Clinical Kidney Journal

Clinical Kidney Journal, 2023, vol. 16, no. 10, 1691–1700

https://doi.org/10.1093/ckj/sfad114
Advance Access Publication Date: 23 May 2023
Original Article

ORIGINAL ARTICLE

Evaluation of advanced imaging biomarkers at kidney failure in patients with ADPKD: a pilot study

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ABSTRACT

Background. Autosomal dominant polycystic kidney disease (ADPKD) presents with variable disease severity and progression. Advanced imaging biomarkers may provide insights into cystic and non-cystic processes leading to kidney failure in different age groups.

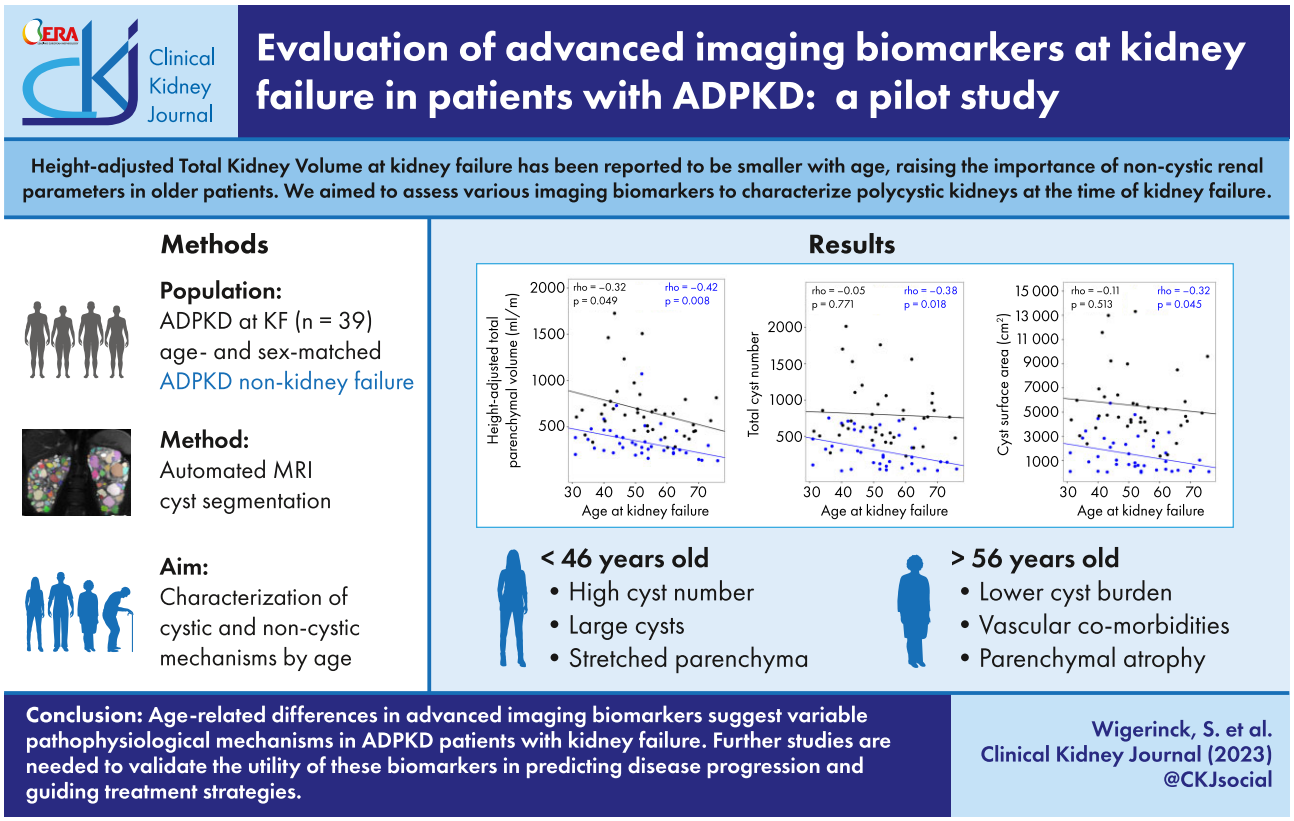
Methods. This pilot study included 39 ADPKD patients with kidney failure, stratified into three age groups (<46, 46–56, >56 years old). Advanced imaging biomarkers were assessed using an automated instance cyst segmentation tool. The biomarkers were compared with an age- and sex-matched ADPKD cohort in early chronic kidney disease (CKD).

Results. Ht-total parenchymal volume correlated negatively with age at kidney failure. The median Ht-total parenchymal volume was significantly lower in patients older than 56 years. Cystic burden was significantly higher at time of kidney failure, especially in patients who reached it before age 46 years. The cyst index at kidney failure was comparable across age groups and Mayo Imaging Classes. Advanced imaging biomarkers showed higher correlation with Ht-total kidney volume in early CKD than at kidney failure. Cyst index and parenchymal index were relatively stable over 5 years prior to kidney failure, whereas Ht-total cyst volume and cyst parenchymal surface area increased significantly.

Conclusion. Age-related differences in advanced imaging biomarkers suggest variable pathophysiological mechanisms in ADPKD patients with kidney failure. Further studies are needed to validate the utility of these biomarkers in predicting disease progression and guiding treatment strategies.

