

# The Longitudinal Study of Liver Cysts in Patients With Autosomal Dominant Polycystic Kidney Disease and Polycystic Liver Disease



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**Introduction:** Although polycystic liver disease (PCLD) is one of the extrarenal complications in patients with autosomal dominant polycystic kidney disease (ADPKD), longitudinal changes and the association with total liver volume (TLV) have not been clearly elucidated yet.

**Methods:** Patients with ADPKD were chosen who underwent computed tomography or magnetic resonance imaging twice or more during August 2003 through December 2015. TLV, each cyst volume, and the proportion of parenchyma were measured. The natural history of liver cysts and the association between TLV and liver cysts were evaluated. To compare with liver cysts in ADPKD patients with PCLD, simple liver cysts in patients without ADPKD were also evaluated.

**Results:** TLV at baseline and its growth rate in all the patients with ADPKD, whose serum creatinine, estimated glomerular filtration rate, and total kidney volume were 1.45 mg/dl (0.76–2.32 mg/dl), 38.5 ml/min per 1.73 m<sup>2</sup> (18.7–57.9 ml/min per 1.73 m<sup>2</sup>), and 1394 ml (773–2861 ml), were 1431 ml (1062–1749 ml) and –0.95%/yr (–3.16 to 4.94%/yr), respectively, in the observation period (median, 1063 days). Neither TLV nor its growth rate was significantly different between ADPKD patients with PCLD and those without PCLD. The growth rate of 79 liver cysts was 39.5%/yr (17.5–80.8%/yr) in PCLD patients with ADPKD. It was significantly larger than that of 60 simple liver cysts in the non-ADPKD group, 11.0%/yr (–2.2 to 33.1%/yr). Moreover, the proportion of parenchyma reduced, whereas that of total cyst volume increased significantly ( $P = 0.001$ ).

**Discussion:** The reduction of parenchyma was accompanied by the growth of liver cysts during time course in PCLD patients with ADPKD.

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KEYWORDS: autosomal dominant polycystic kidney disease; polycystic liver disease

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Before the emergence of tolvaptan, therapeutic strategy consisted of supportive treatment such as blood pressure control in autosomal dominant polycystic kidney disease (ADPKD), and direct treatment against renal cyst enlargement was unavailable. The main cause of ADPKD included renal failure, heart failure, and cerebrovascular disease such as subarachnoid hemorrhage decades ago.<sup>1</sup>

The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) 3:4 trial<sup>2</sup> showed that tolvaptan slowed both the increase in total kidney volume (TKV) and the decline of renal function in ADPKD. This novel treatment will possibly change the clinical course in ADPKD. It is expected that tolvaptan will delay the age of dialysis initiation in patients with ADPKD.<sup>3,4</sup> Because dialysis management has been improved in recent years,<sup>5</sup> patients can undergo better medical treatment even after dialysis initiation. Thus, patients with ADPKD would receive benefit from management of chronic kidney disease in predialysis and dialysis periods. Furthermore, screening of intracranial aneurysm is recommended to improve their prognosis in Japan.<sup>4</sup>

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As a result of the medical advance, the life expectancy of patients with ADPKD would elongate, and nephrologists would have more chance to see patients with ADPKD with or without renal replacement therapy.<sup>5</sup>

Polycystic liver disease (PCLD) is the major extra-renal complication in patients with ADPKD.<sup>6,7</sup> Some ADPKD patients with PCLD present various clinical symptoms such as abdominal fullness, pain, and early satiety that lower their quality of life. They also have some complications such as leg edema and portal hypertension. Moreover, a certain number of patients experience annoying events such as cystic infection, hemorrhage, and rupture.<sup>8,9</sup> Especially, infection including cystic infection was the third cause of death among patients with ADPKD in Japan. Because better management of chronic kidney disease and brain aneurysm is provided, liver involvement will be more frequent in ADPKD henceforth.

Symptoms and complications related to ADPKD have become more frequent in patients with ADPKD at older age.<sup>10</sup> This clinical course suggests that cyst growth may be associated with cyst infection. From this viewpoint, it is clinically useful to clarify the time course of liver and renal cysts. The association between cyst volume and TKV was reported, whereas liver cysts were previously evaluated in a few studies.<sup>11–14</sup> Furthermore, the former reports of PCLD in patients with ADPKD were cross-sectional studies,<sup>11–14</sup> and longitudinal changes and the association with total liver volume (TLV) have not been clearly elucidated yet.

