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Liver Involvement in Early Autosomal Dominant Polycystic Kidney Disease

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The author(s) meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). Drs. Hogan and Abebe had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Abstract

Background & Aims—Polycystic liver disease (PLD), the most common extra-renal manifestation of autosomal-dominant polycystic kidney disease (ADPKD), has become more prevalent due to increased life expectancy, improved renal survival, reduced cardiovascular mortality, and renal replacement therapy. No studies have fully characterized PLD in large cohorts. We investigated whether liver and cyst volumes associate with volume of the hepatic parenchyma, results from liver laboratory tests, and patient-reported outcomes.

Methods—We performed a cross-sectional analysis of baseline liver volumes, measured by magnetic resonance imaging, and their association with demographics, results from liver laboratory and other tests, and quality of life. The data were collected from a randomized, placebo-controlled trial underway at 7 tertiary-care medical centers to determine whether the combination of an angiotensin I converting enzyme inhibitor and angiotensin II receptor blocker was superior to the inhibitor alone, and whether low blood pressure (<110/75mmHg) was superior to standard blood pressure (120–130/70–80mmHg), in delaying renal cystic progression in 558 patients with ADPKD, stage 1–2 chronic kidney disease, and hypertension (15–49 years old).

Results—We found hepatomegaly to be common among patients with ADPKD. Cysts and parenchyma contributed to hepatomegaly. Cysts were more common and liver and cyst volumes were greater in women, increasing with age. Patients with advanced disease had relative loss of liver parenchyma. We observed small abnormalities in results from liver laboratory tests, and that splenomegaly and hypersplenism associated with the severity of PLD. Higher liver volumes were associated with lower quality of life.

Conclusions—Hepatomegaly is common even in early-stage ADPKD and not accounted for by cysts alone. Parenchymal volumes are larger, compared with liver volumes of patients without ADPKD or with those predicted by standardized equations—even among patients without cysts. The severity of PLD is associated with altered biochemical and hematologic features, as well as quality of life.

Keywords

HALT-PKD-A; hepatic cyst; CKD; MRI analysis

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease and the fourth leading cause of end-stage kidney disease worldwide.^{1, 2} Polycystic liver disease (PLD), arbitrarily defined as the presence of any liver cyst, is its most common extrarenal expression.^{3, 4} Liver cysts often remain asymptomatic, but some individuals experience chronic manifestations related to progressive liver enlargement leading to disability and severely impacting quality of life.⁵ Symptoms of PLD relate to effects from the volume of hepatic cysts or complications such as cyst hemorrhage, rupture, or infection. Massive hepatomegaly can cause compression of the adjacent gastrointestinal tract, vasculature, and diaphragm. Highly symptomatic PLD has become more common due to reduced cardiovascular mortality, extended renal survival and life expectancy on renal replacement therapy.⁶⁻¹¹ Some individuals require interventions including cyst aspiration and/or sclerosis, fenestration and/or combined liver resection/cyst fenestration, hepatic artery embolization, or in extreme cases, liver or combined liver-kidney transplantation. Several interventional clinical trials with the objective of delaying the progression of PLD have been published.¹²⁻¹⁷

No studies have fully characterized PLD burden in large cohorts with ADPKD. This characterization is needed, as its full clinical impact is not well understood. The HALT Progression of Polycystic Kidney Disease Study A (HALT-PKD-A) is the largest clinical cohort of ADPKD patients with liver and kidney imaging studied to date and is comprised of 558 individuals with early disease (estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m²) and hypertension, prospectively followed for up to 8 years.^{18,19} The objective of this study was to systematically characterize PLD-associated morbidities in this cohort and correlate the extent of PLD assessed by magnetic resonance imaging (MRI) with relevant baseline clinical and laboratory data.

METHODS

The HALT-PKD A trial is multicenter, randomized, placebo-controlled trial to investigate the effect of blockade of the renin-angiotensin-aldosterone system on total kidney volume and renal function in adults with ADPKD; eligibility criteria and protocol design are published.¹⁸ Full description of methods can be found in the supplemental material.

