

Prevalence of Inferior Vena Cava Compression in ADPKD



Xiaorui Yin^{1,2}, Jon D. Blumenfeld^{3,4}, Sadjad Riyahi¹, Xianfu Luo¹, Hanna Rennert⁵, Irina Barash^{3,4} and Martin R. Prince^{1,6}

¹Department of Radiology, Weill Cornell Medicine, New York, New York, USA; ²Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ³The Rogosin Institute, New York, New York, USA; ⁴Department of Medicine, Weill Cornell Medicine, New York, New York, USA; ⁵Department of Pathology, Weill Cornell Medicine, New York, New York, USA; and ⁶Department of Radiology, Columbia College of Physicians and Surgeons, New York, New York, USA

Introduction: Kidney and liver cysts in autosomal dominant polycystic kidney disease (ADPKD) can compress the inferior vena cava (IVC), but IVC compression prevalence and its risk factors are unknown.

Methods: Patients who have ADPKD (n = 216) with abdominal magnetic resonance imaging (MRI) studies and age-/sex-matched controls (n = 216) were evaluated for IVC compression as well as azygous vein diameter (a marker of collateral blood flow) and IVC aspect ratio (left-to-right dimension divided by anterior-to-posterior dimension with a value of 1 corresponding to a circular (high pressure) IVC caudal to compression).

Results: Severe IVC compression ($\geq 70\%$) was observed in 33 (15%) ADPKD subjects and mild compression ($\geq 50\%$ to $< 70\%$) was observed in 33 (15%) subjects; whereas controls had no IVC compression ($P < 0.001$). Severe IVC compression was associated with larger azygous vein (4.0 ± 1.3 mm versus 2.3 ± 0.8 mm without IVC compression; $P < 0.001$) and a more circular IVC cross-section upstream (mean IVC aspect ratio: 1.16 ± 0.27 vs. 1.69 ± 0.67 , $P < 0.001$), suggesting higher pressure upstream from the compression. IVC compression was associated with older age, lower estimated glomerular filtration rate (eGFR), greater height-adjusted total kidney volumes, greater height-adjusted liver volume (ht-LV), and greater liver and renal cyst fractions ($P < 0.001$). No subject younger than 30 years had IVC compression, but ADPKD subjects ≥ 40 years old had 12-fold higher risk of IVC compression (95% confidence interval [CI]: 4.2–42.4), with highest predicted probability for Mayo Clinic classes 1D (59%; 95% CI: 39%–76%) and 1E (74%; 95% CI: 49%–90%) after adjustment ($P < 0.001$). Women with ht-LV ≥ 2000 ml/m had 83% (95% CI: 59%–95%) prevalence of IVC compression. Complications of IVC compression included deep vein thrombosis (DVT) and symptomatic hypotension.

Conclusions: IVC compression is common in ADPKD patients > 40 years old, with Mayo Clinic class 1D/E, and in females with ht-LV > 2000 ml/m.

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KEYWORDS: ADPKD; azygos vein; DVT; hypotension; IVC compression; Mayo Clinic Classification

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Arterial complications of ADPKD, including aneurysm and dissection^{1–9} of the intracranial arteries and thoracic aorta^{1,10–13} are well recognized. Venous complications of ADPKD are rare. But there have been case reports of IVC compression complicated by DVT, pulmonary embolism, hypotension, and hepatic venous outflow obstruction.^{14–20}

Abdominal MRI is used to measure kidney volumes in ADPKD and to assess other manifestations including liver cysts,²¹ pancreatic cysts,²² and splenomegaly.²³ In

our ADPKD repository, in which subjects are scanned biennially with noncontrast abdominal MRI, we have noticed that the IVC is well seen with high signal on MRI steady-state free precession images and as a black flow void on T2-weighted images. These images show the IVC geometry, which is normally oval, can be squeezed flat by cysts and can have a more distended, circular cross section, similar to the aorta, with increased pressure upstream from a compression. Steady-state free precession images also show the diameter of the azygous vein, an important IVC collateral vessel potentially accommodating blood that needs to bypass an IVC compression. Here, we examined MRI studies from 216 patients in this ADPKD research repository and in 216 age-/sex-matched

Correspondence: Martin R. Prince, 416 East 55th Street, New York, New York 10022, USA. E-mail: map2008@med.cornell.edu

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control patients without ADPKD to determine the prevalence of IVC compression in ADPKD, to assess for hemodynamic significance by measuring azygous vein diameter and the upstream IVC diameters, and to identify subpopulations at higher risk of IVC compression.

METHODS

Study Population

This case control study was Institutional Review Board approved. Written informed consent was obtained from all ADPKD subjects. Participants were recruited from the Polycystic Kidney Disease Repository, which is an ongoing, retrospective, longitudinal study of genetic and phenotype characteristics in ADPKD. All subjects met diagnostic criteria for ADPKD,³ had abdominal MRI, and gene mutation analysis (Figure 1).

An age- and sex-matched control group was selected from the radiology picture archiving and communication system comprising patients who had undergone abdominal MRI but did not have ADPKD. Selection of control subjects was approved by the Institutional Review Board and compliant with the Health Insurance Portability and Accountability Act; the requirement for informed consent of the control subjects was waived.

Imaging Protocol

All ADPKD subjects underwent a standardized protocol MRI at 1.5 tesla (Signa Excite 12.0-15.0; GE, Waukesha, WI) using a body phased-array coil for signal reception. T2-weighted coronal and axial single-shot fast spin echo and axial steady-state free precession acquired with standard imaging parameters (Supplementary Table S1). These basic MRI pulse

sequences were also part of the imaging protocols of control subjects.

