Ultrasound Elastography to Quantify Liver Disease Severity in Autosomal Recessive Polycystic Kidney Disease

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Objectives To evaluate the diagnostic accuracy of ultrasound elastography with acoustic radiation force impulse (ARFI) to detect congenital hepatic fibrosis and portal hypertension in children with autosomal recessive polycystic kidney disease (ARPKD).

Study design Cross-sectional study of 25 children with ARPKD and 24 healthy controls. Ultrasound ARFI elastography (Acuson S3000, Siemens Medical Solutions USA, Inc, Malvern, Pennsylvania) was performed to measure shear wave speed (SWS) in the right and left liver lobes and the spleen. Liver and spleen SWS were compared in controls vs ARPKD, and ARPKD without vs with portal hypertension. Linear correlations between liver and spleen SWS, spleen length, and platelet counts were analyzed. Receiver operating characteristic analysis was used to evaluate diagnostic accuracy of ultrasound ARFI elastography.

Results Participants with ARPKD had significantly higher median liver and spleen SWS than controls. At a proposed SWS cut-off value of 1.56 m/s, the left liver lobe had the highest sensitivity (92%) and specificity (96%) for distinguishing participants with ARPKD from controls (receiver operating characteristic area 0.92; 95% CI 0.82-1.00). Participants with ARPKD with portal hypertension (splenomegaly and low platelet counts) had significantly higher median liver and spleen stiffness than those without portal hypertension. The left liver lobe also had the highest sensitivity and specificity for distinguishing subjects with ARPKD with portal hypertension.

Conclusions Ultrasound ARFI elastography of the liver and spleen, particularly of the left liver lobe, is a useful noninvasive biomarker to detect and quantify liver fibrosis and portal hypertension in children with ARPKD. *(J Pediatr 2019;209:107-15)*.

Autosomal recessive polycystic kidney disease (ARPKD) is an inherited hepatorenal fibrocystic disorder characterized by progressive chronic kidney disease and liver disease consisting of dilated biliary ducts, congenital hepatic fibrosis (CHF), and portal hypertension (Caroli syndrome).[1] Liver-related complications in ARPKD can include ascending cholangitis and symptoms of portal hypertension, such as hypersplenism and esophageal varices. Severe bleeding complications and/or the need for portosystemic shunting occur in 10%-40% of patients with ARPKD, and about 7% of patients eventually require liver transplantation.[2-7]

Current clinical methods to monitor the severity and progression of liver disease in ARPKD have significant limitations. Unlike typical cirrhosis, the liver fibrosis in CHF consists of dense, slowly progressive periportal fibrosis that is usually not accompanied by inflammation. Patients typically have well-preserved liver synthetic function despite progressive portal hypertension, making markers of liver synthetic function testing uninformative for quantifying severity of CHF.[3] Performing a liver biopsy is generally not recommended because of the risk of complications and lack of prognostic value.[8] Splenomegaly and thrombocytopenia resulting from hypersplenism correlate with the severity of portal hypertension[3] but are not universally present or may be under-recognized. Indeed, in 1 cohort study, 2 of 4 patients with ARPKD without splenomegaly had esophageal varices on endoscopy,[3] raising concern that serious bleeding complications could occur in patients without clinical examination findings concerning for portal hypertension. The presence of esophageal varices on endoscopy can confirm portal hypertension, but current

ARFI	Acoustic radiation force impulse
AUROC	Areas under the ROC curve
ARPKD	Autosomal recessive polycystic kidney disease
CHF	Congenital hepatic fibrosis
CHOP	Children's Hospital of Philadelphia
ROC	Receiver operating characteristic
SWS	Shear wave speed
TE	Transient elastography
WBC	White blood cell

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The funding and conflict of interest statement is available at www.jpeds.com.

Portions of this study were presented as an oral presentation at the Pediatric Radiology / International Pediatric Radiology Conjoint Meeting, May 15-20, 2016 Chicago, Illinois, and as a poster at the American Society of Nephrology Kidney Week, November 15-20, 2016, Chicago, Illinois.

https://doi.org/10.1016/j.jpeds.2019.01.055

expert recommendations do not advise prospective surveillance endoscopy and primary prophylaxis for children with portal hypertension because of invasiveness and lack of data on risk of variceal bleeding.[9,10] Standard grayscale ultrasound provides only qualitative assessment of liver echotexture and biliary tract dilatation, and Doppler assessments of portal blood flow lack sensitivity for detection of portal hypertension.[11]

Novel noninvasive imaging biomarkers are therefore needed to quantify the severity of CHF and portal hypertension in ARPKD and could inform anticipatory guidance and plans for expediting medical care in case of variceal bleeding.[9,10] The need to develop new imaging biomarkers has been highlighted by an expert panel, which recommended further study of "noninvasive tests…as a means to help triage children for endoscopy to screen for esophageal varices."[9]

Ultrasound elastography with acoustic radiation force impulse (ARFI) imaging has emerged as a valuable method to quantify liver fibrosis. ARFI is integrated into a conventional ultrasound machine and assesses tissue stiffness by measuring shear wave speed (SWS) of transverse waves generated in the tissue following an acoustic pulse, with higher SWS indicating higher stiffness. In adults and children with chronic liver diseases, ultrasound ARFI elastography has been shown to have good diagnostic accuracy for noninvasive staging of liver fibrosis.[12-14]

The objective of this study is to evaluate the use of ultrasound ARFI elastography to quantify the severity of liver fibrosis and portal hypertension in children and young adults with ARPKD. Our specific aims are to determine if liver and spleen stiffness measured by ARFI can distinguish participants with ARPKD from healthy controls; participants with ARPKD without clinical signs of portal hypertension from healthy controls; and participants with ARPKD with vs without clinical signs of portal hypertension.

Methods

In this cross-sectional study, children and young adults ≤21 years old with a clinical diagnosis of ARPKD were recruited from the nephrology practice at the Children's Hospital of Philadelphia (CHOP). Individuals who had received a liver transplant or a portosystemic shunt were excluded from this analysis. A reference population of 24 healthy children with no personal history of hypertension, obesity, hematologic or rheumatologic disease, and no family history of kidney or liver disease, was recruited from CHOP primary care practices. The reference population consisted of an equal number of male and female children in each of the following age groups: <5 years old (n = 6); 5 to <10 years old (n = 6); 10 to <15 years old (n = 6); and ≥15 years old (n = 6). This reference population approach was chosen to allow comparison of our ARFI measurements with the largest published study of ARFI normative values in children.[15] The CHOP Institutional Review Board approved this study (IRB 14-10785), and informed consent was obtained from all participants/guardians.

