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Spleen phenotype in autosomal dominant polycystic kidney disease

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AIM: To evaluate splenic phenotype in autosomal dominant polycystic kidney disease (ADPKD) including presence of cysts and splenomegaly to determine if these are ADPKD related or represent unrelated incidental findings.

MATERIALS AND METHODS: The axial/coronal T2-weighted images of ADPKD patients (n=215) and age/gender-matched controls (n=215) were evaluated for the presence of T2-bright splenic lesions by three blinded observers. Spleen volume (SV) was evaluated in the context of clinical and imaging features as well as results of gene testing for *PKD1* and *PKD2* mutations.

RESULTS: T2-bright splenic lesions were found in 16 of 215 (7%) ADPKD patients compared to 11 of 215 (5%) control patients (p=0.32) and their prevalence was similar in patients with either *PKD1* or *PKD2* mutations. Median SV was significantly higher in ADPKD patients than controls (236 [182; 313 ml] versus 176 [129; 264 ml], p<0.0001). In multivariable analysis, height-adjusted SV (htSV) was not associated with the presence of liver cysts, haemorrhagic cysts, or infections; however, htSV was directly associated with height-adjusted total kidney volume (htTKV), a biomarker for ADPKD disease severity.

CONCLUSIONS: The prevalence of T2-bright splenic lesions is similar in ADPKD patients and non-ADPKD controls, suggesting no relation to the diagnosis of ADPKD; however, splenic enlargement in ADPKD compared to controls could not be explained by liver cystic involvement, by infection/inflammatory conditions, or by haemorrhagic renal cysts. This combined with direct correlation of htSV with htTKV, a biomarker of ADPKD severity, suggests splenomegaly may be related to the pathogenesis of ADPKD.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, affecting approximately 12 million patients worldwide and 1:1,000

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individuals in the United States.[1,2] ADPKD is caused by mutations in *PKD1* or *PKD2*[3,4]; however, in 10–20% a pathogenic *PKD1/2* mutation is not identified,[5–8] and ADPKD is increasingly found to be caused by mutations in other genes.[9] In addition to chronic kidney disease (CKD), ADPKD is also associated with extra-renal features, such as cysts in the liver, pancreas, seminal vesicles, prostate, arachnoid space, and with intracranial aneurysms.[10–13] The spleen in ADPKD patients appears larger than in patients who do not have ADPKD. Splenic cysts occurring in ADPKD have been identified at computed tomography (CT) and by non-contrast T2-weighted magnetic resonance imaging (MRI)[14–16]; however, the prevalence of these T2-bright splenic lesions, e.g., cysts, in ADPKD has not been systematically compared to a control population without ADPKD.

The aim of the present study was to characterise the spleen in ADPKD, comparing prevalence of T2-bright lesions and spleen volume to age/gender-matched control patients without ADPKD, and to determine whether there are associations with other features of ADPKD, including *PKD1* and *PKD2* gene mutations and known causes of splenomegaly.

Materials and methods

Patients

This study was approved by the Institutional Review Board (IRB) at Weill Cornell Medicine, and written informed consent was obtained from all ADPKD patients. Participants were recruited from the Rogosin Institute Polycystic Kidney Disease Repository, which is an ongoing, prospective, longitudinal study of ADPKD patients' genetic and phenotype characteristics. All patients met the diagnostic criteria for ADPKD,[2,17,18] had at least one abdominal MRI examination, and had PKD gene mutation analysis (Fig 1). Data regarding demographic, clinical, radiological, and gene mutation analysis were collected as part of the research protocol. All patients were invited to undergo biennial MRI protocol of the abdomen.

An age/gender-matched control group was selected from the radiology picture archiving and communication system (PACS), comprising patients who had undergone abdominal MRI, but did not have ADPKD or hepatic disease. The selection of controls was approved by the IRB and compliant with Health Insurance Portability and Accountability Act; the requirement for informed consent was waived by the IRB. Data were obtained from the electronic medical record regarding patients medical history including the number of documented infections as well as chemistry and haematology laboratory values.