Received: 20.12.2022; Editorial decision: 18.4.2023

GRAPHICAL ABSTRACT



Keywords: autosomal polycystic kidney disease, cystic burden, genetics, kidney failure, MRI biomarkers

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited and the fourth most common cause of kidney failure [1–4]. ADPKD is mainly caused by pathogenic variants in *PKD1* and *PKD2*, coding for the polycystin 1 and 2 proteins [5]. It is characterized by relentless cyst growth and frequent kidney manifestations include systemic hypertension, cyst infection, and pain caused by cyst bleeds and ruptures [6, 7]. Due to excessive kidney damage, approximately 50% of patients with ADPKD progress to kidney failure by their sixth decade [8, 9]. Glomerular filtration rate (GFR) trajectories are more linear in patients with severe ADPKD and more curvilinear in patients with less severe disease, with long periods of preserved kidney function, followed by rapid decline [9–11]. Compared with other kidney diseases with a more linear GFR trajectory, i.e. diabetic glomerulosclerosis or chronic glomerulonephritis, the rate of GFR decline in ADPKD is heterogenous, depending on multiple factors including, genotype, age and cystic burden [10, 12]. Given the variability in kidney failure onset, there is an unmet need to develop additional biomarkers to increase the accuracy of predicting GFR decline in patients with ADPKD [13, 14].

Multiple prognostic biomarkers can be combined to predict the risk of future GFR decline in adults [13, 15]. Predictors of progression in ADPKD include the annual rate of decline in estimated GFR (eGFR), ADPKD genotype and clinical parameters [13, 16]. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) established that imaging-based biomarkers are critical in assessing cystic disease severity in ADPKD [17–19]. Height- and age-adjusted total kidney volume (HtTKV), integrated into the Mayo Imaging Classification (MIC), has been validated to predict GFR decline [20, 21]. For instance, HtTKV/age can be four times greater in MIC-1E patients compared with MIC-1B patients, resulting in a much higher risk (25×) of reaching kidney failure [9]. However, HtTKV does not provide granular details on the differential role of cystic and non-cystic mechanisms leading to kidney failure [22–24]. Advanced imaging techniques such as automated semantic kidney and cyst segmentation have been developed to quantify cystic parameters [25, 26]. These advancements in technology enable us to explore the role of additional imaging biomarkers in the phenotype and natural course of ADPKD [5, 10].

Recently, Shukoor *et al.* studied the characteristics of patients with ADPKD at kidney failure and showed that HtTKV at kidney failure was smaller by 12.3% with each decade of life [23]. These findings raised the hypothesis that cyst growth is the predominant mechanism causing kidney failure in younger patients, whereas aging-related factors, including vascular disease, become potentially important as patients with ADPKD age [23]. In this study, we aimed to test this hypothesis by assessing multiple advanced magnetic resonance imaging (MRI) biomarkers to understand the characteristics of polycystic kidneys at time of kidney failure.

MATERIALS AND METHODS

Study patients

This retrospective case–control study was conducted in accordance with the recommendations of the Mayo Clinic Institutional Review Board, and all patients provided their consent for research. The study population consisted of a subset of Mayo Clinic patients between January 1992 and January 2018 (Minnesota, Florida and Arizona), who met all pre-established inclusion and exclusion criteria used in the study of Shukoor *et al.* [23]. All patients were diagnosed with genetically proven *PKD1* or *PKD2* pathogenic variants and had complete clinical and imaging data at the time of kidney failure. Inclusion criteria were the following: (i) clinically or genetically proven ADPKD with typical bilateral cystic distribution (MIC-1), (ii) diagnosis of kidney failure, and (iii) available and complete MRI of the kidneys at time of kidney failure: either <24 months before or <3 months after kidney failure. Patients were excluded when imaging had suboptimal quality, interfering with proper cyst segmentation. The control cohort consisted of 39 patients with ADPKD matched for age (±4 years) and sex with available MRI imaging for cyst segmentation and without advanced CKD.

Data collection

Chart review

Data at time of kidney failure were retrieved from medical records. Kidney failure was defined as one of the following: (i) eGFR ≤15 mL/min/1.73 m^2, (ii) permanent dialysis or (iii) kidney transplantation. Other data retrieved from the chart review included age at kidney failure, race, height, sex, serum creatinine level (mg/dL) at kidney failure, body mass index (BMI; g/m^2), history of hypertension, smoking and macrovascular disease. An adjusted BMI (non-kidney mass index) was calculated by subtracting the kidney mass from the body mass, as previously described [27]. The kidney tissue density was assumed as equal to the water density (1000 kg/m^3) [27, 28]. Kidney function (expressed as eGFR) was calculated using the CKD Epidemiology Collaboration formula [29]. Macrovascular disease was defined as a known history of one of the following before kidney failure: (i) myocardial infarction, (a) symptomatic coronary artery disease or (b) ischemic congestive heart failure; (ii) stroke; (iii) abdominal aortic aneurysm; and (iv) ruptured intracranial aneurysm or intervention for intracranial aneurysm [30].

Imaging biomarkers

Automated kidney segmentation [31] and automated instance cyst segmentation [26] were performed as described previously. The automated programs facilitated obtaining the following parameters: total kidney volume (TKV), total cystic volume (TCV), total parenchymal volume (TPV), total cyst number (TCN), cyst surface area (CSA) and cyst parenchyma surface area (CPSA; defined as the combined surface of all cysts adjacent to the parenchyma). Cyst index and parenchymal index were obtained as follows: TCV/TKV and TPV/TKV, respectively. Height at time of imaging was used to adjust imaging biomarkers by dividing the biomarker by height in meter (e.g. HtTKV = TKV/height, in mL/m). The MIC was determined and calculated using the MIC calculator [17].

Genetic analysis

The entire coding and flanking intronic regions of *PKD1* and *PKD2* were screened for pathologic variants by Sanger or next-generation sequencing [32–35]. Patients were classified as follows: *PKD1* truncating ($PKD1^T$), *PKD1* non-truncating ($PKD1^{NT}$) and *PKD2*.