Measurements

Data collected during the single study visit included demographic information, current medications, and medical and family history. Physical examination included measurements of height, weight, and manual blood pressure. Laboratory measurements were performed only in participants with ARPKD, and included complete blood counts and tests of kidney and liver function. Clinical signs of portal hypertension were defined as presence of splenomegaly or thrombocytopenia. "Definitive" portal hypertension was defined as presence of both splenomegaly and thrombocytopenia, and absence of portal hypertension was defined as the presence of neither splenomegaly nor thrombocytopenia. Splenomegaly was defined as spleen length >90th percentile for height,[16] and spleen length index was calculated as actual/90th percentile spleen length. Thrombocytopenia was defined as platelet count $<150 \times 10^3/\mu$L. Known varices were defined as esophageal or gastric varices diagnosed on upper endoscopy. Estimated glomerular filtration rate was calculated based on the bedside Chronic Kidney Disease in Children Study equation.[17]

Ultrasound was performed with the Siemens Acuson S3000 with Virtual Touch tissue quantification system (Siemens Medical Solutions USA, Inc, Malvern, Pennsylvania), using age- and size-appropriate linear or convex transducers (4-9 MHz). Participants were asked to fast prior to ultrasound for age-appropriate durations according to hospital protocols, unless medically contraindicated. Grayscale ultrasound of the liver and spleen were obtained in supine position according to standard clinical protocols, including measurements of liver and spleen sagittal (craniocaudal) length. ARFI elastography was performed in Virtual Touch quantification mode to obtain point SWS measurements (in meters per second, m/s) in the right and left liver lobes and spleen mid-pole, using an inter- or subcostal approach. Regions of interest for SWS measurements were placed perpendicular to the organ capsule at a depth of 2-7 cm, based on participants' organ size and body habitus, avoiding areas of visible bile ducts, cysts, or vessels. The minimum pressure needed to obtain an adequate grayscale image was applied to the transducer. Measurements were performed during a brief breath-hold (without deep inspiration) in participants who were able to comply, and at end-expiration for noncooperative participants. Ten valid SWS measurements were obtained to calculate the mean SWS for each site.

Statistical Analyses

Clinical and demographic variables were reported as median and IQR for continuous variables, and as frequency and percentage for binary variables. Group differences were compared using Wilcoxon rank-sum test for continuous variables and the Fisher exact test for binary variables. Liver and spleen stiffness (measured as SWS) were compared between control and ARPKD groups, between controls and

Table I. Clinical and demographic characteristics of healthy controls and participants with ARPKD

Characteristics	Healthy controls (n = 24)	Participants ARPKD (n = 25)	*P*
Age, y	10.5 [5.2, 15.0]	4.6 [1.9, 13.2]	.1
Male sex	12 (50%)	15 (60%)	.6
eGFR* (mL/min/1.73 m^2)	-	65.2 [42.5, 90.4]	-
WBC count ($\times 10^3/\mu L$)	-	6.3 [4.4, 10.6]	-
Platelets	-		-
Count ($\times 10^3/\mu L$)		269 [139, 318]	
$<150 \times 10^3/\mu L$		9 (36%)	
Spleen length			
Index (actual/90th percentile)	0.83 [0.76, 0.87]	1.10 [0.89, 1.42]	**<.001**
>90th percentile	1 (4%)	14 (56%)	**<.001**

eGFR, estimated glomerular filtration rate.
Continuous variables given as median [IQR]; binary variables as count (%).
*Includes 5 participants with kidney transplant.
P values that were significant ($P < 0.05$) were put in bold.

participants with ARPKD without portal hypertension (neither splenomegaly nor low platelets), and between participants with ARPKD without vs with definitive portal hypertension (both splenomegaly and low platelets), using Wilcoxon rank-sum tests. To perform age-matched analysis, each participant with ARPKD was matched manually 1:1 to the healthy control participant closest in age, dropping any participants with ARPKD or control participants without a match. Following matching, unpaired group analyses were performed. Linear fit plots and Spearman correlation were performed to examine relationships between liver and spleen SWS, age, spleen length index, and platelet counts. Nonparametric bootstrapping with 1000 replications was performed to calculate 95% CI for the Spearman rho. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of ARFI elastography to distinguish between children with ARPKD and controls, and between participants with ARPKD with vs without clinical signs of portal hypertension. Diagnostic value of SWS cut-offs was evaluated using the sensitivity, specificity, and percent of subjects correctly classified. SWS cut-offs were chosen to maximize the percent of subjects correctly classified. Statistical analyses were performed using Stata v 13.1 (StataCorp, College Station, Texas).

Results

Ultrasound measurements were obtained on 26 participants with ARPKD and 24 healthy controls. One participant with ARPKD was excluded from this analysis because of history of a portosystemic shunt, leaving 25 participants with ARPKD in the final analysis. Twenty- three of 24 (96%) healthy controls and 22 of 25 (88%) of the participants with ARPKD were fasting prior to ultrasound. All participants who did not fast were infants ≤16 months old. Five participants with ARPKD had previously received a kidney transplant.

Clinical and demographic characteristics of the ARPKD and control groups are shown in Table I. The median age of the participants with ARPKD was younger than healthy controls (4.6 vs 10.5 years), but this difference was not statistically significant. Participants with ARPKD had median white blood cell (WBC) and platelet counts within the normal range, but 9 (36%) of the participants with ARPKD had low platelets ($<150 \times 10^3/\mu L$). Splenomegaly was significantly more common in the ARPKD group compared with controls (56% vs 4%, $P < .001$), with median spleen length index of 1.10 in the ARPKD group compared with 0.83 in controls ($P < .001$) (Table I).

Of the 25 participants with ARPKD, 11 had no clinical signs of portal hypertension (ie, neither splenomegaly nor low platelets); 14 participants with ARPKD had splenomegaly, and 9 of these individuals also had low platelets. Clinical and demographic characteristics of participants with ARPKD without and with clinical signs of portal hypertension are shown in Table II (available at www.jpeds.com). Participants with ARPKD with either splenomegaly or low platelets had a higher median age than those without signs of portal hypertension. As expected, participants with ARPKD with splenomegaly (n = 14) had lower median WBC and platelet counts than those without splenomegaly (n = 11) (WBC 6.1 vs 11.0 $\times 10^3/\mu L$, $P = .03$; platelets 142 vs 322 $\times 10^3/\mu L$, $P = .0002$). All participants with low platelets had splenomegaly, and were defined as having "definitive" portal hypertension (n = 9). However, 5 participants with splenomegaly had normal platelets, suggesting that low platelets may be a later sign of portal hypertension or that platelet counts may be affected by other clinical factors. Participants with definitive portal hypertension (ie, both splenomegaly and low platelets, n = 9) had a higher median age and lower WBC count than those without portal hypertension (n = 11) (median age 7.7 vs 1.9 years, $P = .03$; WBC 4.4 vs 11.0 $\times 10^3/\mu L$, $P = .01$). Three participants had a history of endoscopically confirmed esophageal or gastric varices, all of whom had both splenomegaly and low platelets. One participant had a history of ascending cholangitis; this individual had both splenomegaly and low platelets, but did not have a known history of varices. Of the 5 participants with ARPKD who had received kidney transplants, all had splenomegaly and 2 also had low platelets (ie, definitive portal hypertension). Recipients of kidney transplant (n = 5) had slightly higher median WBC and slightly lower median platelet counts