Image Analysis

Abdominal MRIs were reviewed independently by three radiologists (MRP, XL, and XY) with 25, 10, and 10 years of experience. These observers were blinded to clinical, laboratory, and PKD gene data. Extrinsic IVC compression from renal or hepatic cysts was identified and percent area narrowing calculated: $1 - (\text{area of narrowest point}) / (\text{average of area measured above and below})$. Mid-IVC cross-sectional area at its narrowest point, as determined by coronal and axial images, was measured using an electronic polygon tool to trace the lumen perimeter. Cross-sectional areas were measured above the mid-IVC (above any narrowing) where the IVC is intrahepatic, and at the common iliac vein confluence. Criteria for the IVC narrowing classification were: "normal" if percent area narrowing $<50\%$, "mild narrowing" if $\geq 50\%$ and $<70\%$ narrowing, and "severe" if IVC percent area narrowing $\geq 70\%$. Location of the IVC compression was noted as intrahepatic when due to a hepatic cyst(s) or infrahepatic when due to compression by a renal cyst(s). Differences in reporting were resolved by consensus. One observer (MRP) evaluated IVC compression twice in 20% of ADPKD subjects after a 6-month interval to evaluate intraobserver variation. To determine the degree of IVC distension inferior to site of maximum narrowing, the long horizontal cross-sectional dimension, referred to as left-to-right and the short cross-sectional dimension referred to as anterior-to-posterior were measured to calculate the IVC aspect ratio (Supplementary Figure S1). An IVC aspect ratio $\gg 1$ indicated a flat/oval IVC as is typically seen with a normal, low pressure IVC. An IVC aspect ratio ~ 1 was interpreted to be a pressurized IVC that had become

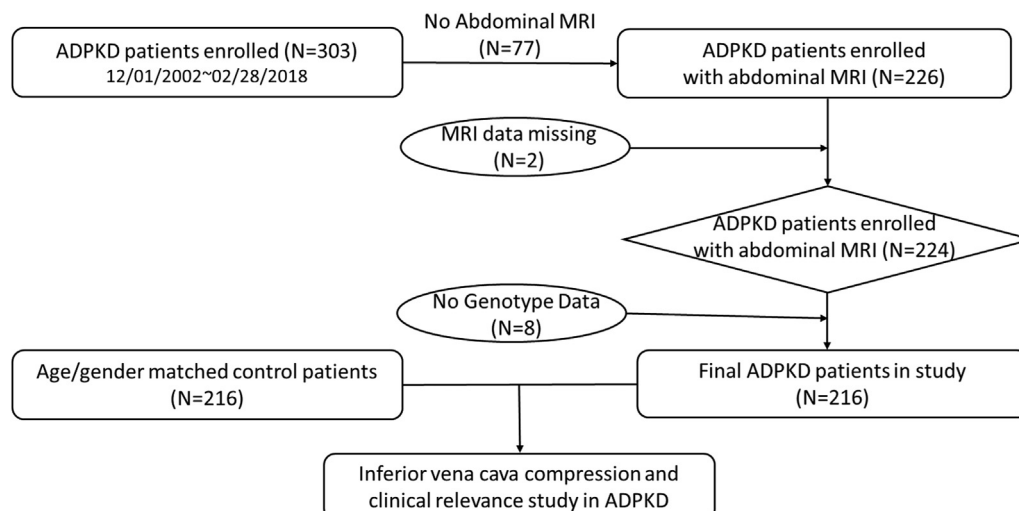


Figure 1. Patient recruitment flow chart. ADPKD, autosomal dominant polycystic kidney disease; MRI, magnetic resonance imaging.

circular to accommodate increased pressure caudad to an IVC compression. The azygous vein, a collateral for IVC stenosis, was too small to measure cross-sectional area, so its lumen diameter was determined at the level of the diaphragm.

Kidney, liver, and spleen volumes were measured by manually contouring organ outer margins to segment the kidneys from the rest of the T2-weighted imaging data. Total kidney volume (TKV) was the sum of right and left kidney volumes. Height-adjusted total kidney volume (ht-TKV) was TKV/height (ml/m). Height-adjusted liver volume (ht-LV) was liver volume/height and height-adjusted spleen volume was spleen volume/height (ml/m). Nerve root ectasia, umbilical hernia, and separation of medial edges of rectus abdominis were determined by the observers. Kidney and liver cyst fractions were estimated using thresholding on organs segmented from T2-weighted images (or using cyst diameter measurements for organs with <10 cysts) to determine cyst volume,²¹ manually adjusting as necessary to add the volume of T2 dark (hemorrhagic) cysts. Cyst volumes were then divided by organ volumes and multiplied by 100 to obtain a percent cyst fraction.

Clinical Data

Electronic medical records were reviewed for levels of serum creatinine, eGFR (ml/min per 1.73 m²), aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, albumin, proteinuria, red blood cell count, white blood cell count, platelets, age, sex, height, weight, body mass index, and any clinical evidence of DVT (e.g., lower extremity edema).

Statistical Analysis

Interobserver and intraobserver reliability was measured using Kappa for presence of IVC compression and interclass correlation coefficient for IVC measurements. Normally distributed variables were reported as the mean \pm standard deviation. Data that were not normally distributed were reported as median (interquartile range).

The χ^2 or Fisher exact test was used to assess the significance of differences in prevalence of IVC compression in ADPKD versus control subjects, and distribution of categorical variables between location (i.e., intrahepatic or renal) and severity (i.e., normal, mild, or severe) of IVC compression. A Student *t* test or analysis of variance were used to assess the significance of differences in continuous variables between ADPKD and control subjects, between ADPKD patients without or with mild and severe compression, and between different locations of IVC compression. In cases of

parametric test assumption violations, Wilcoxon rank sum or Kruskal Wallis test was applied.

Univariate logistic regression was applied to the ADPKD subjects to assess the relationship between presence of IVC compression by hepatic or renal cysts as dependent variables, and the independent variables including age, sex, body mass index, PKD genotype, ht-TKV, ht-LV, height-adjusted spleen volume, renal and hepatic cyst fraction, umbilical hernia width, liver enzymes, DVT, edema, pleural effusion, proteinuria, and free pelvic fluid. Variables were then included in the multivariate analysis based on their univariate *P* < 0.10 to assess their independent effect on the dependent variables. We used backward elimination with the Akaike information criterion as the stopping rule. Established risk factors of rapid ADPKD progression, including male sex, PKD1 genotype, and high ht-TKV, were maintained in the model as potential confounders, regardless of their significance level. To assess possible multicollinearity, the correlation of independent variables and variance inflation factor were determined. Model fits were compared based on Akaike information criterion and Nagelkerke's pseudo-R². Logarithmic transformation was used when appropriate to improve the model fit. Subjects with missing data were excluded from the multivariate analysis. Alpha level was set to 0.05 and all analyses were performed in R, version 3.3.1 (R Core Team, Vienna, Austria).