Statistical analysis

All statistical analyses were done using the JMP 16 pro software. Normally distributed data were reported as mean ± standard deviation. MRI biomarkers were skewed and reported as median [interquartile range (IQR)]. Spearman correlation was used to measure the strength between different variables at the time of kidney failure. Additional analyses using pairwise testing were performed by dividing the patients in tertiles according to age of kidney failure onset: <46 years vs 46–56 years, <46 years vs >56 years and 46–56 years vs >56 years. Continuous variables were tested using analysis of variance for normally distributed variables and Kruskal–Wallis tests for imaging biomarkers that were not normally distributed. Fisher's Exact Test was applied throughout to overcome small, expected counts in contingency tables. The *P*-value was set at ≤.05 for significance. A matched-pair analysis, with two measurements per patient (5 years pre-kidney failure and at time of kidney failure), was conducted to evaluate the longitudinal progression of all MRI biomarkers over 5 years using paired *t*-tests.

RESULTS

Demographics and clinical characteristics at kidney failure

The study flow chart is shown in Supplementary data, Fig. S1. Among 50 patients with ADPKD, available MRI and genotype at the time of kidney failure, 11 were excluded due to suboptimal imaging quality limiting granularity for advanced biomarkers. Thirty-nine patients were included and stratified into three groups (Groups 1–3) by tertiles of age (<46, 46–56, >56 years old) at time of kidney failure (Table 1). Each group consisted of 13 patients and the median age (IQR) at kidney failure across the whole group was 52.1 (42.9–61.9) years. All patients were Caucasian by ethnicity, and 38.5% were male. Patients with kidney failure at a younger age had a more severe MIC compared with older patients. Most patients were classified as MIC-1E in Group 1 (53.8%), as MIC-1D in Group 2 (53.8%) and as MIC-1C in Group 3 (53.8%). The median calculated eGFR at the time of kidney failure was 14.9 mL/min/1.73 m^2 and was similar among the three groups ($P = .196$). Patients received a pre-emptive kidney transplantation more often than dialysis (71.8 vs 28.2%, respectively). $PKD1^T$ pathogenic variants were identified in 53.8%, $PKD1^{NT}$ in 35.9% and *PKD2* in 10.3% of the overall cohort. Adjusted BMI (BMI calculated from an adjusted weight removing the contribution of weight of the kidney) was similar in Groups 1 and 2 (29.7 and 29.8 kg/m^2) but higher compared with Group 3 (24.9 kg/m^2, $P = .012$). Most patients (97.4%) were hypertensive and 61.5% had a history of smoking. Hyperlipidemia was more common in older patients (69.2%) ($P = .041$). By the time of kidney failure, one patient had a history of myocardial infarction, two patients of hemorrhagic stroke and two of an intracranial aneurysm rupture. The control cohort consisted of 39 age- and sex-matched ADPKD patients across all classes of the MIC and with median eGFR of 73.4 (60.5–91.5) mL/min/1.73 m^2. Most patients were classified as MIC-1A (30.8%), MIC-1B (28.2%) and MIC-1C (20.5%).

Table 1: Baseline demographics and clinical characteristics of patients with ADPKD, stratified by age at the time of kidney failure.

	Total, N = 39	<46 years, n = 13	46–56 years, n = 13	>56 years, n = 13	P-value
Caucasian, n (%)	39 (100)	13 (100)	13 (100)	13 (100)	
Male, n (%)	15 (38.5)	5 (38.5)	6 (46.2)	4 (30.7)	
Age at kidney failure (years), median (IQR) [min–max]	52.1 (42.9–61.9) [31.3–75.6]	40.3 (35.3–43.2) [31.3–45.5]	52.1 (50.1–54.6) [46.7–56.4]	65.8 (61.0–68.7) [59.3–75.6]	<.001
MIC, n (%)					<.001
MIC 1B	4 (10.3)	0 (0)	0 (0)	4 (30.7)	
MIC 1C	11 (28.2)	0 (0)	4 (30.7)	7 (53.8)	
MIC 1D	15 (38.5)	6 (46.2)	7 (53.8)	2 (15.4)	
MIC 1E	9 (23.1)	7 (53.8)	2 (15.4)	0 (0)	
Calculated eGFR (mL/min/1.73 m^2), median (IQR)	14.9 (11.0–16.3)	14.9 (12.6–18.3)	12.2 (11.4–16.2)	14.2 (10.5–15.6)	.196
Pre-emptive transplant, n (%)	28 (71.8)	11 (84.6)	8 (61.5)	9 (69.2)	.323
Dialysis, n (%)	11 (28.2)	2 (15.4)	5 (38.5)	4 (30.8)	.550
Genotype, n (%)					.042
PKD1^{T}	21 (53.8)	11 (84.6)	4 (30.8)	6 (46.2)	
PKD1^{NT}	14 (35.9)	2 (15.4)	6 (46.2)	6 (46.2)	
PKD2	4 (10.3)	0 (0)	3 (23.1)	1 (7.7)	
Adjusted BMI (kg/m^2), median (IQR)	26.3 (23.6–31.8)	29.7 (25.1–33.5)	29.8 (25.7–32.3)	24.9 (22.3–26.0)	.012
History of hypertension, n (%)	38 (97.4)	12 (92.3)	13 (100)	13 (100)	1
History of smoking, n (%)	24 (61.5)	8 (61.5)	7 (53.8)	9 (69.2)	.915
History of hyperlipidemia, n (%)	21 (53.8)	3 (23.1)	9 (69.2)	9 (69.2)	.041
Macrovascular disease, n (%)					
Myocardial infarction	1 (2.6)	0 (0)	0 (0)	1 (7.7)	1
Stroke	2 (5.1)	0 (0)	1 (7.7)	1 (7.7)	1
Abdominal aortic aneurysm	0 (0)	0 (0)	0 (0)	0 (0)	1
Ruptured intracranial aneurysm	2 (5.1)	0 (0)	1 (7.7)	1 (7.7)	1

Two patients had atypical ADPKD (5.1%). Nineteen control patients had available genetics. *PKD1* variants were identified in 68.4% (13/19) and *PKD2* variants in 31.6% (6/19) (Supplementary data, Table S1).