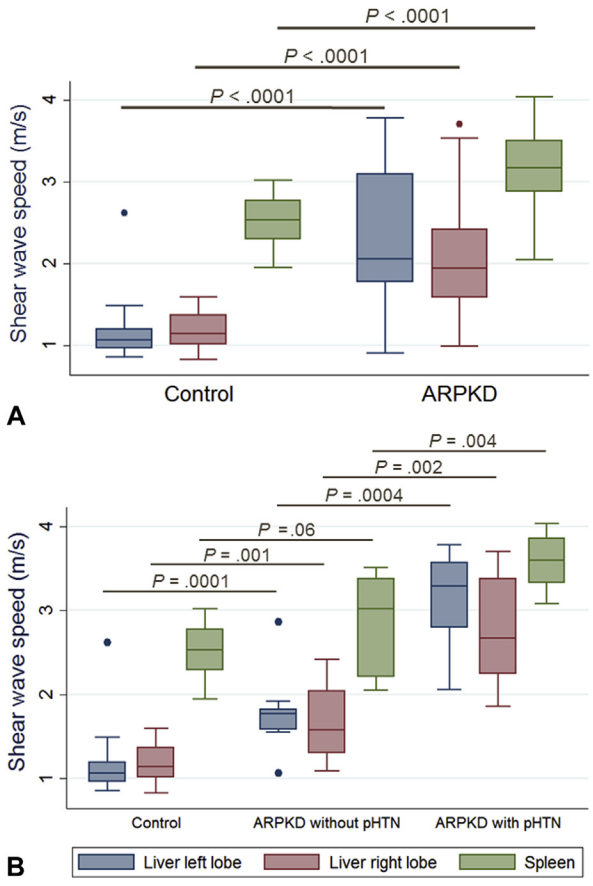

Figure 1. Liver and spleen stiffness in healthy controls and participants with ARPKD. Liver and spleen SWS measured by ARFI ultrasound elastography in **A,** healthy controls (n = 24) and participants with ARPKD (n = 25), and **B,** healthy controls (n = 24), participants with ARPKD without portal hypertension (n = 11), and participants with ARPKD with definitive portal hypertension (n = 9).

than participants without transplant with ARPKD (n = 20), but these differences were not statistically significant (WBC 7.5 vs 6.1 × $10^3/\mu$L, P = .9; platelets 199 vs 271 × $10^3/\mu$L, P = .5, **Table III**; available at www.jpeds.com). Liver and spleen stiffness were not significantly different between recipients with kidney transplant and participants without transplant with ARPKD (**Table III**).

Liver and Spleen Stiffness in Control vs ARPKD Groups

Overall, participants with ARPKD had significantly higher median liver and spleen stiffness than healthy controls. Median SWS for controls (n = 24) vs all participants with ARPKD (n = 25) was 1.07 vs 2.06 m/s in the left liver lobe (P < .0001), 1.15 vs 1.95 m/s in the right liver lobe (P < .0001), and 2.53 vs 3.17 m/s in the spleen (P < .0001) (**Figure 1**, A). To explore whether ultrasound ARFI elastography can detect milder forms of ARPKD liver disease, we compared liver and spleen stiffness between healthy controls and participants with ARPKD without portal hypertension. Median SWS for controls (n = 24) vs participants with ARPKD without portal hypertension (n = 11) was 1.07 vs 1.77 m/s in the left liver lobe (P = .0001), 1.15 vs 1.58 m/s in the right liver lobe (P = .001), and 2.53 vs 3.02 m/s in the spleen (P = .06) (**Figure 1**, B).

Given the older median age of healthy controls compared with the ARPKD group, we performed comparisons of age-matched ARPKD and control groups, and also explored whether there were any age-related changes in liver and spleen stiffness in the ARPKD and control groups. In age-matched analysis, participants with ARPKD again showed significantly higher median liver and spleen stiffness than healthy controls. Median SWS for age-matched groups of controls (n = 18, median age 8.4 [3.8, 14.9] years) vs ARPKD (n = 18, median age 8.1 [4.0, 14.7] years) was 1.07 vs 1.99 m/s in the left liver lobe (P = .0001), 1.15 vs 1.87 m/s in the right liver lobe (P = .0002), and 2.53 vs 3.05 m/s in the spleen (P = .002) (**Figure 2**; available at www.jpeds.com).

In healthy controls (n = 24), liver stiffness did not correlate with age (left liver lobe: rho = 0.12 [95% CI −0.34 to 0.58], P = .6; right liver lobe: rho = 0.18 [95% CI −0.22 to 0.59], P = .4). Spleen stiffness showed a slight positive correlation with age in healthy controls, but this was not statistically significant (rho = 0.32 [95% CI −0.03 to 0.66], P = .1). In the ARPKD group (n = 25), liver stiffness showed a slight positive but statistically nonsignificant trend with age, and spleen stiffness did not correlate with age (left liver lobe: rho = 0.26 [95% CI −0.17 to 0.69], P = .2; right liver lobe: rho = 0.22 [95% CI −0.21 to 0.64], P = .3; spleen: rho = −0.12 [95% CI −0.50 to 0.27], P = .6) (**Figure 3**; available at www.jpeds.com).

Liver and Spleen Stiffness in Participants with ARPKD without vs with Clinical Portal Hypertension

Liver and Spleen Stiffness in Participants with ARPKD without vs with Splenomegaly. Participants with ARPKD with splenomegaly had significantly higher median liver and spleen stiffness than those without splenomegaly. Median SWS for participants with ARPKD without vs with splenomegaly was 1.77 vs 2.94 m/s in the left liver lobe (P = .001), 1.58 vs 2.25 m/s in the right liver lobe (P = .02), and 3.02 vs 3.35 m/s in the spleen (P = .02) (**Figure 4**, A; available at www.jpeds.com).

Liver and Spleen Stiffness in Participants with ARPKD without vs with Low Platelets. Participants with ARPKD with low platelets had significantly higher median liver and spleen stiffness than those without low platelets. Median SWS for participants with ARPKD without vs with low platelets was 1.82 vs 3.29 m/s in the left liver lobe (P = .0003), 1.70 vs 2.67 m/s in the right liver lobe (P = .001), and 2.99 vs 3.60 m/s in the spleen (P = .003) (**Figure 4**, B; available at www.jpeds.com).