RESULTS

Demographic characteristics of 216 ADPKD and 216 age-/sex-matched control subjects are shown in Table 1. The ADPKD and control populations had no significant differences in mean height, weight, body mass index, alanine aminotransferase, or alkaline phosphatase levels. As expected, the mean liver, kidney, and spleen volumes were larger in the ADPKD than control groups and mean eGFR was lower in the ADPKD group. There were small but statistically significant differences in median serum albumin, bilirubin, and aspartate transaminase. No control subjects had ADPKD or clinical evidence of liver disease.

IVC Compression

Interobserver and intraobserver reproducibility for the detection of IVC compression was high with Kappa = 0.9 for both. Reproducibility of IVC diameter measurements was high with interclass correlation coefficient = 0.88 and 0.76 for AP and left-to-right diameters, respectively. IVC cross-sectional area measurement reproducibility was also high with interclass correlation coefficient = 0.92, 0.91, and 0.92 for the area measurements at the site of maximum narrowing as well as above and below the IVC compression.

Table 1. Demographic, clinical, and laboratory data and Prevalence of IVC compression in ADPKD and controls

Parameter	ADPKD	Control	P value
	(n = 216)	(n = 216)	
Age, yr, mean ± SD	48 ± 14	48 ± 14	1.00
Sex, n (%)			
Male	102 (47)	102 (47)	1.00
Female	114 (53)	114 (53)	
Weight, kg	78 ± 18	75 ± 20	0.13
Height, m	1.71 ± 0.11	1.69 ± 0.10	0.06
BMI, kg/m ²	26.2 ± 4.9	26.4 ± 6.6	0.68
Total kidney volume, ^a ml	1380 (728–2581)	329 (78–691)	<0.001
Height-adjusted TKV, ^a ml/m	837 (437–1496)	190 (47–400)	<0.001
Height-adjusted spleen volume, ml/m	151 ± 65	119 ± 58	<0.001
eGFR, ml/min per 1.73 m ²	61.5 ± 28.6	85.0 ± 30.9	<0.001
Presence of IVC compression	66 (31)	0 (0)	<0.001
Liver cysts, ^a n	70 (9–180)	0 (0–0) ^c	<0.001
Liver cyst fraction, ^{a,b} %	1.98 (0.13–16.8)	0 (0–0)	<0.001
Polycystic liver ^d	146 (68)	0 (0)	<0.001
Total bilirubin, ^a mg/dl	0.6 (0.4–0.7)	0.7 (0.5–0.9)	0.012
Albumin, g/dl	4.3 ± 0.28	3.8 ± 0.73	<0.001
Aspartate transaminase, ^a U/L	23 (20–27)	21 (18–28)	0.013
Alanine aminotransferase ^a	20 (16–27)	20 (16–28)	0.92
Alkaline phosphate, IU/l	66.5 ± 21.6	68.4 ± 29.1	0.46
No IVC compression (0–50%)	150 (69.9)	216 (100)	<0.001
Mild IVC compression (50%–70%)	33 (15.3)	0	<0.001
Severe compression (≥70%)	33 (15.3)	0	<0.001
IVC compression reported prospectively	2 (3)	N/A	
IVC lumen area (mm ²)			
Intrahepatic (above)	271 ± 121	313 ± 126	<0.001
Mid-IVC or site of max narrowing	136 ± 90	168 ± 80	<0.001
Iliac vein confluence (below)	264 ± 90	226 ± 79	<0.001

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; IVC, inferior vena cava; N/A, not applicable; TKV, total kidney volume.

^aNonparametric data are presented as median (IQR) and proportions as n (%).

^bCyst fraction (%) = (volume of cysts/volume of organ) × 100.

^cOnly 8 control subjects had liver cysts.

^d>20 hepatic cysts.

All normally distributed data are presented as mean ± SD.

Azygous vein diameter measurement reproducibility was excellent with interclass correlation coefficient = 0.94.

IVC narrowing ≥50% (mild and severe) due to extrinsic compression by renal or hepatic cysts was present in 31% of ADPKD subjects on their baseline scan compared to none of the control subjects ($P < 0.001$) (Table 1). In subjects with either mild or severe IVC compression, the location of the compression was most commonly infrahepatic by renal cysts (Figures 2 and 3; Supplementary Figure S2) ($n = 45$) and, less often, intrahepatic by hepatic cysts (Figure 4) ($n = 21$). Seven patients had compression at both sites.

IVC compression was associated with larger diameter azygous veins as well as a more circular appearance to the iliac vein confluence with an aspect ratio of 1.16 (vs. 1.69 in patients without compression, $P < 0.001$, suggesting increased IVC pressure caudal to the compression) (Table 2). Backward stepwise multivariate linear regression using established confounders (age, sex, ht-TKV, and eGFR) and variables found to be

significant in the univariate analysis showed a significant association of log IVC aspect ratio with azygous vein diameter in ADPKD patients after adjustment for age, sex, eGFR, log ht-TKV, and ht-LV ($P = 0.018$) (Supplementary Table S2). Patients with IVC compression also had a smaller IVC cross-sectional area cephalad to the site of compression ($P < 0.001$), and a larger IVC cross-sectional area caudad to the site of compression ($P < 0.001$) suggesting hemodynamic significance (Table 2).

Comparisons of the multiple variables in patients with and without IVC compression (Supplementary Table S3) showed significant differences in factors associated with severe kidney and liver cystic involvement. Specifically, those with IVC compression were older ($P < 0.001$), had lower eGFR ($P < 0.001$), greater ht-TKV ($P < 0.001$), greater ht-LV ($P = 0.002$), greater renal and liver cyst fractions ($P < 0.001$), and larger separation of rectus abdominis muscles ($P < 0.001$). Mayo Clinic classification²⁴ was associated with IVC compression ($P = 0.009$) (Supplementary Table S4).