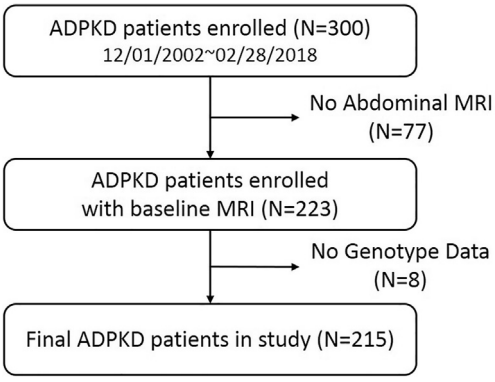

Figure 1 Flowchart showing patient recruitment.

Imaging protocol

All ADPKD patients underwent a standardised imaging protocol at 1.5 T (Signa Excite 12.0–15.0; General Electric, Waukesha, WI, USA) using a body phased-array coil. T2-weighted coronal and axial single shot fast spin echo (SSFSE) acquired with standard imaging parameters as follows: echo time (TE) = 89–185 ms, section thickness = 6–8 mm, matrix = 192–256×256. Additional sequences that were not part of this retrospective evaluation included axial liver accelerated volume acquisition (LAVA; a T1-weighted fat-suppressed three-dimensional [3D] acquisition), diffusion-weighted imaging with b-values of 50 and 800, and two-dimensional (2D) cine phase-contrast renal magnetic resonance angiography.

Image analysis

Abdominal MRI was reviewed independently by three radiologists (MRP, WZ and XY) with 25, 10, and 10 years of experience reading abdominal MRI, respectively. These observers were blinded to the clinical, laboratory, and PKD gene characteristics. Differences in reporting were resolved in consensus on repeat image review. All T2-bright splenic lesions were noted and measured on axial and coronal SSFSE T2-weighted images for every available scan using electronic callipers. A minimum threshold diameter of 2 mm was used for identification of splenic lesions, measuring maximum diameter from inner wall to inner wall with electronic callipers. Where available, contrast-enhanced MRI and CT studies were reviewed to determine if enhancement of T2-bright splenic lesions occurred.

Spleen and kidney volumes were measured on a computer workstation (Advantage Windows 4.3, GE Healthcare) by manually contouring the outer organ boundary on every section of the axial SSFSE acquisition. Splenic fusion anomalies, including splenules and clefts, were noted; clefts were stratified as <1 or ≥ 1 cm. To assess involvement of the liver with ADPKD, up to 10 liver cysts were counted on SSFSE T2-weighted images and grouped as no liver cysts, 1–10 liver cysts or >10 liver cysts.

The effect of dialysis and renal transplantation on spleen volume was determined by identifying ADPKD patients who had measurements of spleen volume available both prior to and after initiating dialysis or undergoing renal transplantation.

Statistical analysis

Interobserver reliability was measured using the kappa statistic for presence of splenic cysts and using interclass correlation coefficient for measurements of spleen volume.

Normality was assessed with the Shapiro–Wilk test. Normally distributed variables were reported as the mean ± standard deviation; non-parametric variables were reported as median (interquartile range). Fisher's exact test was used to assess the association between discrete variables of interest and occurrence of splenic cysts. The *t*-test was used to assess the difference in mean splenic volume between ADPKD cases and age- and gender-matched controls. Spearman's correlation was used to explore bivariate associations between spleen volume and various continuous variables of interest. A multivariate linear regression model was used to assess the independent effect of ADPKD on htSV, controlling for potential confounding variables. Patients with missing data were excluded from the multivariate analysis. Additional multivariate linear regression models were used to assess for the effect of *PKD* gene mutation type on height adjusted spleen volume. Analyses were performed in R Version 3.3.1 (R Core Team, Vienna, Austria). To correct for the effect of spleen volumes being larger with ADPKD compared to controls, an incidence rate ratio was calculated comparing the prevalence of splenic cysts per millilitre of spleen.

Results

Demographic characteristics of 215 ADPKD and 215 age/gender-matched control patients are shown in Table 1. MRI indications for control patients included tumour/mass (*n*=68, 32%), inflammatory bowel disease (*n*=62, 29%), pain (*n*=33, 15%), pancreatic cyst (*n*=13, 6%), gallbladder polyp (*n*=4, 2%), cholecystitis (*n*=5, 2%), pancreatitis (*n*=10, 4.5%), fistula/abscess (*n*=10, 4.5%), appendicitis (*n*=6, 3%), haematuria (*n*=3, 1.5%), and vascular disease (*n*=1, 0.5%). In four control patients, height was not available, and in 17 control patients, serum creatinine and other laboratory data were not available. The ADPKD and control populations had no significant differences in height, weight, body mass index, alanine aminotransferase, or alkaline phosphatase levels. There were small, but statistically significant, differences in serum albumin and aspartate transaminase, which did not appear to be clinically important. Although no control patients had liver disease, a slightly higher total bilirubin in controls was skewed by one spurious case of haematoma with transiently elevated bilirubin to 6.2 mg/dl.