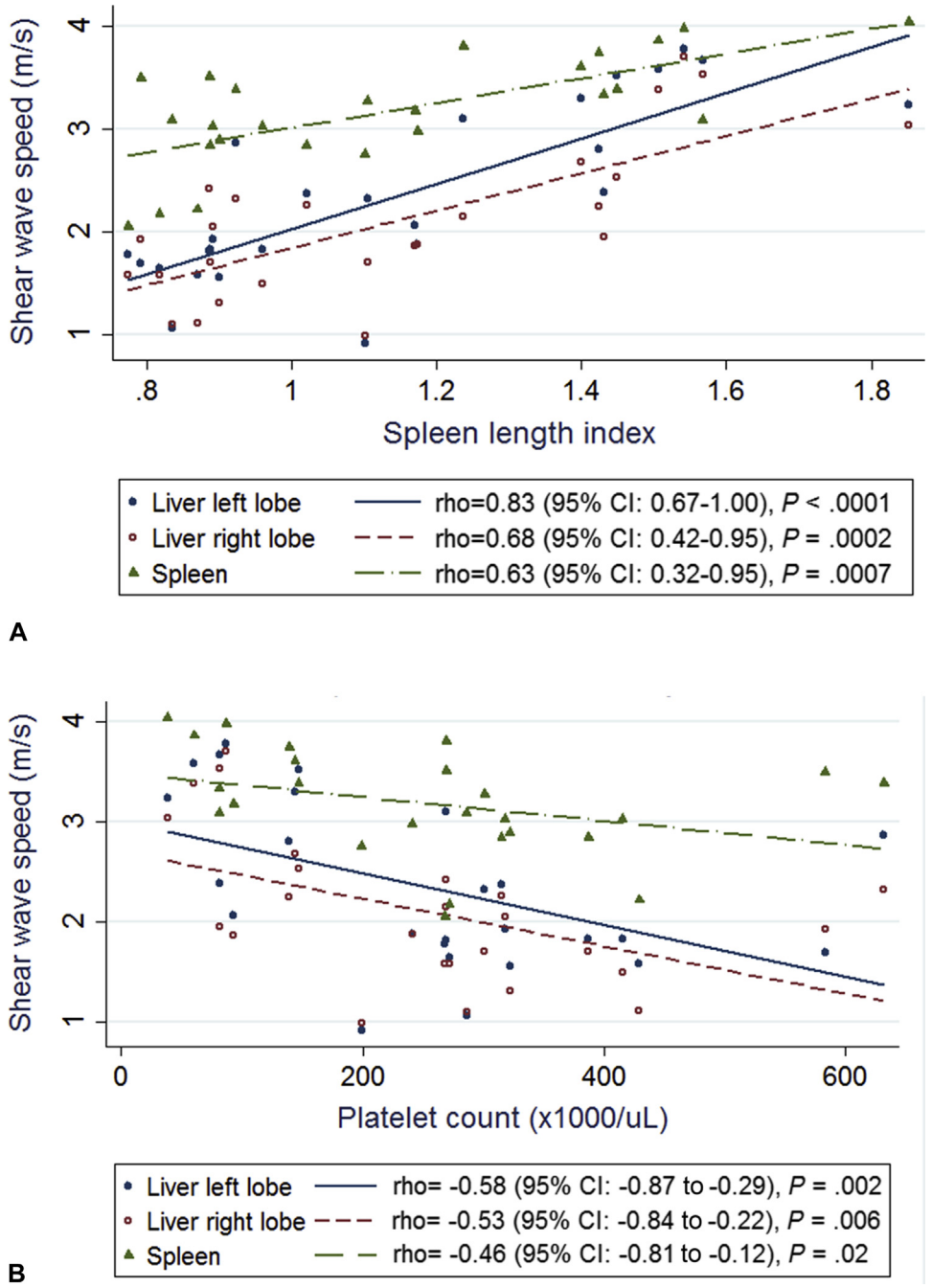

Figure 5. Linear correlations of liver and spleen stiffness with spleen length index and platelet count in participants with ARPKD. Relationship of liver and spleen SWS measured by ARFI ultrasound elastography with **A,** spleen length index and **B,** platelet count.

Liver and Spleen Stiffness in Participants with ARPKD without vs with Definitive Portal Hypertension

Participants with ARPKD with definitive portal hypertension (both splenomegaly and low platelets) had significantly higher median liver and spleen stiffness than those without portal hypertension. Median SWS for participants with ARPKD without (n = 11) vs with (n = 9) definitive portal hypertension was 1.77 vs 3.29 m/s in the left liver lobe (P = .0004), 1.58 vs 2.67 m/s in the right liver lobe (P = .002), and 3.02 vs 3.60 m/s in the spleen (P = .004) (Figure 1, B).

Relationship of Liver and Spleen Stiffness with Spleen Length and Platelet Count in Participants with ARPKD

To further explore the relationship of liver and spleen stiffness with clinical signs of portal hypertension in children