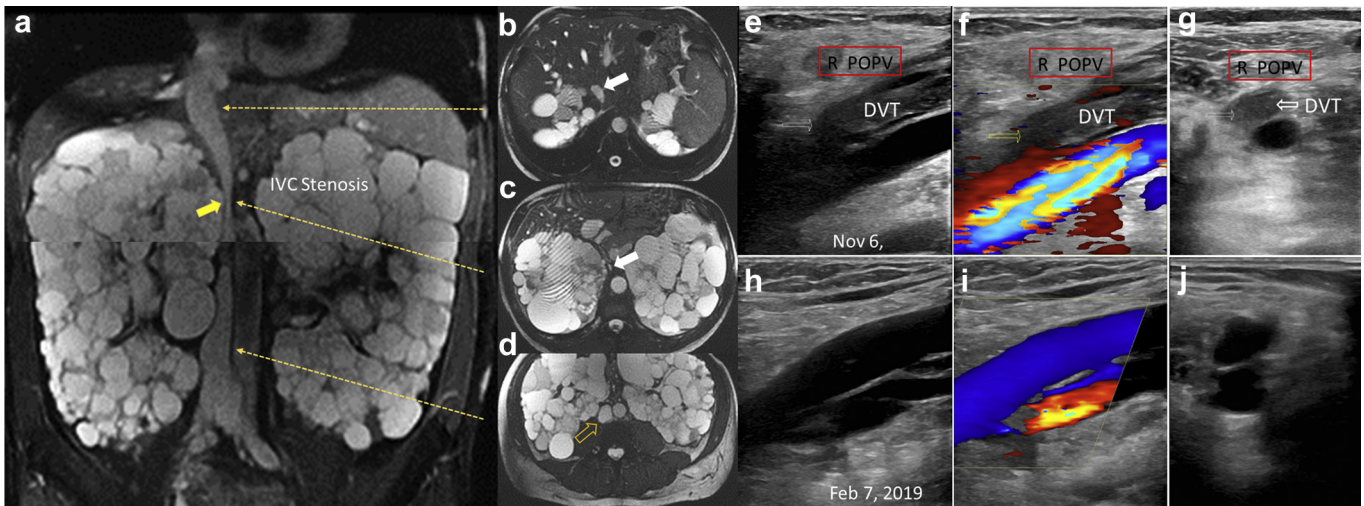


Figure 2. Patient who has autosomal dominant polycystic kidney disease (ADPKD) with renal cysts compressing inferior vena cava (IVC) and lower extremity deep venous thrombosis (DVT). (a) Coronal steady-state free precession (SSFP) shows upper pole renal cysts compressing IVC (solid yellow arrow). (b, solid white arrow) Axial SSFP shows widely patent IVC superior to level of compression. (c) Severe luminal narrowing of IVC at site of IVC compression (solid white arrow). (d) A round IVC cross section caudal to IVC compression just above iliac vein confluence (yellow open arrow). (e–g) Ultrasound in same patient shows occlusive DVT in the right popliteal vein. (h–j) After anticoagulation, normal flow and compressibility of popliteal vein is restored.

Using the age of 40 years as a threshold, IVC compression was significantly associated with age older than 40 years across different Mayo Clinic classes ($P < 0.001$)

(Table 3). The prevalence of IVC compression was 0% below the age of 30 years and plateaued after 40 years old (Supplementary Table S5). Univariate logistic

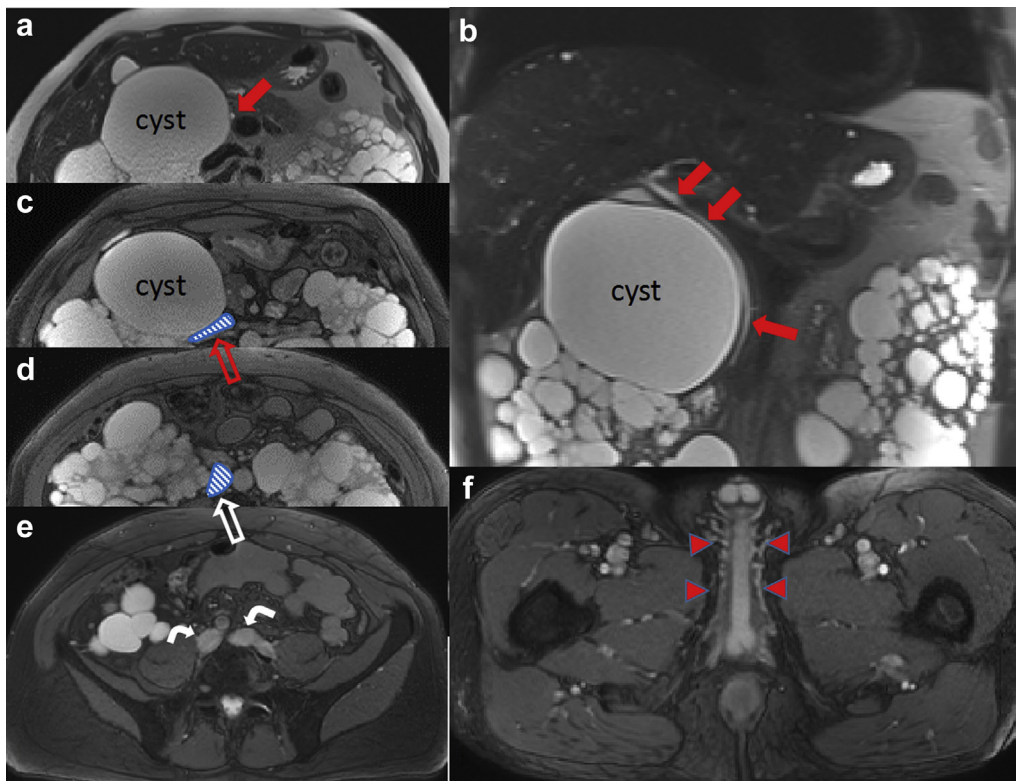


Figure 3. Right upper pole renal cyst compressing inferior vena cava (IVC) and displacing common bile duct. (a) Axial and (b) coronal T2 single-shot fast spin echo magnetic resonance images (MRIs) show right upper pole cyst in a 39-year-old male displacing the common bile duct to the left (solid red arrows). (c–e) Axial steady-state free precession (SSFP) MRIs show renal cyst compressing the IVC (open red arrow). Caudal to compression the IVC (open white arrow) and common iliac veins (curved white arrows) are dilated and there are scrotal varices (f, red arrowheads). (c,d) Cross-sectional axial images of IVC marked with blue shadow.

