CLINICAL GUIDANCE FOR POLYCYSTIC LIVER DISEASE

Thijs R.M. Barten

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Radboud Dissertation Series

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Radboud Dissertations Series
ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS
Postbus 9100, 6500 HA Nijmegen, The Netherlands
www.radbouduniversitypress.nl

Design: Proefschrift AIO | Katarzyna Kozak
Cover: Thijs R. M. Barten
Printing: DPN Rikken/Pumbo

ISBN: 9789493296275
DOI: 10.54195/9789493296275
Free download at: www.boekenbestellen.nl/radboud-university-press/dissertations

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Clinical guidance for polycystic liver disease

Proefschrift
ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op donderdag 14 december 2023
om 10.30 uur precies

door

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General Introduction

Background

What is PLD

Polycystic liver disease (PLD) is a rare hereditary disease diagnosed when >10 cysts are present in the liver. PLD can occur in two distinct forms [1]. First, PLD occurs in an isolated form in autosomal dominant polycystic liver disease (ADPLD) and second with concomitant kidney cysts in autosomal dominant polycystic kidney disease (ADPKD). Liver cysts in PLD develop as a result of an inherited ductal plate malformation and somatic second hit [2, 3]. Together these two hits cause a genetic disturbance in cholangiocytes which results in increased cell proliferation and fluid secretion. On a macroscopic level this can be observed as the presence of intrahepatic fluid-filled cavities: liver cysts. Liver cysts in PLD are benign and the liver's functional capacity remains preserved even in the presence of severe anatomical deformations. Liver growth progresses throughout life and can be observed as hepatomegaly [4].

Liver volume measurements

PLD severity can be quantified by measuring total liver volume (TLV). This objective parameter of disease severity is used in staging systems [5] and also serves as an important outcome measure to assess treatment efficacy. It correlates with symptom burden, which negatively impacts quality of life in the PLD population [6, 7]. Consequently, TLV measurements are an important part of clinical practice as well as therapeutic trials [8-12].

TLV can be obtained from computed tomography (CT) or magnetic resonance imaging (MRI) scans in which the entire liver is depicted [8, 13, 14]. CT scans for TLV measurements do not require high image resolutions and can be obtained with or without contrast enhancement. Manual or automatic approaches are used to calculate TLVs. In manual segmentation, the liver is contoured on every axial CT slice. Liver parenchyma and cystic tissue are included in the contours while the gallbladder and vascular structures are excluded. The corresponding liver volume is calculated by multiplying the contoured areas and slice spacing. In automatic segmentation a similar process is undertaken but the contours are made by automatic segmentation software. Automatic segmentation software is frequently developed with artificial intelligence based learning models and utilizes 3D instead of 2D models [14, 15].

Polycystic liver disease questionnaire

Symptoms in PLD ensue when polycystic livers compress adjacent anatomical structures. These symptoms decrease quality of life and can be captured using the disease-specific polycystic liver disease questionnaire (PLD-Q) [7, 16]. This patient-

reported outcome measure (PROM) quantifies symptom burden in PLD and addresses 16 PLD-related symptoms by expressing the presence and intensity of these symptoms with a score between 0 and 100. The PLD-Q can be used to evaluate cross-sectional symptom burden, but also to assess treatment efficacy [11, 17-19]. Symptom severity plays a pivotal role in PLD treatment since one study demonstrated that reduction in symptoms, and not reduction in cyst volume, represents treatment efficacy [18]. The PLD-Q is currently available in Dutch, English, German, French and Spanish, and part of the PROM repository of the European Reference Network RARE-LIVER.

Treatment

In view of the benign course of the disease, treatment in PLD is only indicated in patients with symptoms or PLD-related complications [1, 20]. Several treatment strategies are available, including radiological, surgical and medical therapies [1, 21-26]. Treatment choice is guided by the perceived symptoms, liver phenotype and availability of treatment options within a center [1, 27]. **Figure 1** illustrates the 5 treatment options currently available for PLD. Aspiration sclerotherapy involves percutaneous drainage of liver cysts, followed by sclerosing the cyst's epithelial lining with a sclerosing agent. The final results of this procedure can be expected after 6-12 months when all postprocedural reactive fluid in the cyst has been resorbed. Aspiration without sclerotherapy has a very high risk of recurrence [24]. Cyst fenestration is most frequently performed by laparoscopy. It encompasses intra-abdominal drainage of liver cysts followed by deroofing of the drained cyst. The main benefit of this procedure is that multiple large cysts can be targeted in a single procedure [23]. In liver resection, severely affected liver segments are resected. This procedure is only indicated in the presence of several cyst-free liver segments and should only be executed in centers with high levels of expertise. Liver transplantation is the only curative treatment option and reserved for severe PLD cases with a compromised quality of life and/or complications that affect survival. Liver transplantation is often preceded by somatostatin analogue treatment. Somatostatin analogues reduce liver volume in highly symptomatic patients with small-to-medium-sized cysts spread throughout the entire liver [8-12, 21]. Young women benefit most from somatostatin analogue treatment [28].

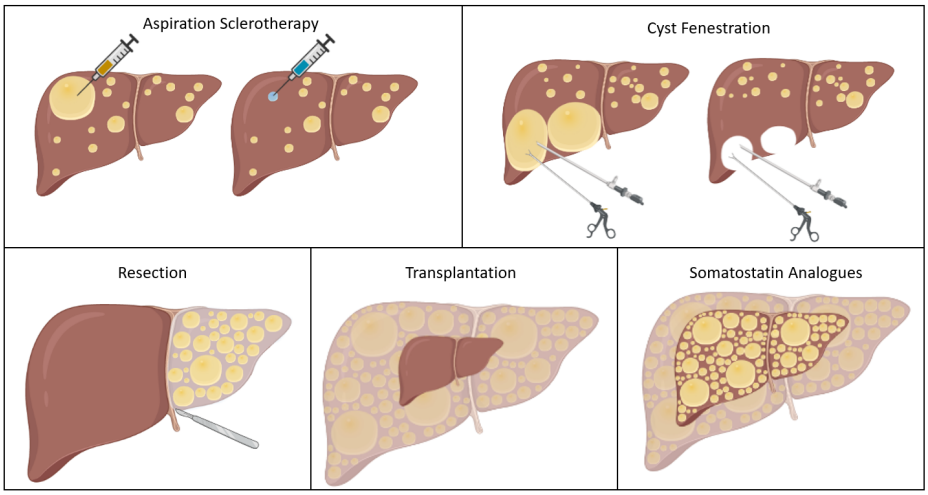

Figure 1 – Treatment options in polycystic liver disease.

Complications

Several complications may occur in PLD patients and can be categorized as intracystic or extracystic. Intracystic complications consist of cyst hemorrhage, cyst infection and cyst rupture. Cyst hemorrhage and rupture are often caused by external trauma to the cysts, while cyst infection is most frequently observed in patients after solid organ transplantation [29]. Extracystic complications are caused by mechanical pressure of (strategically located) cysts and include abdominal wall hernias (AWH), hepatic venous outflow obstruction, obstructive jaundice and portal hypertension [1]. AWHs are a frequent, but scarcely studied complication. In contrast, other PLD complications are rare.

Knowledge gaps

Liver volume measurements

Previous studies have demonstrated that manual segmentation of cystic livers yields accurate and reproducible TLVs [8-12, 21]. However, manual segmentation is time-consuming, expensive and only performed in several referral centers, which limits its availability in clinical practice. As a result, TLV measurements are typically performed in the most severe cases to assess treatment efficacy. In addition, research is hampered by selection bias and the natural growth of TLV remains unclear. Consequently, there is an unmet clinical need for fast and accurate liver segmentation tools in PLD.

PLD parameters

The PLD-Q is an important PROM to quantify symptom severity and assess treatment efficacy in PLD, yet it does not provide clinical guidance regarding initiation of therapies. Current treatment protocols and guidelines dictate that symptomatic patients should be treated, but there is no clear consensus on a threshold of symptom severity that warrants treatment [1, 20]. Consequently, a threshold that identifies patients in need of clinical therapy is needed.

PLD treatment is only indicated in symptomatic patients and previous studies have demonstrated the correlation between TLV and symptom severity [6]. However, the prognostic value of a baseline TLV measurement on treatment initiation in PLD remains unclear. Identification of a prognostic marker for PLD is urgently needed to counsel patients about their prognosis and develop a PLD staging system that differentiates between a mild or severe disease course.

Clinical guidance

Knowledge regarding diagnoses and management of cystic liver lesions has progressed drastically over the past decades. Radiological imaging has advanced to a point where high resolution images allow for accurate and precise discrimination between different cystic liver lesions. In addition, clinical trials have demonstrated the safety and efficacy of medical, radiological and surgical therapies [21, 23, 24]. Consequently a new clinical practice guideline that judges the available evidence and offers practitioners with clear and balanced clinical management advice is warranted.

AWHs are frequently observed in PLD patients in clinical practice, in contrast to other PLD complications. Their epidemiology and risk factors have never been studied, though they may prompt substantial symptom burden in PLD population. The epidemiology and risk factors of AWHs in PLD should be quantified as a first step to assess the impact of this complication on PLD patients.

Currently, the pathophysiology of PLD remains to be completely understood. Basic research has advanced the knowledge regarding pathological pathways involved in hepatic cystogenesis and several signaling paths have been targeted in clinical trials. Consequently lanreotide treatment has been added to the therapeutic options for PLD. An overview of the pathophysiology in PLD is required to identify the most promising therapeutic targets.

Research Aims

This thesis addresses 3 general research aims: 1) To improve disease severity tools, 2) to improve implementation of PLD parameters, and 3) to provide clinical guidance to practitioners who treat PLD patients. These 3 general research aims are supported by study-specific research aims, as described below. The research aims are also summarized in **table 1**.

Research aim 1: To improve disease severity tools

In chapter 2 and 3, we aimed to validate two previously developed liver segmentation tools in a real-world dataset of PLD patients. Chapter 3 comprises a semi-automatic segmentation tool that is based on Hounsfield Unit density of the liver and cystic tissue. Chapter 4 comprises a fully automatic artificial intelligence based segmentation tool.

Research Aim 2: To improve implementation of PLD parameters

In chapter 4 we aimed to develop a threshold for the PLD-Q to identify PLD patients with clinically important symptoms requiring further exploration and possibly intervention. This threshold can be applied in clinical practice or to select patients eligible for inclusion in trials.

In chapter 5 we aimed to assess the prognostic value of TLV on treatment initiation in PLD patients with special emphasis on differences between the two sexes. This study was performed in a prospective, multi-center cohort.

Research aim 3: To provide clinical guidance to practitioners who treat PLD patients

In chapter 6 we aimed to provide guidance in the clinical decision-making process of physicians faced with cystic liver disease patients. Cyst liver diseases include simple hepatic cysts, mucinous cystic neoplasms of the liver, PLD, Caroli disease, Caroli syndrome, biliary hamartomas and peribiliary cysts. All recommendations were based on systematic review of the literature.

In chapter 7 we aimed to assess the prevalence of AWH in PLD in a cross-sectional cohort study. In addition, we explored the risk factors for abdominal wall herniation.

In chapter 8 we summarized the therapeutic targets that are currently available for PLD. In addition, we discussed the pathophysiological pathways involved in hepatic cystogenesis and potential drug therapies that may target these pathways.

Chapter	Research Question	Study Design	Outcome	Measures
2	Does semi-automatic segmentation of polycystic livers using the Siemens Volume tool, yield fast and accurate total liver volume measurements in a real-life population?	Cross-sectional study	Validation of semi-automatic liver segmentation software	Bland Altman (bias, precision)
3	Does automatic segmentation of polycystic livers using the Philips IntelliSpace CT application, yield fast and accurate total liver volume measurements in a real-life population?	Cross-sectional study	Validation of automatic liver segmentation software	Bland Altman (bias, precision) Dice coefficient
4	Which threshold for the a polycystic liver disease questionnaire identifies polycystic liver disease patients in need of therapy?	Cross-sectional study	Development of a threshold for the polycystic liver disease questionnaire	Receiver operator characteristics (area under the curve)
5	What is the prognostic value of total liver volume on treatment initiation in polycystic liver disease?	Prospective cohort study	Determination of prognostic value of total liver volume	Prognostic value (hazard ratio)
6	How to diagnose and manage cystic liver diseases?	Systematic review	Clinical guidance in cystic liver diseases	Evidence level (Oxford center for evidence-based medicine)
7	What is the prevalence of abdominal wall hernias in polycystic liver disease and what are the associated disease-specific risk factors?	Cross-sectional study	Determination of frequency and risk factors of a PLD complication	Prevalence rate (%) Risk factor assessment (odds ratio)
8	What are the existing and potential new therapeutic targets of hepatic cystogenesis?	Narrative review	Overview of therapeutic targets in PLD	Therapeutic targets

Table 1 – Overview of research questions and methods

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2

Validation of a semi-automatic method to measure total liver volumes in polycystic liver disease on computed tomography – high speed and accuracy

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Abstract

Objectives: Polycystic liver disease (PLD) is characterized by growth of hepatic cysts, causing hepatomegaly. Disease severity is determined using total liver volume (TLV), which can be measured from computed tomography (CT). The gold standard is manual segmentation which is time-consuming and requires expert knowledge of the anatomy. This study aims to validate the commercially available semi-automatic MMWP (Multi-Modality-Workplace) Volume tool for CT-scans of PLD patients.

Methods: We included adult patients with one (n=60) or two (n=46) abdominal CT-scans. Semi-automatic contouring was compared with manual segmentation, using comparison of observed volumes (cross-sectional) and growth (longitudinal), correlation coefficients (CC) and Bland-Altman analyses with bias and precision, defined as the mean difference and SD from this difference. Inter- and intra-reader variability were assessed using coefficients of variation (CV) and we assessed the time to perform both procedures.

Results: Median TLV was 5292.2 ml (IQR 3141.4-7862.2 ml) at baseline. Cross-sectional analysis showed high correlation and low bias and precision between both methods (CC 0.998, bias 1.62%, precision 2.75%). Absolute volumes were slightly higher for semi-automatic segmentation, manual 5292.2 [3141.4-7862.2] versus semi-automatic 5432.8 [3071.9-7960.2] mL, difference 2.7%, $p<0.001$). Longitudinal analysis demonstrated that semi-automatic segmentation accurately measures liver growth (CC 0.908, bias 0.23%, precision 4.04%). Inter- and intra-reader variability were small (2.19% and 0.66%) and comparable to manual segmentation (1.21% and 0.63%), $p=0.26$ and $p=0.37$. Semi-automatic segmentation was faster than manual tracing (19 minutes versus 50 minutes, $p=0.009$).

Conclusions: Semi-automatic liver segmentation is a fast and accurate method to determine TLV and liver growth in PLD patients.

Key points

Semi-automatic liver segmentation using the commercially available MMWP-volume tool accurately determines total liver volume as well as liver growth over time in polycystic liver disease patients.

This method is considerably faster than manual segmentation through the use of Hounsfield Unit settings.

We used a real-life CT set for the validation, and showed that the semi-automatic tool measures accurately regardless of contrast used for the CT scan or not, presence of polycystic kidneys, liver volume and previous invasive treatment for polycystic liver disease.

Introduction

Polycystic liver disease (PLD) is characterized by growth of >10 hepatic cysts, leading to hepatomegaly [1,2]. PLD is caused by two inherited diseases: Autosomal Dominant Polycystic Liver Disease (ADPLD) and Autosomal Dominant Polycystic Kidney Disease (ADPKD). In ADPLD, cyst formation is restricted to the liver, while in ADPKD all patients develop cyst kidneys cyst and liver cysts develop in the majority of patients [1,3].

PLD can lead to various symptoms that ultimately impair their quality of life [4,5]. Symptoms are caused by the enlarged liver, which leads to mechanical compression of adjacent structures. This results in PLD-related symptoms such as pain, loss of appetite, abdominal herniation and sometimes a disturbed body image [1,2,6]. Total liver volume is directly associated with symptom severity [5–7].

Total liver volume (TLV) is an important parameter to define disease severity. Longitudinal TLV measurements play a pivotal role in evaluating disease progression and the response to therapies in clinical trials and clinical practice [8]. Liver function remains unaffected, even in severe cases and is not a relevant disease outcome [1,2]. In one of the largest PLD studies, mean liver growth was 3.9% per year in untreated patients [9]. Therefore, precise TLV measurement, with a precision smaller than the mean annual liver growth, is important to determine treatment effects [9,10].

The gold standard to measure TLV involves manual contouring of the liver boundaries on each slice, using dedicated software [11,12]. TLV is calculated by combining the contoured area and slice spacing [11,12]. This method is time-consuming and therefore expensive, requires expert anatomical knowledge and different observers may obtain dissimilar results from the same scan. Complex anatomical deformations and different tissue types present in PLD preclude the application of regular semi-automatic segmentation software. Therefore, there is an unmet clinical need for faster, easier and accurate (semi-)automatic methods to measure TLV on CT [10].

The aim of this study was to show that semi-automatic liver segmentation, using Siemens Multi-Modality WorkPlace (MMWP) tool 'Volume' is reliable and faster

than manual segmentation for both cross-sectional and longitudinal analysis, in a representative, real-life, dataset of PLD patients with a wide variety of CT-scan protocols and liver sizes.

Materials and methods

Study population

In this cohort study, PLD patients were recruited from existing databases from observational studies in two tertiary referral centers in the Netherlands. Patients were included if they had PLD and two axial CT-scans, at least six months apart, were available. All CT-scans had been made in the framework of clinical care in our centers or referral centers, and had therefore been made according to different scan protocols with different phases of contrast. The only exclusion criteria were incomplete CT-scans (e.g. missing slices) or incomplete livers on the CT-scan. CT-scan characteristics (low dose, blanco or phase of contrast) were noted in the database. Baseline parameters on underlying disease (ADPLD or ADPKD), body height and surgical interventions before and between the two CT-scans were collected from study databases or patient records.

Manual TLV measurements

Manual TLV measurements were performed by trained observers using Pinnacle 3 (Philips Radiation Oncology Systems) and Analyze version 9.0 (Analyze Direct, Inc.). Liver boundaries were contoured on each axial slice and TLV was subsequently calculated by multiplying the contoured area by the spacing between slices. Extrahepatic structures (e.g. gallbladder, portal vein and caval vein) were excluded from the liver boundaries if visible. Before inclusion in the database, all liver segmentations were checked for completeness and all reported volumes were recalculated by another independent observer. All observers were blinded for timepoint, patient ID and previous measured volumes for all measurements.

Semi-automatic measurements using MMWP Volume (Siemens)

Semi-automatic TLV measurements were performed by one experienced observer (WC), using the Siemens MMWP tool called Volume version VE61B. This method is referred to as 'semi-automatic measurements'.

Using this tool, the observer coarsely contoured the liver every three slices. The program interpolates all intermediate slices which were adjusted by the observer if necessary. The program excludes structures from the contoured regions if they fall outside predefined Hounsfield Unity (HU) densities. For scans with contrast,

irrespective of contrast phase, HU boundaries are set at -15 and 195; HU limits of -15 and 125 are used for scans without contrast. This ensures exclusion of extrahepatic structures including fat tissue and vascular structures. The program then calculates TLV by multiplying the spacing between slices with the areas of traced volumes, comparable to manual TLV measurements. The observer was blinded for timepoint and patient ID for all measurements.

Additional measurements using Syngo.Via (Siemens)

We performed TLV measurements with the Siemens postprocessing application Syngo.Via VB50 in a randomly selected subgroup of ten patients. This technique lacks HU density options and resembles manual segmentation. However, it allows interpolation between contours reducing the number of slices that require manual contouring. The observer can manually correct the interpolated boundaries. Liver volume is calculated by the program by multiplying the area per slice with the spacing between slices.

Inter- and intra-reader variation per technique

We determined the inter- and intra-reader variation in a randomly selected subgroup of ten CT-scans from ten different patients (cross-sectional) to compare the reproducibility of each segmentation technique. Three readers measured these ten CT-scans twice with manual segmentation and semi-automatic segmentation. Two readers measured the same ten CT-scans twice with Syngo.Via. All readers were blinded to the previous measurements.

Measuring time per technique

We recorded the time needed to perform semi-automatic segmentation, Syngo.Via and manual segmentation measurements.

Statistics

Baseline characteristics are reported as mean ± standard deviation (SD) for normally distributed parameters and as median (IQR) for non-normally distributed continuous parameters. Categorical variables are reported as n (%). Absolute TLV measurements were compared with Wilcoxon Signed Rank test. Using Bland-Altman analyses, we further investigated the agreement of cross-sectional TLV measurements between manual and semi-automatic methods on the first CT-scan of every patient. Mean TLV of manual and semi-automatic measurements was calculated, and the difference between this measurements divided by the mean TLV * 100 to calculate the percentage difference. The bias and precision represent the percentual mean and SD

of this difference between both measurements. We performed a one-sample t-test to test for statistical differences between the segmentation methods.

For our secondary outcome, determination of agreement in longitudinal data, we compared manually determined liver growth with semi-automatically determined liver growth. Again, we used Bland-Altman plots and tested the difference with a one-sample t-test. Liver growth was defined as the percentual growth between the first and second scan, regardless of time between the two scans. Difference in growth percentage was calculated by [semi-automatic growth (%)] – [manual growth (%)] and bias and precision parameters were calculated as the mean of this difference and the corresponding standard deviation. We performed sensitivity analyses in the following predefined subgroups: 1) CT-scans with and without contrast, 2) patients with a height adjusted TLV < 3200 ml and ≥3200 ml, 3) patients with and without a history of surgical interventions, and 4) patients with ADPKD versus ADPLD.

Inter- and intra-reader variability were investigated with coefficients of variance (CV). The CV is the ratio of the SD to the mean. The inter-reader CV was calculated with values obtained by different readers who measured the same CT scan. The intra-reader CV was calculated for each reader separately after measuring the same CT scans twice. The intra-reader CVs of all readers were averaged to yield a mean intra-reader CV plus standard deviation. Wilcoxon signed rank tests were used to determine whether these CVs significantly differed between manual segmentation and semi-automatic or Syngo.Via measurements.

We performed time measurements and calculated the mean from different readers for every scan and every method. In addition, we performed Bland-Altman analyses with bias and precision parameters that compare manual segmentation with semi-automatic or Syngo.Via measurements in the same ten CT-scans.

Ethical statement

All UMC Groningen patients included in this study participated in earlier studies in which they gave approval for the use of their data for future studies. All Radboudumc patients are part of the international PLD registry. Given the non-invasive nature of the data collection, formal ethic's approval was waived by the Radboudumc Ethics Committee. Our study was conducted in accordance with the guidelines for Good Clinical Practice (GCP) and the Netherlands Code of Conduct for Research Integrity.

Results

A total of 60 PLD patients with two CT-scans were included in the study. Volumetry was performed manually for all 120 CT-scans. The semi-automatic method was not able to measure volumes on CT-scans from the companies GE and Toshiba, due to encryption signatures present in these files. Consequently, we were not able to measure one of two CT-scans in 14 patients. Therefore, cross-sectional measurements were obtained in all 60 patients and longitudinal data in 46 patients (Figure 1).

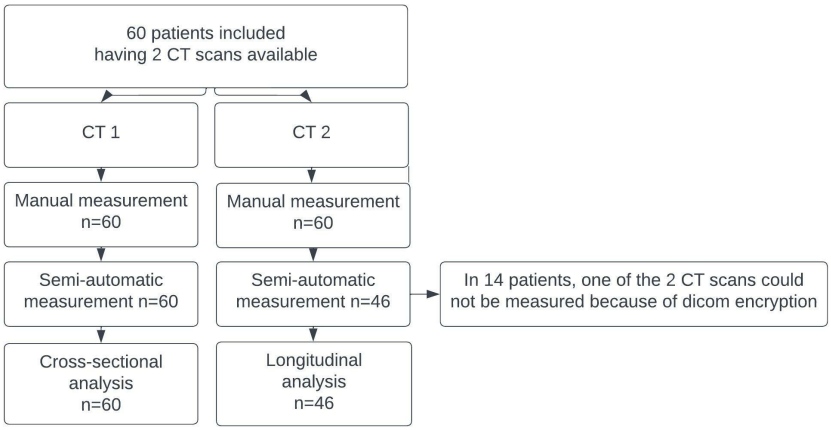

Figure 1 – Flowchart of included patients and scans

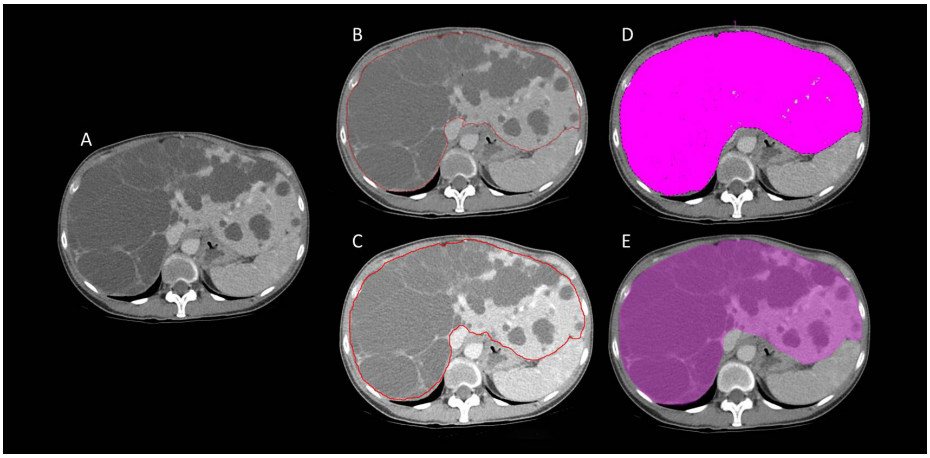

Figure 2 – Image of the segmentation tools. A = unsegmented slice, B = manual segmentation with Analyze, C =manual segmentation with Pinnacle, D = semi-automatic segmentation, E = segmentation with Syngo.Via

Patient characteristics

Baseline characteristics of the patients are shown in Table 1. The mean age of the patients included in the cross-sectional analysis is 51.2 ± 9.4 years (standard deviation SD 9.4) and 85% of patients were female. The majority of patients (58%) suffered from ADPKD, 38% suffered from ADPLD, and two patients (3%) had liver cysts but did not meet the criteria for PLD (>10 hepatic cysts). Median TLV in the cross-sectional analysis was 5292.2 [3141.4-7862.2] ml and 18 patients (30%) received invasive treatment (e.g. aspiration sclerotherapy or cyst fenestration) for PLD before the first scan. In patients having ADPKD, mean creatinine was 106 [71-173] µmol/l. The subset of 46 patients having longitudinal data had comparable baseline characteristics.

	Cross-sectional n=60	Longitudinal n=46
Center		
Radboudumc	43 (71)	29 (63)
UMC Groningen	17 (28)	17 (37)
Sex		
Female	51 (85)	39 (85)
Male	9 (15)	7 (15)
Diagnosis		
ADPLD	23 (38)	17 (37)
ADPKD with PLD	35 (58)	27 (59)
ADPKD without PLD	2 (3)	2 (4)
Age years	51.2 (9.4)	51.7 (9.9)
Creatinine µmol/l *	106.0 [71.0 – 172.5]	110.0 [71.0-202.0]
TLV manual ml	5292.2 [3141.4-7862.2]	4854.1 [2624.9-8104.4]
CT with contrast	32 (53)	26 (57)
Venous contrast	22 (37)	
Late venous contrast	4 (7)	
Arterial contrast	6 (10)	
CT without contrast	28 (47)	20 (44)
Low-dose CT	19 (32)	
Blanco CT	9 (15)	
Invasive treatment PLD	18 (30)	16 (35)
Time between scans years		1.8 (0.8)

Table 1 – Baseline characteristics.*Only for ADPKD patients. ADPLD Autosomal Dominant Polycystic Liver Disease; ADPKD Autosomal Dominant Polycystic Kidney Disease; PLD, Polycystic Liver Disease; TLV, Total Liver Volume; CT, Computed Tomography. Invasive treatment concerns cyst aspiration sclerotherapy or cyst fenestration. Data given as number (%), mean (SD) or median [IQR].

Performance of the semi-automatic tool in cross-sectional TLV assessment

Semi-automatic TLV measurements correlated with manual measurements (CC 0.998) but were slightly larger with a median of 5292.2 vs 5432.8 ml (p<0.001, Table 2). This is also reflected in the bias of 1.62% and precision of 2.75% (p<0.001, figure 3).

	n	Manual TLV	Semi-automatic TLV	p-value
Cross-sectional				
TLV CT 1 ml	60	5292.2 [3141.4-7862.2]	5432.8 [3071.9-7960.2]	<0.001
Longitudinal				
TLV CT 1 ml	46	4854.1 [2624.9-8104.4]	5070.1 [2623.9-8108.9]	0.001
TLV CT 2 ml	46	4852.5 [2656.2-8444.7]	5147.0 [2745.8-8473.5]	0.005
Absolute growth ml	46	99.4 (789.8)	94.7 (855.7)	0.930
Percentage growth %	46	3.1 (14.0)	3.3 (15.5)	0.706

Table 2 – Median total liver volumes using manual tracing and semi-automatic measurement. TLV = total liver volume, CT = computed tomography. TLV presented as median (IQR). Comparison of volumes were made with Wilcoxon signed rank tests; growth was compared with paired t-tests

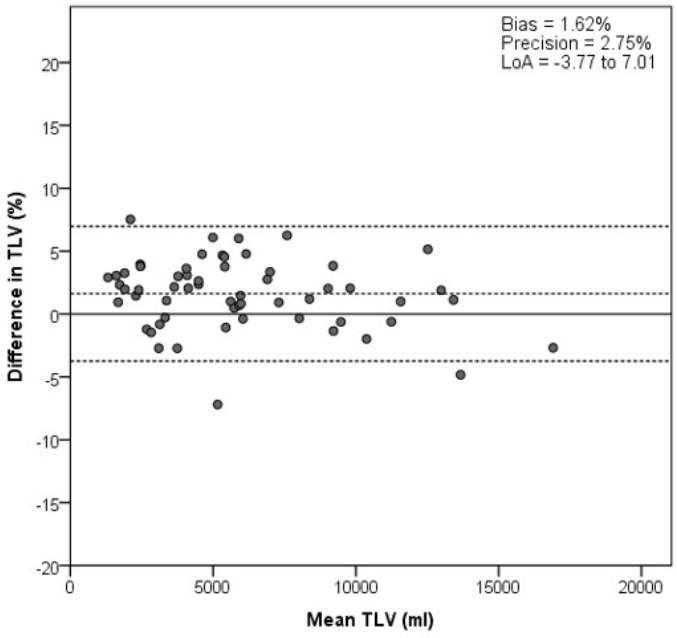

Figure 3 – Bland-Altman plots of cross-sectional TLV measurement, compared between manual tracing and semi-automatic measurement. The solid line represents the reference and the dotted lines the bias and LoA. TLV = total liver volume, LoA = limits of agreement.

Performance of the semi-automatic tool in detecting liver growth

While manual tracing consistently showed significantly smaller TLVs compared to semi-automatic measurements, no difference in liver growth was observed, both for absolute as well as percentage growth (p=0.930 and p=0.706, respectively, Table 2). Figure 4 shows a Bland-Altman plot for the longitudinal analysis of liver growth between the two CT-scans, measured manually and semi-automatically. The bias and precision of total liver growth are 0.23% and 4.04%, respectively.

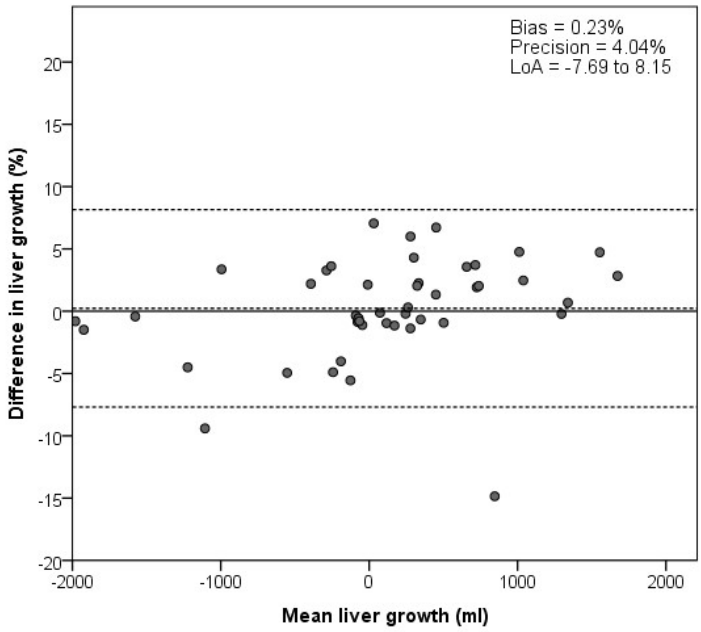

Figure 4 – Bland-Altman plots of total liver growth between the first and second CT scan, compared between manual tracing and Volume measurement. The solid line represents the reference and the dotted lines the bias and LoA. TLV = total liver volume, LoA = limits of agreement.

Figure 4 shows one outlier in the data: manual liver growth of 1701 ml and semi-automatic liver growth of -9 ml. Evaluation of the tracing showed that this was caused by a mistake in the second manual CT-scan, where the right kidney was assigned to the liver (Supplemental Figure 1). If this case is excluded from the dataset, the absolute and percentage growth were not significantly different, with growth rates of 63.8 (±760.5) ml and 2.9% (±14.1) for manual tracing, and 97.0 (±865.3) ml and 3.4% (±15.6) for semi-automatic tracing, (p=0.381 and 0.271, respectively). The correlation coefficient would then be 0.960, with a bias and precision of 0.56% and 3.37%, respectively.

Inter- and intra-reader variability and measuring time

In Table 3, the CVs for the inter- and intra-reader variability are given for manual tracing as well as the semi-automatic segmentation tool. The median segmentation time was 50 [46-78] minutes for manual segmentation and 19 [15-28] minutes for semi-automatic segmentation (p=0.028, Table 3).

	Manual	Semi-automatic	p-value manual vs semi-automatic
Inter-reader Coefficient Variation,%	1.21%	2.19%	0.260
Intra-reader Coefficient Variation,%	0.63%	0.66%	0.374
Measurement Time, hour:minutes:seconds [IQR]	0:50:23 [0:46:42 – 1:18:15]	0:19:06 [0:15:00 – 0:28:29]	0.028

Table 3 – Inter- and intrareader variability for manual and semi-automatic measurements. Comparison for manual versus semi-automatic measurements was made using Wilcoxon signed rank tests.

Syngo.Via

A random subset of 10 CT-scans was selected for measurement with Syngo.Via. In this subgroup the accuracy of the Syngo.Via measurements was comparable to the semi-automatic segmentation method (Supplementary Table 1 and Figure 2). The absolute TLV measurements of Syngo.Via were slightly larger than manual segmentations (median TLV 4265.8 versus 4124.8 ml, p=0.007). Inter-reader CV was not significantly different from manual tracing, with values of 1.01% for Syngo.Via versus 1.21% for manual tracing (p=0.445). The intra-reader CV was also comparable, being 0.54% for Syngo.Via, and 0.63% for manual segmentation (p=0.333). Measuring time was not faster than manual tracing (48 [34 – 56] versus 50 minutes [46 – 78] (p=0.917), while being significantly slower compared to the semi-automatic measurement method of MMWP 'Volume', with a median measurement time of 19 minutes [15 – 28] (p=0.05).

Subgroup analysis

In the cross-sectional dataset, we compared the bias and precision of the semi-automatic tool in four predefined subgroups and found no differences. Results were comparable across CT-scans with contrast (n=32, bias 1.95%, precision 1.94%) and without (n=28, bias 1.24%, precision 3.46%, p=0.338). In addition, we compared performance of the semi-automatic program across different contrast phases, and between low-dose and blanco CT scans (Supplemental Figure 3). We observed no differences across contrast phases, but did observe a significant difference between low-dose and blanco CT scans (median percentage difference -0.3% and +3.8% respectively, p=0.04, Kruskal Wallis test).

Across patients with invasive PLD treatment before the scan (n=18 , bias 1.50%, precision 2.68%) and patients without invasive PLD treatment before the scan (n=42, bias 1.67%, precision 2.81%, p=0.830), results were comparable. We compared PLD patients with ADPKD (n=37, bias 1.45%, precision 2.54%) with patients with ADPLD (n=23, bias 1.89%, precision 3.10%, p=0.549) and observed no differences. Lastly, we found that patients with manual height adjusted TLVs of > 3200 ml/meter (n=31, bias 1.28%, precision 3.02%) were comparable to patients with manual height adjusted TLVs ≤3200 ml/meter (n=27, bias 1.87%, precision 2.48%, p=0.430). Two patients were excluded from this analysis since their height was missing.

Discussion

We demonstrated that semi-automatic segmentation using the Siemens MMWP Volume tool accurately measures TLV (bias 1.62%, precision 2.75%) and liver growth (bias 0.23%, precision 4.04%) in a real-life dataset of patients with polycystic liver disease (PLD). Semi-automatic measurements were faster than manual measurements and were accurate regardless of contrast used in the CT-scan, liver size, invasive interventions and disease etiology. Only for low-dose CT-scans compared to blanco CT-scans, the performance was slightly different (median percentage difference -0.3% and +3.8% respectively, p=0.04), which could probably be explained by the lower quality of the low-dose scans. We observed a minor but statistically significant difference in absolute TLV values between manual and semi-automatic measurements. This difference was consistent for baseline and follow-up scans leading to no difference in liver growth both in absolute (ml, p=0.930) as well as percentage difference (p=0.706). Thus, the semi-automatic method accurately measures liver volumes as well as growth, provided that the same method is used for consecutive measurements.

We determined the inter- and intra-reader variation in a subgroup of ten CT-scans. The CVs were small and not significantly different for manual and semi-automatic segmentation. For semi-automatic segmentation, the intra-reader variability was 0.66%, showing that the same CT-scan is reassessed accurately by the same reader. The inter-reader variability was slightly higher, but still good with a value of 2.19%, showing that the liver volume measurements were comparable between various readers. The inter-reader variability of manual tracing (1.21%), was comparable to the bias of semi-automatic measurements (1.62%), indicating that variation of these methods are quite similar.

In our study, we found a significant difference between observed volumes for the gold standard of manual tracing compared to semi-automatic measurements. However significantly different, this was a numerically small difference. Most importantly, there was no difference observed in the observed liver growth between the two methods. Liver growth is the most important parameter in PLD to assess disease progression. There was no difference in absolute as well as percentage difference in liver growth. Notably, liver growth should be assessed using the same method (either manual or semi-automatic volumetry), due to difference in absolute volumes between the methods.

Over the last years, several (semi-)automatic programs have been developed to measure TLV and/or total kidney volume in ADPKD and/or PLD [13–15]. The only fully automated program is currently only suitable for MRI [15]. This program has comparable bias (-1.6%) and precision (3.1%) to our semi-automatic TLV measurements and is currently used for studies and in clinical practice. CT-scans come with several benefits over MRI as they are quicker, cheaper and more widely available. Patients with contra-indications for MRI (e.g. claustrophobia or metal prosthesis) can also be scanned with CT. In addition, on MRI artefacts can occur that do not occur on CT, especially in patients with large livers [16]. Lastly, abdominal CT-scans are more often made for other purposes related to clinical care, and it would be beneficial if TLV can be measured on the same imaging modality. Therefore, (semi-) automatic volumetry programs are needed for CT.

Recently, Philips developed an automatic segmentation program with this purpose [14]. The bias of and precision (-1.1% and 4.0%) were comparable to our semi-automatic tool. However, the clinical value of this application has yet to be proven, since no longitudinal data on liver growth were shown in this study. In addition, it is unknown whether this program's performance deteriorates when it is applied in real-life CT-scans. Most programs require a standard scanning protocol, which is not always available in clinical practice.

The most important disadvantage of the developed semi- and fully-automatic programs [13–15], is feasibility of implementation in clinical practice. For their use, expert knowledge is required. We chose to validate a commercially available semi-automatic volumetry application, in order to simplify the implementation and transition to clinical practice. We chose the Siemens MMWP Volume tool as main outcome for this study. We observed that the semi-automatic volumes were comparable to the gold standard of manual tracing, while the MMWP Volume was

significantly faster compared to both manual tracing and Syngo.Via (18, 50 and 48 minutes per scan, respectively).

However, since a newer version of this tool is available, we studied the performance of the newest Siemens volume tool 'Syngo.Via' as well. We observed that this tool also measures slightly, but significantly larger TLV compared to manual tracing. The bias and precision for Syngo.Via TLV measurements were comparable to the bias and precision for MMWP measurement. Intra- and inter-reader variability was not significantly different compared to manual tracing. However, Syngo.Via TLV measurements were not faster than manual tracing (the gold standard), despite the option to use interpolation, which was lacking in our manual segmentation procedure. Probably, this could be explained because altering the contour or excluding structures in Syngo.Via was very time-consuming. In addition, every interpolated contour needed to be checked for correctness and adjusted if necessary. The MMWP Volume tool uses HU densities in volumetry, while this feature is no longer available in Syngo.Via. In our opinion it is unfortunate that the HU density option is not available anymore in Syngo.Via, because this feature makes the measurements so much faster.

This study comes with a number of strengths. We used a set of real-life CT-scans (with and without contrast and from different scanning companies) and manual contouring was performed by experienced readers. In addition, we used longitudinal data to validate the performance on liver growth. This is important, because liver growth is used to measure disease progression in clinical practice and is used as the main outcome in many clinical trials [8,9,17,18]. We made a detailed assessment of inter- and intra-reader variability for all methods. This study also comes with limitations. First, the study has a limited sample size. However, the bias and precision presented in our current study are comparable to literature. Second, the manual measurements were performed by several readers, while a single reader performed all semi-automatic measurements. Since the inter-reader variation for manual segmentation was very small, we expect no effect on our study outcomes.

We demonstrated that the semi-automatic Siemens MMWP Volume is tool is reliable, with comparable volume measurements compared to the gold standard of manual tracing, while it is considerably faster and more user-friendly to measure liver volumes as well as liver growth in PLD.

Acknowledgements

We thank Odeke te Kamp for her help with checking all liver segmentations and entering study data in the database.

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3

Validation of fully automatic liver segmentation in polycystic liver disease: the fastest modality to date

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Abstract

Background

Polycystic liver disease is characterized by cyst growth which can lead to hepatomegaly. Disease severity and treatment efficacy are determined with total liver volume (TLV). The current gold standard for TLV measurements is manual liver segmentation, which is time-consuming and costly. In this study we validate a previously developed fully automatic liver segmentation tool.

Methods

In this cohort study we compared manual (gold standard) and automatic liver segmentation in CT scans obtained from adult polycystic liver disease patients. Cross-sectional TLVs and liver growth measurements were compared using Bland-Altman analyses, Dice and correlation coefficients. We evaluated the automatic program's performance in the entire cohort and several predefined subgroups, and measured contouring time.