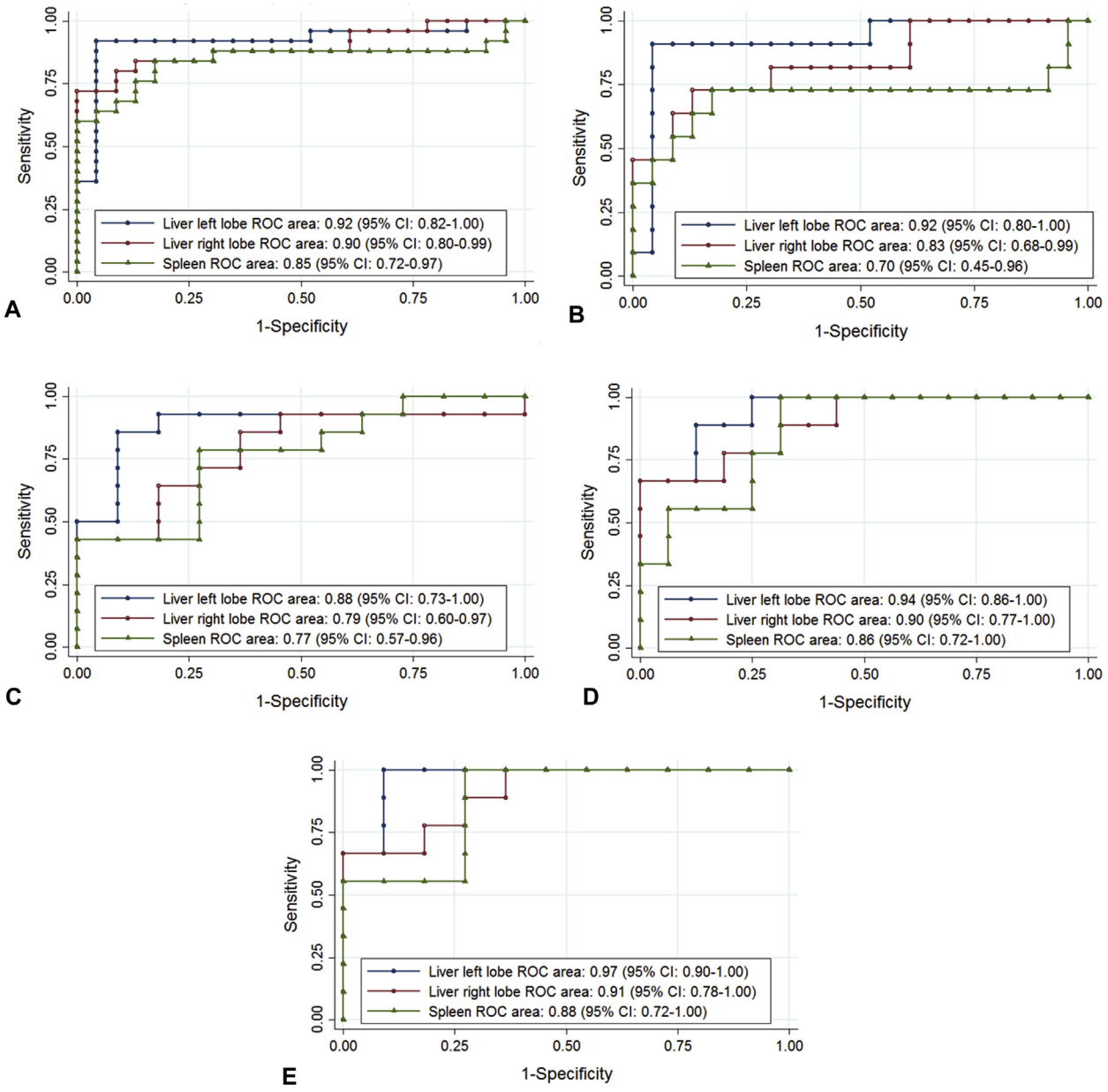

Figure 6. ROC curves to evaluate diagnostic performance of liver and spleen stiffness. ROC curves to evaluate diagnostic performance of liver and spleen SWS measured by ARFI ultrasound elastography to distinguish between **A,** healthy controls vs participants with ARPKD; **B,** healthy controls vs participants with ARPKD without portal hypertension; **C,** participants with ARPKD without vs with splenomegaly; **D,** participants with ARPKD without vs with low platelets; and **E,** participants with ARPKD without vs with definitive portal hypertension (both splenomegaly and low platelets). AUROC with 95% CI are as shown.

with ARPKD, we examined the linear correlations of liver and spleen SWS with spleen length and platelet count. Liver and spleen stiffness were strongly positively correlated with spleen length index (left liver lobe: rho = 0.83 [95% CI 0.67-1.00], $P < .0001$; right liver lobe: rho = 0.68 [95% CI 0.42-0.95], $P = .0002$; spleen: rho = 0.63 [95% CI 0.32-0.95], $P = .0007$) (Figure 5, A). Liver and spleen stiffness were negatively correlated with platelet count (left liver lobe: rho = −0.58 [95% CI −0.87 to −0.29], $P = .002$; right liver lobe: rho = −0.53 [95% CI −0.84 to −0.22], $P = .006$; spleen: rho = −0.46 [95% CI −0.81 to −0.12], $P = .02$) (Figure 5, B).

ROC Analysis

Healthy Controls vs Participants with ARPKD. ROC analysis showed that ARFI ultrasound elastography of the liver and spleen had high accuracy in distinguishing participants with ARPKD from healthy controls, with areas under the ROC curve (AUROC) of 0.92 (95% CI 0.82-1.00) for the left liver lobe, 0.90 (95% CI 0.80-0.88) for the right liver

lobe, and 0.85 (95% CI 0.72-0.97) for the spleen (Figure 6, A). At a proposed SWS cut-off value of 1.56 m/s, the left liver lobe had the highest sensitivity (92%) and specificity (96%) for distinguishing participants with ARPKD from healthy controls (Table IV; available at www.jpeds.com).

Healthy Controls vs Participants with ARPKD without Portal Hypertension. To examine the accuracy of ARFI ultrasound elastography to detect milder forms of ARPKD liver disease, we performed ROC analysis to distinguish participants with ARPKD without portal hypertension from healthy controls. AUROCs were 0.92 (95% CI 0.80-1.00) for the left liver lobe, 0.83 (95% CI 0.68-0.99) for the right liver lobe, and 0.70 (95% CI 0.45-0.96) for the spleen (Figure 6, B). At a proposed SWS cut-off value of 1.56 m/s, the left liver lobe had the highest sensitivity (91%) and specificity (96%) for distinguishing participants with ARPKD without portal hypertension from healthy controls (Table IV).

Participants with ARPKD without vs with Portal Hypertension. Within the ARPKD group, we examined the accuracy of ARFI ultrasound elastography to distinguish between participants without vs with clinical signs of portal hypertension, namely splenomegaly or low platelets.

For distinguishing participants with ARPKD without vs with splenomegaly, AUROCs were 0.88 (95% CI 0.73-1.00) for the left liver lobe, 0.79 (95% CI 0.60-0.97) for the right liver lobe, and 0.77 (95% CI 0.57-0.96) for the spleen (Figure 6, C). At a proposed SWS cut-off value of 2.03 m/s, the left liver lobe had the highest sensitivity (86%) and specificity (91%) for distinguishing participants with ARPKD with vs without splenomegaly (Table IV).

For distinguishing participants with ARPKD without vs with low platelets, AUROCs were 0.94 (95% CI 0.86-1.00) for the left liver lobe, 0.90 (95% CI 0.77-1.00) for the right liver lobe, and 0.86 (95% CI 0.72-1.00) for the spleen (Figure 6, D). At a proposed SWS cut-off value of 2.37 m/s, the left liver lobe had the highest sensitivity (89%) and specificity (88%) for distinguishing participants with ARPKD with vs without low platelets (Table IV).

For distinguishing participants with ARPKD without vs with definitive portal hypertension (both splenomegaly and low platelets), AUROCs were 0.97 (95% CI 0.90-1.00) for the left liver lobe, 0.91 (95% CI 0.78-1.00) for the right liver lobe, and 0.88 (95% CI 0.72-1.00) for the spleen (Figure 6, E). At a proposed SWS cut-off value of 2.06 m/s, the left liver lobe had the highest sensitivity (100%) and specificity (91%) for distinguishing participants with ARPKD with vs without definitive portal hypertension (Table IV).

Discussion

In this study, we found that individuals with ARPKD have significantly higher liver and spleen stiffness than healthy controls. ARFI ultrasound elastography had a high predictive value for differentiating individuals with ARPKD from healthy controls, with a left liver lobe cut-off of 1.56 m/s showing the highest sensitivity (92%) and specificity (96%) (AUROC = 0.92). This high sensitivity and specificity for left liver lobe stiffness in detecting ARPKD liver disease persisted even when comparing healthy controls to participants with ARPKD without evidence of portal hypertension. In clinical settings, ARFI ultrasound elastography, particularly of the left liver lobe, could therefore be useful to detect liver involvement in children in whom the diagnosis of ARPKD is unclear, or to detect early signs of portal hypertension in children with known ARPKD.