RESULTS

LVs (available on 534 individuals) (Figure 1A, 1B; 267 males; 267 females) were higher in men (2022±740 mL) than women (1905±859 mL) ($P=0.0003$). After height adjustment there was no gender difference: 1115±405 mL/m (males) versus 1141±518 mL/m (females) (Table 1, Figure 1A).

Higher prevalence and earlier development of liver cysts in women

LCV (unadjusted for height) was significantly higher in women (311±763 mL) than men (122±648 mL) ($P<0.0001$; Table 1, Figure 1A). Females had higher liver cyst prevalence (78.7%) than males (69.3%) ($P=0.0137$); age adjusted OR=1.54, $P=0.032$ (Table 1). Older men

and women had higher liver cyst prevalence (44%, 68%, and 84% of women 24, 25-34, and 35 years old, compared to 17%, 57%, and 79% of men in the same age groups. Eighty-three percent (20 patients) of those with htLCV >700 mL/m were women, as compared to 49% (275 of 558) in the entire cohort (Figure 1B).

Both LCV and LPV contribute to hepatomegaly

In both sexes, LVs were significantly larger in the ADPKD patients than those reported in a group of potential liver donors and for the general population.²⁰ Using a standardized equation for Caucasians, LVs were also higher than those predicted for the same HALT-PKD ADPKD patients (Table 2).^{20, 21, 22} When adjusted to height, htLPVs were higher in men and htLCVs higher in women (Table 1). To ascertain whether cyst development fully accounts for hepatomegaly, we compared LPVs in the cohort to observed and expected normal LVs in the general population and found that LPVs in our cohort were significantly larger than the LVs in liver transplant living donors ($P<.0001$), LVs reported in healthy controls ($P<.0001$), and predicted LVs in our participants using a standardized equation. Even in those without liver cysts, this was significant ($P<.0001$).²²

Relative reduction in LPV in severe PLD

As expected, htLCV correlated positively with htLV, particularly in severe PLD (Figure 1A) (females $r=0.69$; males $r=0.48$). After reaching an htLCV threshold of ~700 mL/m, htLPV does not continue to increase (Figures 1B, Figure 2A, 2B). Because most of these cases are women, the trends of htLV, htLCV, and htLPV (in Figure 1B) account for the lower LPVs in women with compared to those without liver cysts (1555 ± 289 vs. 1735 ± 448 mL, $P=.0003$, Table 2). Thus, while LPV is normal or larger compared to healthy normals in the majority of ADPKD patients, relative reductions in htLPV occur in a small subset with severe PLD (Figure 1B,).

Classification of PLD into mild, moderate, and severe

We used the data depicted in Figure 1B to classify the extent of PLD into mild, moderate, and severe. We arbitrarily defined mild PLD as htLV <1000 mL/m, and considered htLV between 1000 - 1800 mL/m to represent moderate PLD. We defined severe PLD as htLV >1800 mL/m, (women were 81%) concordant with the plateauing of htLPV at this cutoff point, which approximately corresponds to htLCV >700 mL/m. Table 3 compares demographic, laboratory, and imaging characteristics of patients according to PLD severity. Alternatively arbitrary htLCV cutoffs can be used to define disease (Supplemental Table 5). Patients with severe PLD were older (females in their fourth decade) with lower platelet counts, albumin, eGFR, quality of life, and higher alkaline phosphatase (ALP), alanine aminotransferase (ALT), height adjusted spleen volume (htSV) (Figure 2C).

Determinants of LV, LCV, and LPV

In bivariate analyses, age, eGFR, htTKV (women only), body weight, BSA and BMI, BPs, and caffeine intake associated with htLV (Supplemental Table 1 and data not shown). Variables associated with htLCV were similar, including age, eGFR, htTKV (women only), body weight, BSA and BMI (women only) (Supplemental Table 1). Baseline variables

associated with htLPV were body weight, BSA, BMI, and BPs (Supplemental Table 1). In multivariable analyses (not shown), sex ($P=.004$), age ($P=.001$), weight ($P<.001$), and systolic BP ($P=.010$) were independently associated with htLV; sex ($P<.001$), age ($P<.001$) and lower eGFR ($P=.046$) were associated with htLCV; weight ($P<.001$) and systolic BP ($P=.002$) were independently associated with htLPV.