Results

We included 56 patients with a median manual TLV of 5302 ml. Automatic TLV measurements were slightly smaller in both the cross-sectional (5302 vs 5151 ml, $p<0.001$) and liver growth measurement (3.4% vs 3.4%, $p=0.002$). This was also reflected in our Bland Altman analyses (cross-sectional bias -5.0%, precision 3.0%; liver growth bias -1.9%, precision 4.0%). We found comparable results in all subgroup analyses and no structural segmentation error explained the observed bias. Despite the observed bias, the overall correlation between manual and automatic contours was high (Dice 0.95, correlation coefficient 0.997). Automatic segmentation was considerably faster than manual segmentation (4 vs 2322 seconds, $p<0.001$) and does not have inter-reader variability.

Conclusion

Fully automatic segmentation of polycystic livers is fast and reliable in determining TLV and liver growth. It should be integrated in clinical practice and research.

Introduction

Polycystic liver disease (PLD) is a rare, hereditary disorder in which at least 10 cysts are present throughout the liver (1). It occurs as an isolated disease (autosomal dominant polycystic liver disease, ADPLD) or in combination with kidney cysts (autosomal dominant polycystic kidney disease, ADPKD). Liver function remains preserved, even in advanced cases. However, cyst growth can severely distort the liver architecture and lead to hepatomegaly and symptoms. Symptomatic PLD can be treated with somatostatin analogues, cyst aspiration or surgical procedures (1).

Disease severity in PLD is most frequently quantified using total liver volume (TLV)(2). This objective disease severity parameter correlates with symptom burden and is used as endpoint in trials and clinical practice to assess treatment efficacy (3-8). TLV is measured from computed tomography (CT) and magnetic resonance imaging (MRI) scans (3, 9, 10) and both modalities come with benefits and drawbacks. MRI lacks radiation exposure and can be used to characterize complicated hepatic cysts (11), but the scanning time for MRI is longer than for CT and MRIs are prone to artifacts (12). CT scans are widely available in clinical practice and routinely made in PLD patients.

The current gold standard for TLV measurements is manual segmentation which involves delineation of liver parenchyma and cysts on medical imaging. Manual segmentation yields accurate and reproducible TLV measurements (10, 13) but is labor-intensive, expensive and requires expert knowledge of liver anatomy. Segmentation of polycystic livers is particularly challenging in view of the gross architectural changes with loss of smooth delineation. In addition, it may be difficult to distinguish the origin of cysts in ADPKD patients with liver and kidney cysts. Automatic segmentation aims to overcome the current limitations in time, costs and expertise required for manual segmentations.

A previous study developed an automatic segmentation program that accurately measures TLV in PLD patients (14). This program was developed and tested on cross-sectional CT imaging of PLD patients with limited disease severity and lacks validation in longitudinal data. We hypothesize that this segmentation program accurately determines liver growth across the entire spectrum of disease severity in PLD. In this study we aim to validate TLV and liver growth measurements using an automatic segmentation software in a real-life dataset of PLD patients.

Methods

Patients and design

We included PLD patients that received somatostatin analogue treatment (octreotide or lanreotide) as part of routine clinical care in a tertiary referral center in the Netherlands. All patients were ≥ 18 years old and had ≥ 2 CT scans available, at least 1 year apart. The CT scans were made as part of routine clinical care; no additional CT scans were ordered for this study. Scanning protocols included low-dose and regular dose scans. Regular dose scans consisted of scans without contrast, or with venous, late venous or arterial contrast enhancement. The included scans originate from scanners manufactured by Canon Medical Imaging, GE, Philips, Siemens or Toshiba. All patients were included in the international PLD-registry (15) and demographic data were extracted from this database. Information about the CT scans and treatment status were extracted from clinical files. CT scans were checked for contrast status and completeness of the contours. Incorrect manual contours or CT scans that did not include the entire liver were excluded from our study. Patients were considered to have received invasive treatment if they underwent aspiration sclerotherapy, cyst fenestration or hepatic resection. Medical treatment was not considered as invasive treatment.

Manual segmentation

CT scans were manually contoured using Pinnacle 3 software (Philips Radiation Oncology Systems, Fichburg, WI, USA). This manual segmentation method, involves contouring of the liver on every axial CT slice. Liver parenchyma and cyst tissue are included in the contours; the gallbladder, peritoneal liquid effusion and major vascular structures such as the extrahepatic inferior vena cava and vena porta are excluded from these contours. Small vascular structures such as intrahepatic arteries and veins are included in the contours if they are completely surrounded by liver parenchyma or cysts. Manual segmentation was performed by various different readers. The interreader variability between these readers was extremely low (bias -0.4%, precision 0.6%) (13). Contours were exported from Pinnacle to Philips software (Intellispace Portal 10.1/2019, Philips Healthcare). Volumes were computed with the algorithm used in the Intellispace Portal Multi-Modality Tumor Tracking which combines contoured areas and slice spacing. **Figure 1** shows manual segmentation images.

Automatic segmentation

CT scans were automatically contoured using a previously described method (14). This automatic approach is an artificial intelligence program developed by the Philips Systems company research department. This program is based on a convolutional

neural network and its training dataset included polycystic livers among others. The program uses a 3D approach with U-net localizations of different sizes (5 and 2 mm^3) to identify liver parenchyma and cyst tissue to be included in the contours. TLVs are subsequently calculated by combining the volume of all included contours. The automatic TLV measurements were performed on a standard workstation equipped with 64GB of memory, a Titan RTX (Nvidia) graphics processing unit, and a W-2133 central processing unit (3.60 GHZ, Intel). This software allows for manual adjustment of automatic contours, but in the current study we did not adjust the contours after fully automatic segmentation. The program is available in the pre-release CT liver application Philips IntelliSpace Portal 13. **Figure 1** shows automatic segmentation images.

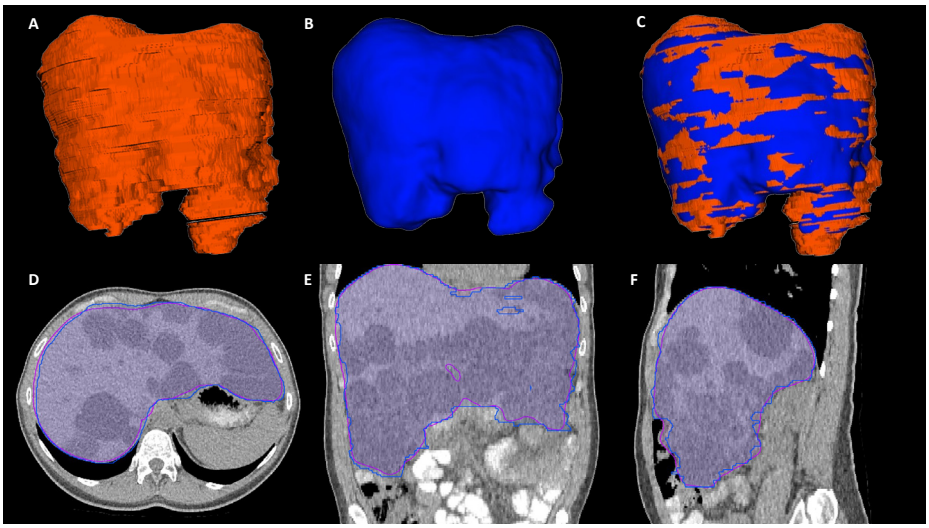

Figure 1 – Automatic and manual segmentation. Panel A: manual segmentation; Panel B: automatic segmentation; Panel C: overlap of manual and automatic segmentation; Panel D (axial plane), E (coronal plane) and F (sagittal plane): blue lines indicate manual contours, pink lines indicate automatic contours

Study outcomes

We assessed the automatic segmentation software's performance with several analyses. First, we compared manual and automatic measurements for cross-sectional CTs, follow-up scans and liver growth. In addition, we determined correlation and Dice coefficients as similarity metrics. We evaluated our primary outcome, comparison between manual and automatic TLVs, with Bland-Altman analyses for cross-sectional CTs and liver growth measurements. Bias and precision in the Bland-Altman analyses were calculated as the mean difference between both measurements and the corresponding standard deviation. We also performed Bland-Altman analyses on cross-sectional CTs in predefined subgroups based on

underlying diagnosis (ADPKD patients), contrast status of the CT, liver size and invasive treatment before the CT scan. These subgroups were chosen to ensure that TLV measurements are accurate in the presence of other anatomical deformations and across different levels and sources of variations in anatomy.

Inter- and intrareader variability

We also determined the inter- and intrareader variability for manual segmentation in a subgroup of 5 randomly selected CT scans using coefficients of variation (CV). CVs were calculated by dividing the standard deviation (SD) of multiple measurements by their mean. For the manual segmentation TLV measurements the interreader variability was determined by comparing measurements from one researcher (TB) with TLV measurements from other readers (interreader variability). The intrareader variability was determined with two measurements by a single researcher (TB). Automatic segmentation does not possess inter- or intrareader variability since every repeated segmentation is the same independent of user.

Measuring time

We recorded the measuring time in seconds for both approaches in the same subgroup of CT scans that was used for the inter- and intrareader variability. For the automatic approach, measuring time was recorded using the central processing unit.

Bias explorations

Lastly, we compared manual and automatic liver contours to explore potential systematic sources of bias.

Statistical analyses

Baseline characteristics were described with mean (SD) or median (interquartile range, IQR) for continuous variables, and n (%) for nominal variables. We compared TLV measurements and liver growth by each method using Wilcoxon signed rank tests. All statistical analyses were performed using IBM SPSS Statistics version 27 (SPSS Inc., Chicago, IL, USA).

Ethical considerations

Formal ethical approval was waived given the non-invasive character of the data collection for this study. The study was conducted following the guidelines for Good Clinical Practice and the Netherlands Code of Conduct for Research Integrity. All authors had access to the study data and approved the final manuscript.

Results

We included 56 patients in our study of which 51 (91.9%) were female. Twenty-five (44.6%) had ADPLD as underlying diagnosis and the median manual cross-sectional TLV was 5302 ml. Follow-up scans were available for all included patients. Baseline characteristics can be found in **table 1**.

	Cross-sectional (n=56)	**Follow-up (n=56)**
Sex		
Male, n (%)	5 (8.9)	
Female, n (%)	51 (91.9)	
Disease		
ADPLD, n (%)	25 (44.6)	
ADPKD, n (%)	31 (55.4)	
Height cm, mean (SD)	171 (9)	
Age years, mean (SD)	47.7 (8.9)	51.2 (9.3)
TLV ml, median (IQR)	5302 (4051 – 8482)	5591 (4312 – 9535)
Contrast enhancement, n (%)	22 (39.3)	4 (7.1)
Invasive treatment before imaging, n (%)	12 (21.4)	18 (32.1)
Slice thickness, mm (SD)	3.5 (0.9)	3.1 (0.4)
Slice spacing, mm (SD)	3.0 (0.9)	2.9 (0.4)

Table 1 – Baseline Characteristics. Continues variables are noted as mean with standard deviation (SD) or median with interquartile range (IQR); nominal variables are expressed as n (%). ADPLD = autosomal dominant polycystic liver disease, ADPKD = autosomal dominant polycystic kidney disease, TLV = total liver volume, mm = millimeter

We first performed automatic TLV measurements and compared them with the corresponding manual TLV. Automatic segmentation yielded smaller TLVs in the cross-sectional (median 5302 versus 5151 ml, $p<0.001$) and follow-up scans (median 5591 versus 5065 ml, $p<0.001$). We then determined liver growth between two scans which was smaller for the automatic method as absolute (median 219 versus 166 ml, $p=0.005$) and percentual liver growth (median 3.4 versus 3.4%, $p=0.002$). However, similarity metrics demonstrated excellent comparability between the two methods with correlation and mean Dice coefficients of 0.95 and 0.997 on baseline and 0.95 and 0.994 on follow-up CTs respectively. Comparisons of manual and automatic segmentations can be found in **table 2**.

	Manual	Automatic	P-value
Cross-sectional TLV ml, median (IQR)	5302 (4051 – 8482)	5151 (3958 – 8114)	<0.001
Follow-up TLV ml, median (IQR)	5591 (4364 – 9440)	5065 (3961 – 8881)	<0.001
Liver growth absolute (IQR)	219 (-292 – 703)	166 (-403 – 754)	0.005
Liver growth % (IQR)	3.4 (-5.0 – 14.5)	3.4 (-5.9 – 15.0)	0.002
Similarity metrics			
	Cross-sectional		Follow-up
Dice coefficient, mean (SD)	0.95 (0.01)		0.95 (0.01)
Correlation coefficient	0.997		0.994

Table 2 – Liver volumes with manual and automatic segmentation. Variables are noted as mean with standard deviation (SD) or median with interquartile range (IQR)

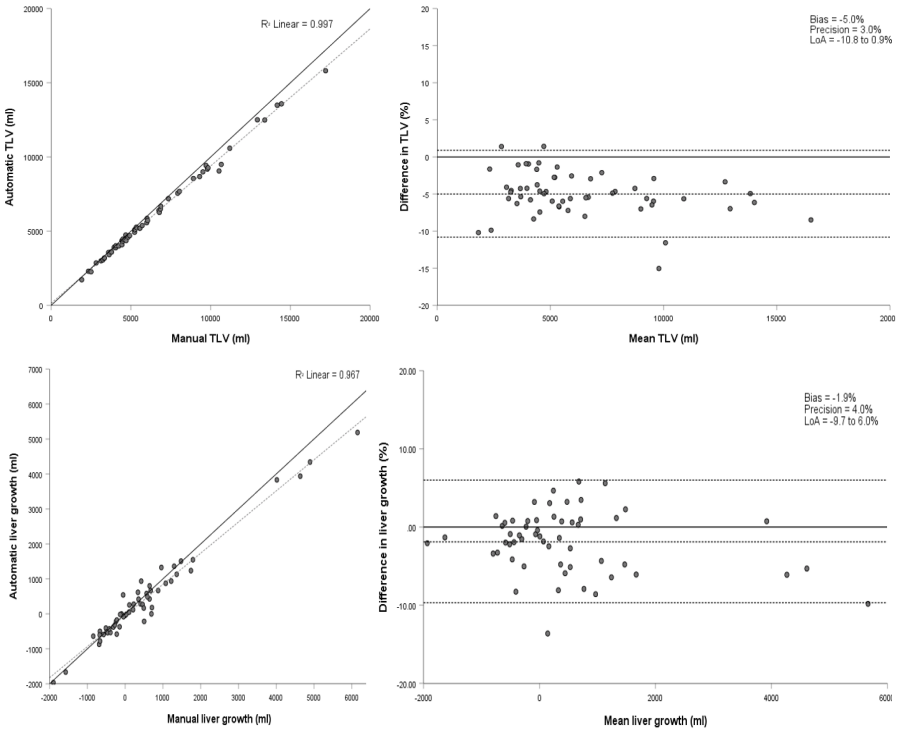

Figure 2 – Correlation and Bland-Altman plots. The upper panels show the cross-sectional analysis, the lower panels show liver growth. The solid line represents the reference line. In the correlation plot, the dotted line represents the correlation. In the Bland-Altman plot the dotted lines represent the bias and LoA. TLV = total liver volume, ml = milliliter, LoA = limits of agreement.

This difference between manual and automatic segmentation was also reflected in the cross-sectional Bland-Altman analysis with a bias of -5.0% and precision of 3.0%. Liver growth however, demonstrated a smaller difference between the segmentation methods with a bias of -1.9% and precision of 4.0%. Correlation and Bland-Altman plots can be found in **figure 2**.

Subgroup analyses

We then determined the automatic segmentation's bias and precision on cross-sectional CT scans in predefined subgroups. These subgroups were chosen to ensure that TLV measurements are accurate in the presence of polycystic kidneys, without and with contrast enhancement of the CT scan and irrespective of liver size or invasive treatment before the CT scan. The bias and precision observed in these subgroups, were similar to the bias and precision in the overall analysis (bias -5.0%, precision 3.0%, **supplementary table 1**). The bias and precision were -5.5% and 2.7% in a subgroup of ADPKD patients (n=31), and -5.5% and 3.1% in CT scans without contrast enhancement (n=34). The bias and precision were also comparable in patients with livers >5302 ml (bias -5.8%, precision 2.8%, n=28), livers <5302 ml (bias -4.1%, precision 2.9%, n=28) and in patients that received invasive treatment before their CT scan (bias -6.0%, precision 3.6%, n=12).

Interreader variability, intrareader variability and measuring time

Median inter- and intrareader coefficient of variation for manual segmentation were 0.5% and 0.3% respectively. The automatic program did not have an inter- or intrareader variability since every repeated segmentation was the same with this fully automatic approach, regardless of the user. Inter- and intrareader variability of the automatic method arise if manual adjustments to the automatic contours are made. However, we only tested the fully automatic approach in the current study. Automatic segmentation was substantially faster than manual segmentation (mean 2322 versus 4 seconds, p<0.001).

	Manual (n=5)	Automatic (n=5)	p-value
Interreader coefficient of variation %, median (IQR)	0.5 (0.3 – 1.8)	N/A	N/A
Intrareader coefficient of variation %, median (IQR)	0.3 (0.2 – 0.6)	N/A	N/A
Measuring time seconds, mean (SD)	2322 (565)	4 (1)	<0.001

Table 3 – Inter- and intrareader variability and measuring time for manual and automatic segmentation. Variables are noted as mean with standard deviation (SD) or median with interquartile range (IQR).

Bias explorations

We further explored the origin of automatic segmentation's bias and categorized our observations in 4 separate groups: 1) The manual contours were placed slightly farther to the edge of the liver/cyst tissue than the automatic contours. This results in slightly larger observations for the manual method. 2) The automatic program made small contouring errors and missed liver parenchyma and cyst tissue. The errors made by the automatic program were random and no specific structures or tissues were excluded with this method. 3) The manual contours contained segmentation errors. While manual segmentation is the current gold standard, this method is not without flaws. Manual TLVs were overestimated in several cases that included tissue without liver parenchyma or liver cysts resulted in their manual segmentations. Inconsistencies in manual segmentation arise in the cranio-caudal direction and can become visible when 2D based contours are visualized in a 3D segmentation model. 4) Differences in difficult cases. In several cases it was difficult to differentiate between cyst tissue or extrahepatic structures (e.g. peri-hepatic ascites). For instance, ascites trapped between the liver and the abdominal wall may mimic hepatic cysts. This caused a discrepancy between both segmentation methods without a systematic error being present. Examples of each type of error can be found in **supplementary figures 1-4.**

Discussion

With this study we demonstrated that fully automatic segmentation is a fast and reliable method to measure total liver volume (bias -5.0%, precision 3.0%) and liver growth (bias -1.9%, precision 4.0%) in PLD patients. Volume measurements with automatic segmentation yield marginally lower TLV values in both cross-sectional and growth analyses. However, the bias and precision of TLV measurements is within accepted limits for application in clinical practice. Automatic segmentation is exceptionally fast (mean measuring time 4 seconds) and, because it is fully automatic, there is no inter- or intrareader variability, which makes it a reproducible and objective parameter of PLD severity.

The bias observed in the automatic liver contours may be attributed to the 4 categories listed in the results section (manual contours outside of automatic contours, errors by automatic method, errors by manual method, and difficult livers). Together these 4 categories result in a bias of -5.0%, but the contribution of each error category to the final volume measurement varies per CT scan. We did not identify a systematic error when exploring the differences between automatic and

manual contours. Correct outlining will reduce a major source of bias as adjusting contours limits the contribution of segmentation errors. Both the automatic and manual segmentation software used in this study allow for manual adjustment of previously made contours.

The measurements by automatic segmentation software obtained in our current validation cohort are comparable to the cohort that was used to develop the method (bias 1.1%, precision 4.0%, Dice 0.95 ± 0.03, correlation coefficient 0.995) (14). The current study addresses two major limitations that were present in the development study: 1) our current study comprises the entire PLD severity spectrum and includes patients with severe PLD in whom TLV measurements are used to assess disease severity and treatment efficacy. 2) the current study validates liver growth measurements for the automatic segmentation tool which can be used to assess natural liver growth or treatment efficacy (3-8). Our findings are further corroborated by studies investigating segmentation in CT (semiautomatic approach, cross-sectional bias 1.62%, precision 2.75%; longitudinal bias 0.23%, precision 4.04%), and MRI (fully automatic approach, cross-sectional bias 1.6% and precision 3.1%, longitudinal bias 1.4% and precision 2.9%) (10, 16).

Our study comes with several strengths and limitations. All patients included in this study originate from a single study center. This is a tertiary referral center that receives referrals from all regions in the Netherlands. The imaging used in this study originated from this study center or the referring hospital, and scans were made with a variety of CT scanners and treatment protocols. Consequently, our study includes a real-world set of CT scans that reflects clinical practice. In addition, the origin of our scans is a major strength as our study confirms and externally validates the diagnostic value of the automatic segmentation software. The artificial intelligence software was trained in another center and with other patients, which makes our cohort an excellent external validation cohort. Our dataset also encompassed the entire spectrum of PLD with a balanced distribution of ADPLD and ADPKD patients. Differentiation between polycystic livers and right-sided cystic kidneys in ADPKD patients is an important obstacle to overcome in automatic liver segmentation (17). The automatic approach adequately distinguished these cystic structures, as demonstrated in the overall analysis and subgroup analysis of ADPKD patients. The automatic segmentation program itself is also extremely fast, accurate and allows for manual adjustments of the contours. The adjustment option can be used to correct mistakes made by the program which can further increase its accuracy. The program is compatible with all CT scan vendors and acquisition protocols, and is fully integrated in radiology software.

In addition to the TLV measurements that we validated in the current study, there is a rising scientific interest to determine total cyst volume in PLD. Volumetric progression in cyst volume is investigated as a promising indicator of disease severity (18) and the ratio between cyst volume and liver parenchyma can be used to stage PLD (19, 20). Consequently, there is an unmet clinical need for an automatic segmentation tool that can measure both TLV and total cyst volume. The segmentation software in our study demonstrates potential to measure total cyst volume, yet a standardized measurement protocol for these measurements is currently lacking. An operating protocol that ensures valid and reproducible measurements should be developed for this purpose. Until this protocol is available, the automatic segmentation program should be used exclusively to determine TLV measurements.

In conclusion, we demonstrated that automatic segmentation of polycystic livers on CT scans is fast and reliable in measuring TLV and liver growth. It should be integrated in clinical practice and research.

Acknowledgements

We thank Myrte K. Neijenhuis, Tom J.G. Gevers, René M.M. van Aerts, Lucas H.P. Bernts for manually contouring polycystic livers in the CT scans.

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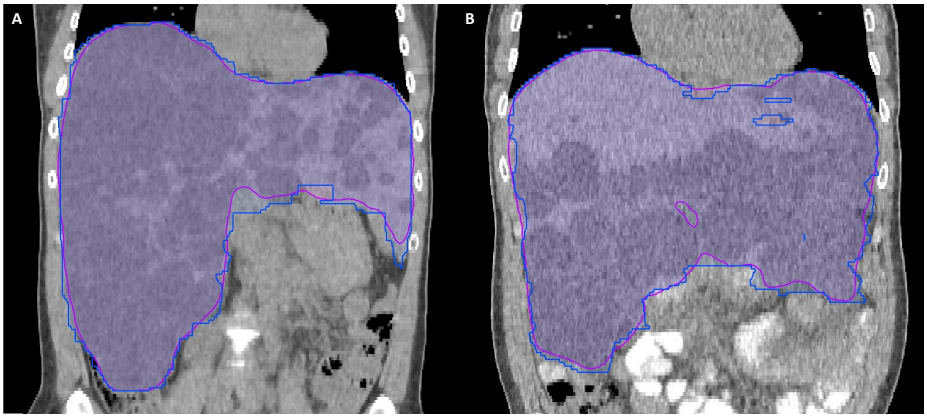
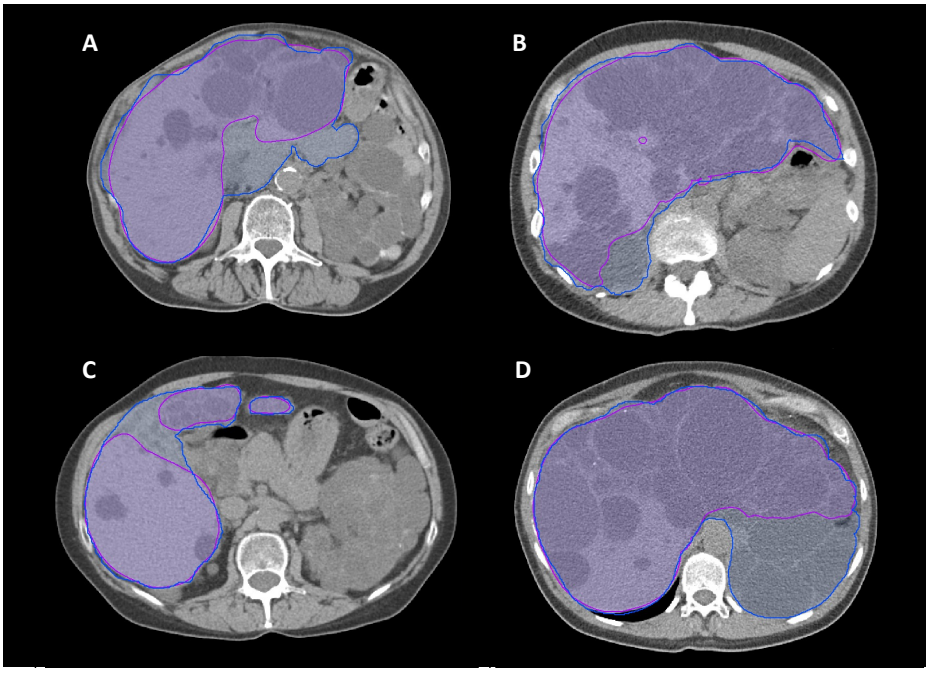
Supplementary files

Subgroup	N	Bias (%)	Precision (%)
ADPKD	31	-5.5	2.7
CT without contrast enhancement	34	-5.5	3.1
Large livers (> 5302 ml)	28	-5.8	2.8
Small livers (< 5302 ml)	28	-4.1	2.9
Invasive treatment before scan	12	-6.0	3.6

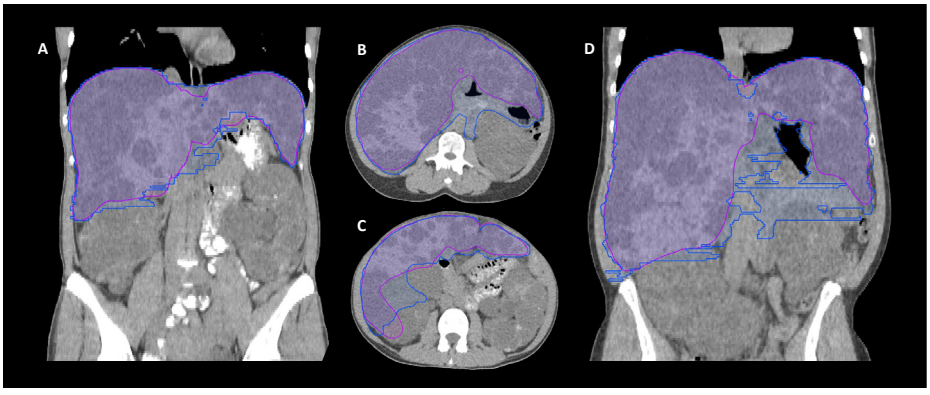
Supplementary table 1 – Bias and precision in subgroups. ADPKD = autosomal dominant polycystic kidney disease, CT = computed tomography, ml = milliliter



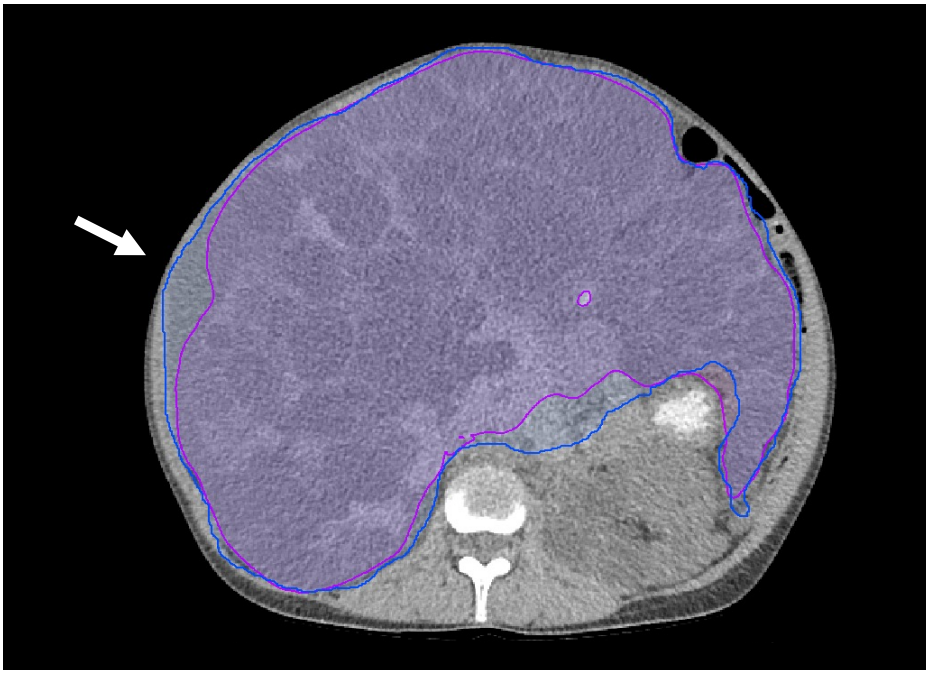
Supplementary figure 1 – Manual contours outside of automatic contours. Panel A and B: coronal computed tomography image demonstrating that manual contours lie slightly outside of the automatic contours. Blue lines indicate manual contours, pink lines indicate automatic contours.



Supplementary figure 2 – Errors by automatic method. Panel A - D: Axial computed tomography images of errors made by the automatic program. The automatic program missed liver parenchyma or cyst tissue. Blue lines indicate manual contours, pink lines indicate automatic contours.



Supplementary figure 3 – Errors by manual method. Panel A - D: Axial and coronal computed tomography images of errors made during manual contouring. The manual contours included tissue that was neither liver parenchyma or liver cyst tissue. Blue lines indicate manual contours, pink lines indicate automatic contours.



Supplementary figure 4 – Difficult liver. This panel shows a difficult liver to segment. It is unclear whether the structure indicated by the white arrow (included by the manual contour, but excluded from the automatic contour) is cystic tissue or perihepatic ascites. Blue lines indicate manual contours, pink lines indicate automatic contours.

4

Expanding the clinical application of the polycystic liver disease questionnaire: determination of a clinical threshold to select patients for therapy

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Abstract

Background

Polycystic liver disease (PLD) causes symptoms resulting from cystic volume expansion. The PLD-specific questionnaire (PLD-Q) captures symptom burden. This study aims to develop a threshold to identify patients with symptoms requiring further exploration and possibly intervention.

Methods

We recruited PLD patients with completed PLD-Qs during their patient journey. We evaluated baseline PLD-Q scores in (un)treated PLD patients to determine a threshold of clinical importance. We assessed our threshold's discriminative ability with receiver operator characteristic statistics, Youden Index, sensitivity, specificity, positive and negative predictive value parameters.

Results

We included 198 patients with a balanced proportion of treated (n=100) and untreated patients (n=98, PLD-Q scores 49 vs 19, $p<0.001$; median total liver volume 5827 vs 2185ml, $p<0.001$). We established the PLD-Q threshold at 32 points. A score of ≥ 32 differentiates treated from untreated patients with an area under the ROC of 0.856, Youden Index 0.564, sensitivity of 85.0%, specificity of 71.4%, positive predictive value of 75.2%, and negative predictive value of 82.4%. Similar metrics were observed in predefined subgroups and an external cohort.

Conclusion

We established the PLD-Q threshold at 32 points with high discriminative ability to identify symptomatic patients. Patients with a score ≥32 should be eligible for treatment or inclusion in trials.

Background

Polycystic liver disease (PLD) is a rare, inherited disorder diagnosed when >10 cysts are present in the liver (1). The disease can occur in isolated form (autosomal dominant polycystic liver disease, ADPLD) or in combination with renal cysts (autosomal dominant polycystic kidney disease, ADPKD) (2). PLD is characterized by a gradual increase in cyst volume, leading to hepatomegaly and symptoms when surrounding structures become compressed (3). When cysts exert pressure against the stomach, this can lead to early satiety, heartburn, and postprandial nausea and vomiting. Compression of cysts against the right diaphragm and ribs results in shortness of breath and pain. Patients may also experience a general feeling of abdominal fullness when the enlarged abdomen reduces mobility. Treatment is usually initiated by symptoms as biochemical biomarkers of liver function such as bilirubin and INR are unrelated to disease severity (4, 5).

A recent guideline determined that treatment choice depends on symptoms and liver phenotype (6). Somatostatin analogue therapy (lanreotide, octreotide, pasireotide) is the only medical therapy currently available that ameliorates liver growth. Mild side effects (mostly transient diarrhea and stomach cramps) are common but diminish over time and in general somatostatin analogues are well-tolerated. Surgical options include cyst fenestration, partial hepatectomy and liver transplantation. These therapies come with varying invasiveness, morbidity and mortality. Aspiration sclerotherapy has the lowest morbidity and mortality. Partial hepatectomy with cyst fenestration (PHCF) can provide substantial relief but not all patients are willing to choose this option and is not available at all surgical centers. Liver transplantation is the only curative option but has a higher morbidity and mortality, and is reserved for the most severe cases.

Adequate selection of patients that may benefit from PLD treatment is paramount. Currently, patients are mainly selected by (expert) opinion of the treating physician. Instead, an objective measure that quantifies PLD-related symptom burden should be used for this purpose. The polycystic liver disease questionnaire (PLD-Q) was developed to objectively quantify PLD symptoms (7). This patient-reported outcome measure scores PLD symptoms with 16 different items. It is a valid and reliable questionnaire that differentiates between complaints originating from hepatic cysts and complaints related to renal cysts. The questionnaire is currently used in clinical practice and as a secondary outcome measure in research (8-10). PLD-Q scores range from 0 to 100. Although its score correlates to liver volume and inversely correlates to quality of life (3, 11), no threshold for clinical significance has been determined

that distinguishes patients requiring treatment. This hampers unbiased selection of patients eligible for treatment or inclusion in clinical trials.

The aim of this study was to determine a PLD-Q threshold for clinical importance to identify PLD patients in need of therapy.

Methods

Study design and patient population

All patients included in our study were ≥18 years and had at least one PLD-Q score available. Patients in this study were included from 4 different cohorts and grouped according to their PLD treatment.

Treated patients received either 1) somatostatin analogues, 2) aspiration sclerotherapy or 3) PHCF. Patients treated with somatostatin analogues (either octreotide or lanreotide) were included from the international PLD Registry. This registry is a prospective cohort that holds data from patients diagnosed with PLD defined by the presence of >10 hepatic cysts (12). The decision to start somatostatin analogues is made during meetings attended by at least two PLD experts and based on the symptoms in combination with liver phenotype. In the absence of a gold standard, this clinical decision-making process is the best available option to initiate somatostatin analogues. Patients treated with aspiration sclerotherapy, were included from a previously described trial that investigated aspiration sclerotherapy (9). Patients with ≤10 hepatic cysts were excluded from this cohort as they were not considered to have PLD. Patients who underwent PHCF were included from another previously described cohort and had a phenotype that consisted of several large hepatic cysts and severely affected liver segments in the presence of less affected segments (8). The flowchart and clinical decision-making proposed by the European Association for the Study of the Liver is followed for all treated patients (6).

As a comparator patients who completed ≥1 PLD-Q were recruited from the 'Developing Intervention strategies to halt Progression of Autosomal Dominant Polycystic Kidney Disease' (DIPAK) observational cohort. This cohort was established as a follow-up of the DIPAK 1 randomized controlled trial and aims to identify factors that predict kidney function decline in ADPKD (13, 14). Hepatic cysts are observed in most ADPKD patients but not all (15), and DIPAK patients with ≤10 hepatic cysts were excluded from our current study. Patients in the DIPAK observational cohort have not been exposed to PLD treatment upon follow-up. In addition, we checked their medical history for PLD treatment. Patients who received volume reducing

therapy for PLD (drug therapy, aspiration sclerotherapy, cyst fenestration, partial hepatectomy, transplantation) prior to their baseline DIPAK visit were excluded. We categorized ADPKD severity using the Mayo Clinic imaging classification based on total kidney volume and age (16). Patients in this comparative group did not require PLD treatment and will be referred to as 'untreated' group.

Data collection

We obtained the following data for this study: age, sex, underlying diagnosis, total liver volume (TLV), total kidney volume (TKV), PLD-Q scores, alanine transaminase (ALT), gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels. We handled PLD-Q scores and missing data according to the user's manual (7). Data were extracted from the International PLD registry, baseline study data and patient files. All measurements were performed as part of routine clinical care for patients included from the international PLD registry. Data were extracted from the outpatient clinic visit prior to starting somatostatin analogue treatment for the symptomatic patients; data that originated from trials were obtained from their baseline study visit.

TLV and TKV measurements were performed using manual segmentation (Pinnacle software) scans as described in other studies for the treated group (17, 18). In the untreated group, TLV and TKV measurements were performed with either manual segmentation (Analyze software) or automatic segmentation (19). TLV and TKV measurements are comparable between automated and manual segmentation methods (19).

Threshold determination

We introduced external anchors to determine thresholds of clinical importance for PLD-Q.

We selected three anchors: somatostatin analogue treatment, aspiration sclerotherapy treatment and PHCF treatment. Thresholds were determined for the entire cohort and tested separately for each treatment modality. In addition, the threshold was tested in three preplanned subgroup analyses: 1) ADPLD patients and ADPKD patients with Mayo class 1A or 1B (16). This subgroup is expected to have limited confounding from polycystic kidneys, and consequently, the PLD-Q may optimally capture disease-specific symptoms. 2) Premenopausal women; this subgroup benefits most from somatostatin analogues and is suggested to have the fastest liver growth (20, 21). Premenopausal status was assumed in all female patients aged ≤50. 3) ADPKD patients; this subgroup was selected to assess whether the threshold can be applied in both ADPLD and ADPKD patients.

To assess the potential negative influence of the questionnaire's recall period, we evaluated an adjusted PLD-Q in a subset of treated patients. These patients received the regular (4 week recall period) and adjusted (1 week recall period) PLD-Q simultaneously.

We also investigated the threshold's ability to discriminate between treatment responders and non-responders. We used previously determined minimally clinically important differences (MCID) between pre- and posttreatment PLD-Q scores for this purpose. MCIDs were available in the aspiration sclerotherapy and PHCF cohorts (8-10).

Finally, we applied the threshold to the PLD-Q's development and validation cohort (7) and tested whether it differentiated between symptomatic and asymptomatic patients. Patients in this cohort were asked the following question: "Do you have symptoms of your polycystic liver?", to identify symptomatic and asymptomatic PLD patients.

Statistical analyses

Baseline variables were noted as mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables and n (%) for nominal variables. Baseline characteristics were compared between the two groups using paired t-tests, Chi-squared tests and Mann-Whitney U tests as appropriate. PLD symptoms were compared between treated and untreated patients with Mann-Whitney U tests. The PLD-Q threshold was determined using receiver operating characteristic (ROC) curve comparing baseline PLD-Q scores between the treated and untreated groups. A minimum area under the ROC (AUROC) curve of 0.8 was considered acceptable. The Youden index was used to establish an optimal threshold value. We also calculated the threshold's positive predictive values (PPV) and negative predictive values (NPV). The regular and adjusted PLD-Q were investigated using correlation coefficients and Bland-Altman analyses with corresponding bias, precision and 95% limits of agreement. Differences between the regular and adjusted PLD-Q were tested with a paired t-test. All statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA). P-values of <0.05 were considered statistically significant.

Ethical considerations

Formal ethical approval was waived for the participants included from the international PLD registry, given the non-invasive character of the data collection in this registry. Participants of the other trial (aspiration sclerotherapy trial) and observational cohorts (DIPAK observational and PHCF cohorts) provided written informed consent before initiation of these studies. Our current study was conducted following the guidelines for Good Clinical Practice, the Netherlands Code of Conduct

for Research Integrity and declaration of Helsinki. All authors had access to the study data and approved the final manuscript.

Results

Patients and study design

We included 198 patients, 100 treated and 98 untreated **(figure 1)**. Baseline characteristics demonstrate several differences between the treated and untreated groups **(table 1)**. Treated patients were more often female (89.0% vs. 68.4%, p<0.001) and had ADPLD as underlying diagnosis more frequently (48.0% vs. 0.0%, p<0.001). They also had higher liver volumes (median 5827 vs. 2185 ml, p<0.001), PLD-Q scores (median 49 vs. 19 points, p<0.001), GGT (median 92 vs. 29 U/l, P<0.001), and ALP values (median 90 vs. 65 U/l, P<0.001) compared to control patients. PLD symptoms were higher for all PLD-Q symptoms in the treated group except for nausea (median scores 4 vs 2, p=0.108, **figure 2**).

	Treated (n=100)	Untreated (n=98)	P-value
Age years, mean (SD)	50.8 (10.3)	48.4 (10.1)	0.095
Sex, n(%)			
Male	11 (11.0)	31 (31.6)	<0.001
Female	89 (89.0)	67 (68.4)	
Diagnosis, n(%)			
ADPLD	48 (48.0)	0 (0.0)	<0.001
ADPKD	52 (52.0)	98 (100.0)	
TLV ml, median (IQR)	5827 (4501 – 9635)	2185 (1798 – 3327)	<0.001
TKV ml*, median (IQR)	1006 (452 – 2028)	1395 (819 – 2264)	0.122
PLD-Q, median (IQR)	49 (36 – 59)	19 (9 – 33)	<0.001
ALT U/l, median (IQR)	22 (19 – 35)	22 (18 – 29)	0.183
GGT U/l, median (IQR)	92 (58 – 170)	29 (18 – 41)	<0.001
ALP U/l, median (IQR)	90 (71 – 141)	65 (53 – 79)	<0.001

Table 1 – Baseline characteristics. * Only determined in ADPKD patients, SD = standard deviation, ADPLD = autosomal dominant polycystic liver disease, ADPKD = autosomal dominant polycystic kidney disease, TLV = total liver volume, TKV = total kidney volume, PLD-Q = polycystic liver disease questionnaire, ALT = alanine transferase, GGT = gamma glutamyl transferase, ALP = alkaline phosphatase, IQR = interquartile range. TLV known in 164/198 (82.8%) patients, TKV in 116/150 (77.3%), ALT in 173/198 (87.4%), GGT in 161/198 (81.3%) and ALP in 173/198 (87.4%) patients.