In this study, we show the characteristics of PCLD in patients with ADPKD, comparing them with non-PCLD patients with and without ADPKD.

## METHODS

### Patients and Definitions

Adult patients (>18 years old) clinically diagnosed with ADPKD were enrolled who underwent computed tomography or magnetic resonance imaging twice or more during August 2003 through December 2015 at the University of Tokyo Hospital. The diagnosis of ADPKD was based on 5 or more cysts in each kidney detected by images, family history, and comorbidity after other cystic kidney diseases could be excluded.<sup>4</sup> These patients were divided into 2 groups: patients with PCLD (PCLD group) and those without PCLD (non-PCLD group). PCLD was defined as having 15 or more liver cysts at computed tomography or magnetic resonance imaging.<sup>15</sup>

Likewise, 34 patients without ADPKD with a few liver cysts were selected as control. All the patients without ADPKD were diagnosed with simple liver cysts.

Parameters checked at baseline were as follows: age, sex, body height, body weight, body mass index, body

surface area, blood pressure, aspartate transaminase, alanine transaminase, alkaline phosphatase, creatinine, sodium, potassium, white blood cell, hemoglobin, and platelets.

### Measurements of Total Liver Volume, Liver Cyst Volume, and Total Kidney Volume

Both TLV and liver cyst volume were measured using the image processing software ImageJ (National Institutes of Health, Bethesda, MD).<sup>16</sup> TLV and each liver cyst volume were calculated as the sum of cross-sectional areas times slice thickness. Liver cysts with the diameter of more than 2 cm were selected at the last computed tomography or magnetic resonance imaging because it was difficult to evaluate the accurate change in the size of small cysts. The parenchymal volume was calculated as the sum of cross-sectional areas after adjusting each liver slice (3–6 mm). Height-adjusted TLV was calculated as the ratio of TLV to body height.<sup>14</sup> In case of multiple scans, we compared the oldest scan with the latest scan.

TKV was estimated from maximum length (L), width (W), and height (H), using the formula for an ellipsoid:  $\pi/6 \times L \times W \times D$ .

All the measurements were performed by 2 independent well-trained nephrologists.

### Analysis

Data were shown as median (interquartile range). Statistical analyses were performed by the Mann-Whitney test when comparing between groups or the Wilcoxon signed-rank test when comparing between baseline and time-proceeding data in the same group because all data were not parametric. The cubic approximation of cyst volume was applied using cyst diameter with analysis of variance. Statistical analyses were performed by JMP Pro 11 for Windows (SAS Institute Japan, Tokyo). The significant difference was defined as  $P$  value < 0.05.

## RESULTS

### Total Liver Volume in the PCLD and Non-PCLD Groups

Of 36 patients with ADPKD in our hospital, 23 patients were eligible for this study. Among them, 13 patients were included in the PCLD group. The observation interval was 1063 days (203–2373 days). Baseline characteristics are shown in Table 1. No parameters were significantly different between the PCLD group and the non-PCLD group with ADPKD at baseline. No patients with ADPKD had elevated liver enzyme and had been treated with somatostatin analog or immunosuppressive agents such as mammalian target of rapamycin inhibitors before.