Subtle liver laboratory test elevations in women with PLD

Liver laboratory tests were mostly within normal range (Table 1). Only 2.3%, 2.7%, and 4.5% of patients had levels of serum ALP, aspartate aminotransferase (AST), and ALT above the upper limit of laboratory normal, and 5.1% had a serum albumin concentration below the lower limit of normal. Serum albumin and blood platelets were lower, whereas serum ALP, spleen volume, and physical role were higher in the severe PLD group (Table 3). In both sexes, ALT correlated with htLV and htLPV (Table 3; data not shown; Supplemental Table 2). ALP (both sexes) and AST (women only) correlated positively with htLV ($P=.0042$ and $P=.0471$, respectively), while serum albumin negatively correlated with htLV ($P=.0042$) and htLPV ($P<.0001$) (Supplemental Table 2). Correlations between ALP, ALT, or serum albumin and htLV in women remained significant after adjusting for age ($P=.001$, $P=.001$, and $P=.003$, respectively). In men, the correlation between ALT and htLV or htLPV persisted after adjusting for age ($P=.006$).

LV, QOL, and pain

Scores on several health-related quality of life (HRQoL) questionnaire subdomains (SF-36) including physical role, general health, vitality, mental health, and standardized component, were lower in women compared to men (Table 1). There was a weak association between htLV and SF-36 role-physical ($P=.0017$) and physical component of health summary score (PCS) in both sexes ($P=.0053$) with general health ($P=.0048$), vitality ($P=.0359$) and mental health ($P=.0450$) in men (Table 3). When analyzed by htLV severity, there was an association with decreased physical role ($P=.0358$) (Table 3). The associations between QOL parameters and htLV did not persist after adjusting for age, BMI, and TKV. When we considered additive effects of htSV+htLV+htTKV (data not shown), we did not see any correlation with QOL measurements in the multivariate analysis, after adjusting for age and BMI for either sex. There were no significant differences across each subdomain according to LCV burden (Supplemental table 5).

Mild splenomegaly and hypersplenism. (see online supplemental results)

Impact of estrogen use and pregnancy number on PLD severity (see online supplemental results)

Prevalence of pancreatic and splenic cysts in ADPKD (see online supplemental results).

DISCUSSION

Despite its significance in ADPKD, few studies have investigated the impact of PLD.²³⁻²⁶ HALT-PKD-A provides an opportunity to correlate MR imaging with clinical, laboratory, and other parameters in a large cohort of patients with ADPKD and CKD stages 1 and 2.

Patient selection criteria did not include presence of or extent of PLD.¹⁸ Therefore, although this cohort represents a highly selected ADPKD population, recruitment was unaffected by biases favoring inclusion or exclusion of patients with severe PLD. Beyond confirming the recognized higher prevalence and severity of PLD in women compared to men, this study reveals a number of novel observations that advance the understanding of PLD.²⁶ Observed LVs (both male and females) were significantly higher than in the general population, and in women, LPVs were significantly larger than LVs predicted for the same patients. The finding of increased LPV compared to normals indicates that hepatomegaly cannot be entirely accounted for by macroscopic cysts detectable by MRI. It is possible that microscopic cysts or bile duct proliferation contribute to LPV.^{27, 28} Alternatively hepatocyte hyperplasia or hypertrophy may also contribute to hepatomegaly.²⁹ Indeed this novel observation is consistent with the recent description of hepatocyte hypertrophy in a mouse model of ADPKD and PLD generated by the insertion of a human *PKD1* mutation, and demonstration that polycystin 1 and polycystin 2 are expressed in hepatocytes where their reduced expression/function may cause the hepatocyte hypertrophy observed by Hopp et al.³¹ Interestingly, many cytokine and growth factors implicated in hepatic regeneration after liver mass reduction are upregulated in PLD.^{30,32-36}