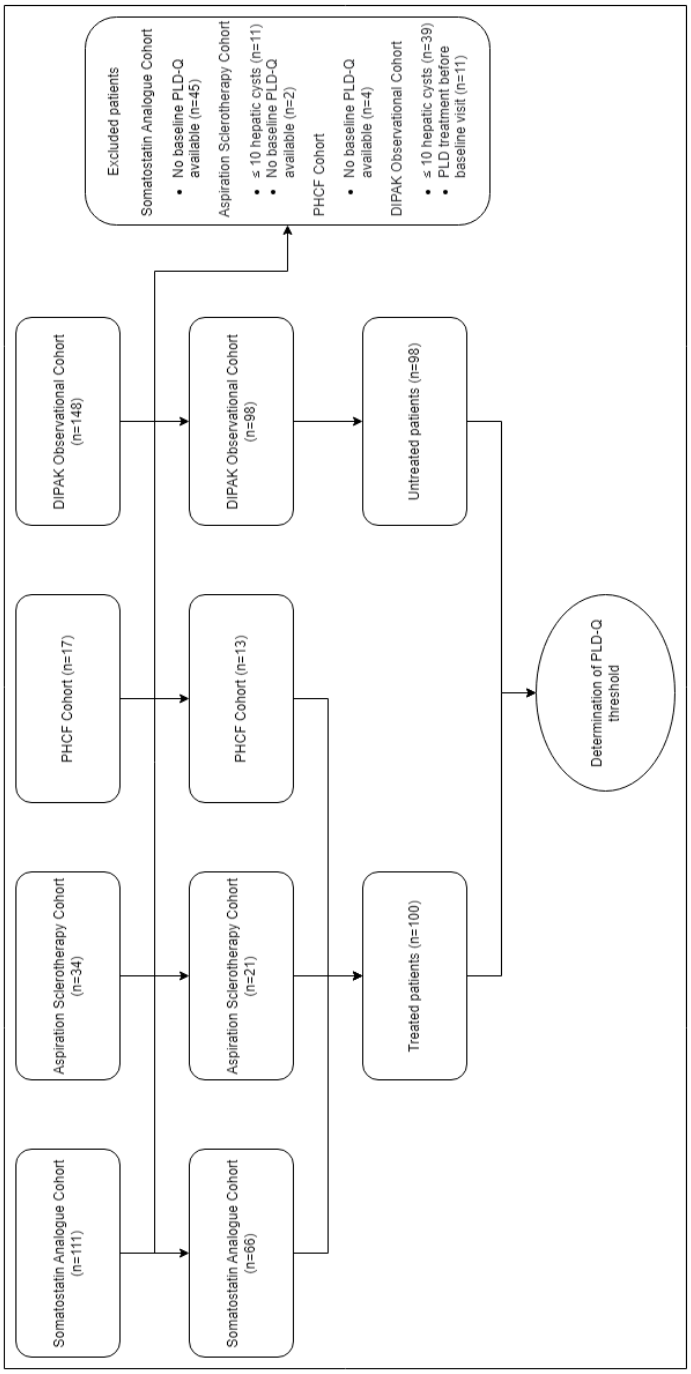

Figure 1 – Flowchart of patients.
PHCF = partial hepatectomy and cyst fenestration, PLD-Q = polycystic liver disease questionnaire

Determination of PLD-Q threshold

We determined the PLD-Q's ability score to differentiate treated from untreated patients with an AUROC (**figure 3, supplementary table 1)**. This model showed a high discriminative ability with an AUROC of 0.856 (confidence interval 0.804 – 0.908). A PLD-Q threshold of ≥32 yielded the highest Youden Index (0.564). This threshold had a sensitivity of 85.0% (85/100 correctly classified), a specificity of 71.4% (70/98), a PPV of 75.2% (85/113) and a NPV of 82.4% (70/85).

We also evaluated the thresholds performance for all three treatment options separately **(figure 3)**. The threshold performed well for somatostatin analogue treatment with an AUROC of 0.875 (confidence interval 0.823 – 0.926), a Youden index of 0.623, sensitivity of 90.9%, specificity of 71.4%, PPV of 68.2% and NPV of 92.1%. PHCF treatment yielded an AUROC of 0.941 (confidence interval 0.887 – 0.996), a Youden index of 0.714, sensitivity of 100.0%, specificity of 71.4%, PPV of 31.7% and NPV of 100.0%. The threshold demonstrated slightly inferior diagnostic parameters in aspiration sclerotherapy patients with an AUROC of 0.743 (confidence interval 0.651 – 0.836), a Youden index of 0.285, sensitivity of 57.1%, specificity of 71.4%, PPV of 30.0% and NPV of 88.6%. The AUROC for aspiration sclerotherapy treatment did not reach our predefined cutoff of 0.8.

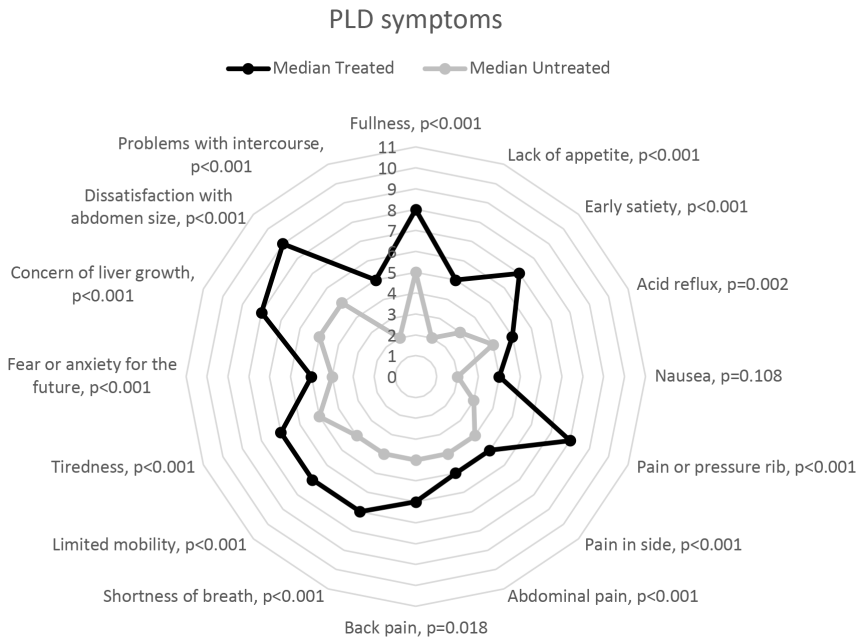

Figure 2 – PLD symptoms in treated and untreated patients.
PLD = polycystic liver disease

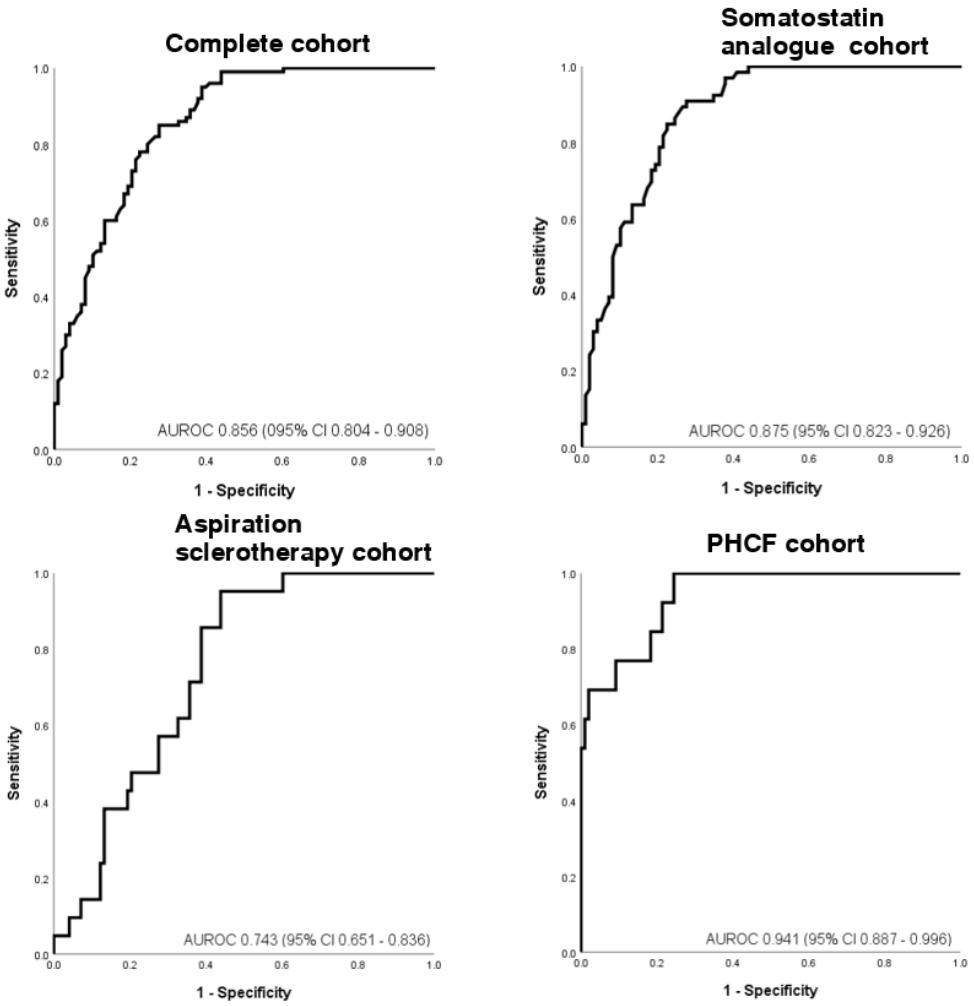

Figure 3 – Receiver Operating Characteristics curves. PHCF = partial hepatectomy and cyst fenestration, AUROC = area under receiver operating characteristics curve, CI = confidence interval

We also applied the overall threshold to three subgroups **(supplementary table 2)**. In ADPLD or ADPKD patients with Mayo Class 1A/1B, the threshold of 32 had an AUROC of 0.827 (0.736 – 0.918) and Youden index of 0.553. In premenopausal women, the threshold showed an AUROC of 0.808 (0.713 – 0.903) with Youden Index of 0.475. This subgroup was selected because premenopausal women benefit most from somatostatin analogues and are considered to have the fastest liver growth. The subgroup ADPKD was selected to assess whether the threshold can be applied in both ADPKD and ADPLD patients. Our threshold of 32 points had an AUROC of 0.897 (0.849 – 0.945) and Youden Index of 0.637 in the ADPKD patients.

Recall 4 vs. 1 week(s)

To check for recall bias, regular (4 week recall period) and adjusted (1 week recall period) PLD-Qs were returned by 37 PLD patients. The two versions of this questionnaire are highly correlated with a correlation coefficient of 0.957 (P<0.001). Using Bland-Altman analyses, we found a bias of -1.3 and precision of 4.1 for the adjusted PLD-Q **(supplementary figure 2).** The two PLD-Q versions were not significantly different (mean 39.4 versus 38.1, P=0.070).

Threshold and treatment response

We applied the established PLD-Q threshold of ≥32 points to the aspiration sclerotherapy and PHCF cohorts to assess the threshold's discriminative ability on treatment response (determined using MCIDs, **supplementary table 3**). Follow-up data were unavailable for the somatostatin analogue group and consequently, treatment response could not be evaluated. In the PHCF cohort, all patients had baseline PLD-Q scores that exceeded our threshold and consequently no reliable treatment response analysis could be performed. In the aspiration sclerotherapy cohort, the MCID was determined at 16 points decrease in PLD-Q. Twelve patients had a PLD-Q score above the threshold and 9 below. Responders were correctly identified in 7/12 cases (58.3%), while non-responders were correctly identified in 8/9 cases (88.9%).

Comparison with development cohort

Finally we compared the PLD-Q scores of our cohort with the original PLD-Q development and validation cohort(7). Patients in this development cohort were asked whether they experienced PLD-related symptoms as a separate question. Symptomatic patients (n=34, unpublished data) had higher PLD-Q scores (median 45) compared to asymptomatic patients (n=124, unpublished data, median PLD-Q score 21). These scores are comparable to our treated and untreated cohorts (median PLD-Q 49 and 19, respectively). Our threshold differentiated well between symptomatic and asymptomatic patients in this external validation cohort (AUROC 0.798, confidence interval 0.712 – 0.884).

Discussion

In this study we established the threshold for PLD treatment using a patient-reported outcome measure, the PLD-Q, at 32 points. This threshold generated a high discriminative ability in the entire cohort (AUROC 0.856) as well as in somatostatin analogue and PHCF treatment (AUROC somatostatin 0.875 and PHCF 0.941). The

discriminative ability for aspiration sclerotherapy was less suitable (AUROC 0.743). We observed comparable results in 3 preplanned subgroup analyses (ADPLD + Mayo Class 1A/1B ADPKD patients, premenopausal women, and ADPKD patients) and the questionnaire's development cohort.

The relevance of health-related quality of life and symptom burden has improved clinical PLD research (22-24), and is increasingly included as outcome measures in randomized controlled trials (https://clinicaltrials.gov/ct2/show/NCT05281328) (25). However, this is the first study that establishes an objective threshold for PLD symptoms. There is one other symptom severity questionnaire available for PLD symptoms, the polycystic liver disease complaint-specific assessment (POLCA) (26) and this questionnaire does not have a threshold. Similarly, an ADPKD specific health-related quality of life instrument that was developed several years ago lacks this threshold (27).

Disease severity can also be quantified using total liver volume measurements. Though liver volume and symptom burden are highly correlated, PLD treatment is initiated as a result of symptom burden. Accordingly, we believe a cutoff value should be based on symptom burden and not on TLV. Using a PLD-Q threshold facilitates appropriate clinical care for PLD patients as the PLD-Q is available in several languages and easily administered. The threshold can be applied as a selection criterium for clinical trials. The alternative, liver volume measurements, are time-consuming, require expert knowledge and are performed on segmentation software that is not widely available (18, 19, 28).

Our study comes with several strengths and limitations. Since PLD is a rare liver disease, the most important strength of our study is the large sample size that encompasses the entire spectrum of the disease. Therefore, we performed our study in a clinically representative set of patients. The main limitation of our study is that most patients (somatostatin analogues, aspiration sclerotherapy and DIPAK observational cohort), originate from a single tertiary referral center. This brings a potential for selection bias as center-specific differences may occur in symptoms that prompt treatment initiation and direct treatment choice. In addition, the availability of treatment and expertise with respect to treatment options may affect treatment choice (29). However, treatment indication was evaluated systematically by ≥ two dedicated PLD physicians using the algorithm described in a clinical practice guideline (6). Another limitation is the lack of ADPLD patients in the untreated group. Our findings were unaffected in two sensitivity analyses that consisted of ADPKD patients only, or patients with ADPLD or ADPKD patients with Mayo Class

1A/1B. Consequently, the presence of concomitant kidney cysts does not affect the PLD-Q threshold. Lastly, we created an overall threshold for PLD treatment and not a threshold for each separate treatment modality. Our responder analysis indicates that aspiration sclerotherapy is the least optimal treatment modality for our threshold (AUROC 0.743 for aspiration sclerotherapy versus 0.856 for overall). This may be explained because aspiration sclerotherapy targets single, large hepatic cysts and does not reduce cyst-induced hepatomegaly like other treatment options. However, even under these conditions, the NPV is very high which is an important parameter in clinical practice.

Our threshold demonstrates excellent overall discriminative ability and yields a particularly high NPV. In clinical practice this suggests that patients with scores <32 do not require treatment. A high NPV, but lower PPV, especially for aspiration sclerotherapy and PHCF treatment, poses a risk of overtreatment. This may be the result of functional abdominal complaints that act as a confounder in the PLD-Q scoring. In patients with a PLD-Q score ≥32, physicians should carefully evaluate whether hepatic cysts are the source of their complaints. They should also assess the patient's liver phenotype and weigh individual patient characteristics (e.g. comorbidity, age) against the risks associated with treatment options to prevent unnecessary treatment. The flowchart from a previously mentioned study may provide guidance in this clinical decision-making process (6).

Our study also paves the way for approval of the PLD-Q by the Food and Drug Administration. We demonstrated that the 4-week recall period is appropriate and shortening this time-frame to 1 week does not affect the outcome of the PLD-Q. Consequently, the PLD-Q conforms to the Food and Drug Administration's requirements for patient-reported outcome measures (7, 30).

In conclusion, we determined the PLD-Q threshold for symptomatic patients at ≥32 points and found similar performance of the 1-week compared to the 4-week recall period. Patients with a PLD-Q score of ≥32 should be eligible for treatment or inclusion in scientific trials.

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5

Higher need for polycystic liver disease therapy in female patients: sex-specific association between liver volume and need for therapy

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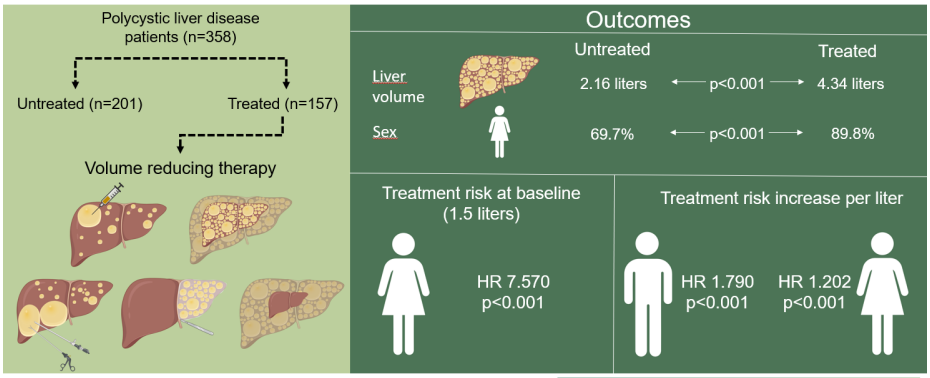
Graphical Abstract

Higher need for polycystic liver disease therapy in female patients: sex-specific association between liver volume and need for therapy



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Abstract

Background & Aim

Prognostic tools or biomarkers are urgently needed in polycystic liver disease (PLD) to monitor disease progression and evaluate treatment outcomes. Total liver volume (TLV) is currently used to assess cross-sectional disease severity and female patients typically have larger livers than males. Therefore, this study explores the sex-specific association between TLV and volume reducing therapy.

Approach & Results

In this prospective cohort study, we included PLD patients from European treatment centers. We explored sex-specific differences in the association between baseline TLV and initiation of volume reducing therapy and determined the cumulative incidence rates of volume reducing therapy in our cohort.

We included 358 patients, of whom 157 (43.9%) received treatment. Treated patients had a higher baseline TLV (median TLV 2.16 versus 4.34 liter, $p<0.001$), were more frequently female (69.7% versus 89.8%, $p<0.001$) and had a higher risk of liver events (HR 4.381, $p<0.001$). The cumulative volume reducing therapy rate at 1 year of follow-up was 21.0% for females compared to 9.1% for males. Baseline TLV was associated with volume reducing therapy and there was an interaction with sex (HR females 1.202, $p<0.001$;HR males 1.790, $p<0.001$; at 1.5 liters).

Conclusion

Baseline TLV is strongly associated with volume reducing therapy initiation at follow-up in PLD patients, with sex-specific differences in this association. Disease staging systems should use TLV to predict need for future volume reducing therapy in PLD separately for males and females.

Introduction

Polycystic liver disease (PLD) is a hereditary disease diagnosed in the presence of > 10 hepatic cysts and is characterized by cyst growth leading to hepatomegaly [1]. It occurs isolated as autosomal dominant polycystic liver disease (ADPLD) or in combination with renal cysts in autosomal dominant polycystic kidney disease (ADPKD). Symptoms in PLD result from hepatomegaly. When cysts grow and compress adjacent structures, mechanical symptoms can occur. PLD symptom burden can lead to a decrease in quality of life and warrant the need for volume reducing therapy (VRT) in selected patients [2, 3]. Somatostatin analogues, aspiration sclerotherapy, cyst fenestration, liver resection and liver transplantation are currently available as VRT while several trials investigate new drug therapies (NCT05478083, NCT05281328 & NCT05500157). VRTs can effectively reduce symptom burden and increase quality of life in PLD patients [4-6].

The most important established risk factor for liver growth in PLD is exposure to estrogens. As a result, the average total liver volume (TLV) is larger in female patients as compared to male patients, also after adjusting for differences in height [7, 8]. It is thought that livers in female PLD patients grow until the menopause and that TLV stabilizes afterwards [7, 9]. This is supported by the predominance of female patients in PLD trials and current clinical practice [10, 11]. In addition, observational studies demonstrate an increase in liver growth after exposure to estrogen-containing oral contraceptives and postmenopausal estrogen therapy [12, 13].

The decision to start VRT for PLD is made through shared decision-making by physicians and patients, and guided by symptom burden and liver phenotype [1, 14]. Currently, there is no objective threshold to initiate therapy and wet biomarkers hold little prognostic value [15]. As a result, there is an unmet clinical need for prognostic parameters that guide physicians in PLD management and counselling. Identification of a prognostic marker for PLD is pivotal in the development and validation of a clinically applicable disease staging system. Adequate staging of PLD is urgently needed to inform patients about the progression of their disease, to select patients who benefit from therapy, and to prevent exposing patients with mild PLD to the risks of therapy.

We hypothesize that TLV possesses substantial prognostic value in PLD since it is the most objective parameter of disease severity. TLV accurately captures disease severity and progression, and is unaffected by random fluctuations [16, 17]. Consequently, this study aims to evaluate the association between TLV and VRT initiation in PLD patients, with special emphasis on sex-specific differences.

Methods

Design and population

Patients in this observational cohort study were included from two cohorts: 1) the international PLD registry [18], 2) a cohort from the University Medical Center Groningen (UMC Groningen). The international PLD registry is a prospective registry that holds data from 1824 patients originating from different medical centers throughout Europe and South Korea. The UMC Groningen cohort contains a group of PLD patients who underwent liver transplantation at UMC Groningen. All female patients were advised to stop exposure to exogenous estrogens.

In- and exclusion criteria

Inclusion criteria for our study were 1) diagnosis of PLD defined as > 10 hepatic cysts, 2) Age ≥ 18 years old, 3) availability of ≥ 1 TLV measurement without prior VRT. The date of first available TLV was considered to be the baseline measurement. We only included patients from European centers as clinical practice may differ regionally and VRT occurred infrequently in non-European patients.

Study outcomes

Primary endpoint

Our primary endpoint, VRT, consisted of aspiration sclerotherapy, laparoscopic fenestration, liver resection, liver transplantation or medical treatment. Medical treatment included either somatostatin analogue therapy (octreotide, lanreotide or pasireotide) or participation in a trial that aimed to reduce liver cyst burden. The decision to initiate treatment was left to the discretion of the attending physician but was driven by presence of volume related symptom burden as a result from hepatomegaly. The choice between treatment options was facilitated by publication of guidance / guidelines [1, 14]. If patients received multiple consecutive occasions of VRT, they were considered to have reached the endpoint at the first occurrence.

Liver volume measurements

TLV measurements were obtained from CT or MRI scans measured with the following segmentation methods. CT scans from Radboudumc were measured using Pinnacle 3 version 8.0 (Philips, Eindhoven, the Netherlands [19, 20]. In UZ Leuven, all scans were measured using Volume software (Siemens, Erlangen, Germany) [21, 22]. UMC Groningen MRI scans were measured either manually using Analyze 11 or with an automated approach as described elsewhere [23, 24]. All TLV measurements were performed as part of routine clinical care or as part of a clinical trial. Estimated annual liver growth rates were calculated between a fixed starting point and baseline TLV.

The fixed starting point was set at a liver volume of 1500 ml at 18 years as this is the average liver volume in the Caucasian population [25].

Liver events

In addition to TLV, we also quantified disease severity by determining the occurrence of liver events in our cohort. Patients were considered to have reached a liver event when they were hospitalized for a PLD related intervention (e.g. aspiration sclerotherapy, laparoscopic fenestration, liver resection or liver transplantation) or conservative management (e.g. hospitalization with liver cyst rupture, hemorrhage or infection), as described elsewhere [26].

Statistical analyses

Study entry was defined as the date of first available VRT-naïve TLV. Patients who did not reach the endpoint were censored at the date of last data collection or death. Descriptive statistics were expressed as median (interquartile range, IQR) or mean (standard deviation, SD) for continuous variables and n (%) for nominal variables. First, we assessed the proportion of patients who received VRT and compared baseline characteristics between treated and untreated groups with independent sample t-tests or Mann-Whitney U tests as appropriate for continuous variables and Chi squared tests for nominal variables.

Next, we analyzed the occurrence and type of liver events in our cohort as a proxy for disease severity. For treated patients, we investigated the first liver event before or after VRT, for untreated patients we investigated the first event that occurred during follow-up after baseline. Liver event rates were compared using Cox proportional hazards models.

We then assessed VRT-free survival of the entire cohort and compared the survival in patients based on sex and baseline TLV using Kaplan-Meier analyses and corresponding log-rank tests. We grouped baseline TLV in tertiles for these analyses to compare TLV severities across this continuous variable.

We determined the association between TLV and VRT initiation with Cox proportional hazards models. We assessed this association with univariate and multivariate models which were stratified for source cohort and corrected for potential confounders. Variables were considered confounders if including the variable in the model altered the hazard rate (HR) for TLV by > 10%. Considering the influence of estrogen on the natural history, we assessed whether sex was an effect-modifier in the association between TLV and VRT initiation by including it as an interaction term to the model. Sex was considered an effect-modifier if the interaction term had a statistically significant

p-value. TLV was centered in all models to improve their clinical interpretation. We assessed the association between TLV and VRT initiation in the complete cohort and separately for male and female patients in the final model. We excluded patients who received VRT within 3 months of their baseline TLV measurement from this analysis because they may have experienced PLD-related symptoms that would have justified VRT prior to their baseline visit.

We further investigated the association in three predefined sensitivity analyses: 1) using height-corrected TLV instead of absolute TLV. This sensitivity analysis was chosen because complaints in PLD originate from mechanical pressure exerted by liver volume and abdominal capacity varies with body size. 2) in all patients with a therapy-naive TLV, including patients who underwent VRT within 3 months of their TLV measurement. In this analysis we included patients who had an indication for VRT at their baseline visit. 3) using estimated liver growth instead of absolute TLV. This sensitivity analysis was chosen since fast liver growth may cause more symptoms compared to slow liver growth, e.g. by stretching Glisson's capsule or pressing on anatomical structures adjacent to the liver.

All statistical analyses were performed using IBM SPSS Statistics version 27 (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

Ethical Considerations

Formal ethical approval of this study was waived by the Institute Review Board Committee on Research Involving Human Subjects Arnhem-Nijmegen as all included data were part of either the PLD-registry or previously performed trials for which informed consent was provided by participants. This study was conducted in accordance with the declaration of Helsinki, the guidelines for Good Clinical Practice and code of conduct for medical research.

Results

We screened 909 patients for inclusion in our study. After applying the in- and exclusion criteria, we ultimately included 467 patients of whom 110 received VRT within 3 months of their baseline TLV measurements. Consequently, 358 patients were included in our analyses (figure 1). Of these patients 281 (78.5%) were female and the median TLV was 2.94 liters (IQR 1.98 – 4.61 liters). One hundred and fifty-seven patients (43.9%) received VRT of whom 37 (23.6%) underwent aspiration sclerotherapy, 8 (5.1%) fenestration, 1 (0.6%) resection, 22 (14.0%) liver transplantation and 89 (56.7%) medical

treatment. Patients who underwent VRT had larger livers at baseline as compared to untreated patients (median TLV 2.16 versus 4.34 liters, p < 0.001), were more frequently female (69.7% versus 89.8%, p < 0.001) and more often had ADPLD as underlying diagnosis (22.9% versus 40.8%, p < 0.001). Eight patients died during follow-up of whom 4 received VRT prior to their death. Baseline characteristics can be found in table 1; treatment types and follow-up times are shown in table 2.

	Overall (n=358)	Untreated patients (n=201)	Treated patients (n=157)	p-value*
Age years, mean (SD)	50.5 (10.7)	50.4 (11.0)	50.5 (10.4)	0.940
TLV liters, median (IQR)	2.94 (1.98 – 4.61)	2.16 (1.75 – 3.32)	4.34 (2.90 – 6.31)	< 0.001
Sex, n (%)				
Male	77 (21.5)	61 (30.3)	16 (10.2)	< 0.001
Female	281 (78.5)	140 (69.7)	141 (89.8)	
Diagnosis, n (%)				
ADPLD	110 (30.7)	46 (22.9)	64 (40.8)	< 0.001
ADPKD	248 (69.3)	155 (77.1)	93 (59.2)	
Cohort, n (%)				
PLD Registry	346 (96.6)	201 (100.0)	145 (92.4)	< 0.001
UMC Groningen	12 (3.4)	0 (0.0)	12 (7.6)	
Radboudumc	279 (77.9)	177 (88.1)	102 (65.0)	<0.001
UZ Leuven	67 (18.7)	24 (11.9)	43 (27.4)	
UMC Groningen	12 (3.4)	0 (0.0)	12 (7.6)	

Table 1 – Baseline characteristics. SD = standard deviation, IQR = interquartile range, TLV = total liver volume, ADPLD = autosomal dominant polycystic liver disease, ADPKD = autosomal dominant polycystic kidney disease, * p-value compares treated and untreated patients.

	Complete cohort (n=358)	Untreated patients (n=201)	Treated patients (n=157)	p-value*
Overall VRT	157 (43.9)			
Aspiration sclerotherapy	37 (23.6)			
Fenestration	8 (5.1)			
Resection	1 (0.6)			
Liver transplantation	22 (14.0)			
Medical therapy	89 (56.7)			
Follow-up months, mean (SD)	89.0 (42.8)	69.3 (34.3)	102.7 (41.6)	< 0.001
Death during follow-up, n (%)	8 (2.2)	4 (2.0)	4 (2.5)	0.723

Table 2 – Follow-up characteristics. Volume reducing therapy overall displayed as proportion of the entire cohort (n=518); individual therapy options displayed as proportion of treated patients at the time-point. VRT = volume reducing therapy. * p-value compares treated and untreated patients.

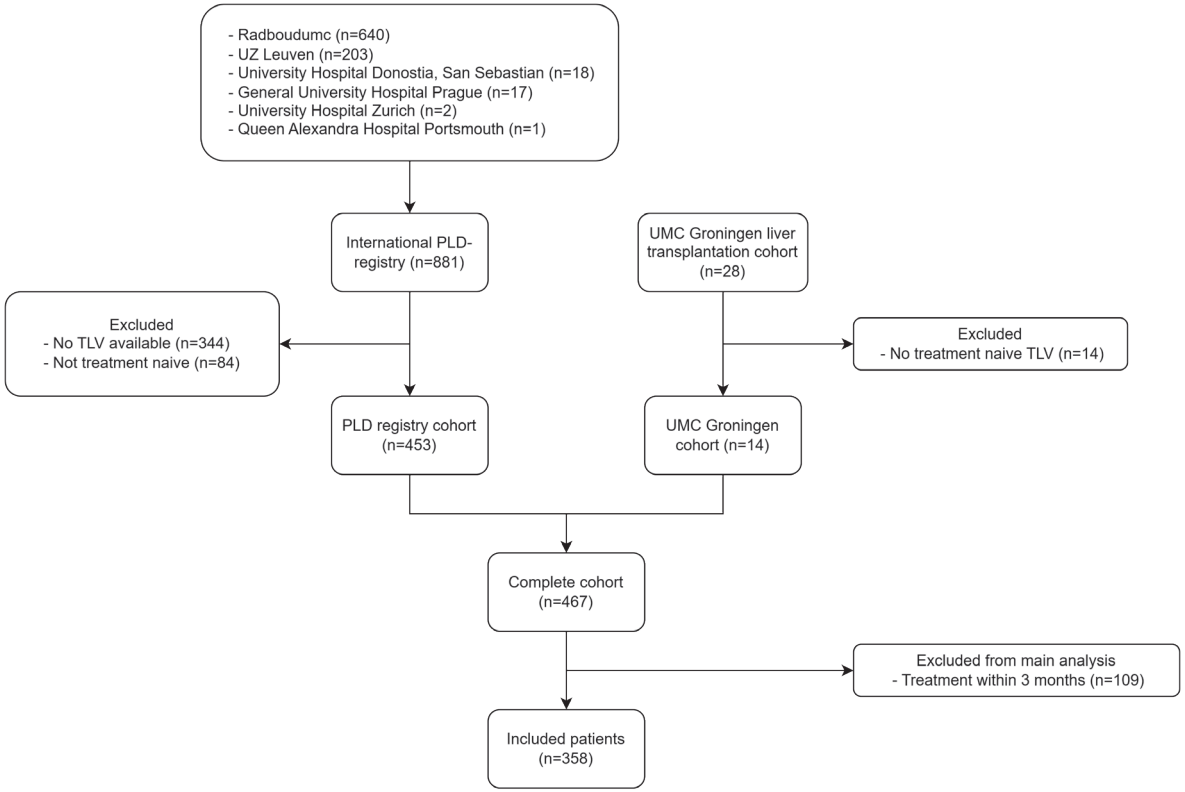

Figure 1 – Flowchart of patients
PLD = polycystic liver disease, TLV = total liver volume

		Treatment status		Sex		TLV		
	Overall (n=358)	**Untreated (n=201)**	**Treated (n=157)**	**Male (n=77)***	**Female (n=281)***	**TLV Tertile 1 (n=119)***	**TLV Tertile 2 (n=120)***	**TLV Tertile 3 (n=119)***
Liver event, n (%)								
Yes	55 (15.4)	10 (5.0)	45 (28.7)	6 (7.8)	49 (17.4)	3 (2.5)	22 (18.3)	30 (25.2)
No	303 (84.6)	191 (95.0)	112 (71.3)	71 (92.2)	232 (82.6)	116 (97.5)	98 (81.7)	89 (74.8)
Time between baseline and liver event months, median (IQR)	69.4 (29.3 – 102.2)	87.5 (53.9 – 125.8)	67.3 (26.6 – 98.4)	68.6 (39.9 – 107.0)	69.4 (29.3 – 99.4)	18.3 (8.3 – 107.0)	67.4 (41.0 – 98.4)	72.6 (29.3 – 102.2)

Table 3 – Liver events. IQR = interquartile range, * in treated patients only (n=5 for male patients, n= 40 for female patients, n=2 for TLV tertile 1, n=14 for TLV tertile 2, n=29 for TLV tertile 3), TLV tertiles: TLV <2213 ml in tertile 1, TLV 2213 – 4124 ml in tertile 2, and TLV > 4124 ml in tertile 3

We observed overall cumulative VRT rates of 18.4%, 32.2%, 38.8% and 48.4% at 1, 3, 5 and 8 years of follow-up respectively. The cumulative VRT rate at 1 year of follow-up categorized according to sex, was 21.0% for female patients and 9.1% for male patients ($p < 0.001$). Cumulative VRT rates at 1 year of follow-up divided by baseline TLV were 6.7% for patients with a baseline TLV in the first tertile (TLV < 2213 ml), 17.5% in the second TLV tertile (TLV 2213 – 4124 ml), and 31.7% in the third TLV tertile (TLV > 4124 ml, $p < 0.001$). We observed cumulative VRT rates of 0.0%, 16.7% and 16.7% at 1 year of follow-up for male patients in TLV tertile 1, 2 and 3 respectively. Female patients in TLV tertile 1, 2 and 3 had cumulative VRT rates of 9.5%, 17.7% and 33.7% at 1 year of follow-up. VRT-free survival and cumulative VRT rates can be found in figure 2, supplementary figure 1 and supplementary tables 1 and 2.

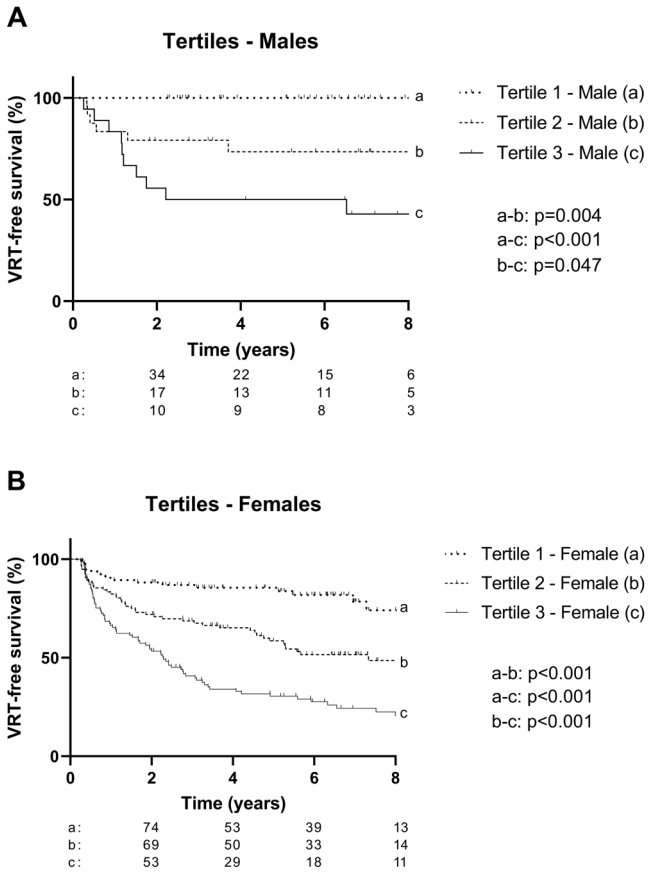

Figure 2 – Volume reducing therapy-free survival
VRT-free survival according to total liver volume for males (panel A) or females (panel B). VRT = volume reducing therapy, TLV = total liver volum

Liver events

Next, we analyzed the occurrence and type of liver events in our cohort (table 3 and supplementary tables 3 & 4) as a measure for PLD disease severity. Liver events occurred in 15.4% (n=55) of our cohort; more often in treated patients (n=45) than those from the untreated group (n=10). Untreated patients were hospitalized for non-VRT liver events exclusively (cyst hemorrhage, n=2; and cyst infection, n=8). The majority of liver events in the treated patients consisted of subsequent VRTs (aspiration sclerotherapy n=10, liver fenestration n=4, liver transplantation n=21). The majority of liver events occurred in female patients (89.1%), and patients with large livers (40.0% in TLV tertile 2, 54.5% in TLV tertile 3). Treated patients were associated with higher risk of liver events (HR 4.381, $p < 0.001$) and with TLV (HR 1.105 at 1.5 liters, $p = 0.026$).

Sex-specific association between TLV and VRT

TLV was associated with VRT initiation in the univariate analysis (HR TLV 1.241 at 1.5 liters, $p < 0.001$; model 1, table 4). Age, sex, diagnosis and originating cohort did not confound the relation between TLV and VRT (models 2-4, table 4) but there was significant effect modification between TLV and sex (model 5, table 4). The final multivariate model, adjusted for age and diagnosis, divided according to sex further shows the sex-specific association between baseline TLV and VRT (HR TLV females 1.202, $p<0.001$; HR TLV males 1.790, $p<0.001$; at 1.5 liters; model 7 table 4). In the entire cohort, this final model also shows an increased treatment risk for female patients at low baseline TLVs (HR sex 7.570 at 1.5 liters, $p < 0.001$; model 6 table 4). Figure 3a shows that relation between TLV and VRT on a continuous scale, for males and females separately. The difference between both sexes in the association between baseline TLV and VRT reduced as baseline TLV increased (Figure 3b).

Sensitivity analyses

We further investigated the association between baseline TLV and VRT in three sensitivity analyses (supplementary table 5). First, we assessed the robustness of the association with height-corrected TLV instead of TLV. In this sensitivity analysis of 343 patients, the sex-specific association between baseline height-corrected TLV and VRT remained robust (HR height-corrected TLV females 1.411, $p < 0.001$; HR height-corrected TLV males 2.684, $p < 0.001$; at 0.869 liter/meter). The second sensitivity analysis included patients who received VRT within 3 months of their baseline TLV measurements. Comparable results were found in this sensitivity analysis with 467 patients (HR TLV females 1.186, $p < 0.001$; HR TLV males 1.376, $p < 0.001$; at 1.5 liters). In a final sensitivity analysis, we investigated whether sex-specific differences were also present using estimated annual liver growth instead of TLV. The sex-specific association remained robust in this last sensitivity analysis (HR annual growth males 2.491, $p <0.001$; HR annual growth females 1.304, $p < 0.001$).

Complete cohort (n=358)				
#	**Variables**	**Hazard Ratio**	**95% confidence interval**	**p-value**
1	TLV (liters)	1.241	1.181 – 1.304	<0.001
2	TLV (liters)	1.242	1.182 – 1.304	<0.001
	Age (years)	1.002	0.986 – 1.018	0.803
3	TLV (liters)	1.232	1.173 – 1.294	<0.001
	Sex (reference = male)	2.384	1.416 – 4.012	0.001
4	TLV (liters)	1.234	1.177 – 1.294	<0.001
	Diagnosis (reference = ADPKD)	1.879	1.350 – 2.615	<0.001
5	TLV (liters)	1.699	1.391 – 2.075	<0.001
	Sex (reference = male)	7.975	2.782 – 22.862	<0.001
	TLV*Sex	0.709	0.577 – 0.872	0.001
6	TLV (liters)	1.708	1.394 – 2.093	<0.001
	Age (years)	0.997	0.982 – 1.013	0.748
	Sex (reference = male)	7.570	2.622 – 21.861	<0.001
	Diagnosis (reference = ADPKD)	1.793	1.285 – 2.504	<0.001
	TLV*Sex	0.703	0.570 – 0.867	<0.001

Cohort divided by sex							
7		**Female (n=281)**			**Male (n=77)**		
	Variables	**Hazard Ratio**	**95% confidence interval**	**p-value**	**Hazard Ratio**	**95% confidence interval**	**p-value**
	TLV (liters)	1.202	1.142 – 1.266	<0.001	1.790	1.391 – 2.302	<0.001
	Age (years)	0.992	0.992 – 1.009	0.367	1.043	0.989 – 1.099	0.120
	Diagnosis (reference = ADPKD)	1.779	1.128 – 2.523	0.001	2.437	0.709 – 8.379	0.158

Table 4 – Cox regression analysis between baseline total liver volume and volume reducing therapy. Multivariate models adjusted for age, sex and diagnosis, and stratified for source cohort. Model 6 divided by sex. TLV = total liver volume, ADPKD = autosomal dominant polycystic kidney disease.