Table 1
Comparison of demographic and splenic features.

Parameter	ADPKD (*n*=215)	Control (*n*=215)	*p*-Value
Age (years) mean± SD	48 ±14	48 ±14	0.93
median (IQR)	48 (37; 58)	49 (37; 58)	
Sex			1
Male	103 (48%)	103 (48%)	
Female	112 (52%)	112 (52%)	
Weight (kg)	78 +18	75 + 20	0.13
Height (m)	170 (162; 178)	169 (162; 176)	0.08
Body mass index (kg/m^2)	25 (23; 29)	25 (22; 29)	0.19
Total kidney volume (TKV) (ml)	1367 (295; 9364)	329 (78; 691)	<0.001
Height adjusted TKV (ml/m)	837 (161; 4867)	190 (47; 400)	<0.001
eGFR (ml/min/1.73m^2)	62 (40–83)	83 (69; 100)	<0.001
Presence of T2 bright spleen lesions			0.32
Yes	16 (7%)	11 (5%)	
No	199 (93%)	204 (95%)	
Number with spleen lesions			0.37
0 T2 bright lesions	199	204	
1 T2 bright lesions	13	7	
2 or more T2 bright lesions[b]	3	4	
Spleen volume (ml)	236 (182; 313)	176 (129; 264)	<0.001
Height adjusted spleen volume (ml/m)	138 (108; 186)	108 (81; 148)	<0.001
Spleen volume excluding dialysis and transplantation (ml)	232 (56; 746)	176 (50; 678)	<0.001
Spleen growth rate (ml/year)[a]	−0.4±18	−7.6±32	0.08
Splenules	12	10	0.84
Large splenic cleft ≥ 1cm	21	9	0.02
Small splenic cleft < 1cm	79	40	<0.001
Total number of liver cysts	70 (9; 180)	0 (0; 0)	<.001
Liver cyst fraction	1.98 (0.13; 16.8)	0 (0; 0)	<.001
Total bilirubin	0.6 (0.4; 0.7)	0.7 (0.5; 0.9)	0.01
Albumin	4.4 (4.2; 4.5)	4.1 (3.7; 4.3)	<.001
AST	23 (20; 27)	21.5 (18; 28)	0.017
ALT	20 (16; 27)	20.5 (16; 28)	0.86
Alkaline phosphate	63 (51; 78)	62 (53; 77)	0.82

TKV, total kidney volume.
[a] 133 ADPKD and 70 control patients were included in the estimation of spleen growth rate.
[b] The most T2 bright lesions in a patient was 4.

Splenic lesions

Interobserver agreement for detection of splenic T2 bright lesions was good (kappa=0.7, $p<0.001$). T2-bright splenic lesions >2 mm were identified in 16 of 215 (7%) ADPKD patients (Table 1; Fig 2). In four of these patients, contrast-enhanced MRI ($n=2$) or CT ($n=2$) were available showing that the splenic lesion had no enhancement in two patients, consistent with a simple cyst. A third patient had a typical splenic haemangioma enhancement pattern and the fourth patient had a lesion that was too small to determine enhancement. The prevalence of splenic lesions in ADPKD patients was not different from controls, (7% versus 5%, 11/215, $p=0.32$).

To correct for differences in spleen volume between ADPKD and controls, the incidence of T2-bright splenic lesion per millilitre of spleen was calculated giving an incidence rate ratio of 1.1 ($p=0.75$) further demonstrating no significant difference in splenic T2-bright lesions between ADPKD patients and controls. In five control patients, contrast-enhanced examinations were available to further characterise their splenic lesions: four had non-enhancing simple cysts and, in the fifth control patient, the splenic lesions were enhancing, indicating they were not cysts. On follow-up, these enhancing lesions showed no growth in over 3 years and were felt likely to be haemangiomas.