Correlation between HtTKV and age in early CKD and at time kidney failure with advanced imaging biomarkers

Previous studies showed differences in HtTKV with advancing age at time of kidney failure [19, 20]. This raised the question of whether different pathophysiological mechanisms are in place among the different age groups in ADPKD. To further elaborate on this hypothesis, we assessed the correlations with age at kidney failure (Fig. 1). Ht-total parenchymal volume was the only biomarker found to be significantly and negatively correlated with age at kidney failure (r = –0.32). TKV and HtTKV are established biomarkers for disease progression in ADPKD [21, 31, 32]. We computed the correlation of advanced imaging biomarkers with HtTKV to better understand how they relate or contribute to the kidney enlargement (Fig. 2 and Supplementary data, Fig. S2). Cystic biomarkers, Ht-total cyst volume (r = 0.97), cyst surface area (0.93) and cyst parenchymal surface area (r = 0.81), and Ht-total parenchymal volume (r = 0.91), correlated strongly with HtTKV. Total cyst number and cyst index were less correlated with HtTKV (r = 0.39 and r = 0.53, respectively), indicating potential value as biomarkers complementary to HtTKV. The parenchymal index was negatively correlated with HtTKV (r = –0.53). In contrast to patients at kidney failure, all biomarkers, except Ht-total cyst volume, did show a significant negative correlation with age in the control cohort. The strongest negative correlation with age at kidney failure was seen in Ht-total parenchymal volume (r = –0.42). Parenchymal index was the only biomarker with a significant positive correlation. The parenchymal index correlated negatively with HtTKV (r = –0.88), similar to the group at kidney failure. All biomarkers correlated strongly with HtTKV. In contrast to the group at kidney failure, cyst index and TCN correlated much more in the non–kidney failure group (r = –0.88 and r = –0.80, respectively).

Analyses by age tertiles

To detect differences between specific age groups, the cohort was divided according tertiles of age at kidney failure (<46, 46–56 and >56 years) (Table 2). Median HtTKV (IQR) at the time of kidney failure was 1482.3 mL/m (1203.3–2117.5) for the overall cohort. HtTKV was numerically higher in patients who reached kidney failure <46 years compared with patients who reached kidney failure at an older age (>56 years) (P = .054). Older patients (>56 years) had a statistically significant lower Ht-total parenchymal volume (P = .02), whereas no significant differences were found for Ht-total cyst volume. Total number of cysts (P = .449) and cyst size based on surface area's (cyst surface area and cyst parenchymal surface area) were similar (P = .364 and .245). The cyst index at kidney failure was comparable among the different age groups (P = .752) and across the various MIC (from 1B through 1E, P = .124) (Fig. 3). Table 3 shows a detailed comparison of the imaging biomarkers between patients at kidney failure and the control group (non–kidney failure). All segmentation biomarkers were significantly elevated at time of kidney failure as compared with the control cohort.

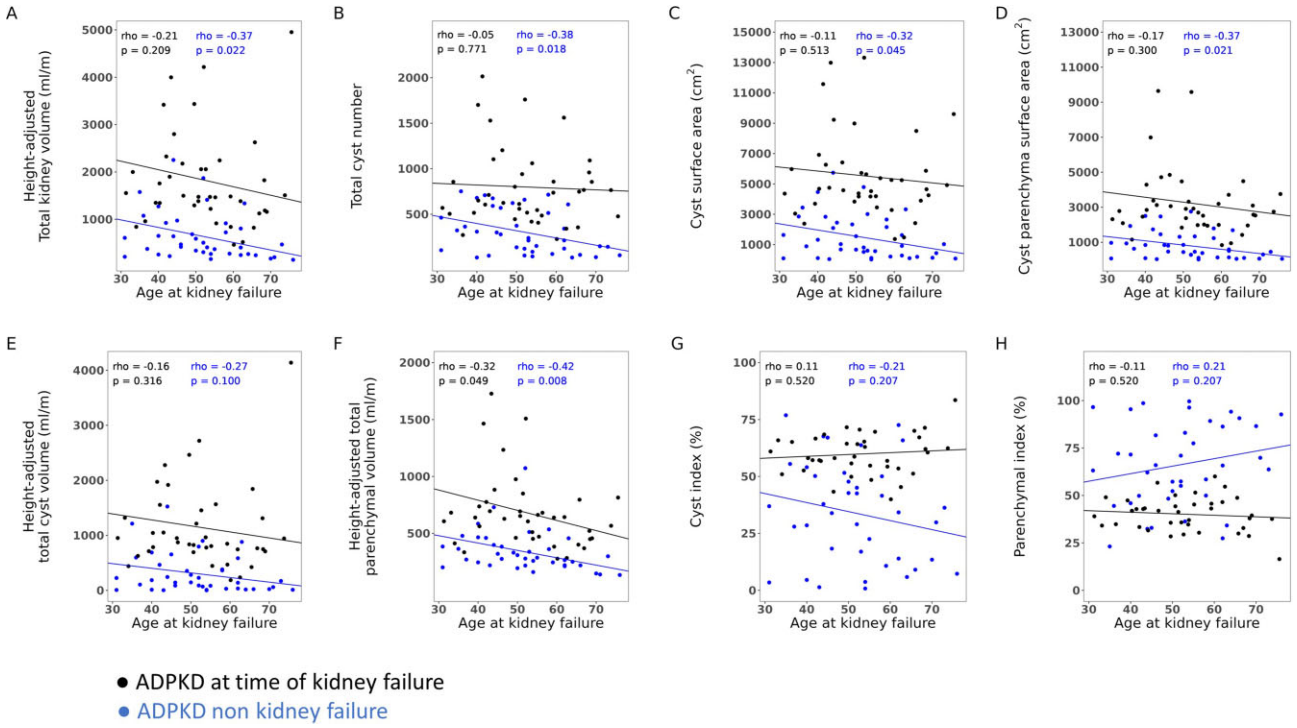


Figure 1: Spearman rank correlation between various advanced imaging biomarkers and age. Interpolated lines are based on Spearman correlation as opposed to a direct linear regression. ● ADPKD at time of kidney failure; ● (blue) ADPKD non–kidney failure.

