDRD] prediction equation [22]. As older measurements of serum creatinine were not IDMS traceable, the CKD Epidemiology Collaboration (CKD-EPI) equation was not used. eGFR was calculated in children using the old Schwartz formula [23] or the new Schwartz equation for time points after the switch to IDMS traceable measurements [24]. Data on eGFR were available in a total of n=50 VEO and n=50 non-VEO patients. Glomerular hyperfiltration was defined as eGFR ≥ 140 mL/min/1.73 m^2. A decline to eGFR <90 mL/min/1.73m^2 was selected as an endpoint in order to detect a more modest decline in renal function, given that GFR is largely preserved in children with ADPKD [3]. As a supplementary analysis, we also evaluated time to 30% decline in eGFR.

Other Measurements—Year of birth, age at diagnosis, race, and ethnicity were determined from self-report. Cause of diagnosis was determined from medical history or self-report. Body mass index (BMI) was determined from height and weight measured during a physical examination (n=51 VEO and n=50 non-VEO). DNA screening of the *PKD1 and PKD2* genes were performed as described previously [25].

Statistical Analyses

The longitudinal association between VEO status and adverse outcomes of interest (development of hypertension, htTKV ≥ 600mL/m, glomerular hyperfiltration, eGFR <90 mL/min/1.73m^2, or progression to ESRD), was analyzed using Kaplan-Meier survival analysis and the log-rank test. The initial time point was defined as birth (0 years of age) for all participants. Participants were censored upon cessation of participation in any ADPKD studies. Differences in demographics and clinical characteristics between groups were assessed using t-tests, Chi-square tests, or rank-based tests. Unadjusted Cox proportional hazards analysis was used to determine the hazard ratio for each outcome of interest. As potential covariates mediating outcomes did not differ between groups, and the progression in patients with VEO-ADPKD is of interest independent of mechanism, adjusted analyses were not performed. Two-tailed values of $P<0.05$ were considered statistically significant. All statistical analyses were performed with SAS version 9.4.

Results

Clinical Characteristics

Demographics and clinical characteristics at the final time point for VEO and non-VEO patients with ADPKD are shown in Table 1. Of note, some pairs of siblings were included in the study (7 VEO pairs, 2 non-VEO pairs, and 3 VEO/non-VEO pairs). Patients were successfully matched for year of birth, sex, and race/ethnicity. Overall, the median follow-up

was until 16.0 (interquartile range: 11.5, 21.0) years of age, which did not differ significantly between groups. By definition, VEO patients were diagnosed at a younger age (i.e. <18 months) than non-VEO patients. VEO cases were more likely to be diagnosed *in utero* or due to an abdominal mass/palpable kidneys, whereas non-VEO patients were more likely to be diagnosed due to other screening or to have not reported a known cause of diagnosis. Presence of the *PKD1* genotype, BMI category, SBP, DBP, eGFR, and htTKV were not significantly different between groups.

Hypertension

42 (61%) VEO and 21 (30%) non-VEO patients developed hypertension in the follow-up period. VEO patients were more likely to develop hypertension during follow-up than non-VEO patients (Figure 1A; $p<0.0001$). The median age at development of hypertension was 18 years earlier in the VEO group compared to the non-VEO group (Table 2). A VEO patient who had not yet developed hypertension was ~3 times as likely to progress to hypertension at the next time point, as compared to a non-VEO patient (Table 2).

Kidney Growth

There were only 7 patients who progressed to htTKV ≥ 600 mL/m during the follow-up period, 4 (17%) in the VEO group and 3 (9%) in the non-VEO group ($p<0.001$; Figure 1B). The median age at time of htTKV ≥ 600 mL/m in the VEO group was 19 years. Due to the low number of events, the median age in the non-VEO group and a hazard ratio could not be calculated. Results were similar in supplementary analysis evaluating progression to htTKV ≥ 300 mL/m (Supplemental Table 1 and Supplemental Figure 2A; HR: 4.00 [95% confidence interval: 1.88–8.74]).