Among ADPKD patients, the median splenic lesion diameter was 5 mm (interquartile range = 4–8 mm) compared to 6 mm (4–8 mm) in control patients ($p=0.42$). Splenic T2-bright lesions were solitary in 13/16 (81%) ADPKD patients and 7/11 (63%) controls ($p=0.32$; Table 1).

PKD gene mutation testing identified pathogenic mutations in either *PKD1* ($n=139$) or *PKD2* ($n=39$) in 178 of the 215 ADPKD patients (83%). The prevalence of splenic T2 bright lesions was similar in those with *PKD1* or *PKD2* mutations (Table 2).

Follow-up imaging was available for 12 ADPKD patients with T2-bright splenic lesions; the mean follow-up duration was 4.4 years. Seven controls with T2-bright splenic lesions had a mean follow-up duration of 2.6 years. The average rate of splenic lesion growth was 0.4 mm/year in ADPKD patients and 0.6 mm/year in controls (Fig 3a and b), excluding one 25 mm outlier cyst that disappeared on follow-up.

Spleen volume

Interobserver agreement in the measurement of spleen volume was high (ICC 0.96). Spleen volume correlated with spleen length for both ADPKD and control patients ($r = 0.73$, $p<0.0001$). The difference in the relationship of spleen length and volume was assessed between ADPKD and control patients by entering the interaction term into the regression analysis (Fig 4). There was no significant interaction effect ($p=0.147$).

Median htSV was 28% larger in ADPKD compared to the control group ($p<0.001$; Table 1). A htSV histogram (Fig 5) for ADPKD and control patients shows that the these two populations have similar distributions of htSV with a shift of the ADPKD curve to larger volumes. This indicates that the larger htSV in ADPKD compared to controls was not skewed by outliers, but rather was affecting the entire ADPKD population. Bivariate analysis (Table 3) applied to ADPKD and control patients showed that spleen volume directly correlated with younger age ($r = -0.28$, $p<0.0001$; see also Fig 6), height (0.47, $p<0.0001$), weight (0.49, $p<0.0001$), htTKV volume (0.21, $p < 0.001$), and liver parenchymal volume (0.51, $p<0.0001$). Furthermore, spleen volume was directly correlated with red blood cell count and haemoglobin level, and was inversely correlated with platelet count (Table 3). Documented infections/inflammatory conditions and the number of haemorrhagic cysts did not correlate with htSV indicating the splenomegaly in ADPKD was not likely due to infections or haemorrhagic cysts.

A multivariate linear regression model, which included ADPKD patients and controls, confirmed that ADPKD was associated with a larger htSV (Table 4). Moreover, larger

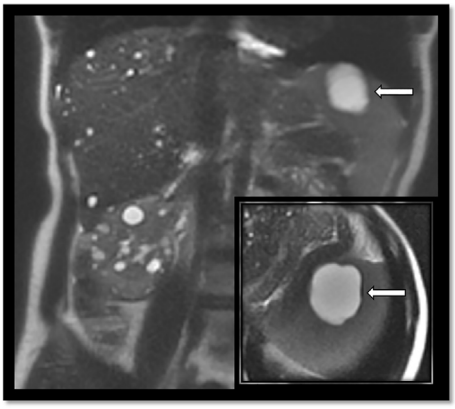

Figure 2 A 32-year-old woman with ADPKD (PKD 1 mutation). Coronal T2-weighted image shows a 44 mm spleen cyst (white arrow). Axial T2-weighted image (inset) confirms that it is arising within the spleen.

Table 2
Prevalence of spleen cysts according to PKD gene mutation.

Parameter	*PKD 1* ($n=139$)	*PKD2* ($n=39$)	*p*-Value
Age (years), mean± SD	45±13	53±13	0.002
Median (IQR)	45 (27; 64)	52 (18; 62)	
Sex: female	77 (55%)	19 (49%)	0.46
Race: white	91%	86%	0.28
eGFR	61 ±30	66 ± 25	0.36
Spleen lesion	7 (5%)	4 (10%)	0.23
No spleen lesion	132 (95%)	35 (90%)	
No. of spleen lesions			
0 cysts	132 (95%)	35 (90%)	
1 cyst	4 (3%)	4 (10%)	
2–10 cysts	3 (2%)	0	
Spleen volume (ml)	245 (56; 747)	203 (56; 457)	0.02
Height adjusted spleen volume	139 (35; 431)	123 (36; 268)	0.014
Spleen growth rate (ml/year)	2.2±17	−3.9±18	0.1
Height adjusted TKV	189 (47; 400)	188 (130; 306)	0.386

TKV, total kidney volume.