A previous small study had shown that hepatic parenchyma and function remain normal even in the presence of hepatomegaly.²⁶ Our study shows a relative reduction in LPV in patients with severe PLD. Furthermore, hepatomegaly is accompanied by subtle changes in LLTs (reflected in positive correlations with liver enzymes and negative correlation with serum albumin) and mild hypersplenism (reflected in the positive correlation with spleen volume and negative correlation with platelet count). Therefore, mild elevations in LLTs and mild thrombocytopenia are associated with hepatomegaly in PLD.²⁸

While the association of pancreatic cysts is well recognized, splenic cysts have only been anecdotally reported.³¹⁻³³ In the current study, the prevalence of splenic cysts was 2.7%, but their origin (epithelial, lymphatic, or other) is unknown. Mild common bile duct dilatation occurs frequently in ADPKD.³⁴ Common bile duct diameter correlated positively with htLV and htLPV, possibly due to shared pathogenic mechanisms. Awareness of this association is important to avoid unnecessary invasive diagnostic procedures.

The correlation between systolic BP and htLPV was unexpected. Angiotensinogen is synthesized in both liver and proximal renal tubules, and overexpression at either site might increase BP, potentially accounting for this correlation. Hormone overproduction at either site is associated with hypertension in mouse transgenic models, and there is some basis for this underlying mechanism in humans.^{35, 36}

Another notable finding is the significant impact of LV on quality of life. Consistent with greater PLD severity in women, the impact was also more pronounced in females. Even though life-threatening hepatic dysfunction is rare in ADPKD, the effect of massive organ enlargement *per se* on QOL provides a strong rationale for medical interventions to retard liver growth. Liver cyst prevalence and LVs were higher in women with a history of pregnancy compared to nulliparous women, regardless of prior birth control pill use. This difference, however, disappeared after adjusting for age. Therefore we could not

demonstrate an independent effect of pregnancy or exogenous estrogens on LV, likely due to the relatively young age and low PLD severity of the patients in our study and the lower estrogen content of contemporary contraceptives.^{37, 38}

The strengths of this study are cohort design, large size, prospective data collection, including QOL assessments, high quality imaging and analysis. LCV is more difficult than total LV measurement.³⁹

There are several study limitations. Cases were selected for early CKD and likely underestimate the burden of PLD because the HALT-PKD-A cohort is limited by its narrow age inclusion criteria (15-49 years). In fact, the patients in this study are more likely to represent the more general PLD population seeking specialty care (for hypertension management, disease specific complications, and counseling) rather than individuals with severe symptomatic PLD and hepatomegaly or other liver-specific complications, which tend to be over-represented in the medical literature and often referred to gastroenterologists. Additional clinical information will emerge from longitudinal analysis of this cohort. Because MR protocols did not use gadolinium, portal, hepatic veins and arteries could not be accurately assessed.

Although we do not have a clear explanation for the observed reductions in QOL, they are most likely due to the impact of progressive liver mass effects, which are more frequent and severe in women than men, as seen in other studies.^{25, 40} The SF-36 questionnaire has not been validated in PLD and better patient-reported outcome tools are needed.

In summary, we have used data from the HALT-PKD-A cohort to better define PLD burden. Previous studies have proven MRI to be a useful tool in assessing kidney volume in ADPKD, and kidney volume is being considered as a biomarker of disease severity. We demonstrate the relationship between MRI-measured LVs with baseline biochemical/hepatologic perturbations and QOL, thus demonstrating their potential for validation as outcome measures for clinical trials in PLD. Over the course of this study, sequential longitudinal imaging will provide liver growth rates and a deeper understanding of spectrum of disease severity in PLD and its complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
AST	aspartate aminotransferase