Glomerular Hyperfiltration

There was no difference in the development of glomerular hyperfiltration (eGFR ≥140 mL/min/1.73 m^2) between groups (n=19 (38%) in the VEO group and n=24 (48%) in the non-VEO group) (Figure 1C; $p=0.86$), with a non-significant hazard ratio (Table 2).

eGFR <90 mL/min/1.73m^2

VEO patients were more likely to progress to eGFR <90 mL/min/1.73 m^2 (Figure 1D; $p=0.034$). 25 (50%) VEO and 15 (30%) non-VEO progressed to eGFR <90 mL/min/1.73m^2 during the follow-up period. The median age at progression to eGFR <90 mL/min/1.73m^2 was 3 years earlier in the VEO group compared to the non-VEO group (Table 2). A VEO patient who had not yet progressed to eGFR <90 mL/min/1.73m^2 was ~2 times as likely to progress to eGFR <90 mL/min/1.73m^2 at the next time point, as compared to a non-VEO patient (Table 2). However, in supplementary post-hoc analyses, there was no difference in time to a 30% decline in eGFR (Supplemental Table 1 and Supplemental Figure 2B; hazard ratio: 1.23 [95% confidence interval: 0.50–3.10]).

ESRD

There were only 4 ESRD events during the follow-up period, all of which occurred in the VEO group (6%; p=0.031; Kaplan-Meier curve not shown). Due to the low number of events, the median age at ESRD and a hazard ratio could not be calculated.

Discussion

In the largest study of VEO-ADPKD patients to date, and the first longitudinal analysis of clinical endpoints, we found a greater hazard of adverse outcomes in a cohort of patients with VEO-ADPKD compared to non-VEO-ADPKD followed until a median age of 16 years. VEO-ADPKD was associated with development of hypertension, increase in htTKV to ≥600 mL/m, eGFR <90 mL/min/1.73m^2, and ESRD, with no difference in glomerular hyperfiltration. Importantly, the patients with VEO-ADPKD were matched for year of birth, sex, and when possible race/ethncity, thus it is unlikely that differences between groups were due to a cohort effect.

A previous cross-sectional analysis from our group also compared outcomes in VEO and non-VEO-ADPKD patients with adjustment for age [5]. At this single time point, VEO patients had a lower eGFR and higher age-adjusted kidney volume measured by ultrasound. 2 VEO and no non-VEO patients reached ESRD, which was a similar low rate to the present study. Additionally, VEO patients were more likely to have hypertension during the follow-up period as evaluated by questionnaire. The current study expands upon these previous findings by following a longitudinal cohort of a larger number of VEO-ADPKD patients with matched non-VEO-ADPKD controls for the development of clinically meaningful outcomes.

The greater development of adverse outcomes in the VEO group supports the need for early identification and intervention of ADPKD in children, particularly in those with VEO. Early intervention may have the greatest effect on the course of the disease by minimizing long-term complications [26,27]. Given that there is great heterogeneity in ADPKD progression, even within a given family [10], early intervention may be of particular significance to patients at the highest risk of progression, which notably includes VEO patients.

The median age of onset of hypertension was 18 years earlier in VEO compared to non-VEO patients. High blood pressure in affected children (above the 75th percentile for age, sex, and height) is associated with faster renal growth [3]. Hypertension is also associated with larger TKV in adults and children [10], as well as a decline in renal function [28,29]. Notably, in the recently completed Halt Progression of PKD (HALT-PKD) blood pressure trial, rigorous blood pressure control slowed the increase in TKV compared to standard blood pressure control [30].

VEO-ADPKD was also associated with progression to htTKV ≥600 mL/min, albeit with a relatively low number of events occurring overall. This value was selected as an endpoint because baseline htTKV ≥600 mL/min predicted progression to stage 3 CKD within 8 years in the Consortium for Radiologic Imaging Studies of PKD (CRISP) [11]. Additionally, increased htTKV at a younger age is clinically significant, as severe renal enlargement at a

young age is associated with faster renal growth [3]. Results were similar in sensitivity analyses considering an earlier endpoint of htTKV ≥300 mL/min. Importantly, as kidney growth is associated with declining kidney function over time [14,31,32], the greater progression to htTKV ≥600 mL/min or ≥300 mL/min would suggest greater risk of progression to ESRD in children with VEO-ADPKD.