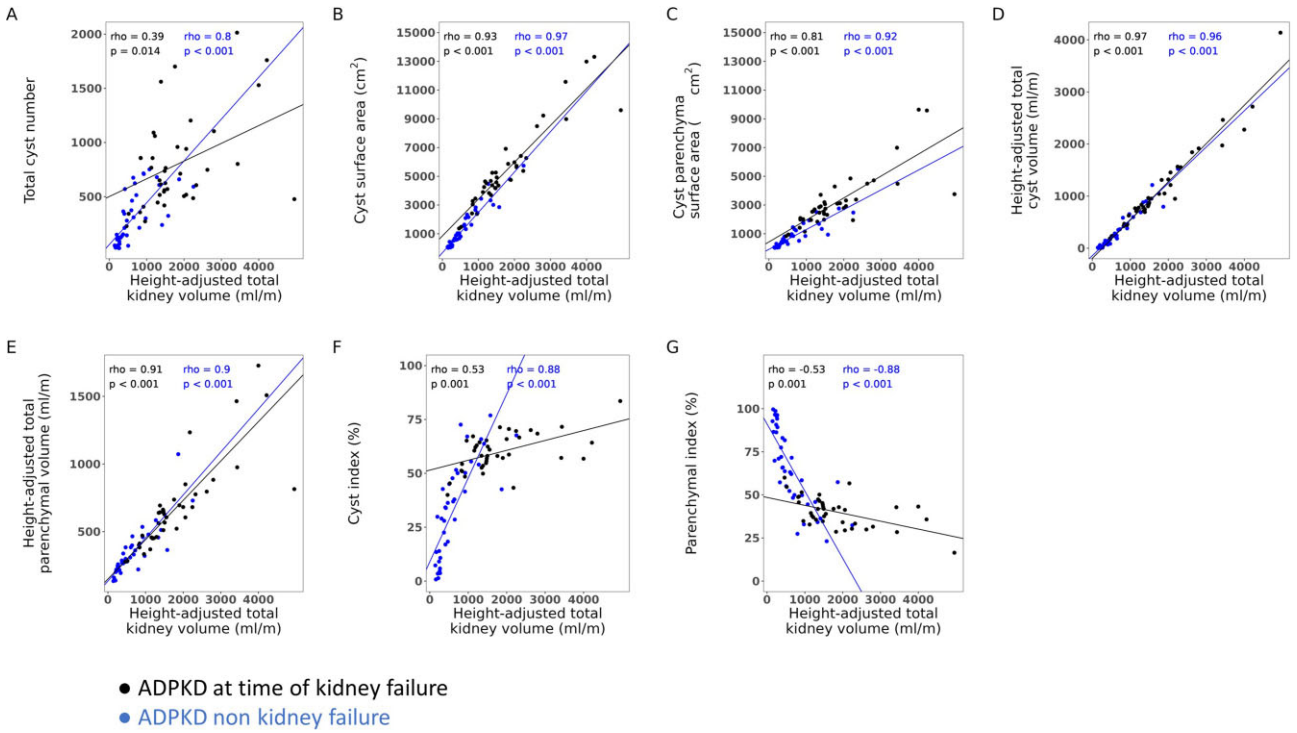


Figure 2: Spearman rank correlation between various advanced imaging biomarkers and HtTKV. Interpolated lines are based on Spearman correlation as opposed to a direct linear regression. ● ADPKD at time of kidney failure; ● (blue) ADPKD non–kidney failure.

Table 2: Comparison of MRI parameters among groups at time of kidney failure.

Biomarker, median (IQR)	All, N = 39	<46 years, n = 13	46–56 years, n = 13	>56 years, n = 13	P-value			
					1 vs 2	1 vs 3	2 vs 3	Overall
HtTKV (mL/m)	1482.3 (1203.3–2117.5)	1898.8 (1349.2–2327.0)	1474.6 (1383.1–2058.3)	1185.8 (839.6–1507.9)	.626	.054	.106	.110
Total cyst number (n)	712.0 (510.5–950.0)	712.0 (570.0–1203.0)	560.0 (486.0–802.0)	765.0 (477.0–858.0)	.174	.573	.626	.449
Cyst surface area (cm^2)	4679.5 (4034.2–6119.7)	5974.7 (4359.8–6914.7)	4520.4 (4171.2–5633.4)	4647.5 (3279.1–5258.2)	.369	.174	.555	.364
Cyst parenchymal surface area (cm^2)	2784.6 (2052.8–3545.5)	3125.9 (2464.6–4715.5)	2696.3 (2014.4–3061.7)	2574.7 (1959.7–3195.7)	.228	.106	.739	.245
Ht-total cyst volume (mL/m)	870.0 (723.0–1384.8)	1021.0 (781.8–1551.0)	870.0 (801.9–1452.4)	740.0 (456.2–941.0)	.858	.086	.130	.169
Ht-total parenchymal volume (mL/m)	639.1 (458.9–756.5)	695.0 (606.4–883.5)	652.9 (510.9–693.3)	457.0 (383.4–639.1)	.369	**.020**	**.026**	**.020**
Cyst index (%)	58.7 (54.5–65.6)	58.1 (56.8–65.2)	63.0 (55.7–65.3)	60.5 (53.5–67.2)	.489	.778	.590	.752
Parenchymal index (%)	41.3 (34.4–45.5)	41.9 (34.8–43.2)	37.0 (34.7–44.3)	39.5 (32.8–46.5)	.489	.778	.590	.752

Longitudinal evolution of biomarkers over 5 years

GFR trajectories are more linear in patients with very severe ADPKD (MIC-1E and -1D) and more curvilinear in patients with less severe disease (MIC-1C, -1B and -1A), with long periods of preserved kidney function, followed by rapid decline [12, 36]. A matched-pair analysis was conducted to assess whether the GFR decline is mirrored by a rapid increase in cyst growth and expansion. Among 39 patients included in this study, 18 had additional MRI available 5 years prior to kidney failure. Distribution according to age at time of kidney failure was as follows: $n = 4$ (<46 years), $n = 6$ (46–56 years) and $n = 8$ (>56 years). The smaller size of the cohort limits an analysis by age groups. We conducted a matched-pair analysis of this whole subset to evaluate the longitudinal evolution in biomarkers over these 5 years. Supplementary data, Table S1 details demographic and baseline characteristics of this subset.