ALP	alkaline phosphatase
ALT	alanine aminotransferase
BMI	body mass index
BP	blood pressure
BSA(m²)	body surface area (corrected for height)
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
DBP home	home diastolic blood pressure
HALT-PKD	Halt Progression of Polycystic Kidney Disease studies
HALT-PKD-A	Halt Progression of Polycystic Kidney Disease Study A
HRQoL	health-related quality of life
htLCV	height adjusted liver cyst volume
htLV	height adjusted total liver volume
htTKV	height adjusted total kidney volume
htLPV	height adjusted liver parenchymal volume
htSV	height adjusted spleen volume
LCV	Liver cyst volume
LLT	Liver laboratory test LPV, liver parenchymal volume
LV	total liver volume
MCS	Mental component of health summary score
PCC	participating clinical center
PCS	physical component of health summary score
PLD	polycystic liver disease
QOL	quality of life SBP home, home systolic blood pressure
SF-36	health-related quality of life (HRQoL) questionnaire short form 36
TKV	total kidney volume
WBC	peripheral white blood cell count

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Figure 1. Effects of sex on height adjusted total liver volume (HtLV) and relationship of HtLV to height adjusted liver parenchymal volume (HtLPV)

(A) Distribution of liver cyst volumes (HtLCV) in relation to HtLVs. A subpopulation of women have more severe PLD with higher HtLCV. (B) Plot of HtLPV and HtLCV versus HtLV. As HtLV increases, HtLPV also increases, but then plateaus. Interrupted diagonal line (slope=1) denotes the maximum values for HtLPV and HtLCV indicating HtLPV closely parallels HtLV for the majority of individuals until HtLV reaches ~1800 mL/m

(vertical interrupted line). To illustrate this, the patient with liver cysts and mildest disease (lower left) had HtLV 475 mL/m (mild disease; HtLV<1000mL/m, vertical interrupted line), HtLCV 1 mL/m, and HtLPV 475 mL/m, and the most severe case (points farthest right) had HtLV of 6382 mL/m, HtLCV of 5287 mL/m, and HtLPV of 1095mL/m but their HtLPV is no different than less severe PLD cases with lower HtLVs. X and Y axes are log scale in both figures. The correlation between log (HtLV) and log (HtLPV) was $r=0.65$ ($P<0.001$). Note second vertical interrupted line (HtLV>1800 mL/m), the cutoff point for HtLV that delineated Group 3 or the group with the highest HtLVs (see Table 3). To the right of the graph are two additional vertical lines delineating HtLVs 2x those of normal female (1x=1858 mL/m) and male (1x= 1986 mL/m) controls.

Figure 2. MR images illustrating

(A) Hepatomegaly (TLV 2677 mL) with larger contribution of LPV (2576 mL) compared to LCV (101 mL); (B) Hepatomegaly (11834 mL) with larger contribution of LCV (9806 mL) compared to LPV (2028 mL); (C) Splenomegaly (601 mL) associated with severe PLD(3388 mL) with LCV (1044 mL); (D) Splenomegaly (542 mL) associated with moderate PLD (LV 2082 mL, LCV 110 mL) (E) Pancreatic cyst (diameter 21.8 mm) (F) Splenic cysts (diameter 12.2 mm).