A decline in eGFR <90 mL/min/1.73m^2 was selected as an endpoint in order to detect a more modest decline in renal function, given that GFR is largely preserved in children with ADPKD [3]. Since GFR is typically maintained in the normal range in ADPKD until the 4th or 5th decade of life [33], a higher risk of progression to eGFR <90 mL/min/1.73m^2 is clinically significant. A higher serum creatinine at baseline has been shown to predict a faster decline in eGFR in a cohort of 200 ADPKD patients [34]. However, unlike decline to <90 mL/min/1.73m^2, there was no difference between groups in time to 30% decline in eGFR, perhaps because it is a less subtle change in renal function. The number of patients that progressed to ESRD (4, all VEO) was low, consistent with earlier data [5]. Of note, the development of ESRD in ADPKD is highly variable, ranging from childhood to a normal life-expectancy without knowledge of disease [33].

There was no difference in glomerular hyperfiltration (eGFR ≥140 mL/min/1.73m^2) between the VEO and non-VEO-ADPKD group. In ADPKD, compensatory hyperfiltration occurs to initially maintain normal or near normal serum creatinine levels, despite progressive destruction of the parenchyma [35]. Glomerular hyperfiltration leads to glomerular hypertension and progressive damage of the remaining unaffected nephrons [36]. In children with ADPKD, glomerular hyperfiltration is associated with an increased rate of kidney growth and a faster decline in eGFR [13]. However, the present results indicate that glomerular hyperfiltration is not an important mechanism differentiating progression in VEO and non-VEO patients with APDKD.

Of note, we feel it is unlikely that the included VEO patients had very severe ADPKD, resulting from coinheritance of a hypomorphic PKD1 allele *in trans* with an inactivating PKD1 allele [37,38]. Such cases present phenotypically similar to autosomal recessive PKD, and no participants in this cohort had such severe symptoms. The inheritance of two incompletely penetrant PKD1 alleles is the likely explanation for early case reports that reported very high mortality in the first year of life for patients with VEO-ADPKD [39,40]. Data were available regarding PKD genotype in a sub-sample of participants in the present study and did not differ between groups. Whether the prevalence of the PKD1 genotype is greater in VEO-ADPKD patients is currently unknown.

There are several important limitations to the present study. As all analysis was retrospective, this introduces various biases and limitations, including selection bias, information bias, loss to follow-up, and missing data. This cohort may not accurately reflect the natural course of disease progression as it is biased by the participation in research studies. Furthermore, as this is an observational study, it can only show association rather than causation. Due to the nature of follow-up, the exact time of each event may have differed slightly from what was reported or measured. Additionally, not all outcomes or covariates were available in all participants, and some outcomes were self-reported.

Similarly, further variables of interest were not available for inclusion in the study, including albuminuria/proteinuria, urinary tract infections, and additional markers of hyperfiltration. The influence of VEO status on progression to ESRD will require longer-term follow-up for more definitive insight. VEO participants may have been followed more carefully or may have been more likely to have outcomes of interest detected earlier due to earlier diagnosis. However, as non-VEO's were also diagnosed nearly exclusively in childhood, this concern is minimized. Of note, the non-VEO patients in our population are possibly more affected than the general ADPKD population, many of whom are affected but undiagnosed. Outside physicians are more likely to refer patients with more severe disease for participation in studies.

Our definition of VEO to include individuals diagnosed due to screening or even *in utero* may have resulted in inclusion of patients who were not truly VEO due to symptoms. However, this definition would have reduced our ability to detect a difference between groups and the disparity between groups may be even greater than assessed. Additionally, mothers of VEO patients were not more likely to receive prenatal ultrasound screening than mothers of non-VEO patients. Last, detailed information on mutation type was unavailable on the vast majority of participants and is an important future direction in this field. Notable strengths of this study include inclusion of the largest *n* of VEO-ADPKD patients to date. Additionally, matching for year of birth, sex, and when possible race/ethnicity minimized potential confounding. Due to the matching by birth year, it is unlikely that difference between groups were due to a cohort effect (e.g. improved ultrasound technology in more recent years leading to increased detection of ADPKD *in utero*). Importantly, this is the first study to examine longitudinal outcomes in VEO-ADPKD patients, with a median follow-up period to 16 years of age.