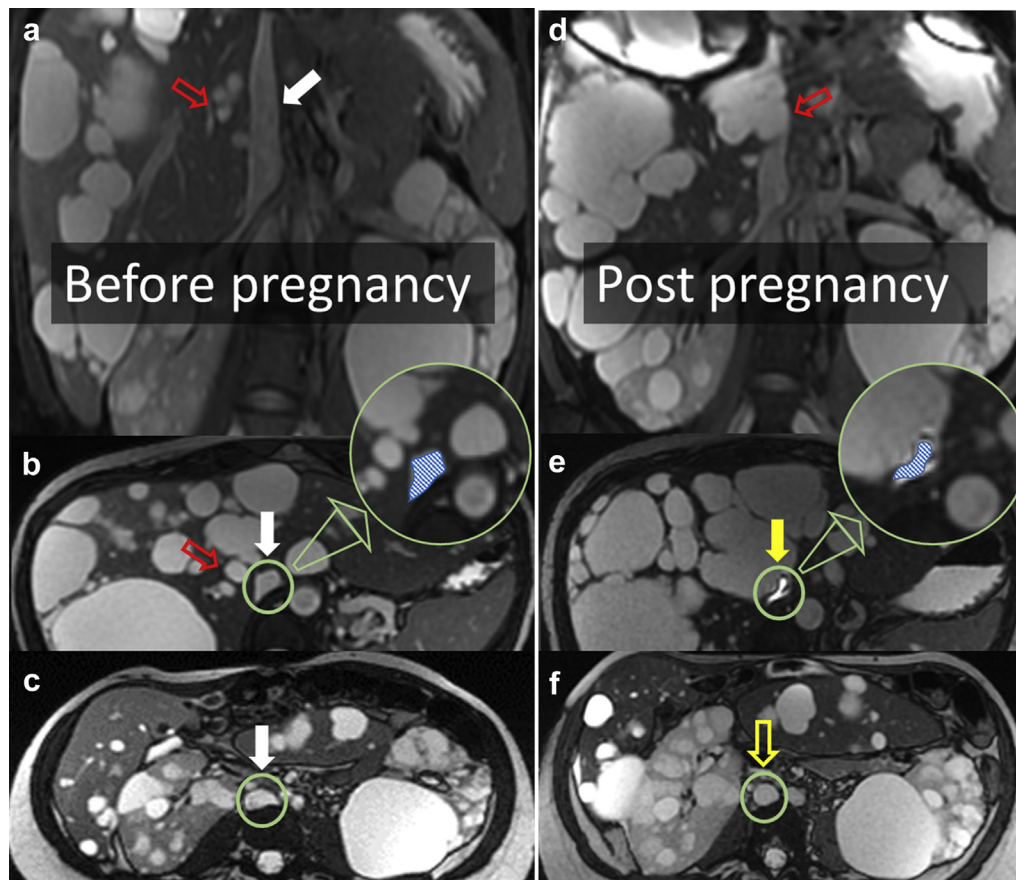


Figure 4. Patient who has autosomal dominant polycystic kidney disease (ADPKD) with hepatic cysts growing during pregnancy and compressing the inferior vena cava (IVC). Before pregnancy (a) coronal, (b) axial of intrahepatic IVC, and (c) axial of IVC at iliac vein confluence show patent IVC lumen (solid white arrow) and small hepatic cysts (open red arrow) which are enlarged post-pregnancy (d, open red arrow) causing severe intrahepatic IVC stenosis (e, solid yellow arrow). Upstream from the intrahepatic IVC stenosis, the IVC is more pressurized and circular at the iliac vein confluence (f, open yellow arrow). (b,c,e,f) Green circles indicate axial IVC images. (b,e) Partially amplified cross-sectional images of IVC are marked with blue shadow.

regression analysis showed a significantly higher prevalence of IVC compression in classes 1D and 1E compared to class 1A, as well as in the age group ≥ 40 years (Supplementary Table S6). We did not find any significant interaction between Mayo Clinic Classification and age (Supplementary Table S6). PKD gene mutation type was not associated with IVC compression ($P = 0.50$) (Supplementary Table S3).

These coefficients remained significant in a multivariate regression model adjusted for age, sex, and genotype (Table 4). Patients ≥ 40 years-old were 12-fold (95% CI: 4.2–42) more likely to have IVC compression compared to the reference: males < 40 years old belonging to the Mayo Clinic class 1A with mean ht-LV = 1200 ml/m and PKD2 or unknown mutation. ADPKD patients with Mayo Clinic

Table 2. IVC compression effects on azygos vein diameter, IVC dimension and aspect ratio upstream from compression and IVC lumen area in 216 ADPKD subject

Parameters	No compression n = 150	Mild compression n = 33	Severe compression n = 33	ANOVA test P
Azygos vein diameter, mm	2.3 ± 0.8	2.5 ± 1.3	4.0 ± 1.3	<0.001
IVC luminal area, mm ²				
Intrahepatic (above compression)	295 ± 127	233 ± 75	200 ± 88	<0.001
Mid or site of max narrowing	157 ± 93	116 ± 69	61 ± 40	<0.001
Iliac vein confluence (below)	260 ± 90	263 ± 83	281 ± 95	0.460
IVC measurements at iliac vein confluence, mm				
Left-to-right IVC dimension	22.2 ± 3.2	19.7 ± 3.2	19.8 ± 3.5	<0.001
Anterior-to-posterior IVC dimension	14.4 ± 3.8	16.5 ± 3.8	17.1 ± 4.2	<0.001
IVC aspect ratio ^a	1.69 ± 0.67	1.27 ± 0.39	1.16 ± 0.27	<0.001

ADPKD, autosomal dominant polycystic kidney disease; ANOVA, analysis of variance; IVC, inferior vena cava.

^aIVC aspect ratio = left-to-right/anterior-to-posterior dimension.