Table 1

Baseline Characteristics of the Study Population

	Male (N=283, 51%)		Female (N=275, 49%)		
Variable	n	mean±std	n	mean±std	P value
Vital Statistics					
Age (years)	283	35.7±8.1	275	37.6±8.4	.006 [*]
Weight (kg)	275	90.5±15.5	273	74.3±16.4	<.0001 [*]
Height (cm)	275	181.0±7.8	271	166.5±6.5	<.0001 [*]
BMI (kg/m2)	274	27.7±4.5	271	26.8±5.7	.044 [*]
BSA (m2)	274	2.1±0.2	271	1.8±0.2	<.0001 [*]
SBP home	192	126.6±9.3	180	121.3±8.9	<.0001 [*]
DBP home	192	82.2±8.1	180	83.0±7.4	.2956
Image analysis					
Patients with liver cysts (%)	185	69.3	210	78.7	.0137 [*]
LV (mL)	267	2021.8±748.5	267	1904.6±859.5	.0003 ^{*1}
htLV (mL/m)	259	1115.2±405.5	263	1141.2±517.6	.7251 ¹
LCV (mL)	267	121.6 (±647.6)	267	310.8 (±763)	<.0001 ^{*1}
htLCV (mL/m)	259	64.6 (±351.3)	263	184.3 (±459.3)	<.0001 ^{*1}
LPV	267	1900.2±343.9	267	1593.8± 336.7	<.0001 ^{*1}
htLPV (mL/m)	259	1050.6±184.5	263	956.9±196.8	<.0001 ^{*1}
TKV (mL)	269	1403.7±752.6	269	1014.6±618.8	<.0001 ^{*1}
htTKV	261	773±408	265	610±368	<.0001 ^{*1}
Spleen volume (mL)	273	339.7±129.2	272	252.6 ±91.4	<.0001 ^{*1}
htSV (mL/m)	265	187.3±69.1	268	151.3±53.7	<.0001 ^{*1}
Laboratory					
eGFR (mL/min)	282	90.4±17.8	275	92.7±17.1	.12
Serum albumin (mg/dL)	280	4.3±0.7	274	4.1±0.5	<.0001 [*]
Serum sodium (mEq/L)	283	139.3± 2.1	275	138.6±7.8	.1371
Hemoglobin (g/dL)	281	15.0±2.1	270	13.8±7.1	.005 [*]
WBC (cells/μL)	281	6.24±1.8	271	6.6±5.9	.295
Platelets (cells/μL)	281	248.2±58.5	272	260.4±60.4	.017 [*]
AST (u/L)	282	26.4±13.1	275	21.8±6.9	<.0001 [*]
ALT (u/L)	282	29.3±17	275	19.1±9.0	<.0001 [*]
Alkaline Phos (u/L)	282	64.7±28.7	275	54.5±17.3	<.0001 [*]

Variable	Male (N=283, 51%)		Female (N=275, 49%)		P value
	n	mean±std	n	mean±std	
Bilirubin (mg/dL)	282	0.85±0.41	275	0.66±0.3	<.0001 *
SF-36 QOL					
Physical functioning	278	91.5±18.2	270	90.5±17.5	.49
Physical role	277	91.6±19.9	269	88.3±21.5	.058
Bodily pain	277	80.8±20.5	268	74.4±22.3	.0006 *
General health	278	67.0±19.7	270	64.5±20.0	.13
Vitality	277	64.7±18.2	269	59.8±20.9	.003 *
Social functioning	277	90.3±2	269	85.5±21.6	.004 *
Role emotional	276	91.9±2	267	88.6±20.6	.04 *
Mental health	278	91.5±18.2	270	90.5±17.5	.49
Standardized mental component	277	51.7±7.9	268	50±9.8	.021 *
Standardized physical component	277	52.8±7.3	268	51.5±7.8	.0503

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA(m²), body surface area (corrected for height); DBP home, home diastolic blood pressure; eGFR, estimated glomerular filtration rate; htLCV, height adjusted liver cyst volume; htLPV, height adjusted liver parenchymal volume; htLV, height adjusted total liver volume; htSV, height adjusted spleen volume; htTKV, height adjusted total kidney volume; LCV, liver cyst volume; LPV, liver parenchymal volume; LV, total liver volume; MCS, Mental component of health summary score; PCS, physical component of health summary score derived from the SF-36 quality of life form; SBP home, home systolic blood pressure; TKV, total kidney volume; WBC, peripheral white blood cell count.

* Significant P value.

Table 2

Comparison of liver and liver parenchymal volumes and predicted liver volumes using a standardized equation versus liver volumes for healthy controls.