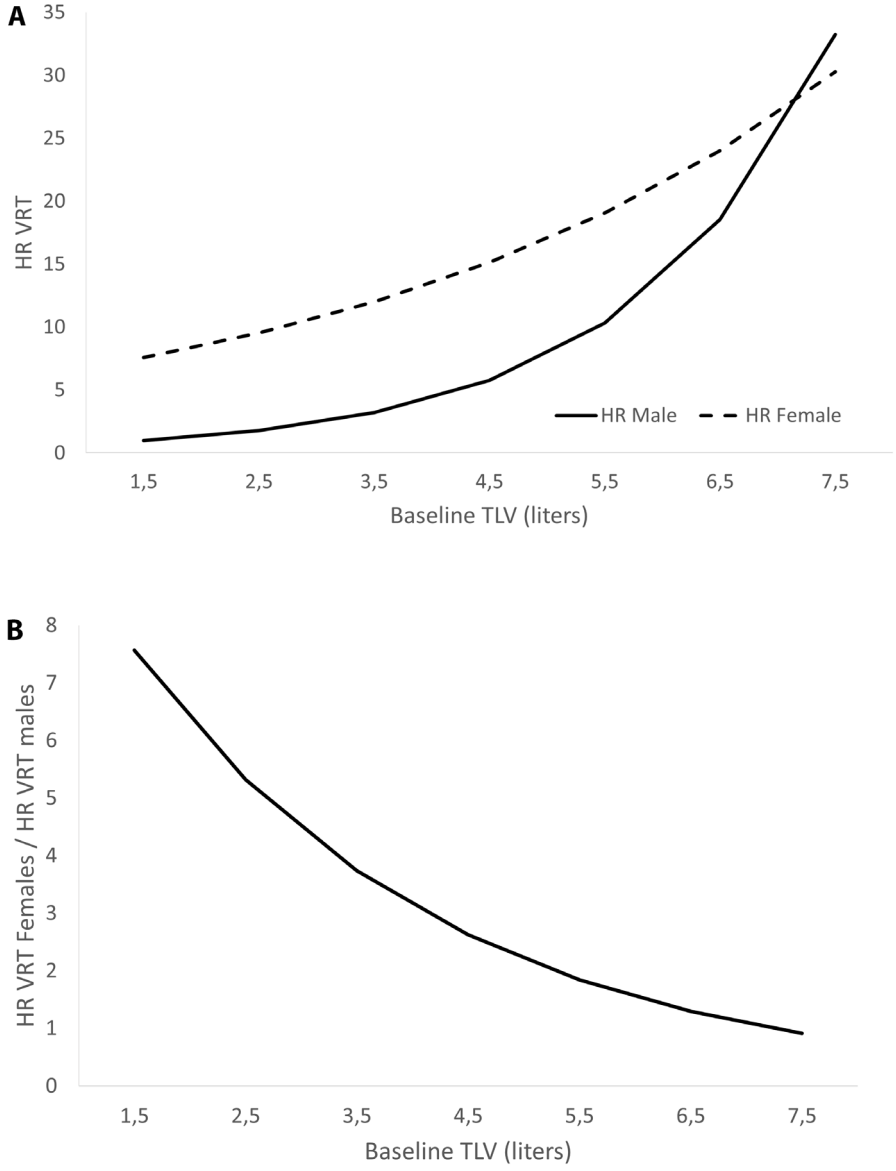

Figure 3 – Hazard ratios total liver volume and volume reducing therapy.
Panel A shows the hazard ratio for volume reducing therapy with total liver volume. The lines indicate hazard ratios for male and female patients separately. Panel B shows the difference in hazard ratio between male and female patients. VRT = volume reducing therapy, TLV = total liver volume.

Discussion

Our study demonstrates that baseline TLV is associated with future VRT in PLD patients and that sex-specific differences are present in this association. Female patients with a low baseline TLV (HR Sex 7.570 at 1.5 liters) carry a higher risk for VRT compared to males, while the risk difference for sex is mitigated at higher TLVs. Cumulative VRT rates were higher in female patients and with larger livers at baseline. The relation between TLV and VRT was robust across the complete disease spectrum and predefined sensitivity analyses. Treated patients have a higher risk for liver events, which emphasizes the more severe disease course in this subgroup.

Our findings are corroborated by previous studies. One study demonstrated that TLV correlates with symptom burden in PLD patients, which is the main indication for VRT [3]. Another study, which divided PLD in three groups according to height-corrected TLV, reported an association between height-corrected TLV and VRTs that is comparable to our current study (0.0% in patients with livers < 1600 milliliter/meter, 13.0% for patients with livers of 1600 - 3200 milliliter/meter, and 36.4% for patients with livers > 3200 milliliter/meter, $p < 0.001$) [8]. However, this last study did not differentiate between sexes when assessing VRT rates.

The most important strength of our study is the size and real-world setting of the cohort. Our cohort comprises a large number of treated and untreated PLD patients with TLV measurements that represent the entire spectrum of disease severity. Though the patients originate from several centers, ADPLD patients with a mild phenotype remain underrepresented in our cohort. This mimics clinical reality as individuals with mild ADPLD are generally asymptomatic and unaware of their disease. In contrast, ADPKD patients with a mild liver phenotype are typically aware of their disease because these patients are monitored for their kidney function. As a result, we have performed our study in a large and clinically representative, real-world cohort of PLD patients.

The main limitation of our study is that our primary endpoint, VRT, is a subjective outcome measure. The indication for therapy is made in conjunction by physicians and patients, and directed by symptoms and liver phenotype. Consequently, symptom perception and expression may have affected the application of the available treatment protocols [1, 14]. However, VRTs were most frequently administered in patients with the most severe PLD phenotype as indicated by the objective disease parameters TLV and liver event.

Our study indicates clear differences in VRT initiation between sexes, which may be explained with several hypotheses: 1) Male patients have higher intra-abdominal capacity compared to female patients, which could mitigate compression of adjacent structures by enlarged polycystic livers. Still, our findings remained robust after adjusting TLV for the patient's height. 2) VRT is initiated because of liver growth rather than absolute TLV. Female patients may experience faster liver growth resulting from (endogenous) estrogen exposure. However, the pronounced sex-specific differences remained present when using estimated annual liver growth instead of TLV. 3) Symptom perception is different for male and female patients. We could not test the last hypotheses because robust data regarding symptom severity were lacking in our cohort.

Currently, our study bears implications for research and clinical practice. In research, prognostic models for PLD that take into account sex-specific differences should be developed. These models are already available for other rare liver diseases (e.g., ADPKD or primary biliary cholangitis), which can serve as a template for prognostic PLD model [27, 28]. In addition, future studies should address symptom severity using validated questionnaires (e.g., the polycystic liver disease questionnaire) to address sex-specific differences in symptom experience and treatment choice [29]. In clinical practice, our study provides clinicians with evidence to counsel patients about their disease prognosis (including risk of requiring VRT) using only the clinical parameters TLV and sex: PLD patients with large TLVs and particularly females are at high risk for future VRT and occurrence of liver events. Historically, obtaining TLV measurements was time-consuming and costly. However, the advent of fully automatic liver segmentation software has facilitated its application in general clinical practice [24, 30]. Consequently, automatic liver segmentation should be applied in all PLD patients to provide them with adequate counselling.

In conclusion, our study establishes the predictive value of baseline TLV for VRT initiation in PLD patients. Sex-specific differences in the association between baseline TLV and VRT are present. Female PLD patients have a higher risk of VRT at a low baseline TLV, yet this sex-specific risk difference is mitigated at high baseline TLVs.

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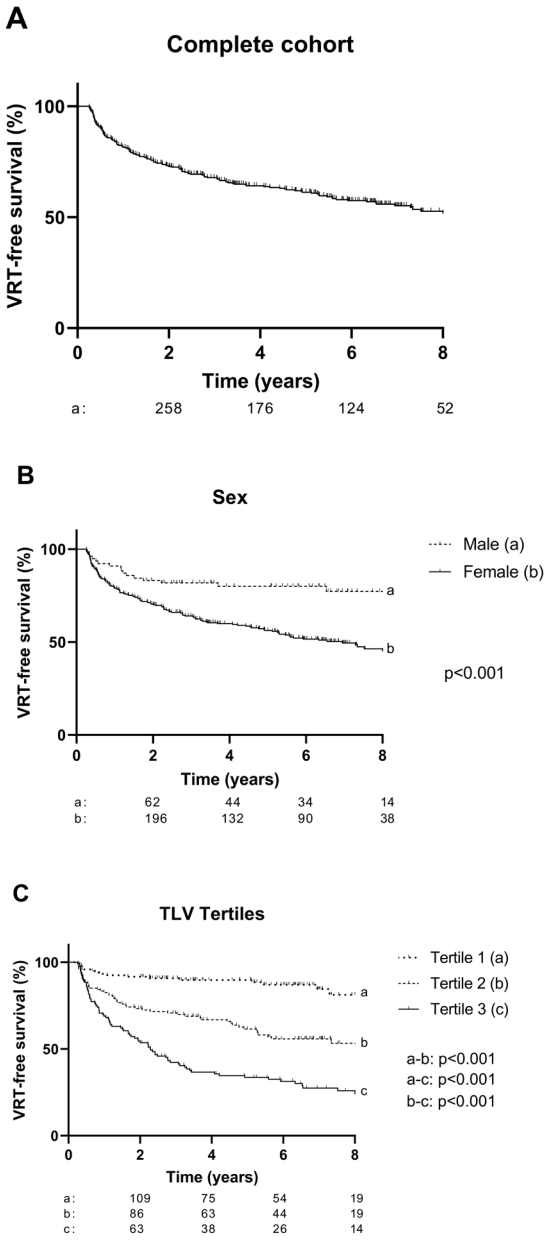
Supplementary Files



Supplementary figure 1 – Volume reducing therapy-free survival
Differences in VRT-free survival are showed for the complete cohort (panel A) and according to sex (panel B) or total liver volume (panel C). VRT = volume reducing therapy, TLV = total liver volume

Time (years)	Overall (n=358)	Females (n=281)	Males (n=77)	TLV tertile 1 (n=119)	TLV tertile 2 (n=120)	TLV tertile 3 (n=119)
1	18.4% (14.5 – 22.3)	21.0% (16.3 – 25.7)	9.1% (2.6 – 15.6)	6.7% (2.2 – 11.2)	17.5% (10.6 – 24.4)	31.7% (22.9 – 39.3)
3	32.2% (23.7 – 37.1)	36.0% (30.3 – 41.7)	18.2% (9.6 – 26.8)	9.3% (4.6 – 14.0)	29.3% (21.1 – 37.5)	57.8% (48.8 – 66.8)
5	38.8% (33.5 – 44.1)	43.8% (37.7 – 49.9)	20.0% (16.7 – 23.3)	10.3% (4.8 – 15.8)	38.6% (29.6 – 47.6)	66.4% (57.6 – 75.2)

Supplementary table 1 – Cumulative rates of volume reducing therapy at different time-points.
TLV = total liver volume. TLV per tertile: TLV <2213 ml in tertile 1, TLV 2213 – 4124 ml in tertile 2, and TLV > 4124 ml in tertile 3.

Time (years)	TLV Tertile 1 - Males (n=35)	TLV Tertile 2 – Males (n=24)	TLV Tertile 3 – Males (n=18)	TLV Tertile 1 – Females (n=84)	TLV Tertile 2 - Females (n=96)	TLV Tertile 3 - Females (n=101)
1	0.0% (0.0 – 0.0)	16.7% (1.8 – 31.6)	16.7% (0.0 – 33.9)	9.5% (3.2 – 15.8)	17.7% (10.1 – 25.3)	33.7% (24.5 – 42.9)
3	0.0% (0.0 – 0.0)	20.8% (4.5 – 37.1)	50.0% (13.2 – 86.8)	13.1% (5.8 – 20.4)	31.4% (22.2 – 40.6)	59.3% (49.5 – 69.1)
5	0.0% (0.0 – 0.0)	26.5% (8.1 – 44.9)	50.0% (13.2 – 86.8)	14.5% (6.9 – 22.1)	41.4% (31.2 – 51.6)	69.6% (60.2 – 79.0)

Supplementary table 2 – Cumulative rates of volume reducing therapy at different time-points.
TLV = total liver volume. TLV per tertile: TLV <2213 ml in tertile 1, TLV 2213 – 4124 ml in tertile 2, and TLV > 4124 ml in tertile 3.

			Untreated		Treated		Untreated			Treated		
	Untreated (n=201)	**Treated (n=157)**	**Male (n=61)**	**Female (n=140)**	**Male (n=16)**	**Female (n=141)**	**TLV tertile 1 (n=103)**	**TLV tertile 2 (n=69)**	**TLV tertile 3 (n=29)**	**TLV tertile 1 (n=16)**	**TLV tertile 2 (n=51)**	**TLV tertile 3 (n=90)**
Type of liver event, n												
Aspiration sclerotherapy	0	10	0	0	1	9	0	0	0	1	3	6
Liver fenestration	0	4	0	0	0	4	0	0	0	1	0	3
Liver transplantation	0	21	0	0	3	18	0	0	0	0	5	16
Liver cyst rupture	0	1	0	0	0	1	0	0	0	0	1	0
Liver cyst hemorrhage	2	3	0	2	0	3	0	2	0	0	2	1
Liver cyst infection	8	6	1	7	1	5	1	6	1	0	3	3

Supplementary table 3 – Types of liver events
TLV = total liver volume

	Hazard Ratio	95% confidence interval	p-value
Treatment			
Treatment (reference = no VRT)	4.381	2.198 – 8.734	<0.001
Sex			
Sex (reference = male)	1.925	0.821 – 4.513	0.132
Liver volume			
TLV (liters)	1.105	1.012 – 1.207	0.026

Supplementary table 4 – Liver event Cox regression analysis.
VRT = volume reducing therapy, TLV = total liver volume

	Female			Male		
Variables	**Hazard Ratio**	**95% confidence interval**	**p-value**	**Hazard Ratio**	**95% confidence interval**	**p-value**
Height-corrected TLV (n=343)						
Height-corrected TLV (liters/meter)	1.411	1.295 – 1.537	<0.001	2.684	1.644 – 4.384	<0.001
Age (years)	0.989	0.972 – 1.006	0.213	1.023	0.966 – 1.083	0.440
Diagnosis (reference = ADPKD)	2.024	1.427 – 2.872	<0.001	2.585	0.432 – 15.450	0.298
Including patients who received volume reducing therapy within 3 months (n=467)						
TLV (liter)	1.186	1.140 – 1.234	<0.001	1.376	1.163 – 1.628	<0.001
Age (years)	0.998	0.985 – 1.011	0.732	1.051	1.011 – 1.094	0.013
Diagnosis (reference = ADPKD)	1.507	1.152 – 1.971	0.003	1.748	0.713 – 4.286	0.223
Liver growth (n=358)						
Liver growth (%/year)	1.304	1.216 – 1.399	<0.001	2.491	1.555 – 3.993	<0.001
Age (years)	1.021	1.002 – 1.042	0.035	1.124	1.047 – 1.208	0.001
Diagnosis (reference = ADPKD)	1.764	1.243 – 2.503	0.001	1.695	0.504 – 5.700	0.393

Supplementary table 5 – Sensitivity analyses.
Models adjusted for age and diagnosis, and stratified for source cohort. TLV = total liver volume, ADPKD = autosomal dominant polycystic kidney disease.

6

EASL Clinical Practice Guidelines on the management of cystic liver diseases

European Association for the Study of the Liver*

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Abstract

The advent of enhanced radiological imaging techniques has facilitated the diagnosis of cystic liver lesions. Concomitantly, the evidence base supporting the management of these diseases has matured over the last decades. As a result, comprehensive clinical guidance on the subject matter is warranted. This Clinical Practice Guideline covers the diagnosis and management of hepatic cysts, mucinous cystic neoplasms of the liver, biliary hamartomas, polycystic liver disease, Caroli disease, Caroli syndrome, biliary hamartomas and peribiliary cysts. On the basis of in-depth review of the relevant literature we provide recommendations to navigate clinical dilemmas followed by supporting text. The recommendations are graded according to the Oxford Centre for Evidence-Based Medicine system and categorised as 'weak' or 'strong'. We aim to provide the best available evidence to aid the clinical decision-making process in the management of patients with cystic liver disease.

Introduction

The advent of enhanced radiological imaging techniques has facilitated the mapping of cystic liver lesions. Following the discovery of these lesions, it is now pertinent to provide guidance on the diagnosis and management of these lesions. The remit of this Clinical Practice Guideline (CPG) by the European Association for the Study of the Liver (EASL) is to provide guidance on the clinical management of non-infectious cystic liver diseases. These lesions encompass simple hepatic cysts, mucinous cystic neoplasms (MCNs) of the liver, polycystic liver disease (PLD), Caroli disease, Caroli syndrome, biliary hamartomas and peribiliary cysts. The disorders described in this CPG are broadly termed fibrocystic diseases. Fibrocystic liver disease encompasses a group of congenital and rare diseases that result from perturbed development of the embryonic ductal plate. Fibrocystic liver diseases are also part of a much wider group of developmental diseases termed "ciliopathies" because they share cilia dysfunction in their pathogenesis [1]. The prevalence of cystic liver lesions varies by disease; simple hepatic cysts are quite common (prevalence rate of 2.5-18.0%) [2,3], while PLD (prevalence rate of 1/10,000 - 1/158,000) and MCNs (estimated prevalence <5% compared to simple hepatic cysts) are rare [4-7].

Hepatic cysts are defined as fluid-filled lesions lined by a single cell layer. The pathogenesis of cysts involves abnormal foetal ductal plate maturation. The ductal plate is a double cylinder of hepatoblasts encircling portal vein branches that provides the scaffold for bile duct development. Cysts arise as a result of ductal plate malformation when the ductal plate disconnects from the biliary tree and progresses into cystic structures. Epithelial cells in the cyst retain a secretory function and fluid production generates a positive luminal pressure that contributes to the cyst's architecture. Cyst fluid consists of water and electrolytes and its composition mirrors that of bile but is devoid of bile acids or bilirubin [8].

MCNs are extremely rare and they may also be referred to as 'biliary cystadenoma' or 'biliary cystadenocarcinoma' in the literature. These lesions present as an important clinical challenge since malignant transformation rates of up to 30% have been described [9].

PLD is defined by the presence of >10 hepatic parenchymal cysts that are unconnected to the bile duct system. It may be inherited in an autosomal dominant fashion and, depending on the most prominent phenotype, 2 different entities have been categorised: autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (ADPLD) [10]. Patients with ADPKD are

diagnosed using previously established criteria based on the presence of kidney cysts; affected patients may develop hepatic cysts [11]. Patients with ADPLD do not meet the ADPKD criteria and cysts are typically restricted to the liver.

Caroli disease (or type V lesions based on the Todani classification) is characterised by dilatation of intrahepatic bile ducts [12]. While Caroli disease is limited to the dilatation of larger intrahepatic bile ducts, Caroli syndrome combines small bile duct dilatation and congenital hepatic fibrosis [13].

Biliary hamartomas, also called Von Meyenburg complexes, are considered to be part of the spectrum of ductal plate malformations [10]. Multiple bile duct hamartomas are typically recognised as tiny (<1 cm) hypodense lesions scattered throughout the liver with normal extra- and intrahepatic bile ducts. Recognition of this entity is crucial because they may mimic liver metastases at first sight.

Currently, comprehensive clinical guidance on cystic liver diseases is lacking, even though there is one guideline that includes PLD [14]. The evidence base supporting clinical management of cystic liver diseases has matured over the last decades to the point that an EASL CPG is warranted.

This EASL CPG covers the diagnosis and management of non-infectious cystic liver diseases. A discussion on choledochal cysts falls outside the remit of this CPG. We aim to provide practitioners with the best available evidence to support the clinical decision-making process when faced with patients with cystic liver diseases.

Methods

The EASL Governing Board initiated this CPG in August 2020 by selecting a panel of experts and describing the remit of the assignment. The development of this CPG followed a standard operating procedure set out by EASL and meets the international standards for CPGs set out by the Guidelines International Network. The process involves identification of a number of key questions pertinent to the subject matter. The CPG panel drafted questions according to the PICO format. P – patient, problem or population, I – intervention, C – comparison, control or comparator, O – outcome. PICO questions were vetted through a simplified Delphi process in the broader community including 41 physicians, scientists, patients and other stakeholders competent in the field of cystic liver diseases beyond the CPG panel and the EASL Governing Board. This was followed by a systematic literature

review process, a literature search was performed using PubMed, and expanding to Embase, Google Scholar and Scopus when needed. Additional articles were obtained through citation snowballing to locate primary sources. Search terms and results can be found in the supplementary information. Each expert took responsibility, made proposals for statements for a specific section of the guideline and shared tables of evidence and text with the full panel. The panel met virtually on 10 occasions, and all recommendations were discussed and approved by all participants. The level of evidence was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) system (Table 1) and the strength of the recommendations was categorised as either 'weak' or 'strong' (Table 2) [15]. The higher the quality of the evidence, the more likely a strong recommendation was made. If no clear evidence was available, recommendations were based on the expert opinion of the panel members. All recommendations were subsequently approved through a second Delphi round and were ultimately brought to the attention of the EASL Governing Board for final approval.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic Reviews (SR) (with homogeneity) of Randomised controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised controlled trials (RCT) or observational studies with dramatic effects;Systematic Reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Systematic Reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (Mechanism-based Reasoning)	Any estimate of effect is uncertain

Table 1 – Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Grade	Wording	Criteria
Strong	Must, shall, should, is recommendedShall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggestedMay not, is not suggested	

Table 2 – Grades of recommendation.

Questions and recommendations

1. Which imaging technique is recommended to diagnose cystic liver lesions?

Recommendations

- Ultrasound should be the first imaging modality used to diagnose simple hepatic cysts and PLD **(LoE 3, strong recommendation, 100% consensus).**
- Hepatic cysts demonstrating complex features (*e.g.* atypical cyst wall or content), either solitary or in the context of PLD, require further evaluation using additional imaging **(LoE 3, strong recommendation, 100% consensus).**
- MRI or CT can be used in PLD to evaluate the distribution of cysts within the liver parenchyma and the relation to hepatic vasculature **(LoE 2, weak recommendation, 100% consensus).**
- Biliary hamartomas should be diagnosed by MRI with heavily T2-weighted sequences and MR cholangiography sequences **(LoE 4, strong recommendation, 100% consensus).**
- The number of lesions (solitary *vs.* multiple) and architecture (simple *vs*. complex cyst) are key elements in the description of hepatic cyst(s) **(LoE 3, strong recommendation, 100% consensus).**

Hepatic cysts are most often discovered incidentally on imaging and accurate diagnosis is needed to differentiate between benign and malignant causes. On ultrasound, hepatic cysts are recognised by their anechoic content with posterior enhancement. A CT image identifies cysts as homogeneous and hypoattenuating lesions on non-enhanced scans, without enhancement of their content after administration of contrast material. MRI helps to identify a strong signal on T2-weighted sequences, similar to other fluids (cerebrospinal fluid) and a low T1-weighted signal. Two features are key to characterise cysts: number of lesions (solitary *vs.* multiple) and architecture (simple *vs*. complicated *vs.* complex cyst). Complicated and complex cysts are defined by the presence of complex features within a lesion, including calcifications, septations, mural thickening or nodularity, debris-containing fluid, haemorrhagic or proteinaceous contents, fluid levels, wall enhancement, and associated bile duct dilatation [16]. Complications of hepatic cysts are referred to as complicated cysts throughout the manuscript; complex cysts are defined as cysts with atypical and complex features.

Ultrasound and MRI are the best imaging modalities to characterise cystic liver lesions. Ultrasound explores content and wall thickness while MRI is able to identify

haemorrhagic or proteinaceous contents and wall enhancement. The sensitivity and specificity of ultrasound for the diagnosis of cystic liver lesions is about 90% [17]. Ultrasound has many strengths: it is widely available, inexpensive and lacks radiation exposure [16]. Contrast-enhanced ultrasound is indicated for complex cysts and helps to identify malignant cystic lesions by demonstrating vascularised septation or wall enhancement, features that are absent in benign lesions [18]. CT may detect gas or calcification but is less accurate for assessing cyst contents. In patients with impaired renal function, administration of contrast-agents may play a role in selecting the appropriate imaging modality.

Among the different MRI sequences, half-Fourier single-shot turbo spin echo sequences are most useful as they allow for differentiation between solid tumours, haemangiomas, and cystic lesions [19]. Conversely, the role of diffusion-weighted MRI in diagnosing cystic liver lesions is more controversial [16]. Indeed, a complete MRI protocol should be performed including contrast-enhanced sequences.

Simple hepatic cyst

Ultrasound is the modality of choice to diagnose a simple hepatic cyst. Simple cysts are round or oval-shaped, anechoic with sharp and smooth borders with thin walls, and strong acoustic posterior enhancement [20]. Once diagnosed on ultrasound, CT and MRI are not indicated to further characterise simple hepatic cysts.

Simple hepatic cysts may induce compression of bile ducts, but this is infrequent. At imaging, the peripheral bile duct dilatation inducing cyst is usually centrally (liver segment 4) located. These patients may present with rising alkaline phosphatase and even jaundice [21].

Complicated hepatic cyst

The most common complications of hepatic cysts are haemorrhage (see question 9) and infection (see question 5). In both, diagnosis requires imaging beyond ultrasound. Cyst haemorrhage is regularly observed in clinical practice but incidence rates remain unknown. The diagnostic criteria for cyst haemorrhage are detailed in question 9. Infected hepatic cysts that result from secondary bacterial infection of simple hepatic cysts are generally assumed to be rare [22]. Current diagnostic criteria rely on clinical, biochemical, microbial and radiological parameters as discussed in question 5 [23,24].

Polycystic liver disease

Current diagnosis of PLD is made in the presence of >10 hepatic cysts. On ultrasound, CT and MRI, PLD will appear as multiple hepatic cysts with the same features as

simple solitary cysts. In the absence of symptoms or complications, no other imaging examination is required. CT or MRI is instrumental to evaluate the distribution of cysts in the liver, the presence of hepatic or portal vein compression and the volume of non-affected liver. Clinically apparent portal hypertension resulting from hepatic venous outflow obstruction is extremely rare. Currently, several systems can be used to classify PLD. These classifications such as Gigot's, Kim's and Schnelldorfer's rely on number, size and distribution of hepatic cysts [25-27]. In this regard, MRI should be preferred over CT, particularly in patients with renal insufficiency. Overall, MRI is superior to ultrasound and CT, and allows for better detection of small cysts in young individuals [28]. Complications of hepatic cysts in patients with PLD are similar to those seen in patients with simple hepatic cysts.

Caroli disease

Caroli disease (or type V lesions based on the Todani classification) is characterised by dilatation of intrahepatic bile ducts[12]. Caroli disease needs to be distinguished from Caroli syndrome [13]. Caroli syndrome features congenital liver fibrosis and kidney cysts in addition to type V biliary dilatations. CT and MRI typically demonstrate segmental intrahepatic saccular or fusiform cystic areas. The central dot sign that represents fibrovascular bundles within the dilated cystic intrahepatic ducts is typical of Caroli disease. Contrast-enhanced imaging reveals the continuity between cystic lesions and draining bile ducts [29]. Diagnostic accuracy is highest with magnetic resonance cholangiopancreaticography, as this allows for the optimal visualisation of the biliary tree. The diagnosis may best be confirmed in expert disease centres.

Biliary hamartomas

Biliary hamartomas may be hypoechoic, hyperechoic or mixed heterogenic echoic structures on ultrasound. The echogenicity is dependent on the presence of dilated bile ducts and fibrocollagenous stroma with biliary hamartomas. The size of hamartomas is typically between 2 to 10 mm [30,31]. In addition, multiple "comet-tail" artifacts (a dense tapering trail of echoes just distal to a strongly reflecting structure) may be present in biliary hamartomas [32-37]. On CT, biliary hamartomas appear as multiple hypoattenuating lesions, predominantly in the subcapsular and periportal areas, that are round or irregular in shape. No enhancement is observed, but they are more clearly visible after intravenous administration of iodinated contrast material [38]. With MRI, biliary hamartomas are hypointense on T1-weighted sequences, and show markedly high intensity on T2-weighted sequences. They often possess an irregular shape with well-defined margins – features which have led to the term "starry sky" appearance. MR cholangiography has a high diagnostic sensitivity and may be used to confirm the absence of communication with the biliary tree [38,39]. On contrast-enhanced MR

sequences, biliary hamartomas may display different patterns: no enhancement, or thin and regular rim of enhancement, or small enhancing mural nodule [40].

Peribiliary cysts

Peribiliary cysts are characterised by their peculiar distribution (predominantly perihilar and on both sides of the bile ducts) and small size (<1 cm). They are often observed in patients with portal hypertension and cirrhosis and may appear as discrete cysts, tubular structures paralleling the portal structures, or a string of cysts that simulate abnormal bile ducts [41]. Ultrasound, CT or MRI may be used as diagnostic modalities (Fig. 1) [42,43].

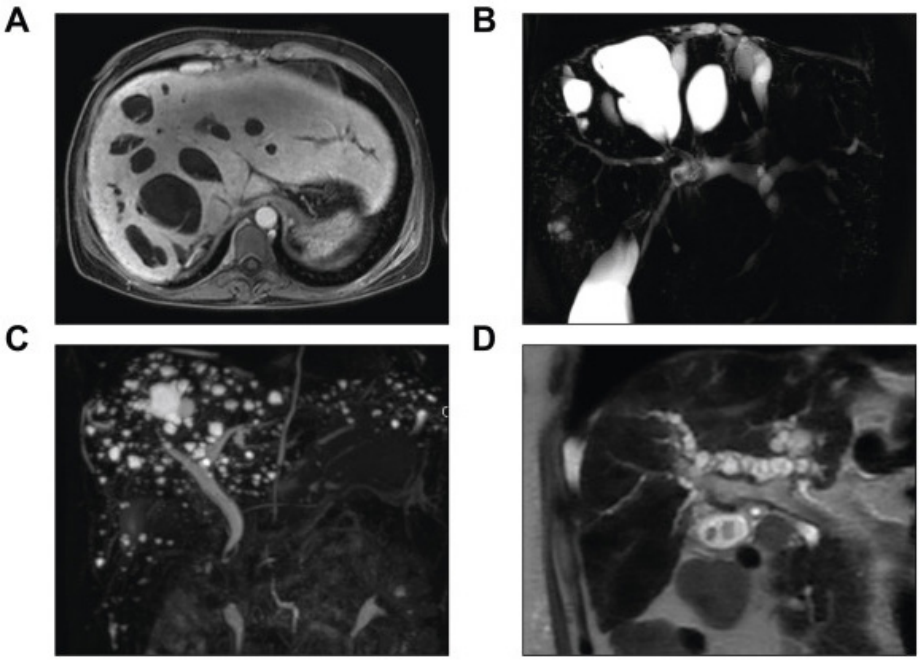

Fig. 1 – Imaging characteristics of Caroli disease, biliary hamartomas and peribiliary cysts. (A,B) Caroli disease, contrast-enhanced T1-weighted MRI and MRI cholangiography showing intrahepatic bile duct dilatation with both saccular and fusiform features; (C) biliary hamartomas, MRI cholangiography showing small innumerable T2 hyperintense cystic lesions scattered throughout the hepatic parenchyma without any communication with bile ducts, which resembles a "starry sky"; (D) peribiliary cysts, coronal T2-weighted MRI showing well-demarcated hyperintense cysts in a hilar distribution.

2. Which imaging technique is recommended for follow-up of cystic liver lesions?

Recommendations

- It is not recommended to follow asymptomatic patients because of simple hepatic cysts, biliary hamartomas or peribiliary cysts **(LoE 3, strong recommendation, 96% consensus).**
- Ultrasound should be the first diagnostic modality used if symptoms occur in patients with simple hepatic cysts **(LoE 3, strong recommendation, 96% consensus).**
- Routine follow-up with imaging after aspiration sclerotherapy or surgical procedures for hepatic cysts is not recommended **(LoE 3, strong recommendation, 92% consensus).**

Follow-up of cystic liver lesions varies depending on the pathologic entity.

Simple hepatic cysts

Simple hepatic cysts are benign lesions that typically follow an indolent course without significant changes in size over time. Incidentally, cysts may grow and it is unclear why some simple cysts grow and others remain stable. There is no indication for follow-up of simple hepatic cysts whatever the size. If patients become symptomatic, imaging (ultrasound first) will assess the size and look for complications and compression. Symptomatic hepatic cysts can be treated surgically or with percutaneous aspiration sclerotherapy (see question 4). Post treatment imaging is not indicated, as treatment success is defined by symptom relief and not by volume reduction of hepatic cysts [44]. If imaging is performed post-treatment, CT or MRI allow for a good estimation of the volume of remnant cyst.

Complicated hepatic cyst

While intracystic haemorrhage within a hepatic cyst resolves spontaneously and does not require any treatment, an infected hepatic cyst necessitates active management. Treatment options for hepatic cyst infection are discussed in questions 6 to 8. Here, the need for imaging is dictated by the presence of symptoms or ongoing acute phase response. These patients may benefit from a contrast-enhanced CT, MRI or, if necessary, 18-fluorodeoxyglucose positron emission tomography-CT (^{18}FDG PET-CT) and/or cyst aspiration. The diagnostic criteria for cyst haemorrhage and infection are discussed in questions 9 and 5.

Polycystic liver disease

Most patients with PLD are, and will remain, asymptomatic; hence imaging follow-up is not indicated. In others, the increasing volume of cysts may result in massive enlargement of the liver with abdominal pain, back pain, early satiety, dyspnoea, malnutrition and a significant impairment in quality of life [45]. Treatment may be considered when quality of life is altered, or in case of local complications as further discussed in question 18 [46]. Routine post treatment imaging is not indicated [44].

Caroli disease and Caroli syndrome

Surveillance in Caroli disease and syndrome is mainly focused on the detection of cholangiocarcinoma. This is further discussed in question 22.

Biliary hamartomas and peribiliary cysts

To date, only a few case studies have reported a possible association between biliary hamartomas and hepatic malignancies, the majority of which were intrahepatic cholangiocarcinoma [47-49]. It is suggested that the presence of persistent chronic inflammation in some of the reported patients might explain the malignant transformation. We do not recommended imaging to follow patients with biliary hamartomas not associated with congenital hepatic fibrosis or Caroli disease. It is not recommended to follow patients because of peribiliary cysts.

3. When should blood and cyst fluid measures of CEA, CA19-9 and TAG-72 be used for diagnosis in cystic liver diseases?

Recommendations

- The tumour markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) in blood or cyst fluid cannot be used to discriminate between hepatic cysts (solitary or in PLD) and MCNs of the liver **(LoE 2, strong recommendation, 100% consensus).**
- Tumour-associated glycoprotein 72 (TAG-72) in cyst fluid may help to distinguish between simple hepatic cysts and MCNs of the liver **(LoE 3, weak recommendation, 95% consensus).**

Serum CA19-9 levels are elevated in up to 50% of patients with simple hepatic cysts or PLD, in 6-100% of patients with biliary cystadenomas and in 28-73% of biliary cystadenocarcinomas. No significant differences in serum CA19-9 levels were consistently observed between simple cysts and MCNs [50-58].

CA19-9 is expressed by the epithelial cells of (even benign) hepatic cysts and is released into serum and cyst fluid. The epithelial expression translates into higher concentrations of CA19-9 in cyst fluid compared to serum. The serum CA19-9 levels correlate with total hepatic cyst volume. However, CA19-9 levels in cyst fluid hardly discriminate between simple and malignant cysts (AUC 0.71, accuracy 19%) or between cystadenomas and cystadenocarcinomas [51,55,57,59-61].

Serum CEA is normal in patients with simple hepatic cysts and elevated in up to 49% of patients with cystadenoma and in up to 75% with cystadenocarcinoma. However, serum CEA levels do not differ between patients with simple cysts and those with a cystadenoma and they had a low diagnostic accuracy for the distinction between cystadenomas and cystadenocarcinomas (AUC 0.69) [50,51,55,58,62].

Similar to CA19-9, CEA levels are elevated in hepatic cyst fluid compared to serum, but intracystic concentrations can hardly differentiate between different cyst entities, *e.g.*, with an AUC of 0.71 and an accuracy of 22% for the distinction between benign and malignant cysts [51,55,59-61].

TAG-72 and carbohydrate antigen 72-4 (CA72-4) in cyst fluid have shown the best diagnostic capabilities for discriminating between malignant cysts (>25 U/ml) and simple hepatic cysts (sensitivity 79%; Specificity 97%, AUC 0.98). However, the number of observations is low and the results are biased because the sample consists of only surgically acquired (symptomatic) cysts [59,63].

4. Which simple hepatic cysts should be treated with volume-reducing therapy?

Recommendation

- Symptomatic simple hepatic cysts without biliary communication should be treated with the best locally available volume-reducing therapy **(LoE 2, strong recommendation, 100% consensus).**

Symptomatic simple hepatic cysts are usually treated by either percutaneous aspiration sclerotherapy, or cyst fenestration as volume-reducing therapy. With aspiration sclerotherapy, the cyst is first drained and temporarily exposed to a sclerosing agent. Cyst fenestration procedures entail a laparoscopy, followed by drainage and resection of the extrahepatic cyst wall. High quality randomised-controlled trials that directly compare these volume-reducing therapies have not yet been published. The available studies have a retrospective single centre design [64-69].

Mere aspiration of cyst fluids invariably results in refilling of the cyst cavity with fluid [70]. Therefore, aspiration of cyst fluid without subsequent sclerotherapy should not be considered as definitive volume-reducing therapy. Sclerotherapy is possible with multiple substances such as 100% ethanol, 20% saline, tetracycline or polidocanol without clear evidence for superiority of any of the agents [68]. It is important to highlight that the volume reduction after aspiration sclerotherapy is slow in onset and may take at least 6 months. We advise against reintervention in the first 6 months after aspiration sclerotherapy. Reported volume reductions after aspiration sclerotherapy range between 76-100%, while symptom relief is obtained in 72-100% of cases and symptom disappearance occurs in 56-100%. The most frequent peri-interventional complications, *e.g.*, ethanol intoxication and local pain, are seen after long duration (>1 hour) sclerotherapy with high-volume ethanol. The combination with the somatostatin analogue pasireotide does not improve the volume-reducing effect or patient-reported outcomes of aspiration sclerotherapy with ethanol [71].

Laparoscopic and open cyst deroofing/fenestration are associated with a low (<8%) recurrence rate [65]. Laparoscopy is preferred over laparotomy in view of the shorter procedural time, reduced postoperative hospital stays and less postoperative pain, while recurrence rates and symptom relief are comparable to the open approach [64,67,69]. More extensive surgical procedures such as partial hepatectomy combined with cyst fenestration in PLD have been associated with a perioperative mortality rate of up to 14% and postoperative liver failure (mean follow-up time up of 6 and 8 years) with the need for liver transplantation in 2-3% of patients [46,72].

Different volume-reducing therapies have not been directly compared in the literature and as a consequence robust evidence on the superiority of any of available volume-reducing therapies is absent. As success of volume-reducing therapies is defined by symptom relief and not volume reduction, volume-reducing therapies should only be performed in symptomatic patients.

Spontaneous rupture is rare, occurs in large hepatic cysts and may result from (minor) trauma. The rupture causes emptying of cyst contents into the peritoneal cavity or more rarely into the pleural cavity or duodenum [73]. Imaging shows cystic liver lesions are often irregular and associated with extrahepatic fluid effusion. The evidence base on the rupture of hepatic cysts comes from a few case reports [74-78]. These studies reported a median cyst size (prior to rupture) of >10 cm (range 2-35 cm). Risk factors for cyst rupture include cyst haemorrhage, cyst infection, trauma and intervention. Imaging demonstrates new onset ascites and signs of ruptured hepatic cyst wall,

accompanied by cyst haemorrhage in about half of cases. It is unclear whether cyst haemorrhage (with increased intracystic pressure) is a cause or consequence of cyst rupture. Given the low number of observations and the relatively high prevalence of simple hepatic cysts in the population (up to 18%), symptomatic cyst rupture must be a rare event. Although most case reports documented a full recovery of patients after cyst rupture, a few fatal outcomes have been reported. These outcomes do not justify a recommendation on pre-emptive volume-reducing therapy.

5. What are the diagnostic criteria for hepatic cyst infection?

Recommendation

- Hepatic cyst infection should be considered as definite in the presence of neutrophil debris and/or microorganisms in cyst aspirate showing evidence of infection **(LoE 4, strong recommendation, 100% consensus).**
- Hepatic cyst infection should be considered as likely in the presence of the features listed in Table 3 **(LoE 4, strong recommendation, 100% consensus).**
- Radiological findings listed in Table 3 may suggest hepatic cyst infections and may be used during the diagnostic work-up **(LoE 3, weak recommendation, 100% consensus).**

Hepatic cyst infection may be a complication of simple hepatic cysts as well as PLD. While the diagnosis may seem elementary, hepatic cyst infections often present a diagnostic conundrum. A cyst aspirate showing evidence of infection (neutrophil debris and/or microorganism) is the golden standard to establish a cyst infection [24,79-82]. However, this finding is relatively rare and does not contribute to the diagnosis in the majority of cases. Cyst infections are more frequently diagnosed using other clinical, laboratory and imaging findings: fever (temperature >38.5° C for >3 days) without other sources of fever detectable, CT or MRI detecting gas in a cyst, ^{18}FDG PET-CT showing increased FDG avidity of the cyst lining relative to normal parenchyma, tenderness in the liver area, increased C-reactive protein, increased leukocyte count (>11,000/L) or positive blood culture [24,79-83]. Other infectious causes, *e.g.* urinary tract infections or pneumonia, should be excluded using urine culture tests and chest x-rays.

Serum liver tests play no role in the diagnosis of hepatic cyst infections [84]. In case reports, elevated serum CA19-9 levels compared to baseline measurements may be observed [54]. However, we do not recommend routine determination of CA19-9 due to the low level of this evidence and the unspecific nature of this disease marker as discussed in question 3.

Criteria definite hepatic cyst infection	Criteria likely hepatic cyst infection (after exclusion of other sources)
• Cyst aspiration showing evidence of infection (neutrophil debris and/or microorganism)	• Fever (temperature >38.5°C for >3 days) with no other source of fever detectable • CT or MRI detecting gas in a cyst[18]FDG PET-CT showing increased FDG activity lining a cyst compared to normal parenchyma • Tenderness in the liver area • Increased C-reactive protein • Increased leukocyte count (>11,000/L) • Positive blood culture
Radiological findings suggestive of hepatic cyst infection	
• Liver ultrasound: debris with a thick wall and/or a distal acoustic enhancement in at least one cyst • Liver CT/MRI: enhanced wall thickening and/or perilesional inflammation in at least one cyst • MRI: high signal intensity on diffusion-weighted images, fluid-fluid level, wall thickening, or gas in at least one cyst • Positron emission tomography scan ([18]FDG PET-CT): increased FDG activity lining a cyst compared to normal parenchyma	

Table 3 – Criteria for hepatic cyst infection and radiological findings suggestive of hepatic cyst infection. [18]FDG PET-CT,18fluorodeoxyglucose positron emission tomography-CT.

Standard radiological imaging is of little help in establishing hepatic cyst infection due to the absence of reliable features that differentiate infected and non-infected hepatic cysts [85,86]. Inflammation parameters, *e.g.* enhanced wall thickening, high signal intensity on diffusion-weighted images, fluid-fluid level, or intracystic gas bubbles observed on CT or MRI may substantiate the diagnosis of hepatic cyst infection. Other non-specific features observed in infected hepatic cysts include heterogenous cyst content and steep increase in the cystic diameter compared to previous evaluations. [18]FDG PET-CT is superior to other imaging modalities and can be used to support the diagnosis of infected cysts in doubtful cases [80,81,87-91]. If the diagnosis of infection is equivocal, fluid aspiration can be performed to confirm the diagnosis.