Within the ARPKD group, participants with either splenomegaly or low platelets had significantly higher liver and spleen stiffness than those without these clinical signs of portal hypertension. Overall, median liver and spleen stiffness measurements were higher in participants with ARPKD with low platelets compared with those with splenomegaly, suggesting that low platelets are sign of more advanced portal hypertension. This is consistent with our observation that only a subset (64%) of participants with splenomegaly also had low platelets. Liver and spleen stiffness both showed strong linear correlations with spleen size and platelet count, suggesting that the ARFI measures track reliably with increasing severity of portal hypertension. Again, the left liver lobe showed the highest accuracy for distinguishing clinical signs of portal hypertension with high sensitivity and specificity.

Overall, our results indicate that ARFI ultrasound elastography of the liver and spleen appears to be a promising biomarker of the severity of congenital hepatic fibrosis and portal hypertension in ARPKD. In particular, elastography of the left liver lobe appears particularly sensitive and specific in detecting ARPKD-related liver disease. Disproportionate involvement of the left liver lobe is consistent with our own clinical observations of left liver lobe enlargement palpable under the xiphoid in our patients with ARPKD. It has also been shown on magnetic resonance imaging in a National Institutes of Health cohort study, where the left liver lobe was disproportionately enlarged in 35 of 51 patients (69%).[3] Our finding of higher sensitivity and specificity of left liver lobe elastography measurements is in contrast to previous studies of ultrasound ARFI elastography in other disease processes in adults. For example, 1 study compared ultrasound ARFI elastography of the left and right liver lobes to histologic grading of fibrosis in adults undergoing hepatectomy for hepatocellular carcinoma, chronic viral hepatitis, and/or alcoholic hepatitis, and found that the left liver lobe had lower AUROC than the right for diagnosing histologic fibrosis.[18] Similarly, some studies in a meta-analysis in which ultrasound ARFI elastography measurements were performed in both liver lobes showed lower AUROC in the left lobe.[13] Our findings of higher diagnostic accuracy of the left liver lobe may represent a unique aspect of ARPKD-related liver disease, or perhaps a finding specific to pediatric liver disease. Further studies in larger ARPKD populations and in children with other liver diseases are therefore needed.

A previous small study evaluating a different type of ultrasound elastography, transient elastography (TE, FibroScan [Echosens North America, Waltham, Massachusetts]), found children with ARPKD had higher liver stiffness than controls.[19] TE is widely used in adults to quantify liver fibrosis in various chronic liver diseases and has the advantage of device portability. However, inability to obtain a reliable reading is about 3 times as common with TE compared with ARFI, with even higher failure rates in obese patients.[20] In addition, TE does not provide any anatomic images and thus does not allow precise region of interest placement. TE also cannot be used in patients with ascites.[20] Therefore, ARFI is likely to be a more useful modality in children with ARPKD across a wide range of body sizes and provides the advantage of a "one-stop" evaluation of both anatomic ultrasound and stiffness measurements in the same examination. In the current study, we were able to successfully perform ARFI ultrasound elastography along with anatomic ultrasound imaging in children ranging in age from 2 months to 20 years. The elastography measurements add only 5-7 minutes to the anatomic ultrasound study, making them easy to integrate into routine clinical imaging examinations.

Current expert guidelines do not recommend routine primary endoscopic surveillance for varices in children with portal hypertension because of the lack of published evidence on the risk of bleeding and efficacy of primary prophylaxis such as nonselective beta blockers or endoscopic ligation.[9,21] However, ARFI ultrasound elastography measures could provide additional data to stratify patients' risk of varices, and could help to more appropriately select patients who may benefit from primary endoscopic surveillance and prophylaxis.[9] Because the number of participants with varices in this study was small, we could not perform ROC analysis to explore an SWS cut-off to differentiate children at risk for varices.

In research settings, ultrasound ARFI elastography of the liver could potentially serve as a surrogate endpoint for clinical trials of disease-modifying therapies in ARPKD. The somatostatin analogs octreotide and pasireotide[22] and the multikinase inhibitor tesevatinib[23] have been shown to ameliorate ARPKD-related liver disease in rodent models, and a Phase 1 clinical trial is now underway for tesevatinib.[24] If any of these agents progresses to efficacy trials, reliable biomarkers of ARPKD liver disease severity will be needed to monitor response to therapy. Because ultrasound ARFI elastography can detect increased liver stiffness even in ARPKD children without clinical signs of portal hypertension, it appears to be more useful than clinical measures such as spleen size and platelet count to monitor ARPKD liver disease severity.

We acknowledge that larger multicenter studies will be needed to further validate the SWS cut-offs identified in the current study and to identify SWS cut-offs that can predict more severe complications such as varices. Another strength of our study was the recruitment of a reference population of healthy control children. The SWS values for liver and spleen obtained in our healthy controls were similar to those obtained in the largest published study of ARFI normative values in children,[15] which supports the external validity of our findings.

A major limitation in any study attempting to investigate a new noninvasive biomarker is the lack of a clinical "gold standard" by which to judge the accuracy of the imaging measure. We, therefore, had to rely on clinical measures of portal hypertension, namely splenomegaly and low platelets, to gauge the reliability of the ARFI elastography measures. However, spleen size and platelet counts are themselves imperfect measures of portal hypertension. As noted previously, esophageal varices have been reported even in patients with normal spleen size.[3] In addition, platelet counts can vary in the context of viral or other illnesses. "Hard" clinical endpoints for portal hypertension, such as esophageal variceal bleeding, are potentially more reliable; however, as observed in the current study, such severe complications are thankfully relatively infrequent in a pediatric population. Another limitation of our study is its cross-sectional nature. Although we found that liver and spleen SWS correlated with clinical signs of portal hypertension across participants with ARPKD, we cannot yet determine whether an individual's liver and spleen SWS will increase over time with progression of liver fibrosis and portal hypertension. Our ongoing longitudinal study of participants with ARPKD will allow us to address this question in the future.

In summary, this study supports the use of ultrasound ARFI elastography of the liver and spleen, an in particular elastography of the left liver lobe, to measure the severity of liver fibrosis and portal hypertension in children with ARPKD. ■

The acknowledgments are available at www.jpeds.com.

Submitted for publication Oct 16, 2018; last revision received Jan 9, 2019; accepted Jan 30, 2019.

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Funding

Funded by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH) (5-K23-DK109203 to E.H.]) and by the National Center for Advancing Translational Sciences (NCATS), NIH, (5-KL2-TR-000139 [PI: Fitzgerald]). The Clinical and Translational Research Center at the CHOP is supported by the National Center for Research Resources and NCATS, NIH (UL1RR024134 and UL1TR000003). The funders did not have a role in study design, data collection, analysis, reporting, or the decision to submit for publication. E.H. served as a consultant for and receives research funding from Kadmon Corporation, LLC. The other authors declare no conflicts of interest.