**Table 1.** Characteristics of patients with ADPKD

	All (n = 23)		PCLD (n = 13)		Non-PCLD (n = 10)		P value
Age	54	(46–67)	65	(46–67)	50	(43–63)	0.47
Male/female	12/11		6/7		6/4		0.51
Body height (m)	1.66	(1.56–1.74)	1.64	(1.55–1.73)	1.66	(1.55–1.75)	0.83
Body weight (kg)	68.2	(49.3–72.0)	55.0	(46.4–70.2)	71.0	(49.8–79.8)	0.15
BMI (kg/m <sup>2</sup> )	22.6	(19.2–25.2)	21.0	(18.5–23.7)	23.9	(21.1–28.0)	0.10
BSA (m <sup>2</sup> )	1.73	(1.39–1.84)	1.58	(1.37–1.78)	1.79	(1.46–1.87)	0.25
Hypertension	21	(91%)	12	(92%)	9	(90%)	1.00
sBP (mm Hg)	130	(120–143)	130	(121–140)	132	(120–150)	0.72
dBp (mm Hg)	80	(76–87)	81	(71–88)	80	(78–87)	1.00
AST (U/l)	19	(15–23)	21	(16–23)	19	(15–24)	0.69
ALT (U/l)	15	(12–20)	17	(13–21)	14	(11–19)	0.40
T-Bil (mg/dl)	0.65	(0.50–0.95)	0.65	(0.43–0.95)	0.65	(0.60–1.02)	0.61
Alb (g/dl)	4.1	(3.9–4.2)	4.0	(3.7–4.2)	4.1	(4.0–4.3)	0.44
Cr (mg/dl)	1.45	(0.76–2.32)	1.45	(0.76–2.21)	1.49	(0.84–3.70)	0.76
eGFR (ml/min per 1.73 m <sup>2</sup> )	38.5	(18.7–57.9)	38.5	(18.5–57.8)	39.9	(18.4–60.8)	0.93
Na (mEq/l)	140	(139–142)	141	(139–142)	140	(135–142)	0.48
K (mEq/l)	4.5	(4.0–4.7)	4.3	(3.8–4.6)	4.7	(4.2–4.9)	0.23
WBC (per $\mu$ l)	5000	(4100–7100)	5000	(4300–6200)	5700	(4000–8500)	0.74
Hb (g/dl)	12.7	(11.3–14.1)	12.7	(11.2–14.4)	12.7	(11.2–14.0)	0.85
Plt ( $\times 10^4/\mu$ l)	20.7	(16.7–24.3)	18.5	(16.9–25.4)	21.2	(16.6–24.7)	0.95
TKV (ml)	1394	(773–2861)	991	(568–2134)	2127	(848–5093)	0.23
htTKV (ml/m)	776	(471–1626)	580	(359–1354)	1234	(526–3179)	0.16
TLV (ml)	1431	(1062–1749)	1538	(1171–1978)	1227	(969–1566)	0.18
htTLV (ml/m)	847	(639–1013)	879	(676–1241)	738	(621–895)	0.18

ADPKD, autosomal dominant polycystic kidney disease; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BSA, body surface area; Cr, creatinine; dBp, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; htTKV, height-adjusted total kidney volume; htTLV, height-adjusted total liver volume; PCLD, polycystic liver disease; Plt, platelet; sBP, systolic blood pressure; T-Bil, total bilirubin; TKV, total kidney volume; TLV, total liver volume; WBC, white blood cell.

TLV and its growth rate in all the patients with ADPKD were 1431 ml (1062–1749 ml) and  $-0.95\%/yr$  ( $-3.16$  to  $4.94\%/yr$ ), respectively. TLV and its growth rate were 1536 ml (1171–1978 ml) and  $-0.95\%/yr$  ( $-2.78$  to  $19.6\%/yr$ ) in the PCLD group, whereas they were 1227 ml (969–1566 ml) and  $-0.38\%/yr$  ( $-8.63$  to  $3.47\%/yr$ ), respectively, in the non-PCLD group. Neither TLV nor its growth rate was significantly different between the groups (Figure 1). In addition, there was no association between TLV and TKV.

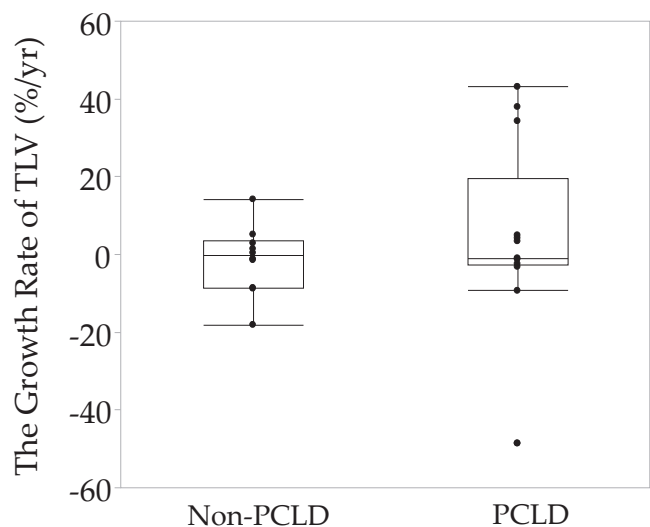
### The Characteristics of Liver Cysts in PCLD Patients With ADPKD