6. Which antibiotic therapy is recommended in cyst infection?

Recommendations

- Fluoroquinolones and third-generation cephalosporins are recommended as empirical first-line antibiotics for hepatic cyst infection **(LoE 2, strong recommendation, 90% consensus).**
- The recommended duration of antibiotic therapy is 4-6 weeks **(LoE 4, strong recommendation, 100% consensus).**

Antibiotic therapy of hepatic cyst infections is of utmost importance and should be administered as soon as possible according to local practice formularies. Without

adequate treatment, hepatic cyst infections can lead to sepsis and ultimately death. Most hepatic cyst infections are caused by gut bacteria. *Escherichia coli* is the most frequent isolate, fuelling the concept that bacterial translocation from the gut is pivotal [92,93]. Antibiotics, in particular monotherapy, are not universally successful and a meta-analysis documented treatment failure in up to 70% [84,94]. Antibiotic penetrance is a key success factor. Carbapenems and cefazolin poorly penetrate into the cyst fluid [95,96]. In renal cysts, trimethoprim-sulfamethoxazole performs better but data in hepatic cysts are lacking [97]. Antibiotic diffusion into infected cysts may be further affected by inflammation-induced hyperpermeability of blood vessels [97,98]. Repeated antibiotic courses, drainage and surgical procedures may contribute to the emergence of resistant bacterial strains [93,99].

Fluoroquinolones (ciprofloxacin) and third-generation cephalosporins remain the standard of care treatment for hepatic cyst infections [84]. Although there is no evidence for combination of ciprofloxacin with a cephalosporin, it may be reasonable in severe cases [79]. There is no data on the efficacy of alternative delivery strategies of antibiotics such as flushing cysts with antibiotics or instillation of antibiotics into cysts.

When faced with hepatic cyst infection, patients and clinicians should adhere to clinical reasoning comparable to other systemic infections: i) use quick sequential organ failure assessment in the clinical algorithm, ii) tailor antibiotic therapy to blood cultures (though these are often negative in hepatic cyst infections), iii) adjust antibiotic therapy to the local resistance profile, iv) adapt drug dosage to renal function and v) suspect fungal infection if antibiotics do not lead to clinical improvement. Efficacy of antibiotic treatment and infection eradication are defined by the disappearance of symptoms such as fever, normalisation of C-reactive protein levels, and at least 2 negative blood cultures. While formal evidence for duration of antibiotic therapy is lacking, a regimen of parenteral treatment followed by a prolonged course of oral antibiotics (4-6 weeks total antibiotic treatment) seems reasonable.

Most cyst infections will be singular events, but some patients, especially those with a compromised immune system, *e.g.* after renal transplantation in ADPKD, are at risk of recurrence. In patients with recurrent cyst infections that severely compromise quality of life, liver transplantation may be considered [100,101].

7. Should antibiotics/probiotics be used in hepatic cyst infection to prevent recurrence?

Recommendations

- We do not recommend secondary prophylaxis for hepatic cyst infection **(LoE 5, strong recommendation, 92% consensus).**
- **Statement:** Robust evidence to recommend selective decontamination of the digestive tract to prevent hepatic cyst infection is lacking **(LoE 4, 100% consensus).**

Different approaches to secondary prophylaxis for hepatic cyst infection can be proposed: i) Continuous use of antibiotics, and ii) selective decontamination of the digestive tract. Currently, no evidence for systematic secondary prophylaxis using antibiotics or probiotics is available. Selective decontamination of the digestive tract controls overgrowth of potential pathogens in the gut and intends to prevent opportunistic infections. It may reduce the incidence of recurrent hepatic cyst infection. Polymyxin with neomycin may be a good option for selective decontamination of the digestive tract [102], but there is currently insufficient evidence available to fully recommend its application to prevent hepatic cyst infection.

8. In which patients is drainage indicated for cyst infection?

Recommendations

- Drainage of infected hepatic cysts may be pursued in the presence of any (combination) of the factors listed in Box 1 **(LoE 3, weak recommendation, 90% consensus).**

Drainage of infected hepatic cysts may be considered in some cases. The main goals for drainage reported are: i) non-response to antibiotic treatment and ii) recurrence of cyst infections after initial antibiotic therapy. In several studies, drainage and antibiotics prove more effective than antibiotics alone [79,80,103]. A meta-analysis found that 64% of infected cysts required drainage [94]. This may be a consequence of the severity of the infection, the inability of antibiotics to adequately penetrate the cyst, or patient-specific factors. Patients with larger cysts, defined as a diameter >5 cm are more likely to require drainage [79]. Drainage may also be pursued in patients who do not respond to empirical antibiotic therapy, after isolation of pathogens from a cyst aspirate, in patients with a severely compromised immune system and when intracystic gas is detected on imaging. [18] FDG PET-CT may aid in the identification of the localisation of infected cysts (see question 5).

- Persistence of temperature >38.5° C after 48 hours on empirical antibiotic therapy
- Isolation of pathogens unresponsive to antibiotic therapy from a cyst aspirate
- Severely compromised immune system
- CT or MRI detecting gas in a cyst
- Large infected hepatic cysts

Box 1 – Factors for drainage of infected hepatic cysts.

We advise caution in pursuing drainage of infected hepatic cysts in patients with PLD. It is difficult to identify the incriminated cyst in PLD and the infection may spread to adjacent cysts if drainage is performed. Percutaneous or laparoscopic drainage should be performed in a similar fashion as for pyogenic liver abscesses.

9. Which imaging technique is recommended to diagnose cystic haemorrhage?

Recommendations

- Imaging to detect intracystic haemorrhage may be performed in patients with sudden and severe abdominal pain **(LoE 4, weak recommendation, 96% consensus).**
- Ultrasound (showing sediment or mobile septations) and/or MRI (heterogeneous and intense signal on both T1- and T2-weighted sequences) may be used to diagnose cyst haemorrhage **(LoE 3, weak recommendation, 96% consensus).**
- CT is not recommended to diagnose cyst haemorrhage **(LoE 4, strong recommendation, 91% consensus).**

Intracystic haemorrhage results from injury to fragile blood vessels of the cyst wall lining and is by far the most frequent complication of hepatic cysts. Cyst haemorrhage is mostly seen in patients with larger (arbitrarily defined as >8 cm) cysts [104] and may occur spontaneously, as a complication of percutaneous aspiration sclerotherapy, or as a consequence of a cyst rupture.

Clinical manifestations consist of sudden, severe pain (observed in 80% of patients) without haemodynamic instability and the risk increases with the size of the cyst [74]. Local abdominal pain will resolve in few days to weeks. A drop in haemoglobin levels is exceptional, but may occur [105]. Serum concentrations of CA19-9 may increase and have been reported to decrease after the acute episode [106]. Conservative management is preferred and interventions such as aspiration (with or without sclerotherapy) of cyst content, or laparoscopic deroofing of the cyst dome should be avoided in active

haemorrhage [74]. At ultrasonography, heterogenous hyperechoic and mobile material, corresponding to clots, and thin mobile septations may be observed in haemorrhagic cysts (Fig. 2). On contrast-enhanced ultrasound, the lack of enhancement of the intracystic structures is highly suggestive of clotting [107]. CT is usually unable to detect intracystic haemorrhage but can be used to detect extravasation of cyst contents in the abdominal cavity in rare cases of cyst wall rupture [16,74,108]. MRI is very specific as haemorrhagic cysts are hyperintense on both T1- and T2-weighted sequences [109] (Fig. 2). The heterogeneous hyperintensity on T1- and T2-weighted sequences may persist for several months [110]. In most cases, the signal is heterogeneous on T1-weighted sequences and thickened wall and fluid-fluid level (represented by blood-filled lakes between septa) may be seen. Very rarely, round mural nodules (some of them enhancing) are seen in haemorrhagic cysts, mimicking MCNs of the liver [111]. Interestingly in a series of 14 patients with haemorrhagic hepatic cysts, all cases showed wall calcifications [112]. In patients with multiple cysts, MRI may show varying intensities in the cyst contents, which is related to different degrees and durations since haemorrhage [113]. Calcification of the cyst lining may ensue after cyst haemorrhage and is visible by high attenuation values on CT scan.

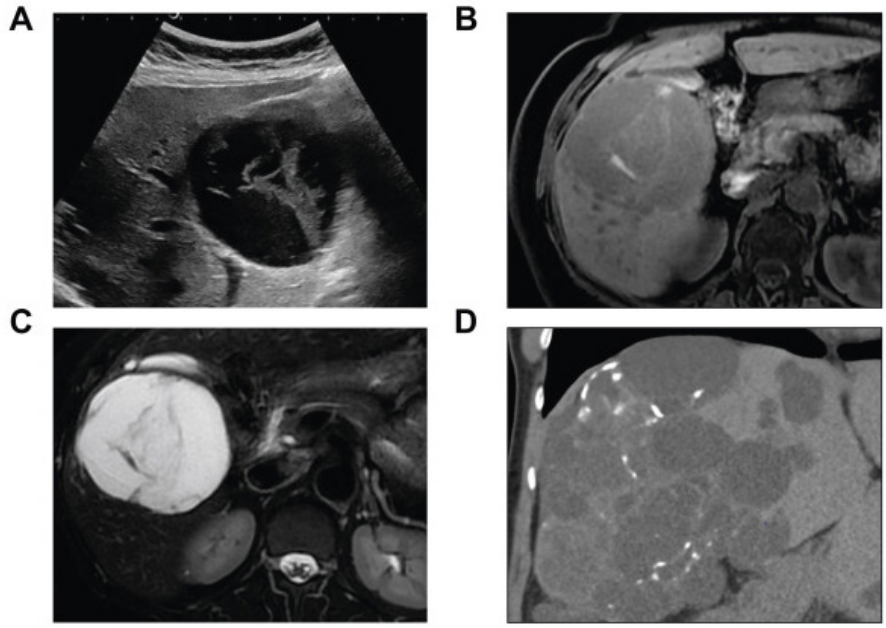

Fig. 2 – Haemorrhagic hepatic cyst and post-haemorrhage calcification. (A-C) haemorrhagic hepatic cyst. Ultrasound (panel A) shows a cystic lesion surrounded by a thin wall. Presence of multiple septations that do not enhance on contrast-enhanced ultrasound (not shown). On MRI (T1- and T2-weighted MRI) the lesion is strongly hyperintense on T2 and has intermediate signal on T1. Internal septations are strongly hyperintense on T1 and correspond to haemorrhagic septations. (D) Calcification after cyst haemorrhage.

10. Should anticoagulants and antiplatelet therapy be stopped in patients with cyst haemorrhage?

Recommendations

- We recommend temporary interruption of anticoagulants in hepatic cyst haemorrhage **(LoE 5, strong recommendation, 96% consensus).**
- Anticoagulants may be resumed between 7–15 days after the onset of hepatic cyst haemorrhage **(LoE 5, weak recommendation, 100% consensus).**

Use of anticoagulation, especially in the setting of supratherapeutic international normalised ratio is an important risk factor for cyst haemorrhage. There are no randomised data that can guide how to handle anticoagulants during cyst haemorrhage, but it is reasonable to extrapolate data from gastrointestinal haemorrhage management. To aid conservative management and to stop ongoing haemorrhage, immediate interruption of all anticoagulants is prudent. There is no role for the administration of vitamin K, intravenous prothrombin complex concentrate or fresh frozen plasma in hepatic cyst haemorrhage, unless in unusual cases of haemodynamic instability [114].

Anticoagulant therapy can be reinitiated in most patients after haemostasis is achieved but is subject to a number of considerations. Available evidence from non-cystic haemorrhage literature indicates that restarting anticoagulants between 7–15 days after the onset of haemorrhage may best balance the risk of recurrent haemorrhage, and thromboembolism [115,116]. Given the non-life threatening nature of cyst bleeding, anticoagulants may be restarted earlier in cases with high risks for thromboembolisms. It seems reasonable to assume that the risks and benefits of resuming newer direct oral anticoagulants are largely similar to those of vitamin K antagonists in view of similar efficacy and safety in clinical trials. Antiplatelet agents include low-dose aspirin and thienopyridines (such as clopidogrel, prasugrel, ticlopidine) that irreversibly inhibit platelet aggregation, ticagrelor a reversible P2Y12 receptor antagonist, and vorapaxar, a protease-activated receptor antagonist that inhibits thrombin. We advise interrupting aspirin for 3 days following the onset of cyst haemorrhage and, in patients receiving double antiplatelet therapy, continuing the P2Y12 inhibitor and interrupting aspirin for 3 days [117].

11. Which worrisome features distinguish hepatic cysts from MCNs of the liver and warrant the need for surgical intervention?

Recommendations

- A combination of ≥1 major and ≥1 minor feature listed in Table 4 may be considered as worrisome features for MCNs of the liver (**LoE 3, weak recommendation, 95% consensus).**
- MRI should be used to characterise hepatic cysts with worrisome features (**LoE 3, strong recommendation, 100% consensus).**

MCNs of the bile ducts are rare cystic lesions of the liver, formerly referred to as "biliary cystadenoma," "biliary cystadenocarcinoma". They are defined as a cystic epithelial neoplasm lined by cuboidal, columnar, or flattened mucin-producing epithelium overlying ovarian-like hypercellular stroma [118]. Presence of ovarian-like hypercellular stroma and absence of bile duct communication are the 2 hallmarks that differentiate MCNs from intraductal papillary neoplasms of the bile duct. Caution is warranted when interpreting the literature published prior to the distinction of these 2 entities.

Major worrisome features mucinous cystic neoplasm of the liver	Minor worrisome features mucinous cystic neoplasm of the liver
Thick septation	Upstream biliary dilatation
Nodularity	Thin septations
	Internal haemorrhage
	Perfusional change
	<3 coexistent hepatic cysts

Table 4 – Worrisome features in mucinous cystic neoplasms of the liver.

MCNs mostly occur in middle-aged women [50,119]. MCNs are commonly symptomatic (86%), with various clinical manifestations: abdominal pain, fullness, or early satiety due to large size and mass effect [50]. MCNs may present with low-grade dysplasia, high-grade dysplasia, or invasive carcinoma. The vast majority of MCNs are benign, 3-6% are invasive carcinoma, usually observed in older patients [120]. Serum tumour markers such as CEA and CA 19-9 may be elevated, particularly in patients with invasive carcinoma, without good diagnostic accuracy (see question 3) [121].

On imaging, MCNs are typically solitary, large, well-circumscribed cystic lesions, either multiloculated (90%) or unilocular, that predominantly form in the left liver lobe. MCNs commonly do not communicate with the biliary tree and upstream

ductal dilatation, if present, is attributed to the mass effect. MCNs often contain enhancing septa, mural calcifications, and mural nodules, the latter being associated with malignancy if larger than 1 cm [122-125]. Typically, the septa arise from the cyst wall without associated wall indentation [126]. Multiloculated MCNs may have different imaging patterns, and T1 signal intensity on MRI may be variable, reflecting differences in protein-rich or haemorrhagic cyst content. Differentiation between benign MCNs and MCNs with invasive carcinoma is difficult, a meta-analysis found that mural nodules, wall enhancement, and calcifications are significantly associated with malignancy [121].

Complicated hepatic cysts (cyst infection or haemorrhage) may present with imaging findings that mimic MCNs, leading to inaccurate attribution [127]. Distinguishing hepatic cysts from MCNs is still challenging and requires expertise of a multidisciplinary team involving hepatogastroenterologists, abdominal radiologists, abdominal surgeons, and expert pathologists.

There are a number of CT and MRI features that may help to differentiate MCNs from simple hepatic cysts. A number of studies reported that septations/thick septations, mural nodules, and biliary dilatation are associated with MCNs [51,127,128] (Fig. 3). A recent study (13 MCNs and 71 simple cysts) saw that thick septations/nodularity, upstream biliary dilatation, thin septations, internal haemorrhage, perfusional change, and fewer than 3 coexistent hepatic cysts were more frequent in MCNs than in simple cysts. The combination of thick septations/nodularity and at least 1 additional associated feature carried high specificity for MCNs (94-98%) [129], and here MRI was more accurate than CT. The morphology of septations may be helpful as septations arising from a cyst wall without external indentation have a very high association with MCNs [126,130]. Internal haemorrhage may be seen in MCNs but is much more frequent in simple hepatic cysts and does not represent a worrisome finding.

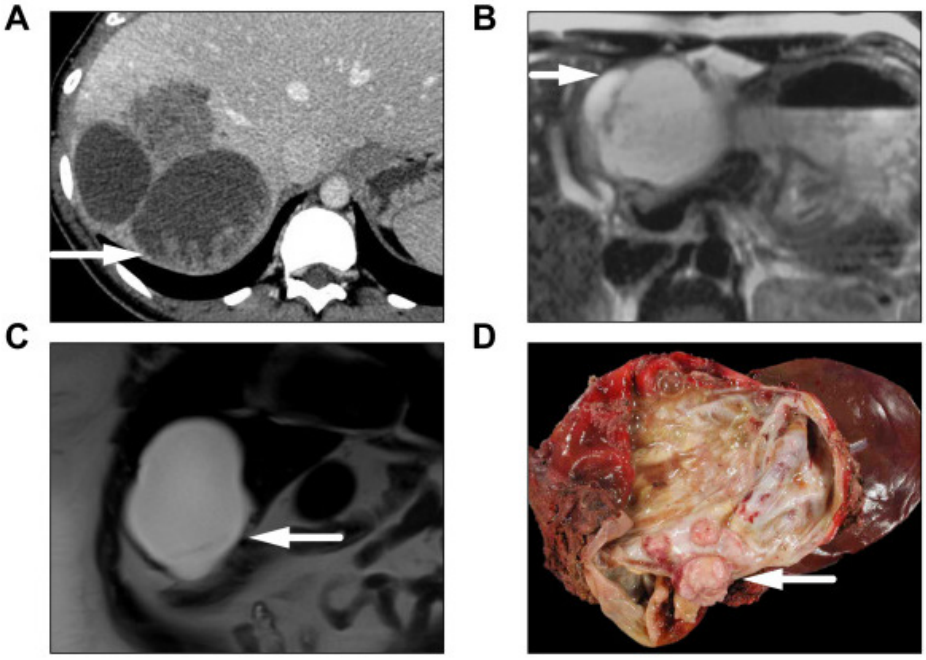

Fig. 3 – Worrisome features in mucinous cystic neoplasms of the liver. (A) Malignant mucinous cystic tumour. Contrast-enhanced CT during the portal venous phase showing multiseptated cystic lesion of the right liver with multiple nodularity. (B,D) malignant mucinous cystic tumour. T2-weighted MRI sequence showing cystic lesion of the left liver with thick septations. Pathologic examination shows thick septations and internal nodularity. (C) Low-grade mucinous cystic tumour. Coronal T2-weighted MR sequence showing cystic lesion of the right liver with a thin septation at the lower part of the lesion.

12. In which situation should surgery be applied for suspected MCNs of the liver?

Recommendations

- Surgical resection is the gold standard for suspected MCNs of the liver, and complete resection should be aimed for **(LoE 3, strong recommendation, 100% consensus).**

The MCN recurrence rates after incomplete resection in the literature are high, but data may be overestimated due to discovery and reporting bias. Similarly, malignant transformation of MCNs is reported frequently, but data may be susceptible to a similar bias [9].

Complete surgical removal of these lesions in reported case series yield good long-term outcomes with a very low recurrence rate. The presence of malignancy is a

significant factor associated with poorer outcome. While recurrences do occur in 0 to 26% of reported cases, recurrences with malignant MCNs in patients who initially had non-malignant MCNs are rare [55,131-138].

Fenestration is associated with higher rates of tumour recurrence [55]. It may be difficult to distinguish simple cysts from cystadenoma even with extensive pre-operative work-up. Indeed, a number of studies found that 20-50% of MCNs had not been properly identified before surgery [132,135,138]. Case reports of recurrence after fenestration provide additional circumstantial evidence to support complete resection.

Major liver resections, including extended hemihepatectomy, have been performed in some cases to allow for complete removal of the cyst. Enucleation with free margins is also considered an option, *e.g.*, for centrally located tumours. More extensive/complex procedures, including total vascular exclusion [139] and liver transplantation [140] after unsuccessful attempts at resection resulting in an intrahepatic biliary injury, have been described in case reports.

As a consequence of the low prevalence of MCNs and the difficulty in establishing a reliable diagnosis on imaging, data is mostly obtained from retrospective studies including only surgically treated patients with pathologic confirmation of the surgical specimen. While head-to-head comparison of outcomes of different treatment options, including surveillance, are absent, the current literature provides compelling evidence to recommend complete surgical resection of MCNs.

13. Who should be screened for PLD and how?

Recommendation

- Abdominal ultrasound to screen for PLD should be offered to all patients diagnosed with ADPKD **(LoE 2, strong recommendation, 100% consensus).**
- Genetic testing should not be used to screen for PLD **(LoE 3, strong recommendation, 100% consensus).**

Screening for PLD can be initiated from different perspectives. Many patients with ADPKD are referred because of a family history of the disease. Indeed, the Kidney Disease Improving Global Outcomes guidelines recommend abdominal ultrasound for all patients diagnosed with ADPKD to screen for PLD [141]. Many others, especially patients with ADPLD, are seen because of the incidental finding of PLD on abdominal imaging or symptoms. Two sources of information are relevant to counsel patients:

i) the anatomy of the liver on imaging and ii) presence of symptoms that can be attributed to PLD.

There is no need to screen for PLD unless symptoms and signs develop that require a change of management. In those cases, volumetry data aids clinical decision making. A pooled analysis showed that liver volume in PLD increases by 1.8% (or by 4.8% in females aged <48 years) within 6–12 months, [142]. Patients with a growth pattern that deviates from the average growth pattern in PLD should be counselled regarding whether a change of management is warranted. There is no need to screen family members of patients with PLD for the presence of hepatic cysts unless symptoms are present.

Genetic testing plays an insignificant role in screening of patients with PLD. While almost all cases of ADPKD can be mapped to *PKD1*, *PKD2*, and *GANAB*, the Kidney Disease Improving Global Outcomes guideline suggests that genetic testing is not required for the diagnosis of ADPKD with the exception of equivocal or atypical renal imaging findings (early and severe PKD, markedly asymmetric PKD, renal failure without significant kidney enlargement, marked discordant disease within family) and sporadic PKD without family history [141]. In ADPLD, at least 6 genes (*PRKCSH, SEC63, ALG8, SEC61B, GANAB, LRP5*) account for 30-45% of ADPLD cases; the other 55-70% remain genetically resolved [143]. The phenotype of patients with ADPLD does not vary with the gene involved or type of mutation. As a result, there is little room for genetic testing of these variants for clinical purposes as results are not likely to inform clinical decision making unless there are questions about the differential diagnosis between ADPKD or ADPLD.

A number of tools help to triage patients with PLD and to design individualised management plans. Liver volume is a prognostic marker and the main endpoint for trials that explore novel therapeutic strategies, as it impacts both symptom burden and quality of life [144]. CT or MRI is necessary to measure volume and assess the extent of PLD. It also allows for measurement of (height-adjusted) liver volume, which is currently used as an endpoint in clinical trials.

14. Which patients with PLD require follow-up?

Recommendation

- We recommend referral and counselling of patients with symptomatic PLD to centres of expertise **(LoE 3, strong recommendation, 100% consensus).**

In PLD, are usually referred to hepatologists for 3 reasons: i) to counsel patients with the incidental finding of PLD, ii) to develop a management plan for patients with symptomatic PLD, and iii) to manage hepatic complications of PLD.

There are 2 populations with PLD, those with ADPKD and ADPLD. Most patients with ADPKD receive regular clinical follow-up given their renal disease, while patients with ADPLD receive clinical attention specifically because of their PLD. While at least 80% of individuals with ADPKD aged >30 years will have hepatic cysts, most will be asymptomatic at the time of screening and these patients will benefit from counselling. Counselling patients with PLD requires an informed clinician who is acquainted with the presentation, natural history, prognosis, and management options. It is relevant to recognise the compressive symptoms that patients may have and to acknowledge the disease burden.

There is an age-dependent increase in hepatic cyst burden, and in particular females may develop progressive disease. It is estimated that some 20% of patients with ADPKD will eventually develop symptomatic PLD [145]. Symptoms in severe PLD are associated with massive abdominal distension as a result of hepatomegaly, leading to a feeling of fullness, abdominal pain and discomfort, abdominal wall hernias, back pain, and dyspnoea in the supine position. Patients reduce their meal size because of early satiety and malnutrition eventually leads to muscle mass loss and sarcopenia [146].

A number of tools help to triage patients with PLD and to develop individualised management plans. CT or MRI is necessary as a tool to obtain an impression of the extent of PLD. It also allows for measurement of (height-adjusted) liver volume which is currently used as an endpoint in clinical trials [147]. While volume measurement accurately quantifies PLD, it does not address symptom burden. The last metric is patient-reported outcome measures and 2 validated scales: the polycystic liver disease questionnaire (PLD-Q) and polycystic liver disease complaint-specific assessment (POLCA) have been developed for PLD. PLD-Q and POLCA are further discussed in question 16.

A number of liver-related complications of PLD require attention from the hepatologist: cyst rupture, haemorrhage and infection (see question 4 and 5) and compression of the portal circulation or hepatic veins due to strategically located hepatic cysts [148]. The latter results in hepatic venous outflow obstruction, which is characterised by reduction of the outflow of venous blood from the liver into the vena cava. These patients develop portal hypertension and ascites and/or hepatic hydrothorax. Of patients with PLD scheduled for a liver resection, 78% (35/45) had

moderate stenosis of hepatic veins and 22% (10/45) had severe venous stenosis [149]. Primary hepatic vein stenting has become the intervention of choice for hepatic venous outflow obstruction with patency rates >80%.

Mitral valve malformations have been reported as possible extrahepatic manifestations of PLD but bear low clinical significance and patients should only be assessed once cardiovascular signs or symptoms arise. Some patients with ADPKD report a history of cerebral aneurysm in their families. According to the Kidney Disease Improving Global Outcomes guideline those patients may be screened for the presence of asymptomatic intracerebral aneurysms while those without a family history should be counselled about the risks of intracerebral aneurysms that are associated with ADPKD [141].

15. What diet or lifestyle adjustments are recommended for patients with PLD?

Recommendations

- CT is suggested to assess sarcopenia in patients with PLD and massive hepatomegaly that displaces adjacent organs (*e.g.* stomach and bowels), as these patients are at risk of malnutrition **(LoE 3, weak recommendation, 87% consensus).**
- Patients with PLD and sarcopenia should receive intensive nutrition and exercise rehabilitation under the supervision of dieticians and physical therapists **(LoE 5, strong recommendation, 100% consensus).**

Malnutrition is the most threatening complication of PLD and is an indication for liver transplantation referral [150]. It is seen in the most severe PLD cases, especially in combination with renal impairment that requires dialysis. In these patients, compression of the liver on the stomach leads to early satiety, nausea and vomiting and precludes consumption of large food portions. Consequently, patients in this situation need to optimise their food intake by eating small portions of food several times a day and are advised to do physical exercise multiple times a week in order to optimise their muscular mass [151]. There are no data from patients with PLD that indicate whether a specific dietary intervention prevents this evolution [152].

Weight loss due to malnutrition in patients with PLD is underestimated due to the extra weight of the enlarged liver. The presence of malnutrition can be assessed by measuring the mid-arm circumference in the non-dominant arm (<23.8 cm for men and <23.1 cm for women) [153]. Though easy to perform, there are several pitfalls with

this measurement. Indeed, this marker has never been validated for patients with PLD, there is a high inter-observer variability and it does not take into consideration the physique of the individual.

Measurement of sarcopenia by CT scan provides an objective measurement of the malnourished status of the patient with PLD. Height-corrected skeletal muscle mass (cm^2) and subcutaneous adipose tissue (cm^2) can be calculated by using a single-slice quantitative image at the lumbar 3 level with 5-mm-thick axial images. This represents the skeletal muscle index (cm^2/m^2). The inter-observer variability and agreement are excellent. Severe skeletal muscle depletion or sarcopenia is defined by a skeletal muscle index <38.5 cm^2/h^2 in females and <52.4 cm^2/h^2 in males, as previously defined in a cancer population[154].

Muscle wasting, malnutrition and functional decline can be assessed with the frailty index (based on grip strength, chair stands and balance). This index is a well validated prognostic test for patients with end-stage liver disease and its utility in PLD should be explored[155]. Standard medical treatment for patients with severe symptomatic disease consists of somatostatin analogues. Although they reduce liver volume and can improve food intake, it is unclear whether somatostatin analogues prevent muscle wasting and sarcopenia [156].

16. When should symptom severity and quality-of-life questionnaires be used in patients with PLD?

Recommendations

- Disease-specific symptom severity questionnaires may be used upon the emergence of symptoms to assess disease severity in patients with PLD **(LoE 3, weak recommendation, 95% consensus).**
- Disease-specific symptom severity questionnaires should be applied in patients with PLD to assess treatment efficacy **(LoE 1, strong recommendation, 96% consensus).**

Most patients with PLD remain asymptomatic, but 2–5% of them will develop symptomatic hepatomegaly as a result of the continuous increase in volume and number of hepatic cysts. The most frequently reported symptoms include abdominal distension, early satiety and abdominal pain. Hepatomegaly-induced complaints represent the single most prominent indication for medical or surgical treatment. Complaints expressed by patients with PLD and their interpretation by clinicians in terms of severity and impact on health-related quality of life are subjective, yet

highly relevant, as they count heavily towards decisions on medical treatment and even the indication for liver transplantation.

Generic questionnaires lack sensitivity to capture PLD-related symptoms, which may explain why some trials failed to identify significant effects on quality-of-life measures [157]. For that reason, disease-specific symptom severity questionnaires were recently developed: the PLD-Q and POLCA. These questionnaires capture disease-specific symptoms in PLD, regardless of treatment side effects, comorbidity or mental problems. The PLD-Q is a valid, reproducible, and sensitive disease-specific questionnaire that has been validated both in a European and American cohort [158]. It is currently used in clinical practice, randomised clinical trials and observational cohorts to evaluate the effect of treatment in patients with PLD[44,159,160]. The POLCA score (https://www.uzleuven.be/polca) has been developed to guide decision making with respect to liver transplantation, and it has been validated in a prospective trial [161]. A POLCA score ≥16.5 predicts the need for liver transplantation, with a sensitivity of 81.3% and a specificity of 88.9%[162]. Both PLD-Q and POLCA distinguish patients on the basis of symptoms and serve as useful outcome measures for clinical trials but they do not define symptom thresholds that could guide decision making in the management of patients with PLD.

17. What is the recommendation for use of exogenous female sex hormones in patients with PLD?

Recommendation

- We recommend stopping exogenous oestrogen administration in female patients with PLD **(LoE 3, strong recommendation, 100% consensus).**

There is a major sex imbalance in PLD, with women overrepresented (>80%) in large cohorts. This effect is independent of the genetic cause of the disease and is seen both in patients with ADPKD and ADPLD. PLD follows a more aggressive disease course, with earlier onset and faster progression, in females. As a consequence, females account for over >80% of liver transplants for PLD [163]. These observations indicate that oestrogen exposure is an important risk factor for PLD.

Liver volume in PLD increases during the reproductive years, and volume stabilises postmenopausally, coinciding with the decrease of endogenous oestrogen production[164]. This finding was corroborated by a controlled trial which demonstrated that 1-year oestrogen treatment in 19 anovulatory postmenopausal patients with ADPKD selectively increased hepatic cyst volume (oestrogen +7%,

control -2%) without an impact on renal cystic disease [165]. Another observational study demonstrated that every year of exposure to low-dose oestrogen-containing oral contraceptives led to a 1.45% larger liver volume in premenopausal patients with PLD, equivalent to a 15.5% higher liver volume for every 10 years of use [166]. There is controversy regarding the effects of pregnancy on PLD severity. Some studies suggest an increase in liver volume after pregnancy [45] while this association is absent in other observational cohorts [141,164,166]. There is a paucity of studies that investigate the effect of *in vitro* fertilisation on PLD. However, *in vitro* fertilisation involves exposure to very high oestradiol levels (<60 pg/ml at cycle baseline to 1,000-4,000 pg/ml during IVF) during a short (2-6 weeks) time frame. Clinicians should be aware that this may aggravate hepatic cyst growth. Pregnancy success is expected to be similar in patients with PLD compared to the general population [167].

Collectively, epidemiological and experimental evidence supports a pivotal role for oestrogens as a driver of PLD. While there is no definitive proof that avoidance of external oestrogen use is beneficial, exogenous oestrogen use is probably deleterious and results in the recommendation to discourage prescribing oral contraceptives to female patients with PLD. Levonorgestrel-releasing intrauterine devices may be an alternative option as a contraceptive. With these devices the systemic exposure to levonorgestrel is 4%–13% of the levels seen with oral contraceptives [168]. However, data on the effect of these devices on PLD growth is unknown. Similarly, no reliable data is available on contraceptive options only containing gestagens (*e.g.*, desogestrel) and no recommendation on the use of these contraceptives can be made.

18. Which treatment should be administered in patients with PLD?

Recommendations

- Choice of treatment should be guided by symptoms and complications related to the presence of cysts, as listed in Table 5, in combination with liver phenotypes, displayed in Fig. 4 **(LoE 2, strong recommendation, 100% consensus).**
- Treatment for PLD should be administered in symptomatic patients exclusively **(LoE 2, strong recommendation, 100% consensus).**
- Symptom relief and improvement in quality of life should be the primary goal of treatment in PLD **(LoE 1, strong recommendation, 100% consensus).**

Since PLD does not compromise the functional capacity of the liver, the aim of treatment is to relieve symptoms and to improve quality of life. While symptoms drive the decision to treat, the choice of treatment option depends on the number, size and localisation of hepatic cysts in combination with the expertise of the treating

centre [144,169]. Cyst infection or haemorrhage are not an indication for volume-reducing therapy. None of the current available treatment strategies are used prophylactically (see question 4). Moreover, previous interventions such as these may make future total hepatectomy or liver transplantation more complex[170]. Liver transplantation for PLD is considered technically difficult from a surgical perspective due to the challenge of removing a (often) huge liver. Potential encasement of the retrohepatic inferior vena cava, traction to very fragile hepatic veins that span out thinly around massive cysts and adhesions due to previous interventions or surgery, may further complicate a liver transplant procedure and increase the risks of massive blood loss.

Polycystic liver disease-related symptoms	Polycystic liver disease-related complications
Abdominal fullness	Jaundice
Lack of appetite or early satiety	Hepatic venous outflow obstruction
Acid reflux	Portal hypertension
Nausea and vomiting	Recurrent cyst infection
Pain in rib cage, sides, abdomen or back	Recurrent cyst haemorrhage
Shortness of breath	
Limited mobility	
Fatigue	
Anxiety about the future	
Concern or dissatisfaction with abdomen size	
Problems with intercourse	
Involuntary weight loss	

Table 5 – Polycystic liver disease-related symptoms and complications.

Interventional (radiological) treatment

When a large or strategically located cyst is the main cause of symptoms, percutaneous aspiration sclerotherapy can also be performed in the context of PLD. Recurrence of symptoms is frequent in the context of PLD [66,169,171] (see question 4). Some series have demonstrated that transarterial embolisation of the hepatic arteries may reduce cyst volume in PLD but the experience with this intervention is limited [172].

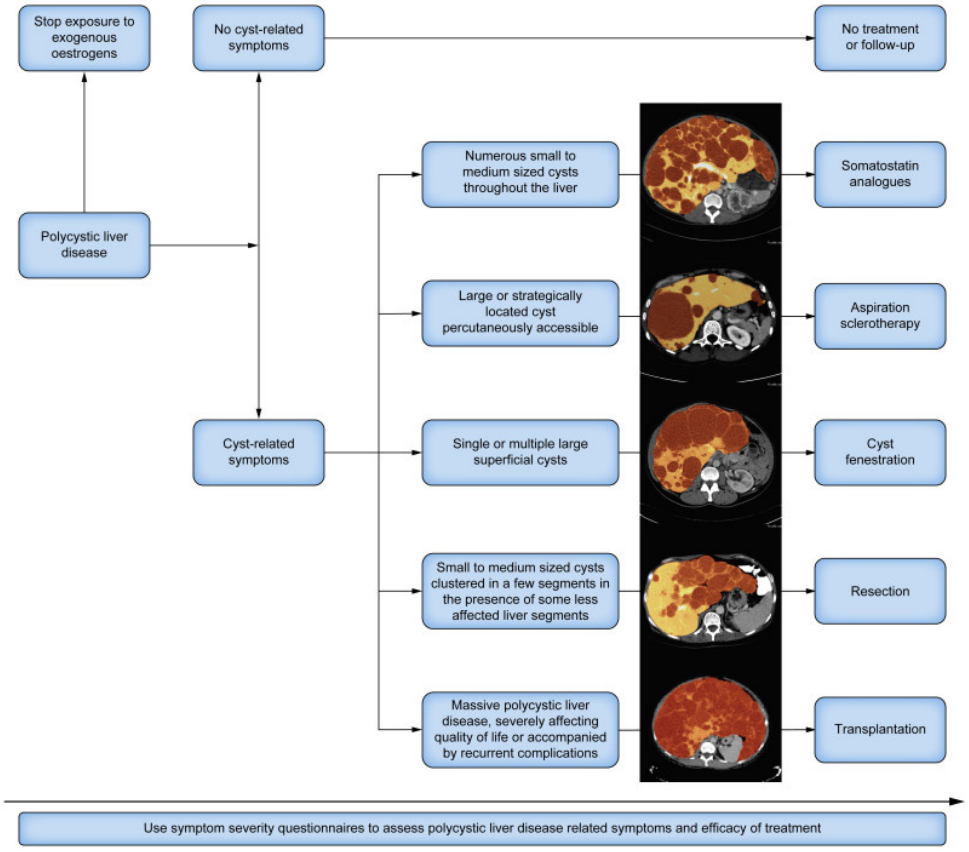

Fig. 4 – Decision-making flowchart for treatment choice in polycystic liver disease.
Adjusted from v. Aerts et al. Journal of Hepatology, 2018.

Surgical treatment

Cyst fenestration, also called deroofing, can be considered in patients with superficial large cysts. Multiple large cysts can be resected simultaneously with this procedure. It provides effective long-term reduction of cyst volume and symptomatic relief but does not change the natural course of the disease [173,174]. The risk of a potential complicating effect of adhesions at the time of a future liver transplantation should be taken into account when considering cyst fenestration.

A liver phenotype with small to medium sized cysts restricted to a few liver segments may be amenable to segmental hepatic resection. The intervention results in a substantial liver volume reduction and improves symptoms. Since surgical resection

in PLD is associated with high morbidity, especially in the presence of vascular abnormalities and biliary dilatation, it is only indicated in patients with severe symptoms in whom liver transplantation is not an option. Several postoperative complications can occur (ascites, haemorrhage, pleural effusion) and mortality rates of more than 2% have been observed while the recurrence rate is high [169,175,176]. The only curative option for patients with PLD is liver transplantation (see question 19) [177].

Pharmacological therapies

Several clinical trials have provided evidence that somatostatin analogues *e.g.*, lanreotide, octreotide or pasireotide can reduce the volume of the liver [157,178-182] (Table 6). They demonstrate a mild reduction in kidney volume but do not affect the rate of kidney function decline[183]. The most important reduction in liver volume is observed in the first 6 months, but a sustained effect can be seen for up to 4 years of treatment [180,184]. Several systematic reviews and meta-analyses have confirmed the beneficial effect of somatostatin analogues on liver volume and quality of life [185-188]. The dosage of somatostatin analogues is balanced between efficacy and side effects. Lanreotide at a dose of 120 mg every 4 weeks is associated with greater reductions in liver volume, but more side effects, than a lower dose of 90 mg every 4 weeks[189]. Patients who benefit most are young women (aged <48 years) who suffer from a rapidly progressive disease [142]. Therapy cessation after short-term treatment usually results in a relapse of liver growth, but patients who discontinued treatment can benefit from retreatment [165]. The therapy is well tolerated and serious adverse events leading to withdrawal are infrequent (<5%). Most patients experience gastrointestinal discomfort (steatorrhea like symptoms) during the first injections which gradually fade over time. Other infrequent side effects of somatostatin analogues include cholelithiasis, hypo- and hyperglycaemia and alopecia [190]. Hyperglycaemia and diabetes are most frequently observed with pasireotide [182].

Pre-clinical data and observational studies in patients with ADPKD, who received a kidney transplantation and were treated with sirolimus, suggested that mammalian target of rapamycin inhibitors had a positive effect on liver volume[191]. These data were not confirmed in a clinical trial, wherein everolimus, a mammalian target of rapamycin inhibitor, did not confer any beneficial effect. Due to the toxicity of these drugs, they should not be used in patients with PLD [192].

Study	Country	Number of patients (males)	Treatment duration (months)	Imaging modality	Drug	Effect on liver volume	*p* value
van Keimpema *et al*. 2009 **LOCK CYST**	The Netherlands and Belgium	54 (7)	6	CT	Lanreotide – LAR120 mg IM every 28 days	-2.9% *vs.* + 1.6%	<0.01
Hogan *et al*. 2010	USA	42 (6)	12	MRI	Octreotide-LAR40 mg IM every 28 days	-4.95% *vs.* + 0.92%	0.048
Caroli *et al*. 2010 ***Post hoc* analysis**	Italy	12 (9)	6	CT	Octreotide – LAR40 mg IM every 28 days	-17 ± 57 ml *vs.* + 14 ± 85 ml	<0.05
Pisani *et al*.2016	Italy	27 (10)	36	MRI	Octreotide – LAR40 mg IM every 28 days	-7.8% *vs.* + 6.1%	0.004
Van Aerts *et al*. 2019 **Post hoc analysis**	The Netherlands	175 (74)	30	MRI	Lanreotide – LAR120 mg IM every 28 days	-1.99% *vs.* + 3.92%	<0.01

Table 6 – Overview of the prospective clinical trials using somatostatin analogues in polycystic liver disease.

Based on pre-clinical data in rodents in which bile acid-induced hyperproliferation of cystic cholangiocytes was decreased with ursodeoxycholic acid, the drug was tested in a phase II study [193]. No significant effect on liver volume was seen after 6 months. In a sub-group analysis restricted to patients with ADPKD, ursodeoxycholic acid appeared to reduce hepatic cyst volume, but these findings need corroborating. Currently, ursodeoxycholic acid treatment is not indicated for the treatment of PLD.

Liver volume

The primary endpoint in all pharmacological and some surgical trials is restricted to change in liver volume [157,159,173,178-182,191,193]. Therefore, accurate and sensitive measurements of liver volume are crucial to evaluate current treatment strategies and to explore new therapeutic options. Manual contouring of the liver by CT or MRI in patients with PLD is the current gold standard for liver volume measurements. This is a challenging and time-consuming endeavour because of the severely deformed liver anatomy in combination with massive hepatomegaly found in PLD. Automatic segmentation of polycystic livers using deep learning methods achieves much faster segmentation with similar performance and will probably find its way into routine clinical practice [194].