Acknowledgment

We thank Norma Latham, Marci Hutchinson, Trudi Morgan, Nina Laney, Daniel Elchediak, and Mohini Dutt for their invaluable assistance with data collection and management. We thank Kathleen Loomes, MD for her advice and critical review of the manuscript, and Rachel Rogers, MS, for biostatistical advice. We also thank the network of primary care clinicians, their patients, and families for their contribution to this project and clinical research facilitated through the Pediatric Research Consortium (PeRC) at CHOP. Study data were collected and managed using REDCap (Research Electronic Data Capture)[25] hosted at CHOP, a secure web-based application designed to support data capture for research studies, providing a validated data entry interface; audit trails for tracking data manipulation and export procedures; automated export procedures to common statistical packages; and procedures for importing data from external sources.

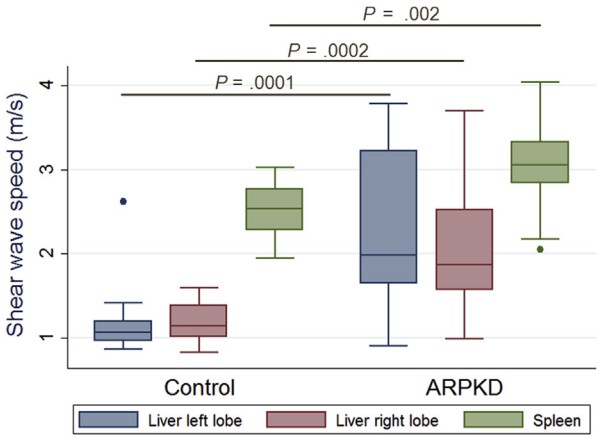

Figure 2. Liver and spleen stiffness in age-matched healthy controls and participants with ARPKD. Liver and spleen SWS measured by ARFI ultrasound elastography in age-matched groups of healthy controls (n = 18) and participants with ARPKD (n = 18).

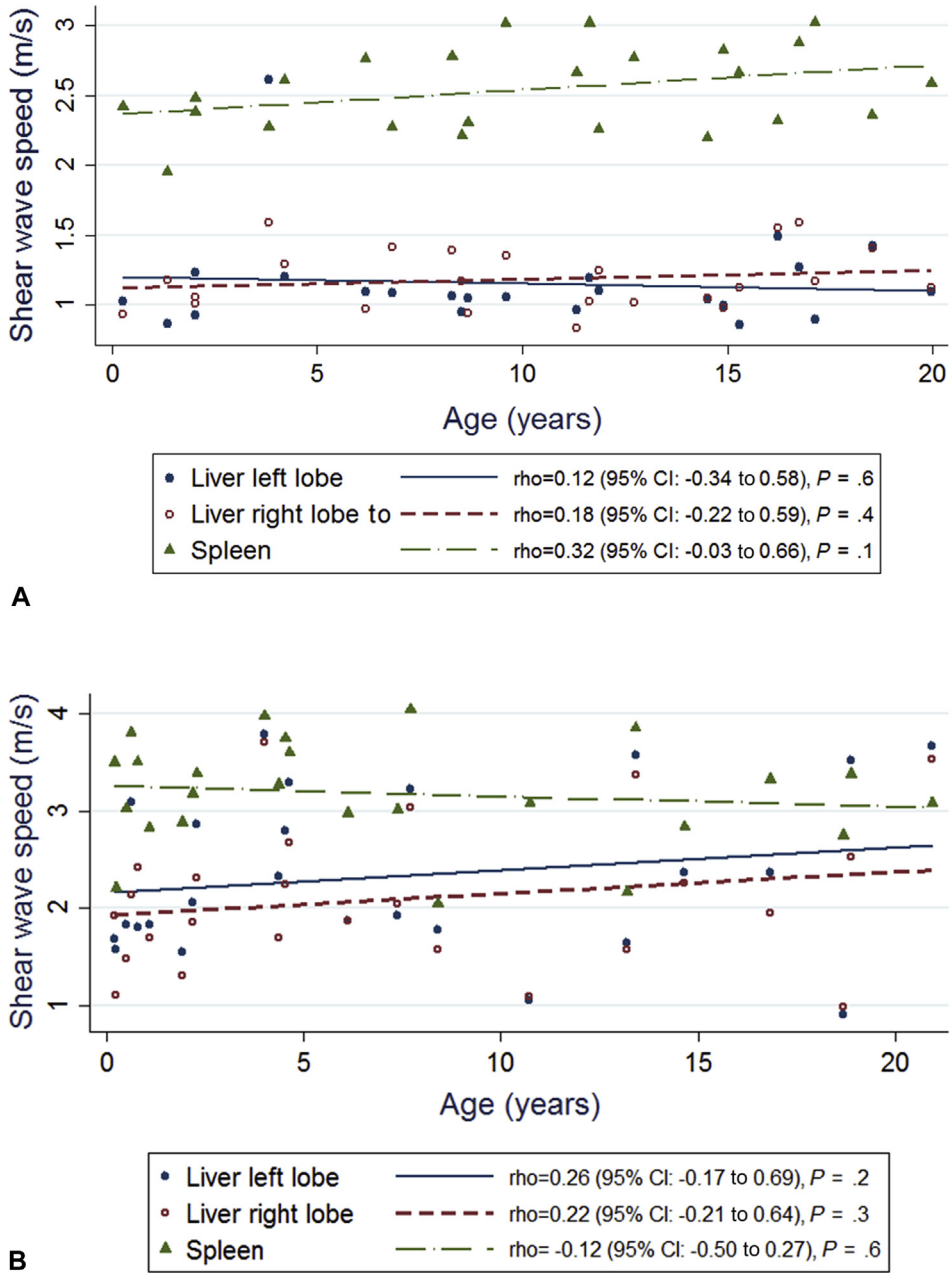

Figure 3. Relationship of liver and spleen stiffness with age. Relationship between liver and spleen SWS measured by ARFI ultrasound elastography with age in **A,** healthy controls (n = 24) and **B,** participants with ARPKD (n = 25).