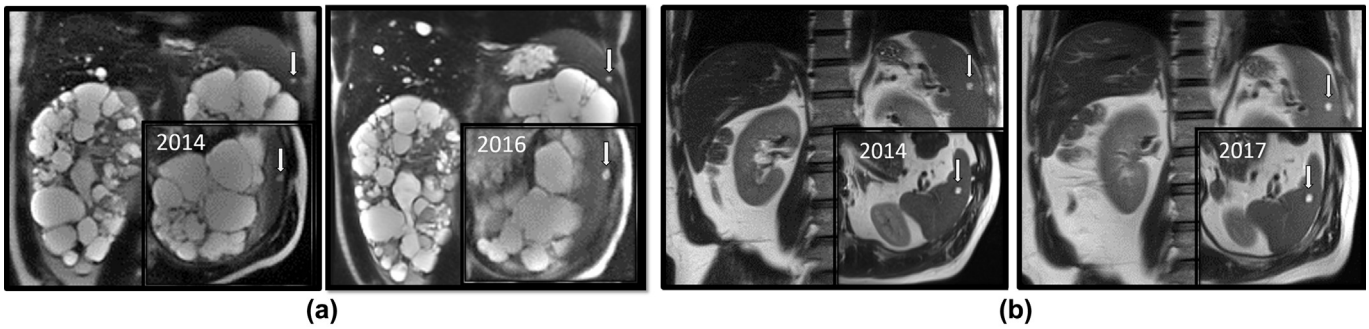

Figure 3 (a) Coronal and (insert) axial SSFSE T2-weighted images of a 39-year-old man with ADPKD in 2014 (left) and 2016 (right) show a splenic cyst measuring 6.7 mm, which increased to 8.3 mm after 2 years. (b) Coronal and (insert) axial SSFSE T2-weighted images of a 61-year-old man from the control group in 2014 (left) and 2017 (right) show a splenic cyst measuring 6.5 mm, which increased to 8.4 mm after 3 years.

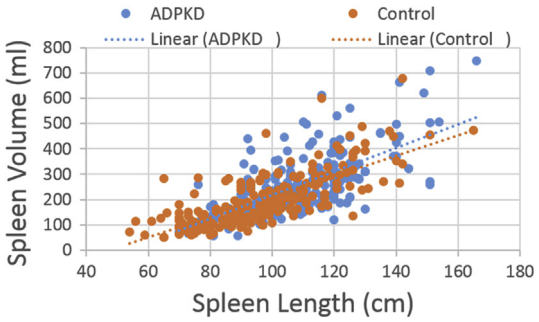

Figure 4 Graph of spleen volume versus spleen length for ADPKD (blue dots) and control patients (orange dots) patients showing a linear correlation. For controls the spleen volume = 4×spleen length (in cm) −192 ml (r=0.75). For ADPKD patients, spleen volume = 4.7×spleen length (in cm) −248 ml (r=0.66); p=0.147.

htSV was associated with younger age, greater htTKV, fewer liver cysts, lower platelet count, and lower serum albumin.

PKD1 gene mutation was associated with a larger htSV compared to patients with *PKD2* mutations in the bivariate analysis (p=0.012), but this was not confirmed by a multivariate analysis model in ADPKD patients. No significant difference in htSV was found between truncating and non-truncating mutations in either *PKD1* or *PKD2*.

Follow-up imaging was available in 133 ADPKD patients and in 70 controls to assess for changes in spleen volume over time. Both populations showed a reduction in spleen volume over time and there was a trend toward greater reduction in spleen volume in control patients over time (−7.6±32 ml/year compared to ADPKD −0.4±18 ml/year; p=0.08).