	Liver Volume (mL)		Liver Parenchymal Volume (mL)			
	Normal living liver transplant donors	HALT (predicted)	HALT (observed)	HALT (all patients)	HALT (patients with cysts)	HALT (patients without cysts)
Men						
mean±std (n)	1772±393 (11)	1875 ±238 (274)	2022±749 (267)	1900±344 (267)	1892 ±331 (185)	1918 ±372 (82)
<i>P</i> value vs. normal donors	-----	-----	<.0001 *	<.0001 *	<.0001 *	<.0001 *
<i>P</i> value vs. predicted LV	-----	-----	.0004 **	.6046 **	.7931 **	.5969 **
Women						
mean±std (n)	1495±357 (21)	1511±235 (271)	1905±860 (267)	1594±337 (267)	1555 ±289 (210)	1735 ±448 (57)
<i>P</i> value vs. normal donors	-----	-----	<.0001 *	<.0001 *	<.0001 *	<.0001 *
<i>P</i> value vs. predicted LV	-----	-----	<.0001 **	<.0001 **	.0001 **	<.0663 **

To determine predicted LV (reported as "HALT predicted") we used the Vauthey formula, a validated equation for the estimation of standard liver volume in the Caucasian population ($LV \text{ in mL} = -794.41 + 1,267.28 \times BSA \text{ in m}^2$).²² Note values in this table are unadjusted for height to permit between group comparisons.

Normal liver transplant donor MRI-derived LVs were obtained at the University of Pittsburgh from patients considering liver donation. Similar results were obtained using LVs from a CT-based study from another published healthy population (males 1710±288 mL (41) and females 1411±263 mL (36)).²⁰

* One-sample *t* test compared to healthy controls.

** Paired *t* test compared to predicted LV.

Table 3

Demographics, laboratory values, image analysis, and SF-36 by htLV category (mild, moderate, severe polycystic liver disease)

Variable	htLV (1) <1000 mL/m (Mild PLD) (n=230)	htLV (2) 1000-1800 mL/m (Moderate PLD) (n=264)	htLV (3) >1800 mL/m (Severe PLD) (n=28)	P value
Vital Statistics				
Age, mean±std, (years)	35.2±9.0	37.2±7.4	42.5±4.5	<i>P</i> <.0001 [*] vs 2, <i>P</i> =.0160 1 vs 3, <i>P</i> <.0001 2 vs 3, <i>P</i> =.0026
Sex, No. (% female)	123 (43.16%)	106 (54.36%)	34 (80.95%)	<i>P</i> <.0001 [*] 1 vs 2, <i>P</i> =.0158 1 vs 3, <i>P</i> <.0001 2 vs 3, <i>P</i> =.0015
Age (median and range)	33.71, 34.22	40.53, 30.70	43.24, 22.01	
Laboratory (mean±std)				
eGFR	95.5±17.8	89.1±16.7	84.2±16.7	<i>P</i> <.0001 [*] 1 vs 2, <i>P</i> =.0010 1 vs 3, <i>P</i> =.0029
sAlbumin, mg/dL (n)	4.3±0.8 (229)	4.1±0.4 (262)	4.0±0.7	<i>P</i> =.0042 [*] 1 vs 2, <i>P</i> =.0135 1 vs 3, <i>P</i> =.046
Bilirubin, mg/dL	0.8±0.4	0.8±0.3	0.6±0.2	<i>P</i> =.1451
Alk phosphatase	57.8±22.2	59.9±26.5	74.0±22.7	<i>P</i> =.0042 [*] 1 vs 3, <i>P</i> =.0028 2 vs 3, <i>P</i> =.0108
AST (u/L)	23.2±8.8	24.8±12.6	26.4±8.3	<i>P</i> =.1531
ALT (u/L)	21.1±3.9	27.4±15.3	26.2±11.4	<i>P</i> <.0001 [*] 1 vs 2, <i>P</i> <.0001
s Sodium, mEq/L	139.2±2.2	138.6±8.0	140.1±2.0	<i>P</i> =.2638
Hemoglobin, g/dL (n)	14.0±2.5 (226)	14.8±7.2 (262)	13.7±0.8	<i>P</i> =.2072
Platelets, cells/uL (n)	254.3±57.5 (227)	259.7±58.9 (263)	219.2±45.6	<i>P</i> =.0020 [*] 1 vs 3, <i>P</i> =.0070 vs 3, <i>P</i> =.0013
WCC, cells/uL (n)	6.5±6.4 (226)	6.4±1.8 (262)		<i>P</i> =.9372
Image Analysis (mean±std)				
LCV, mL	33.4±73.6	140.8±263.3	2358.9±2004.8	<i>P</i> <.0001 ^{*I} 1 vs 2, <i>P</i> <.0001 1 vs 3, <i>P</i> <.0001