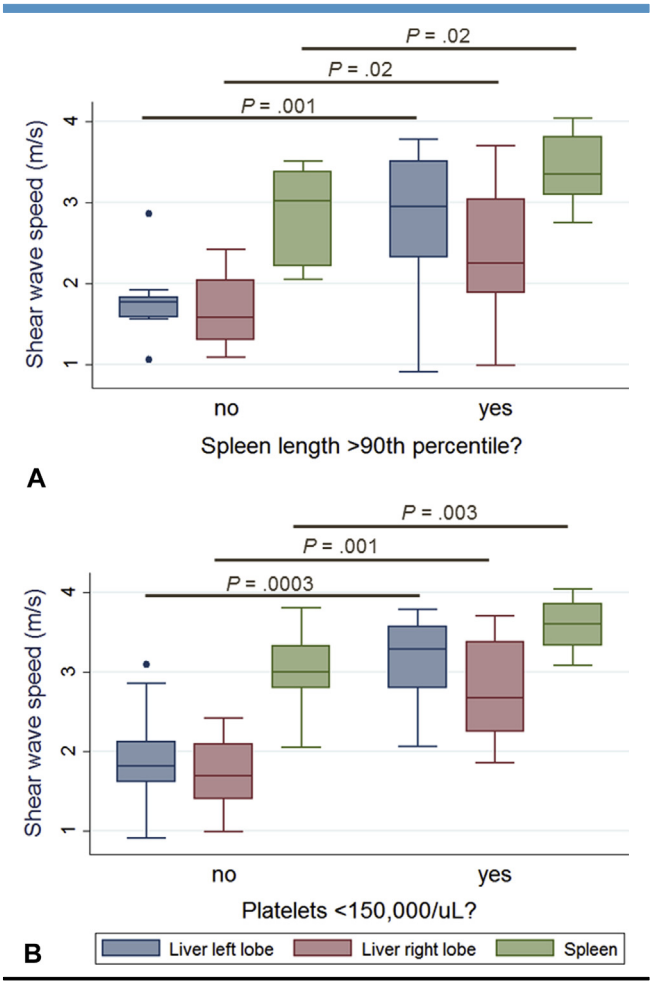

Figure 4. Liver and spleen stiffness in participants with ARPKD without vs with clinical signs of portal hypertension. Liver and spleen SWS measured by ARFI ultrasound elastography in participants with ARPKD **A,** without (n = 11) vs with (n = 14) splenomegaly, **B,** without (n = 16) vs with (n = 9) low platelets.

Table II. Clinical and demographic characteristics of participants with ARPKD without vs with signs of portal hypertension (splenomegaly and low platelets)

Characteristics	Without splenomegaly (Definitive no pHTN) (n = 11)	With splenomegaly (n = 14)	*P*	Without low platelets (n = 16)	With low platelets (Definitive yes pHTN) (n = 9)	*P*	*P* (Definitive pHTN no vs yes)
Age, y	1.9 [0.5, 8.4]	6.9 [4.4, 16.8]	**.02**	3.3 [0.7, 9.6]	7.7 [4.5, 16.8]	.06	**.03**
Male sex	8 (73%)	7 (50%)	.4	9 (56%)	6 (67%)	.7	.9
eGFR* (mL/min/1.73 m^2)	69.8 [30.2, 95.2]	62.3 [48.6, 89.8]	.8	68.0 [42.6, 92.8]	59.3 [42.5, 82.4]	.9	.9
WBC count ($\times 10^3/\mu L$)	11.0 [5.0, 13.5]	6.1 [4.1, 7.5]	**.03**	8.8 [6.2, 12.8]	4.4 [3.1, 5.9]	**.002**	**.01**
Platelets							
Count ($\times 10^3/\mu L$)	322 [272, 429]	142 [81, 241]	**.0002**	308 [269, 401]	87 [81, 139]	**<.0001**	**.0002**
$<150 \times 10^3/\mu L$	0 (0%)	9 (65%)	**.001**	0 (0%)	9 (100%)	n/a	n/a
Spleen length							
Index (actual/90th percentile)	0.89 [0.82, 0.90]	1.41 [1.17, 1.51]	**<.0001**	0.90 [0.85, 1.06]	1.45 [1.42, 1.54]	**.0001**	**.0002**
>90th percentile	0 (0%)	14 (100%)	n/a	5 (31%)	9 (100%)	**.001**	n/a
History of varices	0 (0%)	3 (21%)	-	0 (0%)	3 (33%)	-	n/a
With bleeding	n/a	2 (14%)	-	n/a	2 (22%)	-	
History of ascending cholangitis	0 (0%)	1 (7%)	-	0 (0%)	1 (11%)	-	n/a

eGFR, estimated glomerular filtration rate; *pHTN*, portal hypertension.
Continuous variables given as median [IQR]; binary variables as count (%).
All participants without splenomegaly had normal platelet counts and were categorized as "Definitive no pHTN." All participants with low platelets also had splenomegaly and were categorized as "Definitive yes pHTN."
*Includes 5 participants with kidney transplant.
P values that were significant ($P < 0.05$) were put in bold.

Table III. Comparison of patients with ARPKD with kidney transplant vs those without kidney transplant: clinical and demographic characteristics, and liver and spleen SWS measured by ARFI ultrasound elastography

Characteristics	ARPKD with kidney transplant (n = 5)	ARPKD without kidney transplant (n = 20)	*P*
Age, y	6.1 [4.5, 18.7]	4.3 [0.9, 12.0]	.2
eGFR (mL/min/1.73 m^2)	65.2 [53.7, 82.4]	62.7 [34.7, 102.7]	.9
WBC count ($\times 10^3/\mu L$)	7.5 [6.3, 7.6]	6.1 [4.3, 11.6]	.9
Platelets			
Count ($\times 10^3/\mu L$)	199 [147, 241]	271 [90, 355]	.5
$<150 \times 10^3/\mu L$	2 (40%)	7 (35%)	.9
Spleen length			
index (actual/90th percentile)	1.17 [1.11, 1.42]	0.94 [0.88, 1.41]	.2
>90th percentile	5 (100%)	9 (45%)	**.05**
Definite pHTN†	2 (40%)	7 (35%)	.2
SWS (m/s)			
Liver left lobe	2.32 [1.87, 2.80]	1.99 [1.73, 3.16]	.9
Liver right lobe	1.88 [1.69, 2.25]	1.99 [1.58, 2.54]	.5
Spleen	3.27 [2.97, 3.37]	3.13 [2.86, 3.55]	.9

Continuous variables given as median [IQR]; binary variables as count (%).
†Definite pHTN = splenomegaly + low platelets.
P values that were significant ($P < 0.05$) were put in bold.

Table IV. Diagnostic accuracy of cut-off values for liver and SWS measured by ARFI ultrasound elastography to distinguish between Healthy controls vs participants with ARPKD; Healthy controls vs participants with ARPKD without portal hypertension; Participants with ARPKD without vs with splenomegaly; Participants with ARPKD without vs with low platelet counts; and Participants with ARPKD without vs with definitive portal hypertension (ie, both splenomegaly and low platelet counts)

Group comparison	Sites	Proposed SWS cut-off (m/s)	Sensitivity (%)	Specificity (%)	Correctly classified (%)
Healthy controls vs participants with ARPKD	Liver left lobe	1.56	92	96	94
	Liver right lobe	1.49	84	88	86
	Spleen	2.83	84	83	84
Healthy controls vs participants with ARPKD without portal hypertension	Liver left lobe	1.56	91	96	94
	Liver right lobe	1.49	73	83	83
	Spleen	2.83	73	83	80
Participants with ARPKD without vs with splenomegaly	Liver left lobe	2.06	86	91	88
	Liver right lobe	1.86	86	64	76
	Spleen	3.08	79	73	76
Participants with ARPKD without vs with low platelet counts	Liver left lobe	2.37	89	88	88
	Liver right lobe	2.52	67	100	88
	Spleen	3.60	56	94	80
Participants with ARPKD without vs with definitive portal hypertension	Liver left lobe	2.06	100	91	95
	Liver right lobe	2.52	67	100	85
	Spleen	3.08	100	73	85