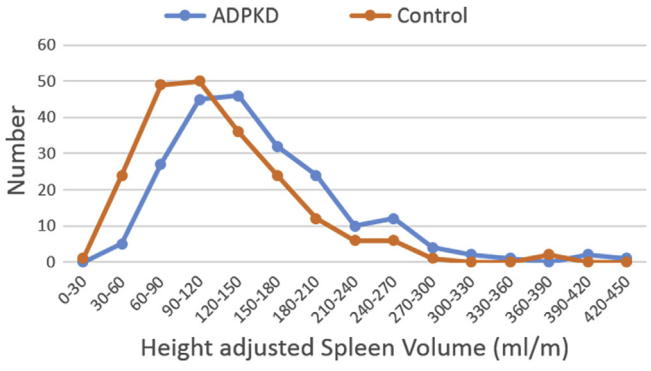

Figure 5 Histogram of height adjusted spleen volume for ADPKD (blue) and control (orange) patients showing similar skewed histograms. The relative shift toward larger height adjusted spleen volumes for ADPKD indicates the difference in mean/median volumes is not due to a few outlier patients or a sub-population but rather something that affects all ADPKD patients.

Effect of dialysis and renal transplantation on spleen volume

In 15 ADPKD patients who progressed to end-stage renal disease (ESRD), MRI data were available before and after treatment initiation of either dialysis (n=6) or transplantation (n=9). There was a 28% increase in spleen volume (198±114 to 253±121 ml; p=0.05) after initiating dialysis. There was a trend toward increased in spleen volume from 328 to 380 ml after kidney transplantation, which was not statistically significant (p=0.1).

Spleen fusion anomalies

Spleen clefts were more prevalent and larger in ADPKD patients than controls (Table 1; Fig 7a and b). Splenules occurred with similar prevalence in ADPKD and control groups.

Discussion

ADPKD primarily affects kidney structure and function, but also commonly has extra-renal manifestations that involve the liver, pancreas, and other organs.[10–13,19–21] ADPKD was previously reported to cause cysts in the spleen.[11] These data from 215 ADPKD patients show the prevalence of T2 bright lesions, cyst-like, in the spleen was similar to an age/gender-matched control group without ADPKD. Although there was no difference in T2-bright splenic lesions regardless of the *PKD1* or *PKD2* mutation locus, spleens were 28% larger in ADPKD with more and larger clefts compared to controls.

Table 3
Bivariate correlations with spleen volume and height-adjusted spleen volume for both ADPKD and control patients.

Continuous variables (Spearman)	Spleen volume		Height adjusted spleen volume	
	Correlation coefficient	*p*-Value	Correlation coefficient	*p*-Value
Height	0.47	<0.0001	N/A	N/A
Weight	0.49	<0.0001	0.4	<0.0001
Age	−0.28	<0.0001	−0.2	<0.0001
Inflammatory conditions	0.06	0.10	0.13	0.13
Liver cyst fraction	−0.12	0.087	0.09	0.08
Liver cyst volume	−0.09	0.205	−0.07	0.307
Largest liver cyst	−0.13	0.057	−0.14	0.048
Number of liver cysts	0.04	0.58	0.16	0.493
Total liver volume	0.35	<0.0001	0.17	0.012
Liver parenchymal volume	0.51	<0.0001	0.43	<0.001
Bilirubin	0.01	0.904	0.06	0.255
Albumin	0.08	0.224	0.09	0.077
Alkaline phosphatase	−0.02	0.777	0.05	0.29
AST (aminotransferase)	−0.04	0.586	−0.04	0.389
ALT (alanine aminotransferase)	0.12	0.085	0.02	0.699
Total kidney volume (TKV)	0.18	0.01	0.21	<0.001
Height adjusted TKV	0.21	<0.001	0.19	<0.001
Kidney cyst fraction	0.01	0.923	0.02	0.862
Haemorrhagic renal cysts	0.07	0.30	0.07	0.28
Creatinine	0.11	0.121	0.11	0.021
Glomerular filtration rate	0.06	0.397	−0.02	0.639
Haemoglobin	0.23	0.0006	0.21	0.003
Red blood cell count	0.22	0.001	0.19	0.004
White blood cell count	−0.06	0.391	−0.08	0.254
Platelets ($\times 10^3/\mu l$)	−0.36	<0.0001	−0.23	<0.0001
Spleen growth rate (ml/year)	−0.12	0.082	−0.2	0.002