19. Which patients with PLD should be referred for liver or combined kidney-liver transplantation?

Recommendation

- Referral for liver transplantation or combined liver-kidney transplantation may be initiated based on the criteria listed in Box 2, taking into consideration local allocation systems, local waitlist criteria, anticipated waiting times and risk of deterioration while waiting for a liver graft **(LoE 3, weak recommendation, 100% consensus).**

Liver transplantation is the only curative treatment for PLD and only the most severe cases with massive PLD are eligible. Allocation of scarce donor liver grafts in most allocation networks is based on a sickest-first principle or transplant benefit score, including incorporation of model of end-stage liver disease (MELD) score which is validated for patients with cirrhosis[195,196]. For patients without end-stage liver failure related to cirrhosis, most allocation systems work with exception points or listing as variant syndromes. PLD represents about 1–1.5% of patients on the waitlist and donor allocation is based on exception points or listing as a variant syndrome because liver function remains preserved even in the most severe cases[197,198].

Criteria to refer patients with polycystic liver disease for liver transplantation

1. Clinically apparent liver disease due to massive polycystic liver severely affecting quality of life
2. Massive polycystic liver disease and complication(s), that can exclusively be treated by liver transplantation

Complications include: severe malnutrition, hepatic venous outflow obstruction, ascites, portal hypertension, variceal haemorrhage, recurrent hepatic cyst infections

3. Failure of non-transplant related interventions and contraindications for non-transplant related interventions

Criteria to consider referral for combined liver-kidney transplantation

1. Creatinine clearance <30 ml/min

Box 2 – Criteria to refer polycystic liver disease patients for liver or combined liver-kidney transplantation.

Several waitlist exception criteria are being used that have considerable overlap. The most important exception criteria for liver transplantation in PLD are: i) clinically apparent liver disease due to massive PLD severely affecting quality of life, ii) massive PLD and complications (*e.g.* severe malnutrition, hepato-venous outflow obstruction, ascites, portal hypertension, variceal haemorrhage, recurrent hepatic cyst infections), that can exclusively be treated by liver transplantation, iii) failure of non-transplant-related interventions and contraindications for non-transplant-related interventions. Referral for liver transplantation may be initiated based on these criteria, taking into account local allocation systems, local waitlist criteria, anticipated waiting times and risk of deterioration while waiting for a liver graft. Assessment for liver transplantation should be performed in multidisciplinary teams in transplant centres that include transplant surgeons, hepatologists and, in case of combined kidney-liver transplantation, nephrologists.

Two studies compared waitlist outcomes between PLD- and non-PLD-initiated transplantations. Waitlist outcomes were determined using liver function-related adverse outcomes: waitlist death, too sick to transplant or deterioration of liver function measured by international normalised ratio or bilirubin. Unsurprisingly, chances of adverse outcomes using these parameters were lower in patients with PLD compared to patients listed based on a MELD-point based allocation [199,200]. Unfortunately, there is very limited data regarding which parameters adequately define waitlistoutcomes for patients with PLD and outcomes are probably unrelated to portal hypertension [201]. In general, liver transplant outcomes for PLD are excellent and comparable to other indications for liver transplantation [177,200,202].

Because of the volume of livers with massive polycystic disease, manipulation of the liver for explantation and access to the suprahepatic vena cava and hepatic veins is considered difficult, with the risk of massive bleeding. It is generally advised not to make any attempt to control access to the inferior vena cava at the beginning of the dissection phase. Instead, the structures of the liver hilum are dissected first and some form of inflow control achieved [203,204]. After transection of the hepatic artery, other strategies include deviation of the portal venous inflow by preparing a porto-caval shunt or to place patients on full veno-venous bypass. Surgeons should avoid excessive traction on the liver downwards and to the left to prevent tearing of the fragile hepatic veins. The liver is then progressively mobilised, from below upwards or from left to right to avoid turning the liver to the left, until the suprahepatic vena cava can be safely controlled. Both, cava-sparing techniques and caval replacement have been described with good outcomes. Techniques describing liver explantation under total vascular exclusion have also been described [205]. In summary, surgeons should aim for a preferred strategy to prevent massive blood loss during the hepatectomy phase.

There is some notion of superiority of combined liver-kidney transplantation over sequential procedures in patients with PLD that require both procedures, but robust evidence is lacking [206-208]. In combined liver-kidney transplantation concerns have been raised about high rates of short-term kidney graft loss of up to 20% [209]. Delayed renal graft function and renal allograft failure in this setting has been attributed to major perioperative haemodynamic and metabolic instability associated with liver transplantation. Current approaches to balance the potential futility of kidney transplantation in the combined setting of end-stage hepatic and renal failure, include the use of hypothermic machine perfusion with delayed implantation of a kidney from the same donor [210], or metachronous living-donor kidney transplantation after recovery from liver-only transplantation which avoids subsequent long waiting times for a deceased organ. All approaches take into account: i) potential better survival rates with combined liver-kidney transplantation, ii) blunted immunological response/immunoprotection due to absorption of donor-specific antibodies by the liver allograft and use of the same donor, iii) increased risk of failure of kidney graft with combined liver-kidney transplantation, iv) anticipated waiting times given the availability or absence of a local allocation policy targeted at combined liver-kidney transplantation, and v) availability of a live kidney donor.

20. Should preconception carrier screening be offered to patients with PLD and when?

Recommendations

- Patients with PLD should receive preconception counselling concerning the risk of passing on PLD to the newborn **(LoE 4, strong recommendation, 96% consensus).**
- Patients with PLD should not be counselled against pregnancy **(LoE 3, strong recommendation, 96% consensus).**

Patient with PLD, both in the context of ADPKD and ADPLD, should receive preconception counselling concerning the risk that their newborn will develop the disease. PLD is passed on in an autosomal dominant fashion, giving a 50% chance that the newborn inherits the mutation. Genetic testing for PLD is available, though screening mutations of the genes causing PLD can only confirm the genetic diagnosis and not exclude the disease. The genes responsible for PLD are different for ADPKD and ADPLD. ADPKD is mainly caused by 2 genes: *PKD1* and *PKD2*. In contrast, ADPLD is caused by at least 6 different genes which combined do not even explain the disease development in over half of the affected population [211]. Genetic testing is not routinely performed because knowledge about the genotype-phenotype correlation is currently limited and does not affect the therapeutic management of PLD. Incomplete penetrance and variable expressivity cause wide variation among family members with the same genotype.

Oestrogen exposure is considered the most important driver of cyst growth and is further discussed in question 17. Controversy still exists regarding the fluctuations in oestrogen that occur during pregnancy and the effects of pregnancy on liver growth. Patients with PLD should not be counselled against pregnancy.

21. How to differentiate between Caroli disease and Caroli syndrome?

Recommendation

- The finding of multiple segmental cystic or saccular dilatations of bile ducts should initiate a search for congenital hepatic fibrosis in order to differentiate Caroli disease from Caroli syndrome **(LoE 4, strong recommendation, 100% consensus).**

Multifocal segmental dilatation of the intrahepatic ducts is present both in Caroli disease and Caroli syndrome. The cystic dilatation results from ductal

plate malformation of the large intrahepatic bile ducts. This is a failure of proper remodelling and resorption of the ductal plate during foetal development and results in persistence of embryonic biliary structures. On imaging, these bile ducts appear as saccular or fusiform cystic dilatations that can grow up to 5 cm in diameter. These lesions are mainly located in the intrahepatic large sized bile ducts and correspond to type V choledochal cysts (part of the Todani classification). However, extrahepatic dilatations are commonly seen in Caroli disease and are thought to result from recurrent episodes of cholangitis and stone passage.

Hepatic fibrosis is the key histological lesion that separates Caroli syndrome from Caroli disease. Caroli syndrome is likely part of the phenotypical spectrum of autosomal recessive polycystic kidney disease (ARPKD) which is inherited as an autosomal recessive trait. Here, the clinical picture is dominated by the consequences of congenital hepatic fibrosis. During the course of their disease many patients develop portal hypertension with venous portosystemic shunting and development of oesophageal varices and splenomegaly [212]. The presence and degree of hepatic fibrosis may be investigated using non-invasive liver stiffness measurements.

The histological renal manifestations in Caroli syndrome are fusiform dilatations of renal collecting ducts and distal tubuli lined by columnar or cuboidal epithelium that usually remain in contact with the urinary system. The presence of renal cystic lesions can be assessed using radiological imaging including ultrasound, CT or MRI. While the majority of patients with Caroli syndrome possess renal cystic lesions and renal impairment may ensue, there is no correlation between the severity of renal and hepatic manifestations [213].

The phenotypical overlap seen in cases of ARPKD and Caroli syndrome has led to mutational screening for *PKHD1* mutations in these populations. In ARPKD, the presence of 2 pathogenic mutations establishes the genetic diagnosis. in certain cases of Caroli syndrome, *PKHD1* mutations have been discovered [214]. However, in view of the considerable size of the *PKHD1* gene, and its complex splicing pattern, and difficulties in interpreting the functional consequences of the mutational findings there is little role for genetic testing in routine clinical practice [215].

22. How should surveillance for cholangiocarcinoma be performed in patients with Caroli disease?

Recommendation

- Patients with Caroli disease and syndrome may receive surveillance for cholangiocarcinoma with magnetic resonance cholangiopancreaticography every 12 months after diagnosis **(LoE 4, weak recommendation, 90% consensus).**

Several studies report that the prevalence of cholangiocarcinoma in Caroli disease and Caroli syndrome is ~7% [216-218]. This is considerably higher than in the general population (prevalence rates 0.05%; incidence rates of 0.5-1.5 per 100,000 person-years) [216,219]. The reason is unclear but may be related to the carcinogenic effects of chronic inflammation due to recurrent cholangitis [220], carcinogenic effects of biliary stasis [216], or formation of carcinogens due to permanent biliary irritation caused by gallstones [221].

Pre-operative detection of cholangiocarcinoma is difficult in patients with Caroli disease and syndrome because of the abnormal anatomy associated with biliary dilatation [216,222,223]. There is no disease-specific literature regarding cholangiocarcinoma imaging in Caroli disease and syndrome [218]. Diagnostic accuracy for cholangiocarcinoma (in the absence of Caroli disease or syndrome) is highest with MRI including magnetic resonance cholangiopancreaticography [224,225]. Analogous to the American College of Gastroenterology guideline for primary sclerosing cholangitis, patients with Caroli disease or syndrome may undergo surveillance for cholangiocarcinoma using magnetic resonance cholangiopancreaticography every 12 months after diagnosis [226].

We do not recommend endoscopic retrograde cholangiopancreaticography for cholangiocarcinoma screening because this procedure is associated with increased risk of biliary infection [227]. In view of the discussion on biomarkers in question 3, the diagnostic properties of CA19-9 testing for cholangiocarcinoma screening are poor [228]. A definitive diagnosis of cholangiocarcinoma relies on pathological examination of affected tissues.

Cholangiocarcinoma recurrence rates of up to 75% have been reported for patients with Caroli disease or syndrome who underwent liver resection or transplantation [223,227,229-232]. Notably, this number likely overestimates the true cholangiocarcinoma recurrence rate since overall cholangiocarcinoma rates in these studies were very low and recurrence only occurred in patients who underwent liver resection not transplantation. Therefore, patients who undergo liver transplantation

should only receive follow-up for metastasised disease if histological examinations of liver explants confirm the presence of cholangiocarcinoma.

23. Which patients with Caroli disease or syndrome should be referred for liver transplantation and when?

Recommendation

- Referral for liver transplantation should be considered in patients with Caroli disease or syndrome with recurrent cholangitis and i) bilobar involvement, or ii) monolobar involvement in combination with liver fibrosis or portal hypertension, when the possibility of liver resection has been excluded **(LoE 3, strong recommendation, 96% consensus).**

Dilatation of bile ducts in Caroli disease can lead to various symptoms. The main presentation of Caroli disease is cholestasis, which can give rise to stone formation and subsequent biliary obstruction. This results in cholangitis and abscess formation. Differentiation between Caroli disease and syndrome depends on the presence of liver fibrosis and kidney cysts as discussed in question 21. Both Caroli disease and syndrome are associated with an increased risk of cirrhosis and cholangiocarcinoma (discussed under question 22).

Initial treatment of Caroli disease and syndrome should primarily focus on symptoms[233]. Cholangitis is the most frequent symptom observed and can be treated with antibiotics or endoscopic retrograde cholangiopancreaticography. Cholestasis and gallstone formation can be treated with ursodeoxycholic acid and abscesses should be drained (which can be achieved radiologically/ultrasound guided, endoscopically or surgically). Patients can be monitored for osteoporosis resulting from decreased vitamin D intake, which is a consequence of cholestasis.

When initial symptom-based treatment fails, alternative strategies should be sought that can provide symptomatic relief. Though scientific evidence is limited and data is mainly based on retrospective cohorts, Caroli disease and syndrome can be treated surgically by liver resection or liver transplantation. Liver resection adequately relieves symptoms, particularly in patients with Caroli disease with restricted bile duct involvement [222,230,234]. Follow-up after liver resection for cholangiocarcinoma and fibrosis should be performed as described in question 22. Patients with Caroli disease and syndrome should also receive ursodeoxycholic acid therapy (dosage of 13-15 mg/kg/day similar to dosages used for primary biliary cholangitis [235]) even if asymptomatic [207].

The first step in surgical treatment should consist of liver resection [228]. This may be feasible in symptomatic cases with monolobar involvement without liver fibrosis or portal hypertension. Liver transplantation is indicated in patients with recurrent cholangitis and bilobar disease or monolobar disease with portal hypertension or liver fibrosis [207,228,233]. Five-year patient and graft survival rates of 62-100% and 72-100%, respectively, have been reported after liver transplantation [222,227,230,231,233,236]. Compared to patients receiving liver transplantation for other conditions, patient and graft survival is higher for patients with Caroli disease[237]. Cholangiocarcinoma is considered a contra-indication for liver transplantation, though a study in patients with cirrhosis suggests that liver transplantation may be performed for cholangiocarcinoma of ≤2 cm [238]. There is no clear consensus on the timing of liver transplantation wait-listing. Patients should be referred to transplant centres in the absence of acute cholangitis or liver failure and before the onset of physical deterioration [236]. In patients with Caroli syndrome, renal impairment, possibly leading to the need for kidney transplantation, should also be monitored. In patients with Caroli syndrome and renal failure, combined kidney-liver transplantation may offer potential advantages over sequential transplants of the liver and kidney. Immunosuppression after kidney transplantation increases the risk of cholangiocarcinoma and cholangitis [207] and liver transplantation confers immunoprotection for the kidney transplant if transplanted at the same time, but not if these organs have been placed subsequently [208].

24. What information should patients with biliary hamartomas receive?

Recommendation

- Patients should be counselled on the benign nature of biliary hamartomas **(LoE 4, strong recommendation, 100% consensus).**

Biliary hamartomas also referred to as Von Meyenburg complexes are considered part of the spectrum of the ductal plate abnormalities [10]. They may occur in an otherwise normal liver or in association with Caroli disease, congenital hepatic fibrosis, and ADPKD or ADPLD. Multiple bile duct hamartomas are usually detected by pathologists as incidental findings. Biliary hamartomas do not affect liver function and may be confused with miliary liver metastases.

Malignant transformations of biliary hamartomas to hepatocellular or cholangiocarcinoma have been described in incidental cases but then often associated with underlying liver diseases [239-243]. The incidence of malignancies associated with biliary hamartomas is unclear but the relatively low number of case reports [239,244] relative to the 5.6% prevalence of biliary hamartomas in the population

suggest a very low risk [245,246]. However, biliary hamartomas were found in up to 40% of resected liver specimens of intrahepatic cholangiocarcinomas[247]. Detailed histopathological and molecular analyses suggest that a malignant transformation of biliary hamartomas by various genetic mutations is possible and argue against a coincidence of primary hepatic malignancies adjacent to biliary hamartomas [248,249]. The time span from benign biliary hamartomas to the development of detectable liver lesions is not known, although a case report suggests a progression over many years [47]. In summary, there is insufficient data to make recommendations regarding the overall need for and the time interval of surveillance to allow for an early detection of biliary hamartoma-associated malignancy in asymptomatic patients. Asymptomatic patients with biliary hamartomas and concomitant liver diseases should have a follow-up that is determined by the primary liver disease.

Abbreviations

ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ARPKD, autosomal recessive polycystic kidney disease; CA19-9, carbohydrate antigen 19-9; CA72-4, carbohydrate antigen 72-4; CEA, carcinoembryonic antigen; CPGs, clinical practice guidelines; EASL, European Association for the Study of the Liver; MCNs, mucinous cystic neoplasms; MELD, model of end-stage liver disease; PLD, polycystic liver disease; PLD-Q, polycystic liver disease questionnaire; POLCA, polycystic liver disease complaint-specific assessment; TAG-72, tumor-associated glycoprotein 72.

Conflict of interest

Please refer to the accompanying ICMJE disclosure forms for further details.

Acknowledgements

The authors would like to thank the members of the Delphi Panel of this Clinical Practice Guideline for their valuable contribution: Tom Gevers, Maxime Ronot, Maria Papp, Beatrice Aussilhou, Aude Vanlander, Lilia Martinez, Veronica Prado, Claire Francoz, Federica Dondero, Juozas Kupcinskas, Jesus Banales, Uwe Korst, Bobby Dasari, Khalid Sharif, Barbara de Koning, Roy Dwarsaking, Roland Schmitt, Zeno Sparchez, Ulrich Baumann, Vincenzo Cardinale, Anja Geerts, Anna Mrzljak, Domenico Alvaro, Edoardo Poli, Jun Oh, Pavel Strnad.

The authors would also like to thank the Governing Board for their valuable contribution to the review process.

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Appendix

Delphi round agreement on the statements and recommendations of the present CPGs.

Recommendation/statement	Consensus
Ultrasound should be the first imaging modality used to diagnose simple hepatic cysts and PLD **(LoE 3, strong recommendation, 100% consensus).**	100%
Hepatic cysts demonstrating complex features (*e.g.* atypical cyst wall or content), either solitary or in the context of PLD, require further evaluation using additional imaging **(LoE 3, strong recommendation, 100% consensus).**	100%
MRI or CT can be used in PLD to evaluate the distribution of cysts within the liver parenchyma and the relation to hepatic vasculature **(LoE 2, weak recommendation, 100% consensus).**	100%
Biliary hamartomas should be diagnosed by MRI with heavily T2-weighted sequences and MR cholangiography sequences **(LoE 4, strong recommendation, 100% consensus).**	100%
The number of lesions (solitary *vs.* multiple) and architecture (simple *vs*. complex cyst) are key elements in the description of hepatic cyst(s) **(LoE 3, strong recommendation, 100% consensus).**	100%
It is not recommended to follow asymptomatic patients because of simple hepatic cysts, biliary hamartomas or peribiliary cysts **(LoE 3, strong recommendation, 96% consensus).**	96%
Ultrasound should be the first diagnostic modality used if symptoms occur in patients with simple hepatic cysts **(LoE 3, strong recommendation, 96% consensus).**	96%
Routine follow-up with imaging after aspiration sclerotherapy or surgical procedures for hepatic cysts is not recommended **(LoE 3, strong recommendation, 92% consensus).**	92%
The tumour markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) in blood or cyst fluid cannot be used to discriminate between hepatic cysts (solitary or in PLD) and MCNs of the liver **(LoE 2, strong recommendation, 100% consensus).**	100%
Tumour-associated glycoprotein 72 (TAG-72) in cyst fluid may help to distinguish between simple hepatic cysts and MCNs of the liver **(LoE 3, weak recommendation, 95% consensus).**	95%
Symptomatic simple hepatic cysts without biliary communication should be treated with the best locally available volume-reducing therapy **(LoE 2, strong recommendation, 100% consensus).**	100%
Hepatic cyst infection should be considered as definite in the presence of neutrophil debris and/or microorganisms in cyst aspirate showing evidence of infection **(LoE 4, strong recommendation, 100% consensus).**	100%
Hepatic cyst infection should be considered as likely in the presence of the features listed in Table 3 **(LoE 4, strong recommendation, 100% consensus).**	100%
Radiological findings listed in Table 3 may suggest hepatic cyst infections and may be used during the diagnostic work-up **(LoE 3, weak recommendation, 100% consensus).**	100%

Recommendation/statement	Consensus
Fluoroquinolones and third-generation cephalosporins are recommended as empirical first-line antibiotics for hepatic cyst infection **(LoE 2, strong recommendation, 90% consensus).**	90%
The recommended duration of antibiotic therapy is 4-6 weeks **(LoE 4, strong recommendation, 100% consensus).**	100%
We do not recommend secondary prophylaxis for hepatic cyst infection **(LoE 5, strong recommendation, 92% consensus).**	92%
Robust evidence to recommend selective decontamination of the digestive tract to prevent hepatic cyst infection is lacking **(LoE 4, 100% consensus)**	100%
Drainage of infected hepatic cysts may be pursued in the presence of any (combination) of the factors listed in Box 1 **(LoE 3, weak recommendation, 90% consensus).**	90%
Imaging to detect intracystic haemorrhage may be performed in patients with sudden and severe abdominal pain **(LoE 4, weak recommendation, 96% consensus).**	96%
Ultrasound (showing sediment or mobile septations) and/or MRI (heterogeneous and intense signal on both T1- and T2-weighted sequences) may be used to diagnose cyst haemorrhage **(LoE 3, weak recommendation, 96% consensus).**	96%
CT is not recommended to diagnose cyst haemorrhage **(LoE 4, strong recommendation, 91% consensus).**	91%
We recommend temporary interruption of anticoagulants in hepatic cyst haemorrhage **(LoE 5, strong recommendation, 96% consensus).**	96%
Anticoagulants may be resumed between 7–15 days after the onset of hepatic cyst haemorrhage **(LoE 5, weak recommendation, 100% consensus).**	100%
A combination of ≥1 major and ≥1 minor feature listed in Table 4 may be considered as worrisome features for MCNs of the liver (**LoE 3, weak recommendation, 95% consensus).**	95%
MRI should be used to characterise hepatic cysts with worrisome features (**LoE 3, strong recommendation, 100% consensus).**	100%
Surgical resection is the gold standard for suspected MCNs of the liver, and complete resection should be aimed for **(LoE 3, strong recommendation, 100% consensus).**	100%
Abdominal ultrasound to screen for PLD should be offered to all patients diagnosed with ADPKD **(LoE 2, strong recommendation, 100% consensus).**	100%
Genetic testing should not be used to screen for PLD **(LoE 3, strong recommendation, 100% consensus).**	100%
We recommend referral and counselling of patients with symptomatic PLD to centres of expertise **(LoE 3, strong recommendation, 100% consensus).**	100%

Recommendation/statement	Consensus
CT is suggested to assess sarcopenia in patients with PLD and massive hepatomegaly that displaces adjacent organs (*e.g.* stomach and bowels), as these patients are at risk of malnutrition **(LoE 3, weak recommendation, 87% consensus).**	87%
Patients with PLD and sarcopenia should receive intensive nutrition and exercise rehabilitation under the supervision of dieticians and physical therapists **(LoE 5, strong recommendation, 100% consensus).**	100%
Disease-specific symptom severity questionnaires may be used upon the emergence of symptoms to assess disease severity in patients with PLD **(LoE 3, weak recommendation, 95% consensus).**	95%
Disease-specific symptom severity questionnaires should be applied in patients with PLD to assess treatment efficacy **(LoE 1, strong recommendation, 96% consensus).**	96%
We recommend stopping exogenous oestrogen administration in female patients with PLD **(LoE 3, strong recommendation, 100% consensus).**	100%
Choice of treatment should be guided by symptoms and complications related to the presence of cysts, as listed in Table 5, in combination with liver phenotypes, displayed in Fig. 4 **(LoE 2, strong recommendation, 100% consensus).**	100%
Treatment for PLD should be administered in symptomatic patients exclusively **(LoE 2, strong recommendation, 100% consensus).**	100%
Symptom relief and improvement in quality of life should be the primary goal of treatment in PLD **(LoE 1, strong recommendation, 100% consensus).**	100%
Referral for liver transplantation or combined liver-kidney transplantation may be initiated based on the criteria listed in Box 2, taking into consideration local allocation systems, local waitlist criteria, anticipated waiting times and risk of deterioration while waiting for a liver graft **(LoE 3, weak recommendation, 100% consensus).**	100%
Patients with PLD should receive preconception counselling concerning the risk of passing on PLD to the newborn **(LoE 4, strong recommendation, 96% consensus).**	96%
Patients with PLD should not be counselled against pregnancy **(LoE 3, strong recommendation, 96% consensus).**	96%
The finding of multiple segmental cystic or saccular dilatations of bile ducts should initiate a search for congenital hepatic fibrosis in order to differentiate Caroli disease from Caroli syndrome **(LoE 4, strong recommendation, 100% consensus).**	100%
Patients with Caroli disease and syndrome may receive surveillance for cholangiocarcinoma with magnetic resonance cholangiopancreaticography every 12 months after diagnosis **(LoE 4, weak recommendation, 90% consensus).**	90%
Referral for liver transplantation should be considered in patients with Caroli disease or syndrome with recurrent cholangitis and i) bilobar involvement, or ii) monolobar involvement in combination with liver fibrosis or portal hypertension, when the possibility of liver resection has been excluded **(LoE 3, strong recommendation, 96% consensus).**	96%
Patients should be counselled on the benign nature of biliary hamartomas **(LoE 4, strong recommendation, 100% consensus).**	100%

7

Abdominal wall hernia is a frequent complication of polycystic liver disease and associated with hepatomegaly

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Abstract

Background & aim

Polycystic liver disease is related to hepatomegaly which causes an increased mechanical pressure on the abdominal wall. This may lead to abdominal wall herniation. We set out to establish the prevalence of abdominal wall hernia in polycystic liver disease and explore risk factors.

Methods

In this cross-sectional cohort study we assessed the presence of abdominal wall hernias from polycystic liver disease patients with at least 1 abdominal computed tomography or magnetic resonance imaging scan. Abdominal wall hernia presence on imaging was independently evaluated by two researchers. Data on potential risk factors were extracted from clinical files.

Results

We included 484 patients of which 40.1% (n=194) had an abdominal wall hernia. We found a clear predominance of umbilical hernias (25.8%, n=125) while multiple hernias were present in 6.2% (n=30). Using multivariate analysis, male sex (OR 2.727 P<0.001), abdominal surgery (OR 2.575, P<0.001) and disease severity according to the Gigot classification (Type 3 OR 2.853, P<0.001) were identified as risk factors. Height-adjusted total liver volume was an independent polycystic liver disease specific risk factor in the subgroup of patients with known total liver volume (OR 1.363, P=0.001). Patients with multiple hernias were older (62.1 vs 55.1, P=0.001) and more frequently male (22.0 vs 50.0%, P=0.001).

Conclusion

Abdominal wall hernias occur frequently in polycystic liver disease with a predominance of umbilical hernias. Hepatomegaly is a clear disease-specific risk factor.

Key points:

Abdominal wall hernias occur frequently in polycystic liver disease with a predominance of umbilical hernias. Hepatomegaly is an important disease-specific risk factor.

Physicians should pay special attention to abdominal wall hernias in polycystic liver disease patients, especially in severe cases. Hernia repair might be complicated in this patient population.

Introduction

Polycystic liver disease (PLD) is a genetic disease characterized by growth of multiple hepatic cysts. It can occur as an isolated disease known as autosomal dominant polycystic liver disease (ADPLD) or in combination with kidney cysts as autosomal dominant polycystic kidney disease (ADPKD) [1]. Complications in PLD may result directly from cyst related complications (e.g. cyst bleeding, infection or rupture) or result from mechanical pressure by (strategically located) cysts (e.g. abdominal wall hernias, obstructive jaundice, portal vein occlusion, portal hypertension, Budd-Chiari syndrome and compression of the inferior vena cava) [1]. While most extracystic complications are rare, the clinical impression is that abdominal wall hernias (AWHs) occur frequently in PLD, but an accurate estimate of the problem is absent from literature.

In patients with AWH, surgical repair might be considered. Over the last decades, several surgical techniques have been developed for AWH repair, including mesh repair en abdominal wall reconstruction using autologous tissue[2]. Such repair can be a simple or complex surgical procedure depending on a number of clinical features [3]. The indication and appropriate technique for hernia repair is based on factors such as the size of the defect, hernia type, symptoms and the patient's age [4].

We hypothesize that patients with PLD have an increased risk for AWH as PLD is related to hepatomegaly [5] which exerts a permanent increase in mechanical pressure on the abdominal wall [6]. In addition, hepatomegaly can lead to malnutrition and in severe cases to sarcopenia [7]. Sarcopenia is thought to affect the integrity of the abdominal wall and may as such increase the risk for AWH [8,9]. Together these two disease-specific factors could contribute to an increased rate of AWHs in PLD. AWHs are subgrouped according to location: inguinal, femoral, umbilical, paraumbilical, parastomal, cicatricial, Spigelian and epigastric. We hypothesize that the increased hernia risk is most evident for umbilical hernias, in view of the local pressure by the liver on the abdominal wall.

In this study we aim to describe the epidemiology of AWH in a large cohort of PLD patients. We aim to assess the prevalence of AWHs in a PLD population and identify disease specific risk factors associated with AWHs in PLD.

Methods

Study design and patient population

Adult patients from the Radboud University Medical Center, a tertiary referral center for PLD, participating in the international PLD registry were included in this study [10]. The international PLD registry is a prospective cohort and currently holds data from 1825 patients with > 10 hepatic cysts. Diagnosis of ADPLD was made in the presence of > 10 isolated hepatic cysts, ADPKD was diagnosed using the Ravine Criteria [11]. Radboudumc is currently one of the largest contributors to this registry with 641 (35.1%) of the patients. The following inclusion criteria were used: 1) age ≥ 18 years, 2) availability of an abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) scan that captured the entire abdominal wall. For all patients the most recent scan was used.

Data collection

The following data were extracted from the international PLD registry: year of birth, sex, diagnosis (ADPKD or ADPLD). Information on height, weight, total liver volume (TLV), total kidney volume (TKV), abdominal surgery including type of surgery and incision, smoking history and present status, presence of a connective tissue disease, presence of AWH symptoms, and whether a hernia was repaired including type of repair surgery were extracted from clinical files. Body mass index (BMI) was calculated using height and weight. All TLV and TKV measurements were performed as part of regular clinical care or for clinical trial purposes. TKV measurements were only performed in ADPKD patients. Volume measurements on CT scans were performed using manual segmentation in Pinnacle 3 version 8.0 (Philips, Eindhoven, The Netherlands) [12,13]; measurements for MRI scans were performed using automatic segmentation [14].

The presence of AWHs was assessed by two trained researchers (TB & RAB). In this training phase both TB and RAB evaluated 100 scans under supervision of a fellow in abdominal radiology WV, who randomly checked 10 cases. A maximum of 2 errors were allowed in the assessments of TB & RAB to ensure there was no systematic error in abdominal wall assessments. After the training phase, TB & RAB independently evaluated the abdominal wall in all CT and MRI scans. The following hernias were assessed in all imaging: inguinal, femoral, umbilical, paraumbilical, parastomal, cicatricial, Spigelian and epigastric. If both were in agreement, the outcome was noted. If TB & RAB disagreed, a final decision was made by WV. If an AWH was present, the type, size (measured in two dimensions: laterolateral and craniocaudal) and complexity of the hernia according to the Slater criteria were noted [3]. The Slater criteria determine hernia complexity based on 22 patient and hernia characteristics

divided into 4 categories: 1) Size and location, 2) Contamination and soft tissue condition, 3) Patient history and risk factors and 4) Clinical scenario. If a patient fulfills one of the criteria their hernia is considered complex. If a patient had undergone hernia repair surgery before imaging, this patient was also considered to have a hernia.

In each scan the PLD severity was determined using the Gigot classification [15]. In this classification, patients were assigned with type 1 if they have < 10 large hepatic cysts (> 10 cm), type 2 consists of patients with diffuse involvement of liver parenchyma by multiple medium-sized cysts with remaining large areas of noncystic liver parenchyma and type 3 is the severe form of PLD with massive, diffuse involvement of liver parenchyma by small- and medium-sized liver cysts and only a few areas of normal liver parenchyma between cysts. Rectus abdominis thickness was measured at the umbilical level using a methods described elsewhere [16], as approximation proxy of sarcopenia status.

Statistical analyses

Baseline variables were noted as mean (SD) or median (IQR) for continuous variables where appropriate and n (%) for nominal variables. Missing data were imputed using multiple imputation where possible. Multiple imputation was not used in case of > 40% missing values, if data were not missing at random or if no reliable imputations could be made (e.g. due to the scarcity of the event). Baseline characteristics were compared using independent t-tests and Mann-Whitney U tests for continuous variables and Chi-squared tests for nominal variables. Subsequently univariate binary logistic regression analyses were performed to identify potential risk factors for AWHs. Variables with a p-value ≤ 0.2 were included in the multivariate binary logistic regression models. For the multivariate models, backward selection was used. All statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA). A p-value of < 0.05 was considered statistically significant.

Ethical considerations

Formal ethical evaluation of this study was waived by the local Institutional Ethical Review Board of Radboudumc given the non-invasive character of the data collection in the PLD Registry. The study was conducted in accordance with the guidelines for Good Clinical Practice (GCP) and the Netherlands Code of Conduct for Research Integrity.

Results

641 patients with PLD were eligible for inclusion. In 21 patients, no CT or MRI was available and in 136 patients only a portion of the abdominal wall was captured on imaging. These 157 patients were excluded from our study. Finally, we included 484 patients in our study; 49 patients (10.1%) with MRI scans and 435 patients (89.9% with CT scans).

Baseline characteristics

Baseline characteristics for the entire cohort are shown in **table 1**. Mean age for our cohort was 55.4 years and most patients were female (81.0%). Overall, livers were enlarged in our entire cohort since 28.5% of cases were rated Gigot type 1, 37.0% type 2 and 34.5% type 3. Total liver volume was available in only 170 (35.1%) patients and in these patients hepatomegaly was evident with a median height-adjusted TLV (hTLV) of 2645 (IQR 2296) ml/m, compared to a normal hTLV of approximately 816 ml/m for Dutch men and 880 ml/m for Dutch women [17,18]. Baseline characteristics for MRI and CT images separately can be found in the supplementary files (supplementary table 1).

Prevalence of abdominal wall hernias

AWHs were found in 194 (40.1%) of the patients in our cohort with a median diameter of 12 mm (IQR 7 mm) as can be seen in **table 2**. The majority of hernias found were umbilical hernias (n=125), followed by inguinal hernias (n=67). Multiple hernias were found in 30 patients (6.2%). An example of an umbilical and inguinal hernia discovered in our cohort can be seen in **figure 1.**

	Overall (n=484)
Age (years)	55.4 (10.5)
Male sex	92 (19.0)
Diagnosis ADPKD	258 (53.3)
BMI	25.7 (4.1)
hTLV (ml/m)	2645 (2296)
Gigot classification	
Grade 1	138 (28.5)
Grade 2	179 (37.0)
Grade 3	167 (34.5)
hTKV (ml/m)	536 (785)
Rectus abdominis thickness (mm)	8 (2)
Abdominal surgery *	244 (50.4)
Laparoscopy only	106 (21.9)
Laparotomy only	90 (18.6)
Both laparoscopy and laparotomy	44 (9.1)
Smoking	
Present	87 (18.0)
Former	301 (62.2)
Never	96 (19.8)
Connective tissue disease	11 (2.3)
Aneurysm aorta abdominalis	2 (0.4)
Pregnancy**	159 (81.1)

Table 1– Baseline characteristics. Age, BMI and rectus abdominis thickness expressed as mean (standard deviation); Height-adjusted total liver volume (hTLV) and height-adjusted total kidney volume (hTKV) expressed as median (interquartile range) were available in 170 (35.1%) and 51 (10.5%) respectively. TKV was only determined in ADPKD patients. Nominal variables expressed as n (%). *Type of surgery available in 479 (99.0%) cases. **Pregnancy information was only available in 196 women (50.0%).

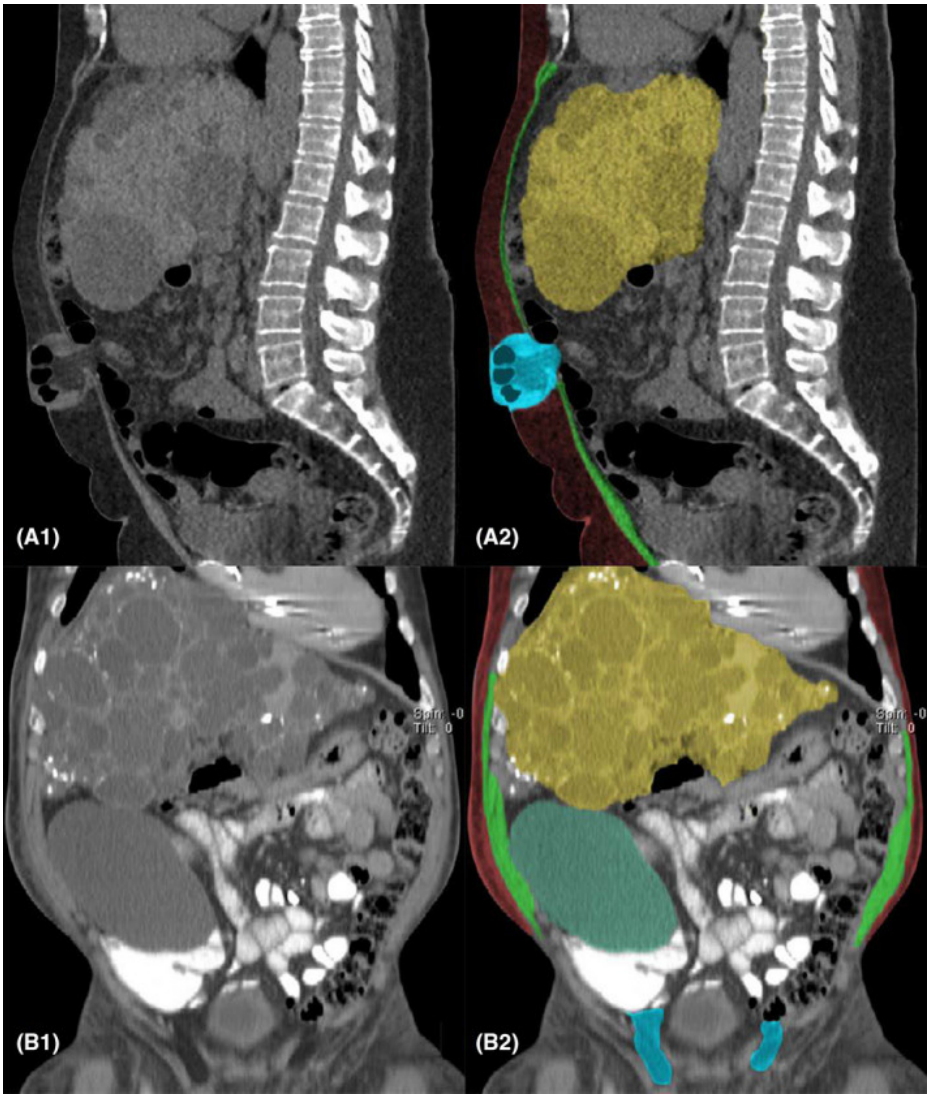

Figure 1 – CT imaging of two patients with abdominal wall hernias. Patient A umbilical hernia, patient B double inguinal hernia. The subcutaneous tissue is colored red, the abdominal muscle tissue light green, the AWH in cyan, the polycystic liver is colored yellow and a single kidney cyst is colored dark green.

Abdominal wall hernia	N (%)	Median diameter in mm (IQR) *
Overall	194 (100.0)	12 (7) n=180
Epigastric	8 (4.1)	18 (6) n=7
Umbilical	125 (64.4)	11 (6) n=109
Cicatricial	3 (1.5)	26 (58)n=3
Inguinal	67 (34.5)	13 (8) n=53
Other hernia	4 (2.1)	10 (1) n=2
Multiple hernias	30 (15.5)	13 (7) n=30
Complex hernia*		
Yes	50 (25.8)	13 (6) (n=43)
No	131 (67.5)	12 (7) (n=109)
Unknown	13 (6.7)	Unknown

Table 2 – Abdominal wall hernias and subtypes. IQR = interquartile range. * N represents the number of hernias in which the diameter could be measured in two different directions (laterolateral and craniocaudal). ** Complex hernia according to Slater criteria; 13 cases were unknown because hernia repair was performed before the imaging.

Baseline characteristics for patients with and without AWH are shown in **table 3**. Patients with an AWH were more frequently male, had larger total liver volumes, higher Gigot types and had undergone abdominal surgery more often. No differences were found with respect to age, diagnosis, BMI, hTKV, rectus abdominis thickness, history of smoking, connective tissue disease, aneurysm aorta or pregnancy rate. Comparable results were found in a subgroup of patients with known hTLV (supplementary table 2).

		No (n=290)	Yes (n=194)	P-value
Age (years)		54.9 (10.5)	56.2 (10.4)	0.160
Male sex		41 (14.1)	51 (26.3)	0.001
Diagnosis ADPKD		146 (50.3)	112 (57.7)	0.110
BMI		25.5 (4.2)	26.1 (4.1)	0.144
hTLV (ml/m)		2413 (1935)	2969 (2881)	0.002
Gigot Classification				
	Type 1	96 (33.1)	42 (21.6)	0.002
	Type 2	111 (38.3)	68 (35.1)	
	Type 3	83 (28.6)	84 (43.3)	
hTKV (ml/m)		510 (565)	898 (939)	0.135
Gigot Classification				
Rectus abdominis thickness (mm)		8 (2)	8 (2)	0.579
Abdominal surgery		121 (41.7)	123 (63.4)	0.000
		No (n=290)	**Yes (n=194)**	**P-value**
Smoking				
	Present	54 (18.6)	33 (17.0)	0.886
	Former	59 (20.4)	37 (19.1)	
	Never	177 (61.0)	124 (63.9)	
Connective tissue disease		7 (2.4)	4 (2.1)	0.511
Aneurysm aorta present		2 (0.7)	0 (0.0)	0.246
Pregnancy*		98 (79.7)	61 (83.6)	0.501

Table 3 – Baseline characteristics for patients with and without hernias. Age, BMI and rectus abdominis thickness expressed as mean (standard deviation); Height-adjusted total liver volume (hTLV) and height-adjusted total kidney volume (hTKV) expressed as median (interquartile range) were available in 170 (35.1%) and 51 (10.5%) respectively. TKV was only determined in ADPKD patients. Nominal variables expressed as n (%). P-values were determined using independent t-tests and Mann Whitney U test for continuous variables and Chi-squared for nominal variables. *Pregnancy information only available in 196 patients (n=123 without AWH and n=73 with AWH).

Compared to patients with a single hernia, patients with multiple hernias were older (62.1 vs 55.1, P=0.001) and were more often male (50.0 vs 22.0%, P=0.001; supplementary table 3).