In conclusion, the results are consistent with the hypothesis that several adverse outcomes are worse in patients with VEO-ADPKD compared to non-VEO ADPKD, thus children with VEO-ADPKD represent a particularly high-risk group of ADPKD patients. Longer-term follow-up is needed to provide even greater insight to the clinical course of patients with VEO-ADPKD. It is likely that even more VEO cases will be identified in the future due to advances in ultrasound imaging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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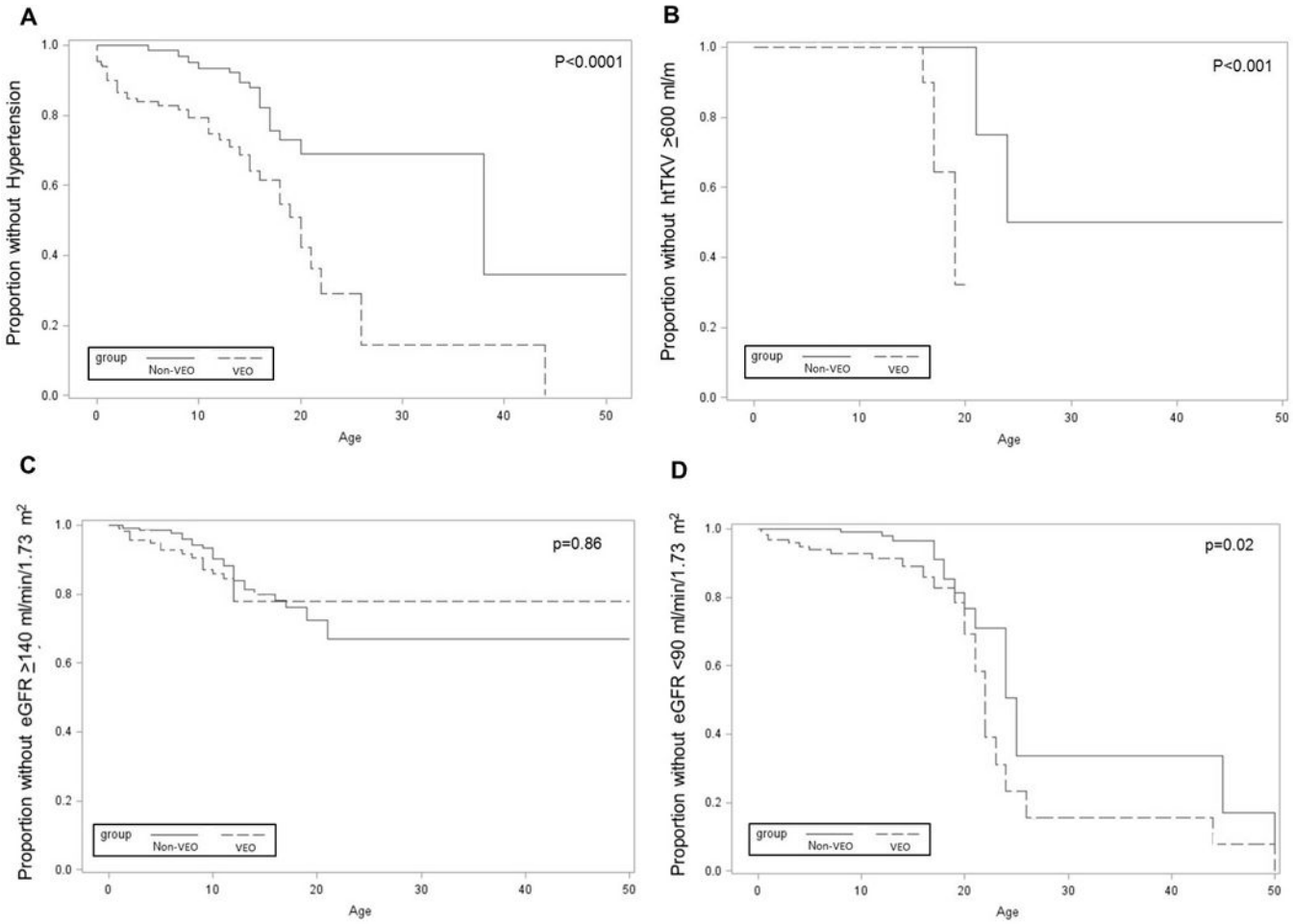

Figure 1.