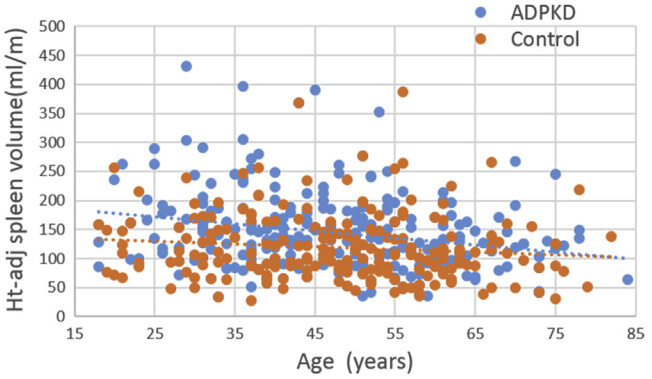

Figure 6 Graph of height adjusted spleen volume (ml/m) versus Age (years) for ADPKD (blue dots) and control patients (orange dots) showing spleen volume decreases with age for both groups. For control patients, the height adjusted spleen volume = 142 ml−0.5 × age (in years) (R^2 = 0.013). For ADPKD patients, height adjusted spleen volume = 214 ml−1.3 × age (in years) (R^2 = 0.086). For all patients combined together, height adjusted spleen volume = 178 ml−0.9 × age (in years) (R^2 = 0.04).

In previous studies of adult ADPKD patients, a splenic cyst prevalence of 6.7% was found using CT imaging, and a prevalence of 2.6% was identified using coronal MRI.[14,16] These prior reports are similar to the present prevalence of 7%; however, neither of the previous studies included a control group without ADPKD. An MRI study designed to determine incidental findings in healthy individuals (without ADPKD), using 10 mm thick sections, estimated the prevalence of splenic cysts/haemangiomas to be 1.4%.[22]

Table 4
Multivariate linear regression model evaluating factors that had significant correlations to height-adjusted spleen volume in the bivariate analysis.

Predictor	Estimate	Confidence interval	*p*-Value
ADPKD	65	40 to 89	<0.001
Age	−1.15	−1.6 to −0.69	<0.001
Platelets	−0.18	−0.25 to −0.11	<0.001
>10 liver cysts	−43	−66 to −19	<0.001
1–10 liver cyst	−31	−57 to −4.4	0.023
Height adjusted TKV	0.01	0.00 to 0.02	0.003
eGFR	0.03	−0.19 to 0.24	0.809
Total bilirubin	9.2	−3.5 to 22	0.156
Albumin	−14	−25 to −2.8	0.015
AST	−0.27	−0.67 to 0.13	0.183

TKV, total kidney volume.

The present control population was 12 years older and a robust SSFSE T2-weighted sequence was utilised, which is not corrupted by respiratory motion with thinner sections in both axial and coronal planes, and likely accounts for the higher (~5%) incidence of T2-bright splenic lesions observed in the present study. These non-parasitic splenic cysts are believed to only rarely result from trauma and are mostly congenital, arising from lymphatic spaces or rests of mesothelial or endodermal cells trapped within the spleen during organogenesis.[23,24]

The present observation of greater median height-adjusted spleen volume in ADPKD patients compared to controls is consistent with findings of Hogan *et al.* in the HALT study of patients with ADPKD, which also reported mild spleen enlargement.[16] In that study, larger spleen volume was associated with hepatomegaly from cystic