Risk Factors

Univariate logistic regression showed that the variables age, sex, diagnosis, BMI, hTLV, Gigot and abdominal surgery were potential risk factors for the presence of AWH ($p < 0.02$; **table 4**). Because hTLV and Gigot could not be included in the same model due to collinearity, we performed multivariate analysis with backward

	P-value	OR	95% CI lower bound	95% CI upper bound
Univariate				
Age	0.161	1.013	0.995	1.030
Sex (reference = female)	0.001	2.166	1.368	3.430
Diagnosis (reference = ADPKD)	0.111	0.742	0.515	1.071
BMI	0.146	1.035	0.988	1.084
hTLV (liter/m)	0.009	1.263	1.059	1.505
Gigot (reference = type 1)				
Type 2	0.162	1.400	0.874	2.244
Type 3	0.000	2.313	1.442	3.711
Rectus abdominis thickness (per mm)	0.579	0.977	0.898	1.062
Abdominal surgery	0.000	2.437	1.671	3.554
Smoking (reference = never)				
Present	0.685	0.895	0.521	1.536
Former	0.694	0.901	0.534	1.520
Connective tissue disease	0.651	0.740	0.200	2.737
Aneurysm Aorta	0.999	0.000	0.000	
Pregnancy*	0.502	0.771	0.361	1.647
Multivariate				
Sex (reference = female)	0.000	2.727	1.659	4.481
Gigot (reference = type 1)				
Type 2	0.178	1.409	0.855	2.322
Type 3	0.000	2.853	1.718	4.740
Abdominal surgery	0.000	2.575	1.741	3.809

Table 4 – Logistic regression AWH overall. ADPKD = autosomal dominant polycystic kidney disease, BMI = body mass index, hTLV = height-adjusted total liver volume *Only investigated in women with known pregnancy status (n=196)

selection in all patients using the Gigot variable and later in a subgroup of patients using the hTLV variable. A final multivariate logistic regression showed that males (OR 2.727, P<0.001), abdominal surgery (OR 2.575, P<0.001) and Gigot classification (Type 3 OR 2.853, P<0.001) were independent risk factors (**table 4)**. Similar results were found in the subgroup of patients with known hTLV (n=170, supplementary table 4), which showed that male sex (OR 12.184, P=0.021), hTLV (OR 1.363 per liter/m, P=0.001) and abdominal surgery (OR 3.571, P<0.001) were risk factors in this group. We performed a sensitivity analysis in the patients with umbilical hernias

due to the close proximity of the liver to this hernia site. This sensitivity analysis showed that Gigot classification and abdominal surgery were relevant risk factors in this subgroup (Gigot classification type 3 OR 2.947, P<0.001; and abdominal surgery OR 2.379, P<0.001; supplementary table 5), while male sex was not a risk factor for umbilical hernias (male sex OR 1.740, P=0.065; supplementary table 5). Since inguinal hernias are known to occur predominantly in older males, we performed a subgroup analysis in this group [19]. Multivariate logistic regression showed that male sex was the strongest risk factor in this group (OR 5.227, P<0.001), but age (OR 1.044, P=0.001), Gigot classification (Type 3 OR 3.195, P=0.002) and abdominal surgery (OR 1.858, P=0.039) were also identified as risk factors (supplementary table 6).

Hernia repair

In our cohort 40/194 (20.6%) of all patients with hernias had received hernia repair surgery. In these patients, 19 umbilical hernias were repaired, 12 inguinal, 11 cicatricial and 5 epigastric hernias. In 30 patients (75.0%) the cross-sectionally evaluated imaging that we evaluated, was performed after their repair. Repair was performed using mesh in 12/30 patients, primary closure was performed in 7/30 patients and in 11/30 patients it remained unknown what type of repair was used. The mean follow-up was 8.0 years (standard deviation 13.4). We found that 14 patients had no AWH after the repair, 7 patients had recurrence of the previously repaired hernia and 11 patients had a new hernia after their repair. A flowchart of patients with hernia repairs can be found in supplementary figure 1.

Discussion

We found that AWHs are a frequent complication in PLD with a prevalence of 40.1%. Umbilical hernia is the most frequent (64.4%) hernia type in our population of PLD patients. We identified male sex and abdominal surgery, as well as severity of PLD (as assessed with Gigot classification (type 3) OR 2.853, P<0.001 and hTLV OR 1.363 per liter, P=0.001) as risk factors for AWH. In addition, using sensitivity analyses, hepatomegaly was confirmed as a risk factor for umbilical and inguinal hernias (Gigot type 3 OR of 2.947, P<0.001 and 3.195, P=0.039 respectively). Male sex was not identified as risk factor for umbilical hernias (OR 1.740, P=0.065). Sarcopenia, measured through rectus abdominis thickness, was not identified as a risk factor (OR per mm 0.977, P=0.579).

There is limited published data on AWHs in PLD patients and a smaller ADPKD study indicates prevalence rates of 13.4% for inguinal and 7.0% for umbilical hernias [20].

Unfortunately, no background information or methodology is provided in this paper, which precludes comparison with our data. Another study investigated hernia incidence in 85 ADPKD patients on renal replacement therapy [21]. While the prevalence of 45% is comparable to our finding, the presence of hernias was evaluated using clinical notes. While the specific method used for hernia identification is unclear smaller and less symptomatic hernias may have been missed. Two other studies assessed the presence of AWHs in the general population by 1) using questionnaires and a physical examination and 2) medical history and clinical examination in combination with ultrasound [22,23]. These studies found prevalence rates of 11.7 and 20.9% respectively which is considerably lower than the prevalence in PLD. Lastly, two other studies describe inguinal hernias to occur most frequently in the general population, followed by umbilical hernias [24,25]. In contrast, we found a clear predominance of umbilical hernias in our cohort. This disparity may be the result of the increased intra-abdominal pressure exerted by the polycystic livers.

The most important strength of our study is the thorough assessment of AWHs. Decisions on the presence of an AWH were made by two investigators independently to minimize the risk of systematic bias. Also, evaluation of AWHs using CT and MRI imaging provides a reliable and objective measure of the AWH prevalence in contrast to subjective measures such as evaluation based on symptoms or physical examination [6]. Furthermore this study was performed in a large real-life cohort of PLD patients. Though patients were included from a single center, this is a tertiary referral center receiving patients from every geographical region within the Netherlands. Therefore the patients seen in this center represent a large, clinically representative cohort.

Our study comes with several limitations. First, as an approximation of intra-abdominal pressure we determined disease severity using two different methods: 1) Gigot classification [15] and 2) hTLV. Both approaches do not directly measure intra-abdominal pressure and it is possible that the effect is mediated through other ways than abdominal pressure. Gigot classification was determined in all patients, hTLV was only available in a subgroup of patients and is typically only measured in severe cases to assess the effect of treatment or before liver transplantation. Since direct intra-abdominal pressure measurements with manometry [26] or indirect measurements in the bladder[27], are both too invasive and unethical for this study we believe Gigot classification and hTLV to be a reliable approximation. Second, our study did not include qualitative measures that determine the impact of hernias such as hernia-related symptoms and quality of life. Our current study is mainly aimed at quantifying the AWH prevalence instead of determining the impact of an AWH on

affected individuals. Future studies should address this. Third, we did not directly compare the AWH prevalence from our cohort with a matched group of healthy controls. However, the prevalence of AWH in our cohort was much higher than reported in general population studies, in accordance to previous ADPKD studies [20-23]. Moreover, there were also profound differences in the prevalences of type of hernia. Lastly, all CT and MRI scans were made in a supine position. Small hernias might not be visible in this position due to the effect of gravity. However, these hernias are not likely to have much clinical relevance and our systematic and thorough methodology minimized the chance of missing small hernias.

While the focus of this study was to determine the prevalence of AWHs, from a clinical perspective the frequency and outcomes after surgical repair are paramount. To accurately determine the outcomes after surgical repair, a study aimed at this goal is needed addressing the specifics of these hernias and the type of repair. However, in our cohort hernia repair was common (20.6%), with frequent recurrence of hernias or development of new hernias after surgery (53.3%) and a high rate of surgically complex patients according to the Slater criteria (25.8%). Recurrence rate of AWH in the general population is estimated between 15-37% for primary repair [28] and around 5-6% for laparoscopic mesh repair [29,30], suggesting that hernia repair is more challenging in PLD patients. In line with hernia guidelines, we recommend hernia repair should be reserved for symptomatic patients [31,32]. Given the high rate of hernia recurrence, PLD patients should undergo AWH repair with mesh or an autologous reconstruction, and not primary closure. Referral to specialized clinics may be considered in PLD patients with Gigot type 3 phenotype or complex hernias according to the Slater

In conclusion we demonstrated that AWHs, especially umbilical hernias, are a frequent complication in PLD. Hepatomegaly is an important disease specific risk factor for AWHs and recurrence after hernia repair is high. Therefore clinicians should pay special attention to AWHs when seeing patients with PLD and refer them to specialized hernia clinics if surgical repair is considered for symptomatic AWH.

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8

New insights into targeting hepatic cystogenesis in autosomal dominant polycystic liver and kidney disease

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Abstract

Introduction: Polycystic liver disease (PLD) is a rare disease defined by growth of hepatic cysts and occurs either isolated or as an extrarenal manifestation of polycystic kidney disease. While surgery has been the mainstay in treatment of symptomatic PLD, recently discovered regulatory mechanisms affecting hepatic cystogenesis provide potential new therapies to reduce hepatic cyst burden.

Areas Covered: This review summarizes intracellular pathways and therapeutic targets involved in hepatic cystogenesis. While drugs that target cAMP, mTOR and bile acids were evaluated in clinical trials, investigation in autophagy, Wnt and miRNA signaling pathways are still in the pre-clinical phase. Recent epidemiological data present female hormones as a promising therapeutic target. Additionally, therapeutic advances in renal cystogenesis are reviewed for their potential application in treatment of hepatic cysts.

Expert Opinion: Further elucidation of the pathophysiology of hepatic cystogenesis is needed to provide additional targets and improve efficacy of current treatments. The most promising therapeutic target in PLD is the female hormone pathway, given the increased severity in women and the harmful effects of exogenous estrogens. In addition, combining current pharmaceutical and surgical therapies can lead to improved outcomes. Lastly, the rarity of PLD creates the need to share expertise internationally.

Article Highlights

- Pathophysiology of polycystic liver disease is complex and remains incompletely understood. However, recent elucidation of pathophysiology has provided new therapeutic targets.
- Currently, somatostatin analogues are the only pharmaceutical therapy available for polycystic liver disease.
- The female hormone pathway is a promising therapeutic target that might prove effective in reducing hepatic cyst growth.
- Combining surgical and pharmaceutical treatments could improve anticystogenic efficacy.
- Low prevalence of autosomal dominant polycystic liver disease creates the need to share expertise through the European Reference Network for Rare Liver diseases.

1. Scope of this review

Polycystic liver disease (PLD) is a rare, progressive liver disease in which hepatic cysts slowly grow and is diagnosed in the presence of >10 hepatic cysts [1]. Several signaling routes such as cyclic adenosine monophosphate (cAMP), mammalian target of rapamycin (mTOR) and female hormones were previously identified as promising targets for therapeutic intervention in PLD [2, 3]. Additionally, other regulatory mechanisms that govern the expansion and growth of liver cysts have been identified more recently, providing various potential new therapies. This review aims to summarize the existing and potential new therapeutic targets of hepatic cystogenesis.

2. Methods

We performed a literature search using the following electronic databases PubMed (MEDLINE), Cochrane Controlled Trials Register (CENTRAL), and clinicaltrials.gov. We used the following keywords: Polycystic Liver Disease, PLD, Autosomal Dominant Polycystic Liver disease, ADPLD, Autosomal Dominant Polycystic Kidney Disease, ADPKD. Only articles published in the last 5 years or landmark papers were included in this search. Additional articles were obtained through citation snowballing to locate primary sources. We focused on articles that discuss pathophysiological pathways of hepatic cystogenesis and included clinical studies, animal models and in vitro cultures of both ADPKD and ADPLD.

3. Clinical Background

PLD can occur as isolated disease in autosomal dominant polycystic liver disease (ADPLD), a rare liver disease with a prevalence of 1/158 000 [1, 4, 5], but it is also the most common extrarenal manifestation of autosomal dominant polycystic kidney disease (ADPKD), which has a prevalence of 1/400 – 1/2500 [5-7]. Although many ADPKD patients develop renal failure due to progressive renal cystogenesis, liver function seems unaffected by growth of hepatic cysts [8]. Disease burden in PLD is mainly defined by symptoms due to hepatomegaly and can include an enlarged abdomen, shortness of breath, early satiety and abdominal pain, which result in impaired quality of life warranting the need for treatment [9, 10]. Hepatic cysts in PLD can be diagnosed with ultrasonography, computed tomography or magnetic resonance imaging [11]. For long, treatment of hepatic cysts was dominated by surgical procedures, which were associated with considerable morbidity, incomplete efficacy and high recurrence rates [12, 13]. These limitations have directed the search for new therapeutic options towards aberrant pathways involved in hepatic cystogenesis, which led to the discovery of somatostatin analogues as the first pharmaceutical treatment for patients with diffuse PLD. Type of treatment is based on symptoms and phenotype of liver disease and can include aspiration sclerotherapy, cyst fenestration, partial

hepatic resection and ultimately liver transplantation in severe cases [1]. Treatment is typically limited to symptomatic cases with moderate to severe phenotypes. Since this review aims to summarize the pharmaceutical treatment of hepatic cystogenesis, surgical interventions are outside the scope of this review.

4. Hepatic Cystogenesis

Hepatic cystogenesis begins during fetal development of the liver, when ductal plates are formed around portal veins. These ductal plates are resorbed later, which leads to the formation of bile ducts. In the event of inadequate resorption of the ductal plate, embryonic biliary structures unconnected to normal bile ducts persist [4]. Hepatic cysts can arise from these biliary structures.

Different genetic mutations account for hepatic cyst formation in ADPLD and ADPKD. In ADPKD, cystogenesis is caused by mutations in PKD1 (approximately 78%), PKD 2 (approximately 15%) or GANAB (approximately 0.3%) [14]. Mutations in DNAJB11 are a very rare cause of ADPKD. While multiple hepatic cysts occur, clinically relevant hepatomegaly has not been observed [15].

Mutations in PKD1 are generally associated with more severe disease than PKD2 [16, 17]. PKD1 and PKD2 encode for the proteins polycystin 1 (PC1) and polycystin 2 (PC2) respectively, which act as a mechanosensor and calcium channel and are located in the primary cilium of cholangiocytes [6, 7]. Additionally, PC2 is also located to the endoplasmic reticulum. Mutations in PKD1 and PKD2 genes result in inadequate formation of PC1 or PC2. Hepatic cystogenesis in ADPLD is caused by mutations in PRKCSH and SEC63 genes in approximately 35% of cases. Recently, GANAB, ALG8 and LRP5 have also been associated with ADPLD with large (>1cm) hepatic cysts, while heterozygous mutations in PKHD1 and SEC61B were found in 10 and 2 PLD patients with numerous diffusely spread small hepatic cysts [18-20]. However approximately 50% of causative genes in PLD still remain unresolved [19].

This difference in phenotype could be explained by the function of these genes since the proteins encoded by DNAJB11, PRKCSH, SEC63, GANAB, ALG8 and SEC61B reside within the endoplasmic reticulum and are involved in maturation and trafficking of PC1. PKHD1 is not present in the endoplasmic reticulum biogenesis pathway, but instead encodes fibrocystin which is an integral membrane protein located in the primary cilium [18]. While fibrocystin has been associated with PC 1 and 2, its exact function remains uncertain [19].

Gene	Protein	Localization	Disease	Phenotype	Reference
PKD1	Polycystin 1	Primary cilium, plasma membrane and cell junctions	ADPKD & ADPLD	Variable with multiple large cysts	[5, 14]
PKD2	Polycystin 2	Primary cilium and endoplasmic reticulum	ADPKD & ADPLD	Variable with multiple large cysts	[5, 14]
GANAB	Glucosidase 2 subunit α or PKD3	Endoplasmic reticulum	ADPKD & ADPLD	Variable with multiple large cysts	[18, 19]
DNAJB11	DnaJ Homolog Subfamily B Member 11	Endoplasmic reticulum	ADPKD & ADPLD	Variable with multiple large cysts	[15]
PRKCSH	Glucosidase 2 subunit β or hepatocystin	Endoplasmic reticulum	ADPLD	Variable with multiple large cysts	[18, 19]
SEC63	Translocation SEC63 homolog	Endoplasmic reticulum	ADPLD	Variable with multiple large cysts	[18, 19]
ALG8	A-1,3-glucosyltransferase	Endoplasmic reticulum	ADPLD	Variable with multiple large cysts	[18, 19]
SEC61B	Protein transport protein Sec61 subunit β	Endoplasmic reticulum	ADPLD	Multitude of small cysts	[18, 19]
LRP5	Low density lipoprotein receptor-related protein 5	Plasma membrane	ADPLD & ADPKD	Variable with multiple large cysts	[19, 20]
PKHD1	Fibrocystin or polyductin	Primary cilium	ARPKD & ADPLD	Multitude of small cysts	[18, 19]

Table 1 – Overview of genes and phenotype associated with PLD. Dysfunction of PC1 and PC2 in ADPLD and ADPKD leads to impaired sensoring in the cholangiocyte's primary cilium. This may cause cyst formation through perturbation of several intracellular signaling pathways [22]. Impaired sensoring can lead to lowering of intracellular calcium levels, which subsequently results in an increase of intracellular cAMP [23]. Increased levels of cAMP are associated with increased cell proliferation and fluid secretion through activation of the MAPK/ERK pathway causing the development of cysts.

LRP5, encodes a plasma membrane protein (also called LRP5), not located to the endoplasmic reticulum nor primary cilium, is involved in the highly conserved Wnt canonical pathway [19]. The Wnt pathway can, in addition to its function in various other pathways, influence the destruction complex that can degrade β-catenin. Upregulation of β-catenin can in turn lead to upregulation of several target genes [19]. However, the exact role of LRP5 in hepatic cystogenesis remains unclear, though it has been suggested that PC1 itself is a Wnt receptor [21]. Table 1 shows a comprehensive overview of the genotypes and corresponding phenotypes involved in PLD [19].

Another important cellular pathway in cystogenesis is the mTOR pathway. This protein kinase complex plays an important role in cell proliferation and activation of tuberous sclerosis complex 2 (TSC2). TSC2 can activate guanosine triphosphatase proteins, which subsequently increases fluid and ion secretion into cysts [2, 24].

Several targets are worth noting such as farnesyl pyrophosphate (FPP), activation of estrogen receptors (ER) and microRNAs (miRNA). These molecules may be targeted with pharmaceutical therapies (Figure 1). Identification of these molecules and the corresponding physiological mechanisms has opened opportunities to intervene using strategically targeting agents (Table 2 & 3). Other unexplored but potentially interesting pathways involve fenofibrate, PPARa, PPARg, innate immunity and long-term exercise. Albeit interesting, these pathways have not been included in this review since they have not been researched extensively. Important pre-clinical models for PLD include PCK rats, PKD2 mice and PKD1 mice [25]. Han:SPRD rats are used in ADPKD research and Madin-Darby canine kidney cells are used as a model for cystogenesis.

5. Therapeutic targets in Hepatic Cystogenesis

5.1 Somatostatin analogues

One way to reduce cAMP in cholangiocytes is by using somatostatin, a naturally occurring hormone that targets somatostatin receptors (SSTR) 1-5. Since natural somatostatin has a half-life of approximately 3 minutes, somatostatin analogues (SAs) with longer half-lives have been developed (e.g. octreotide with a high affinity for SSTR2 and SSTR5 and lanreotide with a high affinity for SSTR2 and minor affinity for SSTR5). Octreotide long-acting release (LAR) showed a reduction of both hepatic and renal cystic growth at 1 year and 3 years of administration in several studies with ADPKD patients [3, 26, 27]. These studies did not observe any beneficial effect on the estimated glomerular filtration rate (eGFR) decline, but one trial documented that fewer patients progressed from chronic kidney disease stage 4 to stage 5 [27].

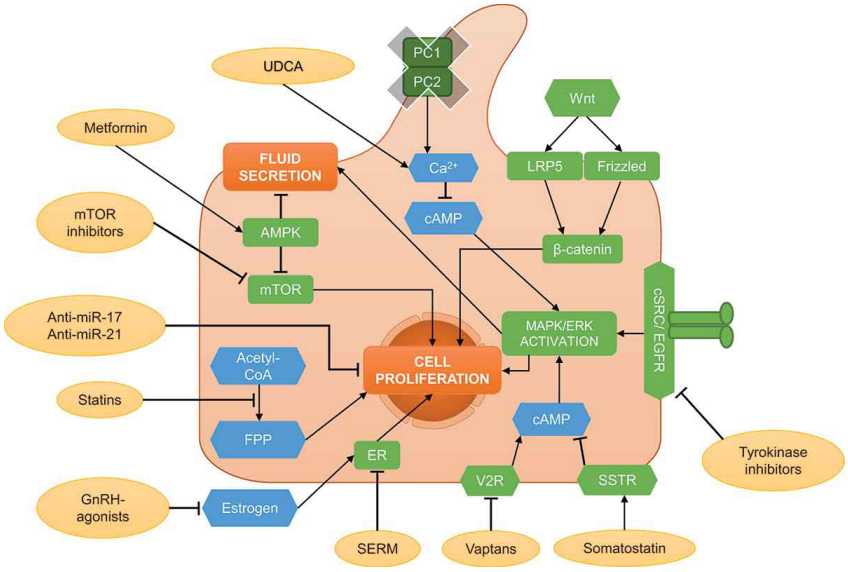

Figure 1 – Pathophysiological pathways in PLD and their therapeutic targets in a human cholangiocyte. AMPK= adenosine monophosphate-activated protein kinase, mTOR=mammalian target of rapamycin, anti-miR=antagonist for miRNA, FPP=farnesyl pyrophosphate, GnRH=gonadotropin-releasing hormone, SERM=selective estrogen receptor modulator, ER=estrogen receptor, V2R=vasopressin 2 receptor, SSTR=somatostatin receptor, cAMP=cyclic adenosine monophosphate, MAPK/ERK= mitogen-activated protein kinase/extracellular signal-regulated kinase cSRC=cellular SRC, EGFR=epidermal growth factor receptor, UDCA=ursodeoxycholic acid, PC=polycystin.

Similarly, lanreotide reduced both hepatic and renal cyst growth in ADPLD and ADPKD patients in several large studies [3, 28-30]. As total kidney volume (TKV) predicts disease progression in ADPKD, it was assumed that preventing renal cyst growth would also prevent eGFR decline [31]. This was refuted when a randomized trial showed that lanreotide did not affect eGFR decline but did reduce kidney and liver volume [28]. However, since only small changes in total liver volume (TLV) and TKV were observed over prolonged periods of time, alternative treatment options are needed.

One of these alternatives, the more recently developed SA pasireotide (high affinity for SSTR1, SSTR2, SSTR 3 and SSTR5) was found to be more effective in reducing hepato-renal cystogenesis than octreotide in rodent models. In this study, polycystic kidney (PCK) rats (a rodent model used for PLD) and polycystic kidney disease (Pkd2) mice (rodent models for ADPKD) were sacrificed 6 weeks after treatment with octreotide or pasireotide. Several indices for both hepatic and renal cystogenesis showed a statistically significant decrease in rodents treated with pasireotide

compared to octreotide and controls, indicating that pasireotide was more potent than octreotide in reducing cyst burden [32].

This led to the initiation of a phase 2 clinical trial investigating the effect of 60mg pasireotide alone on TLV in 48 polycystic liver disease patients, which was recently completed (ClinicalTrials.gov Identifier: NCT01670110). This study assesses the absolute percentage change in liver volume from baseline to 12 months. Additional efficacy and heath related quality of life parameters will be assessed after 1 year, as well as safety since hyperglycemia is a known side-effect of pasireotide [33].

Of note, in an attempt to prevent pasireotide associated hyperglycemia, the efficacy of co-administration of octreotide with pasireotide in PCK rats was investigated. In contrast to increased levels of glucose in the pasireotide group, normal glucose levels with concomitant administration. This led to the conclusion that addition of octreotide to pasireotide potentially nullifies the hyperglycemic effect of pasireotide while preserving its anticystogenic effect, which could be a promising strategy in case severe hyperglycemia occurs with long-term pasireotide monotherapy [34].

5.2 Vasopressin

Vasopressin increases cell proliferation and fluid secretion by upregulating intracellular cAMP. Since it was thought that receptors for vasopressin were only expressed in renal collecting ducts and thick ascending limbs of the loops of Henle, vasopressin research primarily focused on renal cystogenesis [35, 36]. The TEMPO 3:4, TEMPO 4:4 and REPRISE trials showed us that tolvaptan, a potent vasopressin receptor 2 (V2R) antagonist, is a safe and effective method to reduce renal cystogenesis and delays decline in eGFR [37-39]. Another selective V2R antagonist, lixivaptan, is currently being investigated in several clinical trials as an alternative treatment for ADPKD (ClinicalTrials.gov Identifier: NCT03487913, NCT04064346 and NCT04152837).

A recent study also showed the presence of V2R in both rodent and human cholangiocytes, suggesting that targeting vasopressin could be a viable option to reduce hepatic cystogenesis [40]. Indeed, two recent case reports of ADPKD patients with PLD showed a reduction in liver volume while using tolvaptan (dosage of 60mg/day) [41, 42]. Post-hoc analyses of the TEMPO 3:4, TEMPO 4:4 and REPRISE trials could potentially show us the effect of tolvaptan on liver volumes with a larger sample size.

In addition to polyuria, another limiting factor of using V2R antagonists for PLD patients in clinical practice is hepatotoxicity. Tolvaptan is estimated to induce liver failure in 1/4000 ADPKD patients on long-term tolvaptan therapy, occurring between

3 and 18 months [43]. In addition, tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases with infrequent cases of concomitant elevations in bilirubin. While these elevations were reversible with discontinuation of tolvaptan, they represent a potential for significant liver injury. While PLD is considered a benign condition that does not cause liver damage, pathology evaluation of 125 liver samples (obtained after either transplantation or partial hepatectomy) showed several abnormalities including fibrosis [44]. Although the pathophysiological mechanism of this fibrosis remains unknown, this challenges the paradigm that PLD does not affect non-cystic liver parenchyma. Therefore, clinicians should exercise caution when administering potentially hepatotoxic drugs such as tolvaptan in severe PLD. At present, lixivaptan has been evaluated insufficiently to draw valid conclusions on hepatotoxicity

5.3 mTOR inhibitors

Inhibition of mTOR, which can be achieved by everolimus or sirolimus, reduced hepatic and renal cyst formation and cyst size in PKD rodent models [45, 46]. This prompted the initiation of several clinical studies investigating mTOR inhibitors, which showed ambiguous results. Liver volumes of sixteen ADPKD patients receiving two different immunosuppression regimens after kidney transplantation were retrospectively compared. A reduction in liver volume of 11.9% was observed in the sirolimus treated group, whereas an increase in liver volume was seen with tacrolimus [47]. A major limitation of this study was the retrospective, single center design which created a biased patient selection and precluded a direct evaluation of the effect of sirolimus on liver volume, leading to spurious results. In contrast, a randomized clinical trial comparing octreotide alone to octreotide and everolimus in 44 PLD patients did not find a beneficial additive effect of everolimus on liver volume [48]. Finally, a meta-analysis including 9 randomized controlled trials found a statistically significant benefit of administration of the mTOR inhibitors sirolimus and everolimus on TKV and eGFR, but did not evaluate effects in PLD [49]. A major limitation of the included trials were the low doses of mTOR inhibitors. While animal studies showed promising results with high sirolimus doses, increasing the dosage of mTOR inhibitors in order to establish adequate levels to prevent cystogenesis was not feasible in clinical practice due to side effects including stomatitis, edema and thrombocytopenia. Therefore, it is unlikely that mTOR inhibitors will be viable options for the treatment of PLD.

5.4. Ursodeoxycholic Acid

Bile acids became a potential therapeutic target for PLD after a study showed that accumulation of bile acids in bile duct-ligated rats triggered cholangiocyte

proliferation through the cAMP pathway. Ursodeoxycholic acid (UDCA) inhibited cholangiocyte proliferation and ductal secretion in these rats by increasing intracellular calcium and decreasing cAMP levels [50]. Subsequent research showed that UDCA inhibited hepatic cystogenesis and fibrosis in PCK rats, and demonstrated decreased intrahepatic accumulation of cytotoxic bile acids and normalized bile acids levels in bile after UDCA administration [51]. Studies in PCK rats showed promising results, but these rats received early treatment and had mild disease at the time of initiation of treatment [51]. The CURSOR trial, a phase 2 multicenter randomized controlled trial, investigated the effect of 24 weeks of UDCA treatment (15-20 mg/kg/day) on liver and kidney volume in 34 patients with PLD (both ADPKD and ADPLD). However, this trial observed that UDCA did not reduce TLV in PLD patients [52]. Explanations for the lack of effect could be the differences in molecular mechanisms leading to PLD between rodent models and humans, the short-term administration of UDCA (6 months) or that only patients with severe PLD were included. A post-hoc analysis in the CURSOR trial showed reduced liver cyst growth in a subgroup of ADPKD patients in the UDCA-arm. Although this study was not powered for subgroup analyses, this finding raises the question whether differences exist in hepatic cystogenesis between ADPLD and ADPKD. Future research should explore differences in responses to UDCA in ADPKD and ADPLD patients, bearing in mind safe and sufficient drug dosages and adequate follow-up time.

5.5 Estrogen and progestogen

Female hormones are hypothesized to play an important role in hepatic cystogenesis since the majority of PLD patients are female (80%) [1]. Indeed, several studies observed stabilization of polycystic liver volume after the menopause in contrast to pre-menopausal growth, which supports this hypothesis [3, 53].

However, the molecular pathways through which female hormones influence cystogenesis are not fully understood. Bile duct-ligated rats showed that cystic cholangiocytes overexpress estrogen receptors α and especially β in contrast to normal rats [54]. Cholangiocyte proliferation was activated through the ERK pathway in cells that express estrogen receptors. Tamoxifen, a selective estrogen receptor modulator, reduced cholangiocyte proliferation and induced apoptosis in bile duct-ligated rats [55]. Although these studies suggest that aberrant expression of estrogen receptors could be a key factor in hepatic cystogenesis, it is paramount to further unravel the exact molecular characteristics of the estrogen pathway in PLD.

Next to preclinical studies, several clinical studies showed the effect of exogenous estrogens on hepatic cystogenesis. Hormonal replacement therapy with conjugated

estrogens in 19 post-menopausal ADPKD patients was associated with an increase in TLV, compared to a volume reduction in controls [56]. In addition, a recent large cross-sectional cohort study showed that every ten years of oral contraceptive use in pre-menopausal women was correlated with a 15.5% higher height-adjusted TLV compared to unexposed women [57]. These findings led to the clinical advice to discourage use of exogenous estrogens in female PLD patients. Whether progestogens exert a similar negative effect on hepatic cystogenesis remains unknown. Clinical trials that target estrogen receptors have not been initiated at this moment, but can be approached in two ways. First, several drugs (e.g. tamoxifen, fulvestrant) can directly inhibit estrogen receptors present in cholangiocytes. Second, by targeting gonadotropin-releasing hormone (GnRH) receptors (e.g. leuprorelin), systemic estrogen and progestogen levels can be reduced to resemble a postmenopausal status.

5.6 Histone Deacetylase Inhibitors and Autophagy

While dysregulation in autophagy and apoptosis appear to play a role in hepatic and renal cystogenesis, the exact pathogenic pathway has yet to be elucidated [58, 59]. Histone deacetylase (HDAC) 6 is a transporter involved in transporting misfolded proteins to aggresomes, which are later destructed by autophagy [60]. In ADPKD upregulation of PC1 results in increased autophagy of PC2, which could be prevented by inhibiting HDAC6 [61]. Inhibition of HDAC6 was found to decrease cAMP levels, inhibit cell proliferation and inhibit chloride secretion in Madin-Darby canine kidney cells (an in vitro model of cystogenesis) and also reduced renal cyst growth in a PKD1-conditional ADPKD mouse model [62]. Trischostatin A, a broad HDAC inhibitor also reduced renal cyst growth and inactivated mTOR in PKD1 -/- mice, but only when autophagy pathways remained intact [63].

Another study confirmed the role of autophagy in hepatic cystogenesis by analyzing PCK rats [64]. Analysis of cholangiocytes from this model showed increased markers of autophagy, which might be triggered by activation of the cAMP-PKA-CREB signaling pathway. Since the exact anticystogenic mechanisms of HDAC6 inhibition is unknown, no clinical trials have been initiated presently.

Inhibition of sirtuin 1 (SIRT1), another HDAC can be achieved with nicotinamide, also known as vitamin B3. A Pkd1-mutant mouse model found that nicotinamide inhibited Rb deacetylation and phosphorylation, resulting in reduced cell proliferation and regulated cell death through the p53 apoptosis pathway [65] and prompted the initiation of two clinical trials. In 2014 the NIAC-PKD1 trial was initiated to look at the sirtuin 1 inhibition capacity of nicotinamide in ADPKD patients, but its results have not

been published so far (ClinicalTrials.gov Identifier: NCT02140814). The more recently initiated NIAC-PKD2 study focusses on downstream effects of sirtuin 1 inhibition by measuring the acetylated/total p53 ratio (ClinicalTrials.gov Identifier: NCT02558595).

5.7 Wnt pathway

LRP5 has been discovered as a membrane-bound coreceptor (coupled with Frizzled-receptors) involved in hepatic cystogenesis, which is activated when Wnt ligands bind and subsequently increases cytosolic β-catenin protein. This pathway, also called the Wnt canonical pathway, is associated with cellular developmental processes including cell proliferation [19]. Extensive attempts to block the Wnt canonical pathway have not yielded any useful clinical interventions thus far [66]. Since PC1 itself is suggested to be another receptor in the Wnt canonical pathway, interventions in this pathway could provide therapeutic targets for both ADPKD and ADPLD.

5.8 miRNA

In recent years, miRNAs have presented themselves as new potential therapeutic targets for several forms of cancer, hepatitis C and Alport syndrome [67]. MiRNAs are small non-coding pieces of RNA that regulate translation of mRNA by binding to complementary sites of specific mRNA sequences. The complementary mRNA sequence is then either degraded or its translation is repressed, both resulting in the inhibition of translations of the mRNA sequence [68]. Interactions between cholangiocyte cilia and biliary exomes, including microRNA miR-15A, were shown to affect cholangiocyte proliferation and cyst growth [69]. When miR-15A was overexpressed in PCK rats, cell proliferation was inhibited and hepatic cyst growth was reduced [70].

In contrast, upregulation of two other miRNAs, miR-17 (associated with pro-proliferative effects) and miR-21 (associated with antiapoptotic effects), is associated with ADPKD progression in murine models [71]. Indeed, deletion of miR-17 or miR-21 attenuated ADPKD progression and renal cyst burden in mouse models [72, 73]. Based on these results it was hypothesized that miRNAs can serve as a target in hepatic cystogenesis. Indeed, specific miRNAs can be targeted by anti-miRs, which are complementary synthetic oligonucleotides. Importantly, an anti-miR-17 drug has advanced through preclinical ADPKD studies [74] and a phase 2 trial with an anti-miR-21 drug is currently being performed for Alport Syndrome (ClinicalTrials.gov Identifier: NCT02855268). In the future it will be interesting to explore the effects of anti-miRs on ADPKD and ADPLD.

6. Therapeutic targets in Renal Cystogenesis

All previously mentioned pathways were investigated in clinical or pre-clinical models of hepatic cystogenesis. However, given the overlap with renal cystogenesis, findings in studies aimed at renal outcomes in ADPKD could also be valuable for treatment of PLD. Given that most ADPKD patients will have a PLD phenotype, this would provide the ideal setting to investigate effects of potential drugs on renal and liver endpoints simultaneously. We will discuss the most promising strategies currently available for renal cystogenesis.

6.1 Tyrokinase inhibitors

Tyrokinase inhibitors such as tesevatinib and bosutinib inhibit proto-oncogene tyrosine-protein kinase Src (c-Src) and have originally been developed as drugs to treat several malignancies including chronic myeloid leukemia and non-small cell lung cancer [75, 76]. C-Src activation promotes hepatic and renal cystogenesis in two ways. Firstly, c-Src is required for cAMP dependent ERK activation of cholangiocyte proliferation and fluid secretion [77]. Secondly, c-Src is involved in the ErbB2 (epidermal growth factor receptor) pathway, which is one of the major triggers for renal tubular epithelial cell proliferation and thus renal cystogenesis [78]. A recent study with two rodent models for PLD showed that tesevatinib effectively reduced both hepatic and renal cystogenesis without morphological evidence for toxicity [79]. In addition, a phase 2 clinical trial found that bosutinib in a dose of 200mg/d was found to significantly reduce the rate of kidney growth when compared to placebo. Adverse events were comparable to earlier chronic myeloid leukemia studies [80]. At present, two different trials are being conducted with tesevatinib (ClinicalTrials.gov Identifier: NCT03203642 and NCT01559363). Both are phase 2 studies, evaluating the safety and tolerability of tesevatinib in combination with the efficacy on GFR and TKV at several time points in ADPKD patients. Presently research focuses only on renal outcomes, but hepatic cystogenesis might also be suppressed by tyrokinase inhibitors. However, high rates of gastrointestinal and liver toxicity could impede the use of tyrokinase inhibitors in clinical practice.

6.2 Metformin

Metformin inhibits renal cyst formation by downstream effects of activating adenosine monophosphate-activated protein kinase (AMPK), which negatively regulates the cystic fibrosis transmembrane conductance regulator pathway (involved in epithelial fluid secretion) and the mTOR pathway (involved in cyst formation) [81]. Currently, the TAME-PKD study evaluates the safety and tolerability of metformin in ADPKD patients (ClinicalTrials.gov Identifier: NCT02656017). This

study will also assess cystogenesis parameters such as TKV and TLV as secondary outcomes [82]. The METROPOLIS study (ClinicalTrials.gov Identifier: NCT03764605) is currently running and compares the additive effect of metformin combined with tolvaptan on renal cystogenesis. Since metformin is inexpensive and safe, it would be interesting to investigate as a potential treatment for hepatic cystogenesis.

6.3 Statins

Lovastatin (an HMG-COA reductase inhibitor) prevents cell proliferation by inhibiting the conversion of acetyl-CoA to farnesyl pyrophosphate (FPP). FPP is required for the activation of guanosine triphosphatase binding proteins that cause cell proliferation in mammalian cells [83]. Treating Han:SPRD rats (a rodent model for ADPKD) with lovastatin leads to structural changes in renal composition, including decreased cystic kidney size and volume density of cysts [83, 84]. In addition, another statin (pravastatin) was effective in slowing progression of structural kidney disease in children with ADPKD [85]. In contrast, a recent post-hoc analysis of the HALT-PKD trial found no differences in TKV and TLV between patients with and without statins. However, limitations of this post-hoc analysis were the small number of statin users, the use of different statin types and non-randomized allocation of doses [86], which precludes definitive answers on the effect of statins on hepatic and renal cystogenesis. The efficacy of pravastatin is currently investigated in adult ADPKD patients (ClinicialTrials.gov Identifier NCT03273413), in a trial that will compare the effect of pravastatin 40mg with placebo on TKV in ADPKD patients, but does not include hepatic outcomes.

Drug	Target	Hepatic or Renal cystogenesis	Current stage of evidence	Main outcomes	Reference
Octreotide	cAMP (SSTR)	Hepatic and Renal	Clinical Phase 3	Reduced hepatic and renal cyst size in PLD patients	[3, 26, 27, 34, 48]
Lanreotide			Clinical Phase 3	Reduced hepatic and renal cyst size, no effect on eGFR in PLD patients	[3, 28-30]
Pasireotide			Pre-clinical animal studies	Reduction of hepatic and renal cystogenesis in animal models	[32, 34, 64, 87]
Tolvaptan	cAMP (V2R)	Renal, possibly also hepatic	Clinical Phase 4	Reduces TKV and attenuates the rate of decline in eGFR in ADPKD patients	[37-40, 87]
Lixivaptan			-		
Sirolimus	mTOR	Hepatic and Renal	Clinical Phase 2	Reduces hepatic and renal cystogenesis in animal models. Doesn't affect cyst volume in PLD patients	[45-47, 49]
Everolimus			Clinical Phase 2	Reduces hepatic and renal cystogenesis in animal models. Doesn't affect cyst volume in clinical setting	[45, 46, 48, 49]
Ursodeoxycholic acid	Calcium	Hepatic	Clinical Phase 2	Reduces hepatic cystogenesis in animal models, but does not affect hepatic cyst size in clinical settings	[50-52]
Female hormone targeting	Female hormone pathway	Hepatic	No experimental studies performed yet		

Table 2 – Current clinical evidence.

Drug	Target	Hepatic or Renal cystogenesis	Current stage of evidence	Main outcomes	Reference
Tubacin	Histone Deacetylase	Hepatic and Renal	Pre-clinical animal model	Reduces cyst formation in ADPKD models	[61, 62]
Trichostatin A			Pre-clinical animal model	May prevent cyst formation in ADPKD models	[63]
Nicotinamide			Pre-clinical animal model	Delayed cyst formation in several ADPKD models	[65]
Anti-miR15	miRNA	Hepatic and Renal	Pre-clinical animal model	Regulation of miR15 reduces cholangiocyte cell proliferation and cyst growth in animal models	[69, 70]
Anti-miR17			Pre-clinical animal model	Anti-miR17 attenuates cyst growth in PKD mouse models	[71, 72]
Anti-miR21			Pre-clinical animal model	Genetic deletion of miR21 leads to attenuated cyst burden in animal models	[73]
Tesevatinib	C-Src	Renal	Pre-clinical animal model	Reduces both biliary and renal cystogenesis in animal models	[79]
Bosutinib			Clinical Phase 2	Reduction of kidney enlargement in animal models and ADPKD patients. No effect on eGFR decline.	[77, 80]
Statins	Farnesyl Pyrophosphate	Renal	Pre-clinical animal model	Decreases cyst volume density in animal models. Might decrease HtTKV in young ADPKD patients	[83-86]

Table 2 – Continued. SSTR=somatostatin receptor, V2R=vasopressin 2 receptor, mTOR=mammalian target of rapamycin, miRNA=micro ribonucleic acid, c-Src= proto-oncogene tyrosine-protein kinase Src

Drug	Target	Hepatic or Renal cystogenesis	Stage of upcoming clinical trial	ClinicalTrials.gov Identifier
Pasireotide	cAMP (SSTR)	Hepatic and Renal	Clinical Phase 2	NCT01670110
Tolvaptan	cAMP (V2R)	Renal, possibly also hepatic	Clinical Phase 3	NCT03764605
Lixivaptan			Clinical Phase 3	NCT03487913, NCT04064346 & NCT04152837
Tesevatinib	C-Src	Renal	Clinical Phase 2	NCT03203642 & NCT01559363
Nicotinamide	Histone Deacetylase	Renal	Clinical Phase 2	NCT02140814 &NCT02558595
Metformin	AMPK	Renal	Clinical Phase 3	NCT02656017 & NCT03764605

Table 3 – Upcoming clinical trials. SSTR=somatostatin receptor, V2R=vasopressin 2 receptor, c-Src= proto-oncogene tyrosine-protein kinase Src, AMPK=adenosine monophosphate-activated protein kinase

7. Conclusion

Progress in the pathophysiological understanding of hepatic and renal cystogenesis has led to discovery of new potential pharmaceutical interventions. At present, SAs are the only proven pharmaceutical intervention for treatment PLD. Other promising results from animal models, including UDCA or mTOR inhibitors, were not reproduced in clinical practice or possessed safety issues. Promising new targets are female hormones, vasopressin, miRNA and autophagy, but their efficacy and safety will have to be determined in clinical trials. No therapeutic targets for the Wnt canonical pathway are currently being investigated. Finally, developments in renal cystogenesis could provide new therapeutic targets in hepatic cystogenesis, for example vasopressin, tyrokinase inhibitors, metformin and statins. Further elucidation of existing and new pathophysiological mechanisms involved in hepatic and renal cystogenesis could provide additional treatment strategies, and future clinical trials should reveal whether these treatments will be useful for clinical practice. Trials combining different treatment strategies with the aim to achieve a synergistic effect need to be developed.