The number of calculated cysts in PCLD patients with ADPKD was 79, and the median volume was 3.05 ml (1.69–5.84 ml). If the maximum diameter of cyst was defined as  $X$  (mm), the volume of cyst  $Y$  (ml) was approximated by the following formula:  $Y = 0.0007X^3 - 0.0318X^2 + 0.5137X$  ( $r^2 = 0.92$ ,  $P < 0.001$ ) (Figure 2).

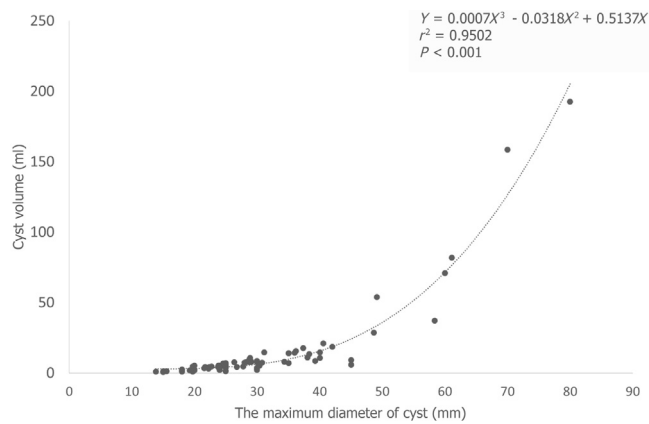
All liver cysts in PCLD patients with ADPKD enlarged in the observation period, and the increasing rate of liver cysts in the PCLD group was  $39.5\%/yr$  ( $17.5$ – $80.8\%/yr$ ). This was significantly larger than  $11.0\%/yr$  ( $-2.2$  to  $33.1\%/yr$ ) in the control group without ADPKD ( $n = 60$ ) (Figure 3). The growth rate of liver cysts did not correlate with that of TLV and TKV (data not shown).

### The Proportion of Parenchyma and Liver Cysts in PCLD Patients With ADPKD

The proportion of parenchyma and cysts were evaluated because TLV was unchanged despite the enlargement of each cyst volume. The proportion of parenchyma decreased significantly from  $71.7 \pm 18.0\%$



**Figure 1.** TLV change in patients with ADPKD. The vertical axis represents the change of TLV compared with baseline (%), whereas the horizontal axis represents time (days). ADPKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease; TLV, total liver volume.



**Figure 2.** Association between liver cyst volume and the diameter of cyst in PCLD patients with ADPKD. ADPKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease.

at baseline to  $65.0 \pm 16.8\%$  at proceeding time. On the other hand, the proportion of cysts increased significantly from  $28.3 \pm 18.0\%$  at baseline to  $35.0 \pm 16.8\%$  at proceeding time ( $P = 0.001$ , Figure 4a and b).