Cyst parenchymal surface area (13.6% per year), Ht-total cyst volume (12.9% per year), TCN detectable by MRI (9.9% per year) and, to a lesser extent, Ht-total parenchymal volume (4.6% per year) increased significantly during the 5 years prior to kidney failure, all contributing to the significant increase in HtTKV (8.6% per year). Ht-total cyst volume growth is a combination of increased TCN and increased volume of pre-existing cysts (cyst parenchymal surface area increased by 13.6% per year). Over 5 years, cyst index and the corresponding parenchymal index were relatively static with a growth rate of only 3.8 ± 5.0% and decline rate of –2.5 ± 2.4% per year. (Supplementary data, Table S2 and Fig. S3). We computed the correlation between annual change in each biomarker and age at kidney failure. Annual change in HtTKV (r = –0.41) and Ht-total parenchymal volume (r = –0.6) were negatively correlated with age at kidney failure (Fig. 4A–H).

DISCUSSION

In this pilot study, granular and advanced imaging biomarkers provide further insight into cystic and non-cystic processes leading to kidney failure in ADPKD that vary with age. Using an automated instance cyst segmentation tool, we analyzed cystic and parenchymal characteristics of polycystic kidneys at time of kidney failure and compared them with an age- and sex-matched ADPKD cohort in early CKD. In this pilot study, the differences between the control and the kidney failure group illustrated how these advanced imaging biomarkers granularly measure the evolution in cystic development throughout the CKD stages. Interestingly, we observed in this study a negative correlation between Ht-total parenchymal volume and age at kidney failure. Age correlated significantly in both the cohorts. This decline of Ht-total parenchymal volume at kidney failure with advancing age could be explained by the development of interstitial fibrosis and parenchymal atrophy contributing to the loss of renal function in conjunction with the cystic burden. This finding possibly explains the recent observation that HtTKV at kidney failure decreased with each decade of life [23]. In early CKD, age correlated more negatively with Ht-total parenchymal volume as compared with age at time of kidney failure. Parenchymal atrophy physiologically increases with age [37]. Cyst development is a continuing process and cystic burden in patients at kidney failure is higher as compared with age-matched PKD patients in early CKD. Besides age-related vascular burden, mechanical pressure of cysts plays a more important role in parenchymal atrophy at time of kidney failure as compared with early CKD. Therefore, the negative correlation

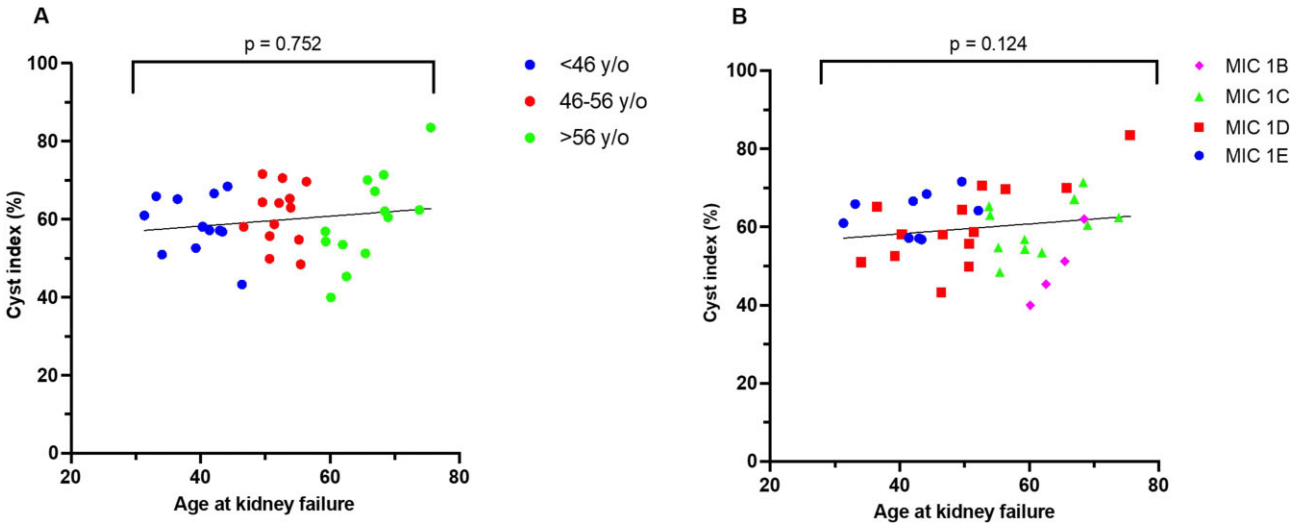


Figure 3: Cyst index is similar in patients grouped by age tertile or MIC at the time of kidney failure.

Table 3: Comparison of MRI parameters between ADPKD patients at kidney failure and non–kidney failure ADPKD patients.