Table 3. Prevalence of IVC compression based on age and Mayo Clinic Classification 1 for 214 subjects

Age, yr	Mayo Clinic Classification					Sum
	1A	1B	1C	1D	1E	
<40	0% (0/4)	6% (1/16)	0% (0/14)	8% (1/13)	21% (3/14)	8% (5/61)
≥40	12% (2/17)	26% (10/38)	40% (23/58)	64% (18/28)	67% (8/12)	40% (61/153)
Total	10% (2/21)	20% (11/54)	32% (23/72)	46% (19/41)	42% (11/26)	31% (66/214)

IVC, inferior vena cava.

Mantel-Haenszel χ^2 ($2 \times 2 \times 5$ matrix) $P < 0.001$.

Two subjects were excluded: 1 with missing height data and 1 with renal transplantation at baseline.

Classifications 1D and 1E were 13-fold (95% CI: 2.4–116) and 26-fold (95% CI: 4.3–255) more likely to have IVC compression compared to the. Figure 5 shows that IVC compression was strongly associated with older age and with more severe Mayo Clinic Classifications, a predictor of rapid progression to end-stage renal disease.

IVC Compression by Hepatic Cysts

Intrahepatic IVC compression occurred almost exclusively in females, possibly reflecting their greater hepatic cyst fraction (Supplementary Table S7). In women with height adjusted liver volume (ht-LV) exceeding 2000 ml/m (corresponding to liver cyst fraction ~ 60%), the majority, 77% [95% CI: 54%–91%], had intra-hepatic IVC compression and 83% (95%CI: 59%-95%) had intra-hepatic or renal IVC compression (Supplementary Figure S3).

Supplementary Table S7 shows that subjects with intrahepatic compression of the IVC were older, female and had greater ht-LV, greater liver cyst fraction, lower height and weight and a more circular IVC below the compression ($P < 0.05$) that was consistent with higher IVC pressure caudal to the site

Table 4. Multivariable models of overall IVC compression in ADPKD patients

Predictors	Multivariate		
	OR	95% CI	P
Female	1.1	0.50–2.35	0.843
Age ≥40 yr	12.0	4.21–42.43	<0.001
PKD1	1.7	0.74–3.90	0.218
ht-LV ^a	0.6	0.26–1.23	0.195
Mayo Clinic class			
1B	2.9	0.55–24.04	0.250
1C	4.3	0.91–34.33	0.101
1D	13.3	2.44–115.73	0.007
1E	26.3	4.29–254.54	0.001
Interaction			
Female * ht-LV ^a	5.53	2.29–15.96	0.001

ADPKD, autosomal dominant polycystic kidney disease; CI, confidence interval; ht-LV, height-adjusted liver volume; IVC, inferior vena cava; OR, odds ratio.

Predictors are compared to the reference: Male, <40 years old, PKD2 or unknown mutation, with mean ht-LV (1200 ml/m) and Mayo Clinic class 1A.

^aht-LV was standardized to mean=0 and SD=1, odds ratio is reported for 1 SD change in ht-LV.

The interaction term, female*ht-LV, is highly significant showing female ADPKD subjects with large livers have 3.3-fold (OR_{interaction} * OR_{ht-LV} = 5.5*0.6) greater odds of IVC compression.

of compression. Multivariate analysis to assess the independent effect of ht-LV or liver cyst fraction, found that intrahepatic compression of the IVC was associated with female sex (odds ratio [OR]: 20, 95% CI: 1.72–235.61, $P = 0.017$) and ht-LV (OR: 5.63, 95% CI: 2.81–11.28, $P < 0.001$). In the regression model where ht-LV was removed and substituted for by liver cyst fraction (%), female sex (OR: 20.13), and liver cyst fraction (OR: 1.12) were significantly associated with intrahepatic compression of IVC (Table 5).

IVC Compression by Renal Cysts

IVC compression by renal cysts was more prevalent in males ($P = 0.0015$), and in those with greater renal cyst fraction, higher ht-TKV, lower eGFR, and larger rectus muscle separation width (Supplementary Table S8). Multivariate analyses (Table 6) showed that both higher log ht-TKV (OR: 8.65; 95% CI: 3.95–18.94; $P < 0.001$) and larger renal cyst fraction (OR: 1.05; 95% CI: 1.03–1.08; $P < 0.001$) were associated with a higher likelihood of IVC compression by renal cysts. In the

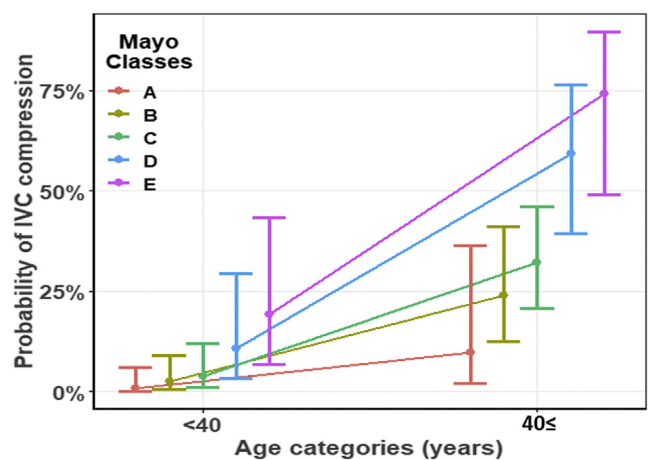


Figure 5. Predicted probability of inferior vena cava (IVC) compression based on age and Mayo Clinic Classification using multivariate logistic regression after adjustment. Probability (95% confidence interval [CI]) of IVC compression for patients with age <40 years and Mayo Clinic classes 1A: 1% (95% CI: 0.1%–6%), 1B: 3% (95% CI: 0.6%–9%), 1C: 4% (95% CI: 1%–12%), 1D: 11% (95% CI: 3%–29%), and 1E: 19% (95% CI: 7%–43%); and for patients with age ≥40 years and Mayo Clinic classes 1A: 10% (95% CI: 2%–36%), 1B: 26% (95% CI: 13%–41%), 1C: 32% (95% CI: 21%–46%), 1D: 59% (95% CI: 39%–76%), and 1E: 74% (95% CI: 49%–90%).