## DISCUSSION

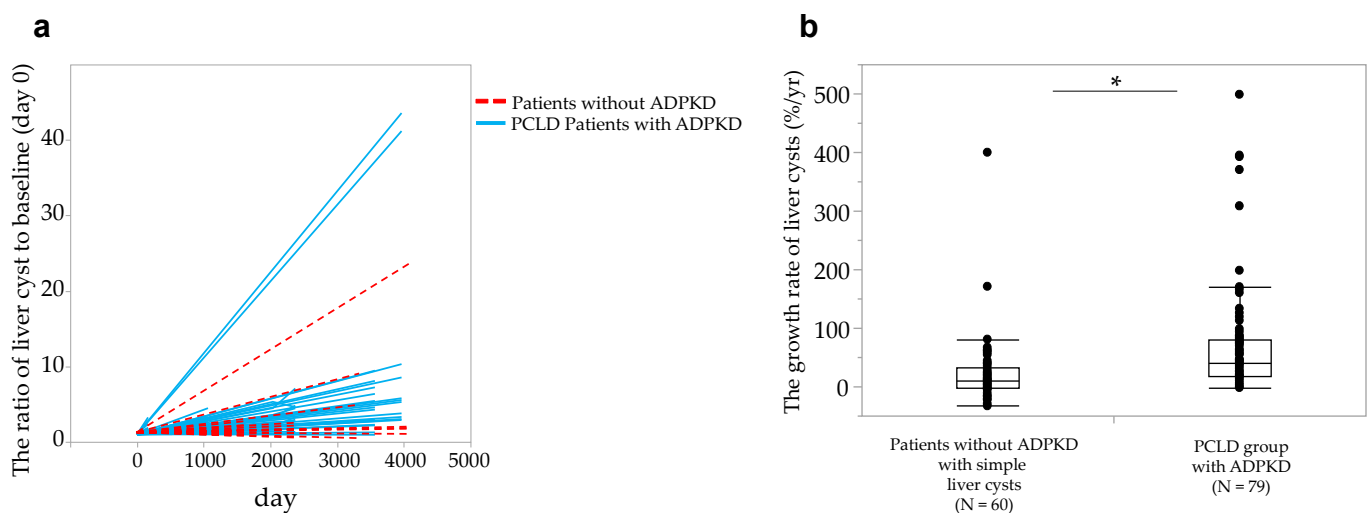
PCLD is the major extrarenal complication in patients with ADPKD. This study showed the clinical course of liver cysts in patients with ADPKD, and clarified some characteristics.

First, liver cysts in patients with ADPKD were increasing and never shrinking. As shown in Figures 4 and 5, all liver cysts in patients with ADPKD enlarged with various growth rates, whereas not all simple liver cysts enlarged. This characteristic was supported by the result in a previous report that liver cyst volume was associated with age.<sup>6</sup>

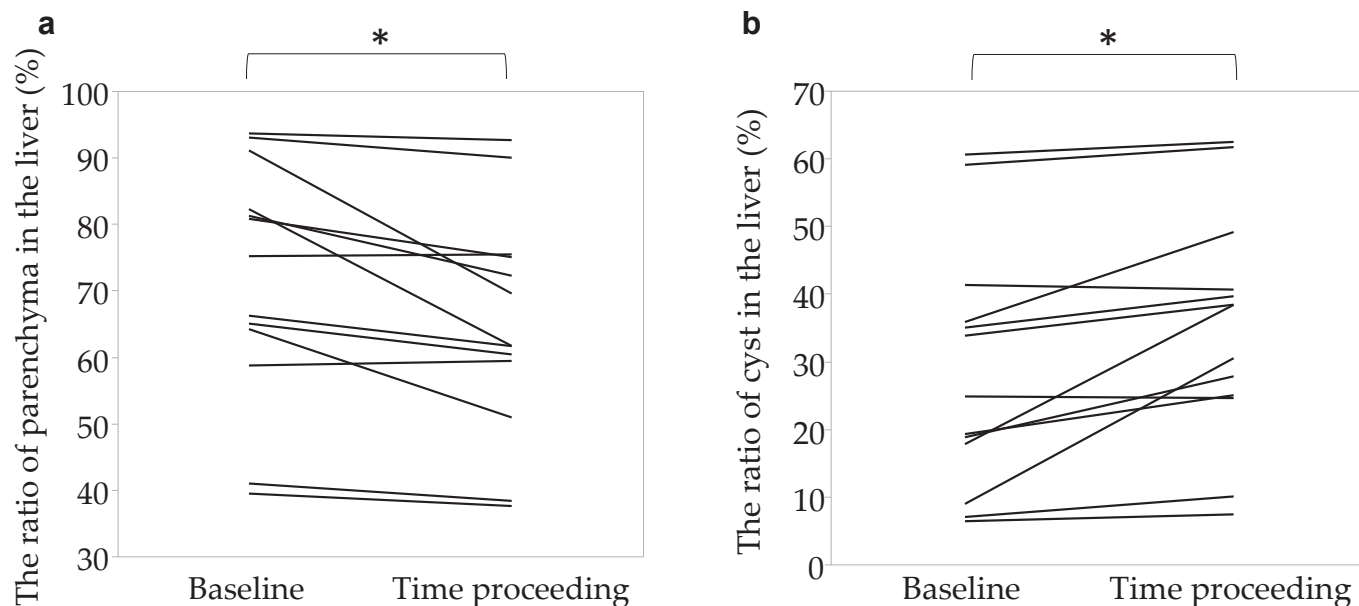
Second, the growth rates of liver cysts did not correlate with the change of TLV. The result was unchanged in a case with the lowest growth rate in the PCLD group. This was inconsistent with some former studies that concluded that liver cyst volume was associated with TLV.<sup>14,17</sup> However, it is of note that TLVs in our study were smaller than those in the previous studies. Unlike the relationship between renal cysts and TKV, TLV would not reflect liver cyst volume when liver cysts were not enormous. Moreover, focusing on patients without severely developed liver cyst volume, it seemed that there were no associations with cyst volume and TLV. The result was similar to ours, and it is speculated that cyst volume increased and parenchymal volume reduced despite unchanged TLV when TLV was mild to moderate. Indeed, this speculation could explain the fact that the proportion of parenchyma volume reduced and the proportion of cyst volume increased in spite of unchanged TLV, as shown in Figure 4. When the total liver cyst volume severely developed, both total cyst volume and TLV increased, as shown in Figure 5b.