Biomarker, median (IQR)	ADPKD at KF, N = 39	Non-KF ADPKD, N = 39	P-value
HtTKV (mL/m)	1482.3 (1203.3–2117.5)	469.0 (267.5–860.3)	<.001
Total cyst number (*n*)	712.0 (510.5–950.0)	239.0 (96.5–542)	<.001
Cyst surface area (cm^2)	4679.5 (4034.2–6119.7)	917.1 (246.9–2390.1)	<.001
Cyst parenchymal surface area (cm^2)	2784.6 (2052.8–3545.5)	508.5.5 (136.5–1275.0)	<.001
Ht-total cyst volume (mL/m)	872.8 (728.7–1386.7)	144.9 (31.8–422.6)	<.001
Ht-total parenchymal volume (mL/m)	639.1 (458.9–756.5)	286.4 (219.9–391.3)	<.001
Cyst index (%)	58.7 (54.5–65.6)	34.2 (13.7–50.1)	<.001
Parenchymal index (%)	41.3 (34.4–45.5)	41.3 (34.4–45.5)	<.001

KF: kidney failure.

between age and Ht-total parenchymal volume is lower, yet significant [23, 37]. The negative correlation in Ht-total parenchymal volume with age in both cohorts further supports that age-related factors become more important in developing kidney failure at older age. Several mechanisms may lead to lower Ht-total parenchymal volume. Mechanical pressure from cysts and obliterative arteriosclerosis likely play a key role [38]. Kidney interstitial fibrosis might be another mechanism in the setting of increased expression of matrix metalloproteinases [39, 40]. Furthermore, patients with ADPKD and late-onset kidney failure have increased vascular sclerosis, resulting in suboptimal vascularization of the kidney parenchyma [41, 42]. In our study, Ht-total parenchymal volume correlated negatively with age in both early CKD and at time of kidney failure. These findings further support the existing hypothesis on differential pathogenetic mechanisms by age, as vascular disease becomes more prevalent in elder patients [23, 38, 43–46].

Spearman correlations between HtTKV and other imaging biomarkers are informative as they capture the strength of rank-based, non-linear relationships. Ht-total cyst volume and HtTKV correlated strongly in our study, which is consistent with CRISP-I study (241 patients aged 15–46 years and creatinine clearance >70 mL/min/1.73 m^2) [19]. Increase in total cystic volume is the main driver of kidney growth [47, 48]. Imaging biomarkers that have weaker correlation with HtTKV are also of interest as they could add granularity in stratifying patients. In our study, TCN, cyst index and parenchymal index at kidney failure had low correlation with HtTKV, suggesting that these biomarkers might add complementary information to HtTKV. Interestingly, in early PKD, the correlation between TCN (R = 0.8), cyst index (R = 0.88) and parenchymal index (R = –0.88) was much higher as compared with at the time of kidney failure (R = 0.39, R = 0.53 and R = –0.53, respectively). In a recent study, we explored the utility of TCN among others using data from the CRISP study [49]. Similarly, TCN showed a low correlation with HtTKV and superior prediction of the change in future GFR compared with TKV [49]. Higher cyst number at young age predisposes to rapidly progressive ADPKD [48, 50]. In our study, cyst and parenchymal index are two imaging biomarkers at kidney failure that showed weak correlation with HtTKV. At time of kidney failure, they were comparable across all age groups and MIC. Moreover, the inter-individual variability within the cyst index was low as compared with HtTKV and Ht-total cyst volume. In both groups, cyst and parenchymal index did not correlate with age. These findings provide the basis to explore this promising imaging biomarker in larger cohorts across the various CKD stages.

Other imaging biomarkers detailing cyst characteristics were explored. Cyst surface area and cyst parenchymal surface area correlated strongly with HtTKV but were similar across age groups at time of kidney failure. These biomarkers have shown utility in improving GFR predictions in a recent study [49]. As enlarging cysts exert more stress on the surrounding parenchyma, cystogenesis is potentiated and the cystic surface areas vastly increase towards kidney failure [51]. These cystic surface areas allow an objective measure of cyst expansion. Characterizing the longitudinal progression of these advanced imaging biomarkers