Variable	htLV (1) <1000 mL/m (Mild PLD) (n=230)	htLV (2) 1000-1800 mL/m (Moderate PLD) (n=264)	htLV (3) >1800 mL/m (Severe PLD) (n=28)	P value
htLCV, mL/m (n)	19.8±44.3 (230)	82.4±156.0	1389.9±1127.4	2 vs 3, $P<.0001$ $P<.0001^{*I}$
TKV, mL (n)	1197.3±748.7 (226)	1204.1±72.9 (259)	1303.6±744.8	1 vs 2, $P<.0001$ 1 vs 3, $P<.0001$ 2 vs 3, $P<.0001$
htTKV, mL/m (n)	685.9±412.3 (226)	683.6±370.5 (259)	766.0±430.6	$P=.4181^I$ $P=.3409^I$
LPV, mL	1488.7±205.4	1948.4±329.2	1972.8±517.7	$P<.0001^{*I}$ 1 vs 2, $P<.0001$ 1 vs 3, $P<.0001$
htLPV, mL/m	858.9±92.2		1165.5±292.0	$P<.0001^{*I}$ 1 vs 2, $P<.0001$ 1 vs 3, $P<.0001$
Spleen Volume, mL (n)	255.4±97.9 (224)	328.5±125.8	318.0±126.7	$P<.0001^{*I}$ 1 vs 2, $P<.0001$ 1 vs 3, $P=.0148$
htSV, mL/m (n)	147.0±52.5 (224)	186.5±66.3	186.7±70.6	$P<.0001^{*I}$ 1 vs 2, $P<.0001$ 1 vs 3, $P=.0032$
SF-36 QOL (mean±std)				
Physical functioning (n)	90.4±19.3 (226)	91.8±15.7 (260)	89.8±18.1	$P=.6325$
Physical role (n)	92.0±17.0 (225)	88.8±23.2 (259)	82.4±22.3	$P=.0358^{*}$
Bodily pain (n)	78.4±21.5 (224)	77.8±21.7 (259)	68.9±23.5	$P=.0881$
General health (n)	66.9±20.4 (226)	65.0±19.5 (260)	59.8±20.4	$P=.1699$
Vitality (n)	63.1±19.5 (225)	61.7±20.3 (259)	58.2±22.8	$P=.4266$
Social functioning (n)	88.2±19.6 (225)	88.0±20.4 (259)	80.8±21.4	$P=.1781$
Role emotional (n)	90.2±18.4 (223)	90.4±19.8 (258)	84.5±20.5	$P=.3040$
Mental health (n)	77.8±15.8 (225)	77.3±14.5 (259)	74.5±12.4	$P=.5419$
Standardized mental component (n)	51.0±9.6 (224)	50.7±8.6 (259)	48.4±9.4	$P=.3542$
Standardized physical component (n)	52.5±7.3 (224)	52.1±7.4 (259)	49.8±8.4	$P=.1905$

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; htLCV, height adjusted liver cyst volume; htLPV, height adjusted liver parenchymal volume; htLV, height adjusted total liver volume; htSV, height adjusted spleen volume; htTKV, height adjusted total kidney volume; LCV, liver cyst volume; LPV, liver parenchymal volume; LV, total liver volume; TKV, total kidney volume; WCC, white cell count.

^I P value calculated using log transformed variables.

* Significant P value. For quality of life data, despite an overall $P<.05$, there were still no statistically significant pairwise comparisons values (probably due to the marginal P value $P=.0358$).