Third, the growth of liver cysts did not correlate with TKV. The defect of polycystin, encoded by the causal gene of ADPKD, may contribute to the development of liver cysts<sup>18,19</sup>; however, the factors promoting cyst growth are not clarified. Our result suggested that the growth factors of liver and kidney cysts will be different.

Fourth, the growth rate of TLV in some patients was negative. This was consistent with the previous large cohort.<sup>20</sup> Total liver volume shrinks with aging in healthy population.<sup>21</sup> Shrinkage of parenchyma may have a stronger impact than cyst growth in some patients.



**Figure 3.** (a) Clinical course of cyst growth in PCLD patients with ADPKD and patients without ADPKD. The vertical axis is the ratio of cyst volume to baseline (day 0) volume. (b) Cyst growth rate in PCLD patients with ADPKD and patients without ADPKD.  $*P < 0.001$ . ADPKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease.



**Figure 4.** The proportion of (a) parenchyma and (b) cyst at baseline and time proceeding in PCLD patients with ADPKD. \* $P = 0.001$ . ADPKD, autosomal dominant polycystic kidney disease; PCLD, polycystic liver disease.

There were some limitations of our study. First, the sample was small. Although previous studies about PCLD with ADPKD are limited, the fact that the median of TLV in our report was similar to that in a previous study<sup>22</sup> indicates that selection bias was unlikely in this study. Second, heterogeneous observation intervals might have affected the change of TLV because this was a retrospective study. However, liver volume and its growth rate were consistent with the previous cohort and these differences had little impact on our results. A prospective and large clinical study with the same interval will help develop the perception in this study. Third, we evaluated only liver cysts with the maximum diameter of more than 2 cm because the volume of smaller cysts could not be measured accurately.

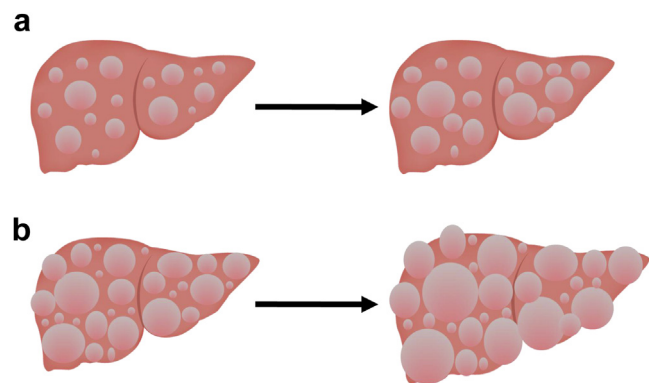
In conclusion, the change of TLV and liver cysts in mild-to-moderate PCLD patients with ADPKD was not paralleled because cyst volume was growing with the reduction of parenchyma. This is the first report that demonstrated the change of TLV and liver cysts among PCLD patients with ADPKD.

## DISCLOSURE

All the authors declared no competing interests.

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**Figure 5.** The relationship between TLV and cyst volume. (a) When cyst volume is mild to moderate, parenchymal volume decreases and TLV does not change, whereas the cyst grows. (b) When cyst volume is severely developed, cyst volume and TLV correlate. TLV, total liver volume.

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