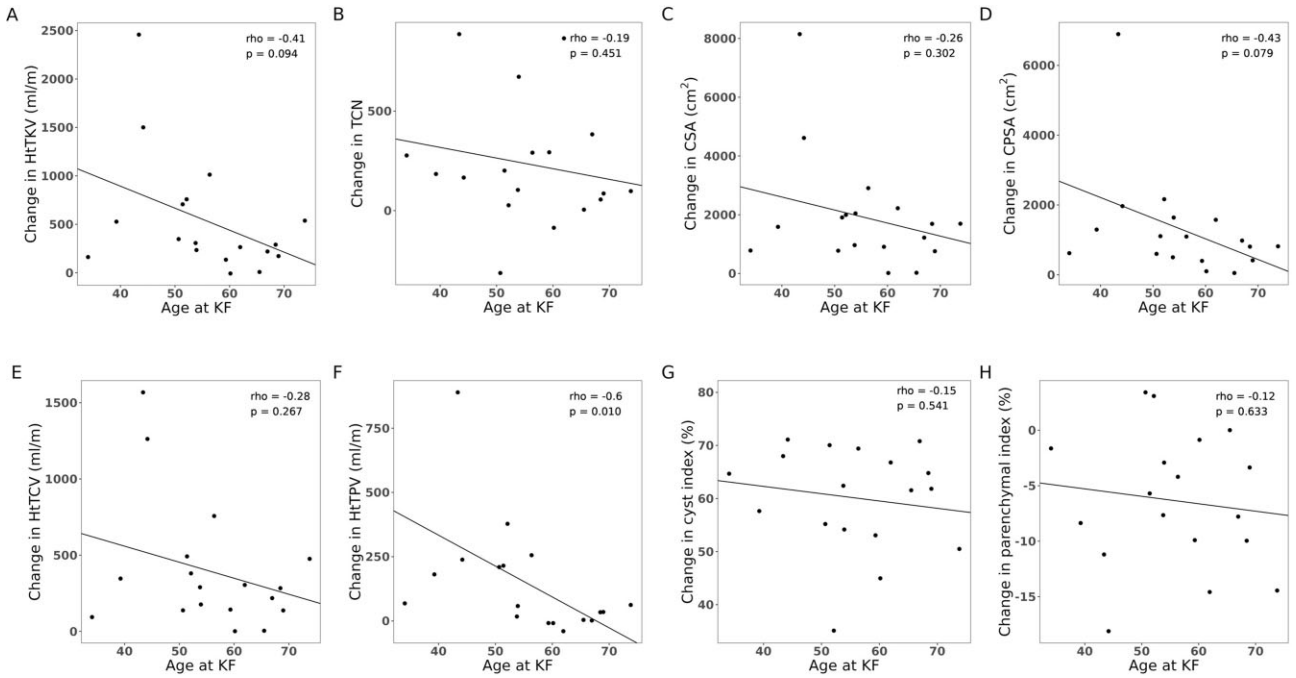


Figure 4: Spearman rank correlation between the annual changes in imaging biomarkers and age at kidney failure. Interpolated lines are based on Spearman correlation as opposed to a direct linear regression.

provides insight into the driving force of renal function decline which may be different in early and severe disease as compared with late and mild disease. Our study showed that the main driver of TKV growth is cystic volume growth from both increase in number of cysts detectable by MRI and growth of preexisting cysts. The parenchymal index declined with time. Furthermore, the growth rate of the parenchyma (Ht-total parenchymal volume) was much lower in patients who reached kidney failure at older age, consistent with the hypothesis of pronounced parenchymal atrophy with aging. Another interesting finding is the lower adjusted BMI in patients reaching kidney failure at older age, demonstrating again the importance of nutrition and obesity in modulating APDKD [27]. This study is the first to assess newly developed imaging cystic parameters in patients with kidney failure, with the aim of improving the accuracy of future predictive models in ADPKD. The biomarkers identified in this study hold great promise, and it is prudent to investigate them further in larger cohorts across all CKD stages, including both slowly progressive typical ADPKD (MIC-1A and -1B) and atypical ADPKD (MIC-2). The heterogeneity and baseline variability among patient groups may present challenges in clinical trials despite promising results in mouse models. Therefore, further research is required to address these issues and ultimately improve outcomes for patients with ADPKD.

This study has been designed as a pilot study to explore the wealth of information that a cyst segmentation tool can offer and to investigate the relevance of these new imaging biomarkers in understanding the pathogenesis of ADPKD. While the small size of the cohort limits the generalizability of the results, it highlights the need for larger confirmatory cohort studies. All patients in this cohort are white, therefore the applicability of this study's results to other ethnic and racial groups may be limited. Although a referral bias could be present given that Mayo Clinic is a tertiary center, almost two-thirds of the patients are from Minnesota and surrounding states. The cohort is representative of the general ADPKD population except for the race limitation.

In conclusion, we evaluated advanced imaging biomarkers at the time of kidney failure, using an automated instance cyst segmentation tool. Parenchymal volume and its rate of growth decreases with age, possibly accounting for the previously reported observation of lower TKV at kidney failure in older patients. Our results further support the hypothesis that cyst growth is the predominant pathogenic mechanism in younger patients with kidney failure, whereas parenchymal atrophy likely becomes more important as patients age [20]. This technical advancement of automated segmentation provides additional biomarkers that could complement TKV, the hallmark of ADPKD progression, in enhancing prognostication. Furthermore, each biomarker may provide specific insight into the pathogenesis of ADPKD and offer new opportunities to discover mechanism-specific biomarkers paving the way for studying these biomarkers as potential endpoints in future clinical trials. Additional studies will be needed to validate the predictive power of these novel biomarkers.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

We acknowledge all caregivers who previously collected the MRI scans and blood samples, allowing us to conduct genetical and imaging analysis.

FUNDING

We received no funding for conducting this study.

CONFLICT OF INTEREST STATEMENT

V.E.T. receives grants for preclinical research and clinical trials from Palladio Biosciences, Mironid, Blueprint Medicines, Tribune, Sanofi, and Reata and Regulus. He reports consultancy agreements with uResearch Technology and MFMER for imaging analytics for PCKD and repurposing of probenecid to treat PCKD. He reports royalties for system and method of classifying ADPKD. He is a member of the International Society of Nephrology Kaplan award committee, the *American Society of Nephrology* editorial board and the PKD Foundation advisory board. P.C.H. reports receiving grants and/or research reagents from Amgen, Inc., Bayer AG, Genzyme Corporation, GlaxoSmithKline, Mitobridge Inc., Otsuka Pharmaceuticals, Palladio Biosciences, Regulus Therapeutics and Vertex Pharmaceuticals, all outside of the submitted work. P.C.H. also reports a position on the Clinical Advisory Board of Mironid, honoraria from Otsuka Pharmaceuticals and Vertex Pharmaceuticals, and other fees from Otsuka Pharmaceuticals. F.T.C. receives research funding from Natera Inc. and Otsuka Pharmaceuticals. He is Chair of the educational advisory panel at the PKD foundation in the USA. All others authors declared no conflict of interest.

AUTHORS' CONTRIBUTIONS

F.T.C., V.E.T., P.C.H. and T.L.K. designed the study. S.W., M.C., A.V.G., H.-D.N.K., S.R.S. and S.S. were involved in data acquisition and analysis. A.V.G and T.L.K. optimized the segmentation algorithm and ran all cyst segmentations. B.H.S. performed all the statistical analyses. S.W. and I.-A.I. interpreted the data and wrote the manuscript. F.T.C. and C.H. critically revised all the manuscript drafts and provided further intellectual contribution. All authors read and approved the final article.

DATA AVAILABILITY STATEMENT

The data underlying this article can be shared on reasonable request to the corresponding author.

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