Kaplan-Meier curve of hypertension **(panel A)**, height-adjusted total kidney volume (htTKV) ≥ 600 mL/m **(panel B)**, glomerular hyperfiltration (estimated glomerular filtration rate [eGFR] ≥ 140 mL/min/1.73m^2) **(panel C)**, and eGFR < 90 mL/min/1.73m^2 **(panel D)** according to group (very-early onset [VEO] or non-VEO autosomal dominant polycystic kidney disease [ADPKD]). VEO patients were more likely to develop hypertension, to progress to htTKV > 600 mL/m, and to decline to eGFR < 90 mL/min/1.73m^2 than non-VEO patients, but did not differ in progression to glomerular hyperfiltration.

Table 1

Clinical characteristics of very-early onset (VEO) and non-VEO patients with autosomal dominant polycystic kidney disease at the final time point. Data from the final time point for each variable are shown and may represent a slightly different time point for each variable. SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; htTKV, height-adjusted total kidney volume; IQR, interquartile range. Data were not reported for SBP and DBP (n=21 VEO, 21 non-VEO), eGFR (n=20 VEO, n=20 non-VEO), htTKV (n=46 VEO, n=37 non-VEO).

Clinical characteristics	VEO	Non-VEO
N (M/F)	70 (29/41)	70 (29/41)
Year of birth (median [IQR])	1992 (1986, 1996)	1992 (1986, 1995)
Age, years (median [IQR])	15 (9, 21)	17 (13, 21)
Age at diagnosis (median [IQR])	<18 months	10 (6, 14) yrs
Race/Ethnicity, % (n)		
Non-Hispanic White	64% (45)	73% (51)
Other	7% (5)	10% (7)
Not reported	29% (20)	17% (12)
Cause of Diagnosis, % (n)		
In Utero	40% (28)	0% (0)
Screening by imaging (other than *in utero*)	19% (13)	34% (24)
Abdominal Mass/Palpable Kidneys	13% (9)	4% (3)
Hypertension	0% (0)	1% (1)
Other Symptoms	7% (5)	16% (11)
Not reported	21% (15)	44% (31)
PKD1 genotype, % (n)		
Yes	47% (33)	31% (22)
No mutation detected	1% (1)	1% (1)
Unknown	51% (36)	67% (47)
Body mass index category, % (n)		
Normal or underweight	46% (33)	42% (30)
Overweight	14% (10)	13% (9)
Obese	11% (8)	15% (11)
Not reported	27% (19)	28% (20)
SBP, mm Hg (mean±SD)	116±23	120±14
DBP, mm Hg (mean±SD)	71±13	71±10
eGFR, mL/min/1.73m^2 (median [IQR])	109 (81, 128)	108 (93, 128)
htTKV, mL/m (median [IQR])	370 (214, 544)	281 (224, 471)

Table 2

Median time to events for included very-early onset (VEO) and non-VEO patients with autosomal dominant polycystic kidney disease. N/A = the median estimate could not be calculated because the failure probability never exceeded 0.5. Hazard ratios and p-values are for unadjusted Cox proportional hazards analysis comparing VEO to non-VEO.

Event	N (%) VEO	Median Age VEO	N (%) Non-VEO	Median Age Non-VEO	Hazard Ratio (95% CI)	*P*-Value
Hypertension	42 (61%)	20	21 (30%)	38	3.15 (1.86–5.34)	<0.0001
eGFR ≥140 mL/min/1.73m^2	19 (38%)	N/A	24 (48%)	N/A	1.06 (0.58–1.93)	0.86
eGFR <90 mL/min/1.73m^2	25 (50%)	22	15 (30%)	25	2.3 (1.08, 3.95)	<0.05