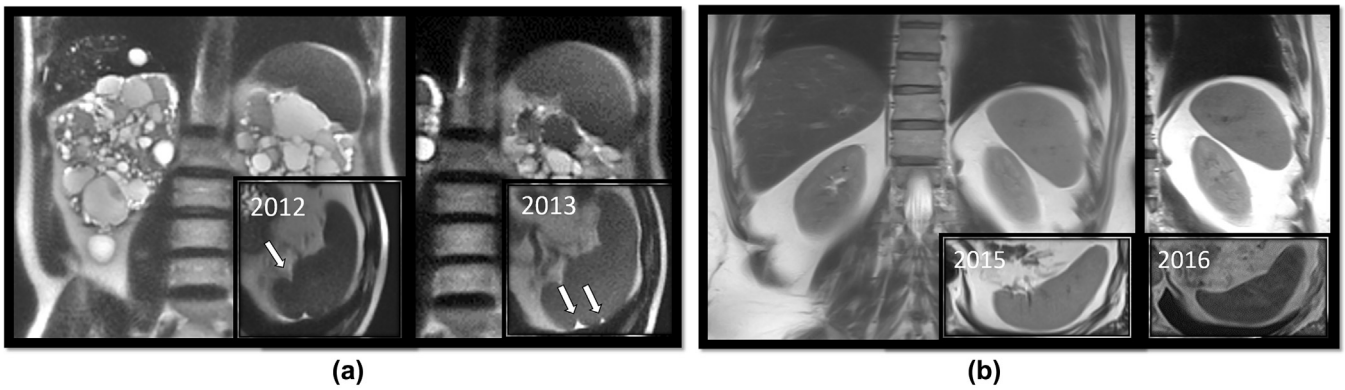

Figure 7 (a) ADPKD patient with 61ml/year spleen with more lobular shape, multiple clefts (arrows) and volume growth rate from 240 ml on 23/01/2012 (left) to 348 ml on 25/10/2013 (right) after initiating dialysis. (b) Control patient with −68 ml/year spleen volume growth rate from 280 ml on 08/07/2015 (left) to 197 ml on 22/09/2016.

involvement of the liver. Similar to Hogan *et al.*, an inverse association of spleen volume and platelet count was also found in the present study, which is consistent with their proposed mechanism of platelet sequestration in the larger spleens of patients with ADPKD. By contrast, a direct positive correlation between spleen volume and the magnitude of cystic liver changes was not found in our study indicating that the increased spleen volume was not associated with hepatomegaly from cystic liver disease. The histogram analysis suggests that the entire population of ADPKD patients had increased spleen volume not just a few outliers. Although inflammatory/infectious conditions can cause splenomegaly, no correlation with inflammatory/infectious conditions listed in the electronic medical record and htSV was found. Furthermore, there was no relationship between haemorrhagic cysts and htSV. An association of greater htTKV with htSV was identified, which may support the hypothesis that splenomegaly is directly related to the ADPKD disease process.

Interestingly, both ADPKD and controls showed decreasing spleen volume with age suggesting that the splenomegaly occurs early prior to diagnosis of ADPKD and enrolment in the study, but htSV increased in ADPKD patients after initiating dialysis[25] and, to a lesser extent, in the subset of ADPKD patients who had kidney transplantation.

There is a well-established association of *PKD* gene mutation locus and severity of chronic kidney disease. Patients with *PKD1* mutations, particularly those with truncating *PKD1* mutations, progress to ESRD at a younger age than those with a non-truncating *PKD1* mutations or a *PKD2* mutation.[26] Mutations at the *PKD1* gene locus have been associated with intracranial aneurysm[27] and seminal megavesicles,[21] whereas an association of increased prevalence of pancreatic cysts with mutations at the *PKD2* gene locus.[20] In the present study, a multivariable model identified an association of ADPKD with htSV; however, no association was found between *PKD1/2* gene loci and the presence of splenic T2 bright lesions or with spleen volume.

ADPKD is thus in the family of diseases related to ciliary dysfunction.[28,29] In this study, splenic clefts were more prevalent in the ADPKD group than in the control group. Anatomical variants of the spleen have also been reported with other ciliary dysfunction syndromes,[30,31] such as Kartagener's disease, also known as ciliary dyskinesia, which causes asplenia and polysplenia[32] and has been reported to occur in ADPKD.[33]

Strengths of this study include a large sample size, with an age/gender-matched control group. The ADPKD group was especially well characterised, including *PKD* gene mutation analysis. All of the MRI interpretations were provided by observers with extensive experience with ADPKD. Limitations of this study included the lack of contrast enhancement of protocol MRI examinations and, therefore, discrimination between cysts and other splenic lesions that can also be T2 bright could not achieved; however, the same criteria for identifying splenic cysts in the ADPKD and control populations were used. Other potentially confounding features included the lower eGFR in the ADPKD group than in the control group; however, a multivariable model found no association of eGFR with htSV in the ADPKD group.

In summary, this study found increased spleen volume in ADPKD, which was not related to cystic involvement of the liver, infectious/inflammatory conditions, or haemorrhagic cysts raising the possibility that is part of the ADPKD disease process. The data also show that T2-bright splenic lesions, which include spleen cysts, had similar prevalence in ADPKD patients and controls without ADPKD and were equally likely with *PKD1* or *PKD2* mutations indicating splenic cysts are not part of ADPKD pathogenesis. This is clinically important because identification of splenic cysts does not support a diagnosis of ADPKD. Further work is needed to investigate the extent to which spleen volume may be a biomarker for the severity and progression of ADPKD.

Conflict of interest

The authors declare no conflict of interest.

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