Table 5. Intrahepatic IVC compression multivariate analysis

Using ht-LV				Using liver cyst fraction			
Predictors	ORs	CI	P	Predictors	ORs	CI	P
Female	38.39	2.03–725.13	0.015	Female	20.13	1.72–235.61	0.017
<i>PKD1</i>	2.93	0.52–16.49	0.222	<i>PKD1</i>	2.89	0.42–20.00	0.283
Age, yr	1.05	0.99–1.11	0.110	Age, yr	1.05	0.98–1.13	0.147
log ht-TKV	0.51	0.17–1.52	0.229	log ht-TKV	0.31	0.08–1.12	0.075
ht-LV ^a	5.63	2.81–11.28	<0.001	Liver cyst fraction (%)	1.12	1.07–1.18	<0.001

CI, confidence interval; ht-LV, height-adjusted liver volume; ht-TKV, height-adjusted total kidney volume; IVC, inferior vena cava; OR, odds ratio.

^aht-LV is standardized to mean = 0 and SD = 1, i.e., 1 unit change in ht-LV = 1 SD.

PKD1 was compared to *PKD2* and indeterminate mutations.

model with renal cyst fraction, sex retained its significance with males having higher risk of developing IVC compression by renal cysts (OR: 2.85; 95% CI: 1.33–6.25; $P = 0.007$). Men had greater ht-TKV than women (median [interquartile range]: 985 [1199]–678 [758]; $P < 0.001$) but their renal cyst fraction was similar (median [interquartile range]: 87.5% [48.5]–82.2% [45.8]; $P = 0.195$), thereby accounting for the difference in effect of sex between these 2 models. An association with borderline statistical significance was identified whereby height-adjusted liver volume was inversely associated with the likelihood of intrarenal compression of the IVC in both models (Table 6).

Pregnancy, Parity, and Hormone Replacement Therapy

Considering the strong association of intrahepatic IVC compression with female sex ($n = 114$), we also evaluated whether sustained high levels of exposure to estrogen, including hormone replacement therapy, prior pregnancy, and multiparity were risk factors for IVC compression. No significant associations of these measures with IVC compression were found (Supplementary Table S9). However, multivariate regression analysis showed an association between parity and IVC compression by renal cysts (OR: 1.45; 95% CI: 1.03–2.12; $P = 0.039$) (Supplementary Table S10) where each birth increased the odds of extrinsic IVC compression by renal cysts by 45%. In this regression model, there

was also an association of greater ht-TKV and risk of renal compression of IVC.

Clinical Events Related to IVC Compression

We found severe intrahepatic IVC compression caused by hepatic cysts that had grown substantially during pregnancy (Figure 4) in an ADPKD patient presenting with symptomatic hypotension. Although DVT occurred in four ADPKD patients, three of these also had disorders associated with hypercoagulability: 1 each with antiphospholipid antibodies, factor V Leiden deficiency, and human immunodeficiency virus infection.^{25,26} The sole ADPKD patient who developed DVT in our study, without having risk factors for thrombosis identified by an extensive hematologic evaluation, had severe IVC compression by renal cysts (Figure 2). DVT was diagnosed in 2 control patients, each of whom had risk factors including rectal cancer²⁷ and post-traumatic stress disorder.²⁸ Another control patient with diabetes had pulmonary embolism without DVT.

Follow-up MRI scans were available for 143 of 216 ADPKD patients ranging from 2 to 15 years (median: 5 years). Nine of 100 (9%) ADPKD patients with no IVC compression at baseline progressed to IVC compression on follow-up (range: 2–14 years; median: 6 years). For 2 of 23 (9%) ADPKD patients with mild IVC compression at baseline, it became severe during follow-up. The remaining 129 of 143 patients were unchanged; none of those with severe compression at baseline regressed to

Table 6. IVC compression by renal cysts multivariate analysis

Using log ht-TKV				Using renal cyst fraction			
Predictors	OR	CI	P	Predictors	OR	CI	P
Male	1.45	0.60–3.45	0.405	Male	2.85	1.33–6.25	0.007
<i>PKD1</i>	1.56	0.59–4.09	0.369	<i>PKD1</i>	1.37	0.58–3.25	0.479
Age, yr	1.01	0.98–1.05	0.421	Age, yr	1.02	0.99–1.05	0.173
log ht-TKV	8.65	3.95–18.94	<0.001	Renal cyst fraction (%)	1.05	1.03–1.08	<0.001
ht-LV ^a	0.59	0.34–1.02	0.057	ht-LV ^a	0.62	0.38–1.02	0.058

ht-LV, height-adjusted liver volume; ht-TKV, height-adjusted total kidney volume; IVC, inferior vena cava; OR, odds ratio.

ht-TKV has a higher OR because of amplification by log scaling.

^aht-LV is standardized to mean = 0 and SD = 1, i.e., 1 unit change in ht-LV = 1 SD.

PKD1 was compared to *PKD2* and indeterminate mutations.

normal at follow-up. IVC compression of any magnitude was not observed to become less compressed during follow-up imaging.

DISCUSSION

Arterial complications of ADPKD include intracranial aneurysms (10%),^{5–7} aneurysm or dissection of the aorta (0.9%),^{8,11,12} coronary arteries,^{10,13} and dolichoectasia of carotid/vertebral arteries.^{9,29,30} However, there is a paucity of information regarding venous abnormalities in ADPKD. In this case control study of 216 ADPKD subjects and 216 age-/sex-matched controls, we found the prevalence of IVC compression by renal or hepatic cysts was dramatically higher in those older than 40 years in Mayo Clinic classes 1D/E and in females with ht-LV \geq 2000 ml/m. Radiographic features indicate that IVC compression in this study was hemodynamically significant including (i) IVC compression was associated with increased diameter of the azygous vein, a collateral vessel known to enlarge during IVC obstruction; and (ii) distension of the IVC at the iliac vein confluence into a larger, more circular cross section, suggesting increased venous pressure compared to the usual flat, low-pressure IVC cross section. Serious complications in affected patients included DVT and hypotension. Although none of the patients in this series developed ascites or hepatic veno-occlusive disease, these potential complications represent additional clinical concerns for ADPKD patients with intrahepatic IVC compression.