8. Expert opinion

The pathophysiological process of cystogenesis in PLD remains complex. Recent advances with in vitro cell cultures and rodent PLD models have proven that cystogenesis can be targeted and cyst burden can be reduced with drugs. The ultimate goal is to develop a safe and inexpensive pharmaceutical therapy that

effectively controls polycystic liver growth and renders surgical interventions obsolete. However, the journey to a clinically viable treatment is still long. Indeed, promising treatment options in cell cultures and rodent models did not make their way into clinical practice due to impaired efficacy or harmful side-effect profiles [34, 52]. We therefore propose several strategies to maximize results.

We believe that the female hormone pathway is the most promising future therapeutic target due to several reasons: 1. the majority of PLD patients is female [1] 2. female patients express a more severe phenotype compared to males [13, 56] 3. growth of polycystic liver declines after menopause [3, 53] 4. exogenous estrogens are a risk factor for hepatic cyst growth in PLD [57] 5. postmenopausal hormone administration increases cyst volume [56]. Altogether, these arguments suggest that inducing a post-menopausal status in female PLD patients, for example with GnRH agonists, would be a logical next step. However, since these therapies are associated with serious side-effects, effects should be large to achieve a favorable benefit-to-risk ratio.

Another important approach to improve outcomes is by combining different therapeutic targets to create a synergistic effect. We have already shown in this review that combining different treatment modalities (octreotide and pasireotide) can reduce side effects while maintaining efficacy [34]. Similarly, a study with Pkd1 mice showed that concomitant administration of tolvaptan and pasireotide reduced cystic volumes and decreased cAMP to wild-type levels [87]. Both studies aimed to reduce cyst growth by simultaneous administration of drugs that target the cAMP pathway. A synergistic effect could further be enhanced when combining treatments that target distinct pathways, as demonstrated by a study that combined hydroxychloroquine and pasireotide in PCK rats and found that the combination achieved better repression of cystogenesis compared to each drug alone [64]. We believe that when targeting the female hormone pathway appears effective, combining this strategy with SAs is a key strategy that could provide a viable treatment option in PLD.

Although surgery is associated with morbidity and mortality, surgical treatment of hepatic cysts remains the most effective treatment presently available. Concomitant administration of pharmaceutical treatment could potentially maximize the effects of surgical treatment and prevent recurrence of cyst growth. This was already demonstrated almost three decades ago, when reduction of ascites was observed when SAs were administered after cyst fenestration [88]. A recent trial tried to apply this strategy in patients with dominant hepatic cysts, and evaluated the addition of a pasireotide injection before and after aspiration-sclerotherapy, but proved

ineffective [89]. Nevertheless, combining surgical and pharmaceutical therapies might prove advantageous in PLD when applied strategically, for example in combination with cyst fenestration or partial hepatic resection.

Lastly, the low prevalence of patients with clinically significant PLD impedes progression in developing the optimal treatment. Sharing knowledge in the field of hepatic cystogenesis and collaborations between liver centers are of vital importance in finding a treatment for PLD patients. In an attempt to increase collaboration between European centers that treat patients with rare liver diseases, the European Reference Network RARE-liver has recently been established [90]. This network will increase research collaborations between ERN RARE-liver centers and can bring the specialized knowledge from all over Europe into local clinical practice. Additionally, insight in hepatic cystogenesis could be improved through collaborations between nephrologists and gastroenterologists when hepatic parameters in ADPKD patients are analyzed.

Acknowledgments

This work is generated within the European Reference Network for Rare Liver diseases.

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9

General Discussion

Research Aims

The primary aim of this thesis was to provide clinical guidance to physicians faced with polycystic liver disease patients. This goal was pursued by improving disease severity tools, application of clinical parameters and providing recommendations for clinical practice. The aims, main outcomes and limitations of each study in this thesis are discussed in **table 1**. This chapter further discusses the study results, strengths and limitations, clinical relevance and directions of future research.

"Research aim 1: To improve disease severity tools"

Chapter 2: Semiautomatic liver segmentation

Background: Total liver volume (TLV) is an important parameter to quantify PLD severity and assess treatment efficacy. Manual total liver volume measurements are time-consuming, costly and have limited availability in clinical practice.

Results: We demonstrated that semi-automatic liver segmentation yields accurate TLV and liver growth measurements. Semi-automatic segmentation is also considerably faster than manual segmentation for two reasons. First, this method requires coarse contouring instead of detailed contouring; the non-cyst and non-liver tissue that is included in the contour will be excluded by the program. Second, not every slice needs to be contoured since the program interpolates between contours.

Implications: Validation of the Siemens Volume application increases the clinical application of TLV measurements. It is commercially available and more user-friendly than manual segmentation but still requires coarse contouring which takes approximately 20 minutes per CT scan. For this reason a clinical need for automatic segmentation tools remains. A previous study in MRI demonstrates that this it is feasible to develop and validate such tools [1].

Chapter 3: Automatic liver segmentation

Background: The previous chapter established that semiautomatic segmentation yields accurate and moderately quick TLV measurements. In spite of this improvement, the need for automatic segmentation software that computes TLVs in a single click remains.

Results: We provided compelling evidence that reliable, automatic segmentation of polycystic livers can be applied in clinical practice. The artificial intelligence based software in our study can be applied on every CT scan, irrespective of CT

manufacturer, scanning and contrast injection protocol or liver size. It is integrated in radiology software and measures the liver in a matter of seconds.

Implications: Automatic segmentation software drastically improves the time needed to obtain TLV measurements. As a result determining TLV is not limited to expert centers anymore and liver volume data become increasingly available for research. Using TLV, we can determine 1) cross-sectional disease severity [2], 2) historical growth in PLD patients and 3) treatment efficacy. These measurements improve clinical care for individual patients, but also provide valuable data to progress PLD research.

"Research Aim 2: To improve implementation of PLD parameters"

Chapter 4: PLD-Q threshold

Background: Symptom burden in PLD can be captured with the PLD-Q [3]. A previous study also demonstrated the correlation between PLD-Q score and liver volume [4]. However, clinical practice lacks a PLD-Q threshold to identify patients with symptoms requiring further exploration and possibly intervention.

Results: In this study we established the PLD-Q threshold at 32 points with a high discriminative ability to identify symptomatic patients. The threshold has a particularly high negative predictive value.

Implications: The PLD-Q is an easily administered, economical and non-invasive tool to assess symptom severity in PLD. In contrast to TLV measurements, the PLD-Q is widely available and can be applied in every setting. This study quantifies the severity of symptoms that is needed to initiate PLD treatment and provides clinicians with clear guidance. Patients with a PLD-Q score that exceeds our threshold should be eligible for treatment or inclusion in trials.

Chapter 5: Prognostic value of TLV

Background: PLD can be classified using cross-sectional TLV [2]. Patients with larger livers experience more symptoms and treatment is most frequently administered in patients with the large livers [4, 5]. However, the prognostic value of TLV in PLD patients is lacking.

Results: Baseline TLV is associated with future treatment in PLD patients. In addition, female patients have a higher risk of treatment at low baseline TLVs compared to male patients, but this sex-specific increase in treatment risk is mitigated as baseline TLV increases.

Implications: This study confirms the prognostic value of TLV and highlights sex-specific differences in treatment initiation. Consequently, this improves counselling for PLD patients and may serve as a basis to develop a staging system for PLD.

"Research Aim 3: To provide clinical guidance to practitioners who treat PLD patients"

Chapter 6: Clinical practice guideline cystic liver diseases

Background: Cystic liver lesions are frequently identified on radiological imaging and the evidence base for cystic liver diseases has advanced over the past decades. Subsequently, a clinical practice guideline on this subject is warranted.

Results: This guideline provides clinicians with 45 practical recommendations regarding cystic liver lesions. The recommendations are focused on clinical dilemmas that physicians face when treating cystic liver disease patients.

Implications: The current guideline marks a shift from expert-based medicine to evidence-based medicine for cystic liver diseases as it provides a clear overview of their diagnosis and management. Concomitantly, the guideline unveils the knowledge gaps and confronts physicians with the need for (clinical) research in cystic liver diseases.

Chapter 7: Abdominal wall hernias in PLD

Background: Umbilical hernias are frequently observed in PLD patient at the outpatient clinic. This led to the hypothesis that PLD patients are prone to develop abdominal wall hernias from hepatomegaly-related increased intra-abdominal pressure.

Results: We observed that abdominal wall hernias, with a predominance of umbilical hernias, are a frequent complication of polycystic liver disease. In addition, we identified hepatomegaly as a disease-specific risk factor.

Implications: This study confirms the association between abdominal wall hernias and PLD and encourages clinicians to be vigilant about this complication in clinical practice. Hepatomegaly is an important disease-specific risk factor. Future studies should address whether reduction of TLV could be a therapeutic target to prevent abdominal wall hernia formation.

Chapter 8: Therapeutic targets in hepatic cystogenesis

Background: The pathophysiological mechanisms of hepatic cystogenesis in PLD are not completely uncovered. Several pharmacological treatment options have been studied.

Results: In this study we provided an overview of the pathophysiology and subsequent therapeutic targets in PLD. The largest previous clinical trials have targeted cyclic adenosine monophosphate through somatostatin receptors [6-10] and ursodeoxycholic acid [11]. As a result, somatostatin analogues are currently applied in clinical practice [12]. We identified the estrogen receptor as the most promising future therapeutic target. This receptor is targeted in the most recent clinical trial for polycystic liver disease: the AGAINST-PLD trial [13].

Implications: This study can be used to identify new therapeutic targets and new treatment strategies for PLD. Patients may benefit from therapies that target different aspects of hepatic cystogenesis similar to the design of the ELATE trial [14]. This manuscript also emphasizes the need to collaborate(internationally) and share expertise within the field of PLD.

Limitations and strengths

All included studies in this thesis are observational or (systematic) reviews. Several forms of bias (e.g., confounding bias, selection bias, information bias) are inherent to observational studies [15].

A potential source of confounding is the lack of an objective disease endpoint. This can be observed in **chapter 4 and 5** which utilize PLD treatment as study parameter. PLD is a benign disease that does not affect the liver's functional capacity. Consequently, there are no uniform criteria to start PLD treatment, and treatment is initiated based on symptoms, liver phenotype and its availability within a center. Symptoms can be captured using the PLD-Q which may be affected by the presence of mental distress or comorbidities with symptoms similar to PLD (e.g. abdominal complaints in irritable bowel syndrome). TLV partially addresses liver phenotype but lacks information regarding size and distribution of liver cysts and their relation to adjacent structures. This heterogeneity in clinical decision-making brings forth a bias that remains difficult to correct for in research. In contrast, these objective endpoints are present in other diseases: e.g. renal replacement therapy in ADPKD or liver transplantation in primary biliary cholangitis [16, 17].

Selection bias could also have affected our study results. TLV measurements, which are used in **chapter 2, 3, 4 and 5**, are historically performed in patients with large livers to evaluate treatment efficacy. This is the case in **chapter 2 and 3** which both include large polycystic livers. We believe that the effects of selection bias to be limited in these studies since liver segmentation is most difficult in large anatomically deformed livers. The effects of selection are larger in **chapter 4**, in which the control group consisted of ADPKD patients exclusively as a comparative group, and which did not incorporate all types of treatment in the treated group. We aimed to limit the effects of bias on our study results, by performing sensitivity analyses if appropriate and addressing potential sources of bias in the manuscripts.

This thesis also comes with important strengths. Robust and appropriate research designs were used for the included manuscripts, though all designs were observational. In **chapter 2 and 3**, we compared the new intervention with the current gold standard. In **chapter 7** the presence of abdominal wall hernias was evaluated by 2 (or in ambiguous cases 3) independent researchers. This rigorous approach reduced the risk of bias in our studies. In addition, we used a thorough Delphi process in a large group of cystic liver disease experts to achieve consensus on the recommendations of **chapter 6.** With this method we established the first set of clinically applicable recommendations, endorsed by the scientific community.

Our findings were also obtained in large cohorts that comprise the entire spectrum of PLD. This limits the risk of selection bias or performing underpowered analyses, which is particularly important since PLD is a rare liver disease. The formation of international collaborations in the international PLD registry, the European Reference Network RARE-LIVER and European Association for the Study of the Liver play a pivotal role in the collection of large cohorts with high quality data [18, 19].

Future perspectives

The studies presented in this thesis provide clinical guidance to physicians and answer their predefined research questions. Simultaneously, this thesis in combination with discussion of complex cases evokes new questions that should be subject to future research. A summary of the research agenda is provided in **table 2**.

Improvement of disease severity tools

In **chapter 2 and 3** we demonstrated that semiautomatic liver segmentation provides accurate and fast TLV measurements. First, this method will drastically

improve the availability of TLV measurements and decrease the selection bias that currently accompanies research with this parameter. Many PLD patients that visit the outpatient clinic have undergone 1 or more CT scans during their patient journey. Automatic segmentation of available CT scans will aid in assessing the natural liver growth in PLD patients. Knowledge regarding the natural growth leads to distinguishing between patients with fast and slow growth which improves counselling in the outpatient clinic.

The segmentation tool used in **chapter 3** is an artificial intelligence based tool that was developed specifically to measure TLV. This raises the question which other PLD-related disease parameters can be identified using artificial intelligence based tools. First, they could measure cyst growth in addition to TLV, which showed promising discriminative power for PLD progression [20]. Second, artificial intelligence based applications could be used to automatically measure sarcopenia status on radiological imaging. Currently, sarcopenia status can only be measured manually [21]. Third, artificial intelligence could identify mucinous cystic neoplasms of the liver on radiological imaging. The diagnosis of mucinous cystic neoplasms is extremely challenging and pathology assessment remains the gold standard for diagnosis. In **chapter 6**, we proposed major and minor worrisome features for mucinous cystic neoplasms, yet these criteria only overlap partially with a machine-learning based classification system that was published afterwards [22]. An artificial intelligence based tool that directly evaluates radiological imaging should be developed for this purpose.

Implementation of PLD parameters

In **chapter 4**, we established a threshold for treatment initiation using the PLD-Q in cohorts of patients that underwent somatostatin analogues, aspiration sclerotherapy and partial hepatectomy + cyst fenestration. Whilst this study indicates the start criteria for somatostatin therapy, its stop criteria are not yet established. A previous trial demonstrated that somatostatin analogues reduce liver volume in 60.2% of the patients that received somatostatin treatment [9]. In the patients that demonstrated liver growth during somatostatin treatment, it remains unclear whether the somatostatin analogues decreased the natural growth rate, or if treatment was completely ineffective. There is an unmet clinical need to define stop criteria for somatostatin analogues, particularly in view of the side-effects and costs associated with this treatment [6, 23].

The PLD-Q threshold in **chapter 4** was developed without patients receiving liver transplantation. The invasiveness of this procedure and the associated morbidity and mortality makes the threshold less suitable to identify liver transplantation

candidates in PLD populations. Consequently, identifying and implementing uniform liver transplantation criteria for PLD patients should be the subject of future research. The importance of this subject is further supported by **chapter 6** which attests that there is large variation between geographical regions regarding liver transplant criteria for PLD.

Chapter 4 also emphasizes the high negative predictive value of its PLD-Q threshold. This indicates that patients with a score below the threshold should not receive PLD treatment. The limited positive predictive value does not imply that treatment should be administered in all PLD patients with a PLD-Q score that exceeds the threshold. Confounding factors (e.g. irritable bowel syndrome or an unfavorable liver cyst phenotype) should be excluded before proceeding to PLD treatment in these patients. Future studies should further specify the therapeutic threshold in these patients.

Chapter 5 establishes the value of TLV in predicting treatment initiation for PLD. This association should be used to develop a staging system that predicts a patient's risk of future treatment. A similar prognostic staging system is already available in ADPKD patients and serves as the basis for tolvaptan treatment [16, 24]. Similarly to the ADPKD classification, a staging system for PLD paves the way to 1) provide patients with valuable prognostic information, 2) administer pre-emptive treatment in severely affected patients at high risk for severe symptom burden and 3) assess treatment efficacy by comparing a patient's disease stage before and after treatment.

Clinical guidance

Chapter 4 and 6 both emphasize that only patients with clinically relevant symptom burden should be treated. This prevents exposing patients with mild disease to the risks of therapy. PLD trials should include symptom burden in their study parameters, preferably as their primary outcome measure. An open label, clinical trial that compares aspiration sclerotherapy and laparoscopic fenestration (the ATLAS trial; NCT05500157) uses the PLD-Q as its primary outcome. This trial will include 70 patients with large ventral and caudal liver cysts, randomized in a 1:1 ratio. Lastly, future clinical trials with therapeutic targets, e.g. as described in **chapter 8**, should also incorporate symptom severity questionnaires.

Chapter 7 described the prevalence of abdominal wall hernias in PLD patients. This study quantifies the prevalence of this complication, but does not address the impact of hernias on quality of life and outcomes after hernia repair. These topics

should be addressed in future studies, including the effects of volume reducing treatment options.

Part	Chapter	Aim
Disease severity tools	2	To show that semiautomatic liver segmentation, using Siemens Multi-Modality WorkPlace tool 'Volume' is reliable and faster than manual segmentation
	3	To validate total liver volume and liver growth measurements using automatic segmentation software in a real-life dataset of polycystic liver disease patients
Implementation of PLD parameters	4	To determine a polycystic liver disease questionnaire threshold of clinical importance that identifies polycystic liver disease patients in need of therapy
	5	To evaluate the prognostic value of total liver volume on treatment initiation in polycystic liver disease patients, with special emphasis on sex-specific differences
Clinical Guidance	6	To provide the best available evidence to aid the clinical decision-making process in the management of patients with cystic liver disease
	7	To assess the prevalence and disease-specific risk factors of abdominal wall hernias in polycystic liver disease patients
	8	To summarize the existing and potential new therapeutic targets of hepatic cystogenesis.

Table 1 – Overview of aims, main findings and limitations

	Main findings	Limitations and comments
	• Semi-automatic liver segmentation using the Multi-Modality WorkPlace Volume tool accurately determines total liver volume as well as liver growth over time in polycystic liver disease patients • This method is considerably faster than manual segmentation by excluding non-cystic and non-liver tissue based on Hounsfield Unit density	• Semiautomatic liver segmentation requires coarse contouring of CT slices
	• Automatic segmentation yields accurate total liver volumes in polycystic liver disease • Automatic total liver volume measurements are extremely fast • There is no variability in automatic liver volume measurements	• Manual adjustments of automatic contours not included in the study
	• The optimal polycystic liver disease questionnaire threshold for symptomatic patients is 32 points • Patients with a polycystic liver disease questionnaire score of ≥ 32 should be eligible for treatment or inclusion in scientific trials • There is no difference between the polycystic liver disease questionnaire with a 1- or 4-week recall period	• Potential selection bias as patients originate from tertiary referral centers and an observational ADPKD cohort • Positive predictive value may be limited particularly in the most invasive treatment options (e.g. liver transplantation)
	• Total liver volume is an important predictor for initiation of polycystic liver disease treatment • Female patients have a higher risk of treatment at low baseline total liver volumes, yet this sex-specific risk difference is mitigated at high baseline total liver volumes.	• The primary endpoint, polycystic liver disease treatment, is a subjective outcome measure
	• This manuscript provides clinical guidance in 45 graded recommendations that answer diagnostic and therapeutic questions	• Recommendations based on low level evidence
	• Abdominal wall hernias occur frequently in polycystic liver disease with a predominance of umbilical hernias. • Hepatomegaly is an important disease-specific risk factor. • Physicians should pay special attention to abdominal wall hernias in polycystic liver disease patients, especially in severe cases. Hernia repair might be complicated in this patient population.	• Clinical impact of abdominal wall hernias not evaluated • Research design unsuitable to assess perioperative outcomes in hernia repair
	• This study identifies the pathophysiological pathways involved in hepatic cystogenesis • The female hormone pathway is the most promising therapeutic target in polycystic liver disease	• Narrative review and not a systematic review. • Large section of expert opinion

Research Aim	Research Agenda	Proposed research design
Development of tools	Determine the natural growth in PLD patients	Prospective cohort study
	Develop and validate an automatic tool to measure liver cyst volume	Cross-sectional cohort study
	Develop and validate an automatic tool to measure sarcopenia status	Cross-sectional cohort study
	Develop and validate a tool to identify mucinous cystic neoplasms on radiological imaging	Cross-sectional cohort study
Improve clinical parameters	Develop stop criteria for somatostatin analogue treatment	Delphi survey
	Define uniform criteria for liver transplantation in polycystic liver disease	Delphi survey
	Develop and validate a PLD staging system	Prospective cohort study
Clinical Guidance	Compare the relative efficacy and safety of aspiration sclerotherapy and cyst fenestration	Randomized controlled trial
	Determine the impact of abdominal wall hernias on quality of life in PLD patients	Cross-section survey
	Assess the peri-operative outcomes of hernia repair in PLD patients	Prospective cohort study

Table 2 – Overview of research agenda

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10

Summaries

English Summary

Fluid secretion and cell proliferation trigger the formation of hepatic cysts in polycystic liver disease (PLD). Cysts can vary in size and occur in any liver segment. When cysts grow and compress surrounding structures, they may cause symptoms. PLD-related symptoms can be treated with radiological, surgical or drug therapies.

Research aim 1: To improve disease severity tools

Chapter 2 validates a clinically available semiautomatic segmentation method. This tool reduces the time needed to obtain total liver volume (TLV) measurements with similar accuracy compared to the current gold standard, manual segmentation.

Chapter 3 validates a fully automatic artificial intelligence based segmentation method. This software yields slightly smaller TLV measurements compared to manual segmentation, but produces reliable TLV measurements in several seconds.

Research Aim 2: To improve implementation of PLD parameters

In **chapter 4**, we developed a threshold for the polycystic liver disease questionnaire (PLD-Q) that identifies patients with symptoms requiring further exploration and possibly intervention. Patients with a PLD-Q score ≥ 32 should be eligible for treatment or inclusion in trials, while patients with a PLD-Q score < 32 should not be subjected to PLD therapy.

In **chapter 5** we assessed the association between TLV and initiation of volume reducing therapy in PLD. This study confirms the association and found sex-specific differences in this association. Future PLD staging systems should incorporate TLV and provide sex-specific prognostic information.

Research aim 3: To provide clinical guidance to practitioners that treat PLD patients

In **chapter 6** we studied the frequency and risk factors for abdominal wall hernias in PLD. We confirmed that abdominal wall hernias occur frequently, with a predominance of umbilical hernias. Hepatomegaly is an important disease-specific risk factor. Consequently, physicians should pay special attention to hernia-related symptoms, particularly in patients with large polycystic livers.

Chapter 7 is the first European Association for the Study of the Liver clinical practice guideline (CPG) on the subject of cystic liver diseases. This CPG covers the diagnosis and management of hepatic cysts, mucinous cystic neoplasms of the liver, biliary

hamartomas, PLD, Caroli disease, Caroli syndrome, biliary hamartomas and peribiliary cysts in 45 clinically applicable recommendations.

Chapter 8 provides an overview of the pathophysiological pathways that cause hepatic cystogenesis in PLD and identifies the estrogen pathway as most promising future therapeutic target.

In conclusion, this thesis progresses the implementation liver segmentation tools. It also improves the clinical application of the PLD-Q and demonstrates the prognostic value of TLV. Lastly, this thesis provides clinical guidance with respect to abdominal wall hernias, diagnosis and management of cystic liver disease, and future therapeutic targets for PLD.

Nederlandse Samenvatting

Vochtsecretie en cel proliferatie leiden tot de vorming van levercysten bij polycysteuze leverziekte (PLD). Cysten kunnen in grootte variëren en in elk leversegment voorkomen. Wanneer cysten groeien en omliggende structuren samendrukken, kunnen ze symptomen veroorzaken. Deze PLD gerelateerde symptomen kunnen behandeld worden met radiologische, chirurgische of medicamenteuze therapieën.

Onderzoeksdoel 1: Verbeteren van instrumenten voor de ernst van de ziekte

In **hoofdstuk 2** wordt een klinisch beschikbare semiautomatische segmentatiemethode gevalideerd. Dit hulpmiddel vermindert de tijd die nodig is om het totale levervolume (TLV) te meten en heeft een nauwkeurigheid die vergelijkbaar is met de huidige gouden standaard, handmatige segmentatie.

Hoofdstuk 3 valideert een volledig automatische, op kunstmatige intelligentie gebaseerde, lever segmentatiemethode. Deze software resulteert in iets kleinere TLV-metingen op dan handmatige segmentatie, maar produceert deze betrouwbare TLV-metingen in enkele seconden.

Onderzoeksdoel 2: Verbetering van de implementatie van PLD-parameters

In **hoofdstuk 4** ontwikkelden we een afkapwaarde voor de polycysteuze leverziekte vragenlijst (PLD-Q). Deze afkapwaarde identificeert patiënten met symptomen die nader onderzoek en mogelijk therapie vereisen. Patiënten met een PLD-Q score ≥ 32 zouden in aanmerking moeten komen voor behandeling of inclusie in trials, terwijl patiënten met een PLD-Q score < 32 geen PLD-therapie zouden moeten ondergaan.

In **hoofdstuk 5** hebben wij de associatie onderzocht tussen TLV en de start van volume verminderende therapie bij PLD. Deze studie bevestigt deze associatie en vond geslacht specifieke verschillen in deze associatie. Toekomstige PLD-stadiëringssystemen moeten TLV omvatten en sekse specifieke prognostische informatie verschaffen.

Onderzoeksdoel 3: Klinische begeleiding bieden aan behandelaars van PLD-patiënten

In **hoofdstuk 6** bestudeerden we de frequentie en risicofactoren voor buikwandbreuken bij PLD. Wij bevestigden dat buikwandbreuken frequent voorkomen, in het bijzonder navelbreuken. Hepatomegalie is een belangrijke ziekte specifieke

risicofactor. Als gevolg van deze studie zouden artsen speciale aandacht moeten besteden aan buikwandbreuk-gerelateerde symptomen, vooral bij patiënten met grote polycysteuze levers.

Hoofdstuk 7 is de eerste clinical practice guideline (CPG) over cysteuze leverziekten van de European Association for the Study of the Liver. Deze CPG behandelt de diagnose en behandeling van levercysten, mucineus cysteuze neoplasmata van de lever, biliaire hamartomen, PLD, de ziekte van Caroli, het syndroom van Caroli, biliaire hamartomen en peribiliaire cysten in 45 klinisch toepasbare aanbevelingen.

Hoofdstuk 8 geeft een overzicht van de pathofysiologische routes die vorming van levercysten bij PLD veroorzaken en identificeert de oestrogeenroute als meest veelbelovend toekomstig therapeutisch doelwit.

Concluderend kan worden gesteld dat dit proefschrift de implementatie van leversegmentatie-instrumenten bevordert. Het verbetert ook de klinische toepassing van de PLD-Q en toont de prognostische waarde van TLV aan. Ten slotte biedt dit proefschrift klinische richtlijnen met betrekking tot buikwandbreuken, diagnose en behandeling van cysteuze leverziekten, en toekomstige therapeutische doelen voor PLD.

11

Appendices

Dankwoord

Met het schrijven van dit dankwoord is een einde gekomen aan mijn tijd als arts-onderzoeker. Graag bedank ik in dit hoofdstuk eenieder die mij, bewust of onbewust, heeft ondersteund in het schrijven van dit proefschrift. Dit proefschrift zou niet mogelijk zijn geweest zonder jullie hulp.

Prof. dr. Drenth, beste Joost, bedankt voor het fantastische promotietraject dat jij me hebt geboden. Jouw passie voor het onderzoek is onmiskenbaar en je begeleiding kan ik niet anders beschrijven dan excellent. Jouw deur staat altijd open voor overleg en mijn manuscripten werden steevast binnen 48 uur van feedback voorzien. Een kwaliteit waar menig ander promotor wat van kan leren. De nadruk die je legt op de klinische boodschap van een artikel zorgt ervoor dat deze daadwerkelijk in de praktijk toepasbaar zijn. Toch ben je niet alleen een wetenschapper, maar ook absoluut een mentor. Je zag mijn kwaliteiten, stimuleerde me om uitdagingen aan te gaan en steunde me bij tegenslagen, zowel gedurende mijn promotie als daarna. Het vertrouwen en de autonomie die je me gaf daagde me uit om mijzelf te blijven ontwikkelen.

Dr. Gevers, beste Tom, bedankt voor de begeleiding die je me de afgelopen jaren hebt geboden. Je bent een zeer betrokken copromotor en jouw passie voor het onderzoek spatte altijd van mijn scherm af. Dit klinkt misschien wat raar, maar enkele maanden na de start van mijn promotie maakte jij de overstap van het Radboud naar het MUMC+. De fysieke overleggen maakten hierdoor plaats voor Zoom-vergaderingen, waarin je mij leerde 'grasduinen' door een grote dataset. Ik vind het indrukwekkend hoe je de complexe data doorgrondde met de beperkte data die ik aan je voorlegde. Ook daagde je me uit om kritisch te blijven over mijn eigen artikelen en voorkwam dat ik kortzichtige conclusies trok.

Members of the manuscript committee, **prof. dr. Nijenhuis, prof. dr. Fütterer and prof. dr. Lüdde,** thank you for your careful evaluation of this PhD thesis.

Ook dank ik graag alle arts-onderzoekers met wie ik de afgelopen jaren heb samengewerkt: Ali, Ayla, Britt, Christa, Daan, Dorien, Edo, Elsa, Fenna, Fenna, Gijs, Jasmijn, Julia, Lia, Lieke, Lisa, Lotte, Lucas, Maarten, Marleen, Melissa, Menso, Michiel, Michiel, Milou, Monica, Naomi, Pepijn, Renée, Romée, Sabien, Veerle, Vince, Yonne. Waar de gemiddelde Nederlander een promotietraject beschouwt als een solistische activiteit achter een computer, bewijst deze onderzoekersgroep het tegendeel. Ik heb genoten van onze eindeloze middagpauzes en VrijMiBo's. Ook tijdens congressen heeft dit sociale aspect van promoveren de boventoon gevoerd.

Met de PLD-onderzoekers in het bijzonder heb ik vele uren samengewerkt. **Lucas**, je maakte mij wegwijs in het onderzoek en benadrukte direct het belang van 'niet te vroeg beginnen' en de welbekende 'second lunch'. Ik zie dit als een essentiële start voor arts-onderzoekers, bedankt hiervoor. **Melissa**, hoewel we twee compleet verschillende promotietrajecten hadden (jij deed basaal onderzoek in het lab en ik was gericht op de kliniek), bespraken we onze projecten altijd in de PLD-meeting. Juist dit andere perspectief maakte dat we elkaar zinvol konden adviseren. **Renée**, jij hebt het PLD-stokje inmiddels van mij overgenomen. Je doet dit met verve, zeker gezien de flexibiliteit die hierbij nodig is gebleken.

Michiel, jij benoemt haarfijn het verschil tussen een borrel en een feest en weet ook last-minute nog vliegtickets voor een congres te kopen. Ik heb hard gelachten om de manier waarop jij deze 'blunders' met de groep deelde. **Monica**, Moniek, waar jij je eindeloze energie en enthousiasme vandaan haalt is mij soms een raadsel. Ook begrijp ik niet hoe jij géén katers had na onderzoekersavonden. Je bent een verbindende factor binnen de onderzoekers. **Pepijn**, ik kan me jou niet voorstellen zonder glimlach op je gezicht. Zeker niet nadat ik jou en Veerle, tijdens een onderzoekersuitje in Utrecht, betrapte op jullie stiekeme eerste zoen. **Romée**, het is niet minder dan indrukwekkend hoe je Compendium, onderzoek en een uitgebreid sociaal leven met elkaar weet te combineren. Deze ervaringen worden gedetailleerd vastgelegd in groepsfoto's. Ook succesmomenten weet jij als geen ander te vieren. Een les die menig ander van jou kan leren. **Veerle**, toen ik met jou op een kamer zat daalde mijn productiviteit significant. Het werkplezier daarentegen nam direct toe. Samen klagen over de administratieve last van onderzoek leidde bijna tot het oprichten van een eigen onderzoekers-secretariaat. Onderzoek met bloedafname zou hierin niet meer geaccepteerd worden, want zoals je weet: "blood, no funny".

Stafsecretariaat MDL, beste **Lionne**, **Linda** & **Rachelle**. Een MDL PhD is niet compleet zonder jullie betrokkenheid. Jullie deur stond (letterlijk) altijd voor mij open. Jullie zijn een baken van rust in de roerige MDL vakgroep die het Radboud bemant.

Naast deze collega's hebben ook mijn vrienden mij altijd bijgestaan tijdens mijn promotie. **Tom**, Appie, als medepromovendus begrijp je de lusten en lasten van en promotie ten volste. Dank dat je vandaag als paranimf naast mij wil staan en dat ik mijn successen en frustraties met jou kan delen. Ik waardeer je betrokkenheid. Veel van mijn verhalen deel ik met je op de racefiets, dus bij deze alvast een verzoek: Trap alsjeblieft een tandje zachter. **Tom**, Harry, van ongenuanceerde grappen tot

weloverwogen adviezen, ik weet dat jij altijd voor me klaar staat. Bedankt voor je luisterende oor en je begrip. Ik hoop jou met dezelfde openheid van advies te kunnen voorzien. **Thijs**, Boef, jouw nuchterheid en scherpe opmerkingen blijven me verbazen. Met de manier waarop jij complexe (sociale) situaties relativeert, breng je ogenschijnlijk lastige problemen tot een simpele kern. **Koen**, op de racefiets heb jij me vaak geholpen context te plaatsen bij de obstakels waar ik tegenaan liep. Bedankt voor deze vriendschappelijke systeemtherapie-light. **Luc, Reinier, Jorein (AJ), Mats & Wieland**, de obstakels van mijn promotie heb ik misschien niet expliciet met jullie besproken, maar deze heb ik op het lacrosse veld wel degelijk met jullie gedeeld. Excuses voor de blauwe plekken van mijn late checks. Wieland, om je vraag nog eens te beantwoorden: ja ik ben nu (bijna) gepromoveerd. **Bende van Ellende**, we zien elkaar niet vaak, maar ik geniet er des te meer van als we weer samen zijn. Zonder het te weten is de basis van mijn promotie al tijdens de middelbare school gelegd. Mijn interesse in degelijk onderzoek is natuurlijk ontwaakt door het profielwerkstuk dat Merijn en ik deden in het zesde jaar. Saillant detail: dit is de enige keer dat ik daadwerkelijk een power-analyse heb moeten uitvoeren.

Lieve familie, ook jullie wil ik in het bijzonder bedanken. **Eric**, met jouw zelfspot weet je de wereld wat minder serieus te maken. **Anne**, thank you for your kindness and support. Ik ben blij de doctorstitel (straks) met jullie te mogen delen. **Justin en Judith**, bedankt voor jullie betrokkenheid en enthousiasme. Justin, het maken van een cover design was een van de obstakels die ik tegenkwam. Had ik je om hulp gevraagd, dan was dit obstakel waarschijnlijk in no-time verdwenen. **Jeanette**, interesse is de eigenschap die jou karakteriseert. Met eindeloze vragen probeerde jij mijn anekdotes tot in detail te visualiseren. Dit hielp me mijn obstakels te identificeren en overwinnen. **Koen**, bedankt dat je vandaag naast mij wil staan als paranimf. Met jouw relativerende grappen help je me ontspanning te vinden in een spannende dag als vandaag. **Godelieve**, dank voor de rust en kalmte die je altijd uitstraalt. **Janne**, ik denk dat jij het familielid bent dat mijn proefschrift inhoudelijk het beste kent. Je noemde me nooit "poepdokter", maar toonde oprechte interesse in de inhoud van mijn thesis. Onze wandelingen in Heumensoord geven mij nieuwe inzichten en ontspanning. Bedankt hiervoor. **Mam**, je wordt gemist. Wat had ik dit succes graag met jou gedeeld. Ondanks je afwezigheid voel ik me nog altijd door jou gesteund. **Pap**, jouw steun is onvoorwaardelijk en de trots die je naar mij uitstraalt is immens. Toen jij op C5 werkte heb je me aan de hele afdeling voorgesteld, ook al kwam ik alleen een echoapparaat halen dat hier gestald stond. Wat heerlijk om dit enthousiasme van je te mogen ervaren.

Lieve **Sophie**. Tot slot wil ik ook jou bedanken voor de eindeloze steun tijdens mijn promotie. Het was niet zozeer de inhoud van mijn proefschrift die je interesseerde, maar de interacties op het werk en wat het promoveren met mij deed. Hierin gaf je me vaak (on)gevraagd advies en hielp je me buiten de kaders te denken. Met jouw begrip, eerlijkheid en liefde kan ik de wereld aan. Ik kijk uit naar de avonturen die we samen nog gaan beleven. Ik hou van jou.

Portfolio

Name PhD candidate: Thijs R.M. Barten
Department: Gastroenterology and Hepatology
PhD period: From 01-10-2019 until 31-01-2023
Promotor: Prof. Dr. Joost P.H. Drenth
Co-promotor: Dr. Tom J.G. Gevers

	Year(s)	ECTS
Training activities		
Courses & Workshops		
Introduction day Radboudumc	2019	0.5
Graduate school specific introductory course 'In the Lead'	2019	0.75
eBROK course	2020	1.5
Scientific Writing	2020	1.5
Maintaining great relationships in your PhD project	2020	1.0
Scientific Integrity	2021	1.0
Design and Illustration	2021	1.5
Seminars & Lectures		
ERN Webinar 'Hepatic cyst infections' Presentation ERN annual members	2020	0.5
meetings (3 cases and working group presentations)	2020-2022	0.75
Renal disorders Theme lunch meetings (3 presentations)	2020-2022	0.75
ERN Webinar Guideline Cystic Liver Diseases 2022	2022	0.5
(Inter)national Symposia & Congresses		
UEG Week 2019 (full attendance + poster (1.5 punt)	2019	1.5
UEG Week 2020 (full virtual attendance + poster 1.5 punt)	2020	1.5
Meeting Copenhagen 07-2021 QoL	2021	1.5
RIMLS Retreat + New Frontiers (2021 1.5 punt)	2021	1.5
DDD 2021 (full virtual congress + poster presentation)	2021	1.0
RIMLS Retreat + New Frontiers (2022, 1.5 punt)	2022	1.5
EASL 2022 (full congress + poster)	2022	1.5
ERN Rare Liver Members Meeting	2022	1.0
Meeting September 2022 during annual meeting QoL working group	2022	0.25
KDIGO Symposium 2022 (3 full days)	2022	1.5
UEG Week 2022 (full attendance + poster 1.5 punt)	2022	1.5
Other		
PhD Research Meetings (weekly) 5 punten	2019-2023	5.0
PhD intervision sessions (4x per year) 2.5 punten	2019-2023	2.5
Journal club (weekly) 5 punten	2019-2023	5.0
Polycystic Liver Disease meeting (2x per month) 2.5 punten	2019-2023	2.5
Chef du Corridor	2021-2022	2.0

Teaching Activities		
Lecturing		
Lecturer at bachelor course 'Integratieopdracht Q3'	2020	1.0
Supervision of Internships		
Supervision of research students (3 master students, 1 student assistant)	2019-2022	3.0
European Reference Network RARE-LIVER Teaching Materials		
PLD patient leaflet	2020	0.5
Informational PLD videos for patients	2020	0.5
Informational PLD videos for physicians	2021	0.5
Total		**47.0**

Research data management

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands has given approval to conduct these studies, or waived ethical approval due to the nature of the study. Published data generated or analyzed in this thesis are part of published articles and its additional files are available from the associated corresponding authors on reasonable request. To ensure interpretability of the data, all filenames, primary and secondary data, metadata, descriptive files and program code and scripts used to provide the final results are documented along with the data. The patient data for the analyses of studies as presented in Chapters 3, 4, 6, 8, and 9 is stored on the departments' shared drive: https://teamsites.radboudumc.nl/sites/mdl/ra/Onderzoekers/Afgeronde studies/PLD. All data from the aforementioned chapters were anonymously collected and entered by use of Castor EDC (Amsterdam, The Netherlands). Data were later converged from Castor EDC to SPSS (IBM, Armonk, NY, USA). The privacy of the participants in these studies is warranted by use of encrypted and unique individual subject codes. The code was stored separately from the study data.

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Publication list

Barten, T. R., Atsma, F., van der Meer, A. J., Gansevoort, R., Nevens, F., Drenth, J. P., & Gevers, T. J. (2023). Higher need for polycystic liver disease therapy in female patients: sex-specific association between liver volume and need for therapy. Hepatology, 10-1097

Barten, T. R., Staring, C. B., Hogan, M. C., Gevers, T. J., & Drenth, J. P. (2023). Expanding the clinical application of the polycystic liver disease questionnaire: determination of a clinical threshold to select patients for therapy. HPB.

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Curriculum vitae

Thijs Robertus Martinus Barten werd op 20 juni 1995 Geboren te Venray. In 2012 haalde hij zijn VWO diploma aan het Stedelijk Gymnasium Nijmegen en startte in hetzelfde jaar met de opleiding Biomedische Wetenschappen Hij haalde in 2013 zijn propedeuse en stapte vervolgens over naar de studie Geneeskunde. In het derde studiejaar vertrok hij in het kader van het Honours programma Medical Sciences naar Toronto, Canada voor een wetenschappelijke stage als onderwerp "Luisteren onder lastige omstandigheden".

In het laatste jaar van zijn studie Geneeskunde volgde hij zijn klinische stages op de afdelingen Maag- Darm- Leverziekten van het Bernhoven ziekenhuis en het Rijnstate ziekenhuis. Wederom volbracht hij zijn wetenschappelijke stage in het buitenland toen hij het effect van immunosuppressiva op nierfunctie na levertransplantatie onderzocht aan het Sahlgrenska Universitetssjukhuset in Göteborg, Zweden. In 2019 behaalde hij zijn arts-examen.

Na zijn afstuderen is hij gestart met zijn promotietraject binnen de afdeling Maag-Darm- Leverziekten aan het Radboudumc. Onder supervisie van prof. dr. J.P.H. Drenth en dr. T.J.G. Gevers deed hij onderzoek naar de klinische behandeling van polycysteuze leverziekte. Aansluitend op zijn promotieonderzoek is hij gestart als ANIOS Maag- Darm- Leverziekten in het Rijnstate ziekenhuis.

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