IVC compression in this study correlated with increased cystic involvement of kidneys and liver. Younger patients (<30 years old) had fewer kidney/liver cysts, and none in this age range had MRI signs of IVC compression. Older patients with more advanced disease had a higher rate of IVC compression; the age of 40 years appeared to be the risk threshold by univariate and multivariate analyses. It is not surprising that intrahepatic IVC compression occurred almost exclusively in women, who are more likely than men to have more numerous and larger liver cysts, possibly due to an estrogen-related mechanism.^{31–33} As the mean ht-LV increased, a larger proportion of female ADPKD patients had MRI evidence of IVC compression, especially with ht-LV \geq 2000 ml/m. In this study, greater parity and ht-TKV were associated with higher risk of IVC compression by the cystic kidneys. Therefore, we propose that hypotension, which occurred in one of our patients at 8 months pregnancy, was likely due to progressive IVC compression from enlarging hepatic cysts, and increased flow to/from the enlarging gravid uterus and diffuse systemic vasodilatation characteristic of pregnancy.^{34,35}

We did not consistently find evidence of peripheral edema during our review of patient medical records or identify subcutaneous edema on the images below the level of compression. For IVC compression caused by intrahepatic and upper pole of kidney, one might expect renal vein outflow obstruction and increased proteinuria.³⁶ However, no correlation with proteinuria was identified. This may reflect development of collateral pathways and other physiological adaptations in these patients. Indeed, the enlarged azygos vein diameter observed here is a well-known collateral pathway for IVC obstruction.³⁷

Case reports have identified IVC thrombosis^{14,16–19,38} in ADPKD, in some cases resulting in pulmonary embolism.^{18,38} Intraoperative hypotension and hypoxia were reported previously in ADPKD from IVC compression exacerbated by general anesthesia interrupting compensatory mechanisms.¹⁹ In that case, surgery had to be aborted but was later completed successfully, with meticulous attention to perioperative volume status to maximize venous return. Hepatic cysts compressing both IVC and hepatic/portal veins has also been reported in ADPKD³⁹ resulting in hepatic venous outflow obstruction with ascites, portal hypertension, and a poor prognosis.

The strengths of this study include the relatively large, well-characterized population of ADPKD subjects with a matched control population of subjects without ADPKD. The patient with a thrombotic event had extensive evaluation that did not find other factors that provoke thrombosis. Limitations of this study included retrospective analysis of data collected prospectively. There was no gold standard for the assessment of pressure gradients across the compressed IVC, which ideally would be measured by an invasive procedure. Instead, this was qualitatively assessed here by evaluating the azygos vein collateral and IVC aspect ratio caudal to compressions. The IVC aspect ratio was limited in patients where lower pole right renal cysts restricted the space available for the IVC to assume its natural cross-sectional shape. Hydration status was not strictly controlled, which could impact the degree of IVC distension. Although patients were instructed to avoid food intake for 4 hours before MRI to reduce peristalsis artifacts, fluid intake was permitted during this period before MRI. During follow-up MRI, we found progressive worsening of IVC compression in some cases, but none had regression of IVC compression. However, the duration of follow-up varied among subjects and, thus, conclusions regarding the natural history, type, and severity of complications of IVC compression are limited.

In conclusion, IVC compression by renal or hepatic cysts is a potentially important vascular complication in autosomal dominant polycystic

kidney disease. IVC compression occurs rarely in those younger than 30 years and is more likely at ages >40 years and for patients at highest risk for progression to end-stage renal disease within a 10-year period (i.e., Mayo Clinic classes 1D and 1E), generally in those with the greatest renal cyst burden. Intrahepatic IVC compression occurs predominantly in women, with a prevalence reaching 77% for ht-LV \geq 2000 ml/m, whereas men are more likely to have IVC compression by renal cysts. IVC compression has the potential for significant cardiovascular complications, including venous thrombosis, pulmonary embolism, hypotension (including during anesthesia that blocks compensatory mechanisms), and hepatic venous outflow obstruction.

MRI is being performed with increasing frequency in patients with ADPKD, particularly as specific treatments become available. Routine evaluation of these MRIs for signs of inferior vena cava compression should be considered, particularly in those with large renal and hepatic cyst burdens. The physiologic impact of IVC compression, including while upright, needs further investigations.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Imaging parameters of IVC MRI scanning.

Table S2. Multivariate linear regression showing association of azygos vein diameter with log IVC aspect ratio adjusted for covariates.

Table S3. Comparison of the means/medians between presences vs. absence of IVC compression in ADPKD subjects.

Table S4. A 5×2 contingency table showing association of IVC compression and Mayo Clinic classes (χ^2 test).

Table S5. Prevalence of IVC compression based upon age and Mayo Clinic Classification for 214 subjects with class 1 symmetrical disease. Two subjects were excluded including 1 with missing height data and 1 with renal transplantation at baseline.

Table S6. Univariate logistic regression showing association between IVC compression and Age >40 years and Mayo

Clinic Classification and likelihood ratio test for analysis of interaction between age and Mayo Clinic Classification.

Table S7. Comparison of the variables between presence and absence of intrahepatic IVC compression in ADPKD subjects.

Table S8. Comparison of the means/medians of the continuous and distribution of the categorical variables between presence and absence of IVC compression by renal cysts in ADPKD subjects.

Table S9. Frequency table for pregnancy status, parity, hormone replacement therapy among female ADPKD patients (N = 114).

Table S10. Multivariate analysis for effect of parity number on IVC compression among female ADPKD patients (N = 114).

Figure S1. Schematic diagram: measuring the left to right (LR) and anterior to posterior (AP) IVC lumen dimensions to get an IVC aspect ratio. (A,B) Flat IVC without compression. (C) Coronal image of IVC compression; we define above as IVC, below as just above the iliac vein confluence. (D–F) Abnormal small aspect ratio with IVC compression.

Figure S2. Coronal (A) and axial (B,C) SSFP of IVC in a 30-year-old male ADPKD patient. Right kidney is enlarged by innumerable cysts and has limited space to expand superiorly. It is pushed down by the liver (solid yellow arrow) rotating counterclockwise (curved open arrow) with the lower pole migrating medially to compress the IVC (open yellow arrow). The left kidney is also expanded by innumerable cysts.

Figure S3. Probability of IVC compression stratified by gender and ht-LV using multiple logistic regression for (A) overall IVC compression and (B) intrahepatic IVC compression. The large error bars in males indicates small number of observations in this category.

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