MANAGEMENT OF COMPLICATIONS IN POLYCYSTIC LIVER DISEASE

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MANAGEMENT OF COMPLICATIONS IN POLYCYSTIC LIVER DISEASE

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INTRODUCTION

BACKGROUND

Polycystic Liver Disease

Polycystic liver disease (PLD) is characterized by the presence of numerous fluid-filled cysts in the liver and a diagnosis is made when >10 hepatic cysts are present.[1] PLD occurs in two distinct genetic disorders, associated with autosomal dominant polycystic kidney disease (ADPKD), or in absence of renal cysts as autosomal dominant polycystic liver disease (ADPLD).[1] Mutations in the following genes are causes of PLD: ALG8, DNAJB11, GANAB, LRP5, PKD1, PKD2, PRKCSH, PKHD1, SEC61B and SEC63.[2,3]

Clinical presentation

There is a wide-ranging clinical phenotype in PLD. As the majority of patients remain asymptomatic, diagnosis is often coincidental. However, in a subset of patients, persistent growth of hepatic cysts may lead to symptomatic hepatomegaly or symptomatic large cysts.[1] In severe cases, liver volume may be enlarged tenfold compared to a normal liver (Figure 1).[4] Symptoms may be related to liver capsule distension, mechanical compression of adjacent vasculature or other organs, and spontaneous hepatic cyst infection. In general, liver function remains preserved, even in severe cases.[1]

Interestingly, despite having an autosomal inheritance pattern, over 80% of patients in cohort studies are female.[1] Therefore it is hypothesized that endogenous female sex hormones (e.g. estrogen) promote cyst growth, which was corroborated in clinical studies as liver volume stabilizes post-menopausally.[5,6] In addition, PLD severity may also be dependent on exposure to exogenous estrogens, either through use of oral contraceptives or hormonal replacement therapy.[7-9] The most robust evidence comes from a case-control study in 19 post-menopausal ADPKD patients which showed that hormonal replacement therapy with estrogens was associated with a significant increase in total liver volume compared to a decline in the control group.[9] Based on this study, counseling advice in the outpatient clinic includes discouraging exogenous estrogen therapy in female PLD patients.[1]

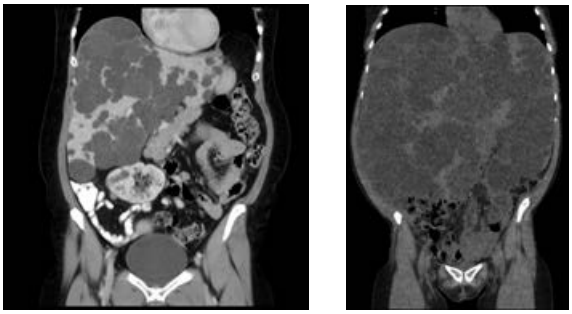

Figure 1. Coronal CT-scans of two female patients with liver volumes of 6 and 13 liters.

Management

Due to the benign disease course, treatment of PLD is only indicated in symptomatic patients and should focus on improving quality of life.[1,10] Current treatment options consist of interventional radiology procedures,[11-13] surgery,[14-16] and drug therapy (Figure 2).[1,17] The choice of therapy is dependent on disease phenotype and local experience.[18-20]

Previous research has primarily focused on these treatment options for symptomatic hepatomegaly and large cysts. This has resulted in limited evidence and clinical guidance for treatment of other complications in PLD: (1) hepatic cyst infections and (2) portal hypertension and ascites. Recurrent cyst infections and refractory ascites are both listed as exception criteria for liver transplantation in PLD, and represent a substantial burden of disease for both patients and healthcare providers.[21]

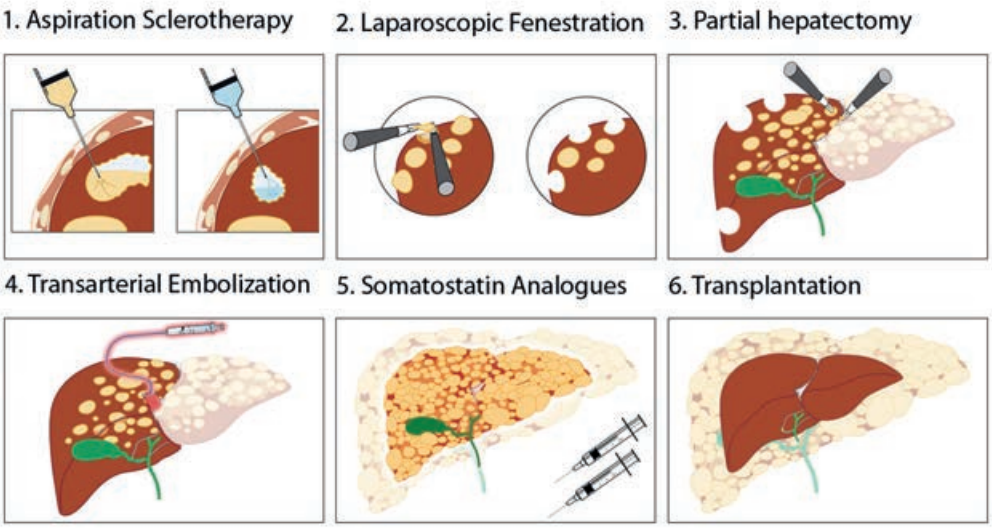

Figure 2. The effects of treatment options visualized. **1. Aspiration sclerotherapy** involves percutaneous drainage followed by instillation of a sclerosing agent (e.g. ethanol). **2. Laparoscopic fenestration** combines drainage with excision of extra-hepatic cyst wall in a single laparoscopic procedure. **3. Partial hepatectomy** consists of removal of segments or lobes of the liver, and is often combined with cyst fenestration of the remaining liver. **4. Transarterial embolization** consists of hepatic angiography and careful embolization of hepatic artery branches (e.g. with platinum microcoils). **5. Somatostatin analogues** are usually administered as monthly injections and impede cyst growth. **6. Liver transplantation** is reserved for patients with severe complications.

Hepatic cyst infections

Spontaneous hepatic cyst infection is a rare but severe complication of PLD, potentially leading to sepsis and death. In a cohort of 1773 PLD patients, 28 (1.6%) developed hepatic cyst infections during 12 years of follow-up.[22] It is most often caused by Escherichia coli or other intestinal pathogens, which implicates bacterial translocation from the gut as root cause.

A definite diagnosis can be made through culture of pathogens from a cyst aspirate. However, this is not often available in PLD patients with an abundance of cysts. Therefore, a combination of clinical, biochemical and imaging findings is used to diagnose cyst infection.[23,24]

First-line treatment is ciprofloxacin, based on one case series with 3 patients that showed tissue penetration into hepatic cysts.[25] However, 10-47% of Escherichia coli strains in Europe are resistant to fluoroquinolones (e.g. ciprofloxacin)[8] and as a corollary, fluoroquinolones fail in 50% of hepatic cyst infections. Even after successful treatment, recurrence is as high as 20%.[22,26-28] These findings highlight the need for novel, diverse and more effective antimicrobial regimens.

Portal hypertension

Although portal hypertension is mostly associated with liver cirrhosis, it can also occur in severe cases of PLD. Patients may be confronted with vascular obstruction of hepatic veins, portal veins or the inferior caval vein because of cystic mass effect or unfavorably located cysts.[29,30] These conditions can lead to non–cirrhotic portal hypertension and as a consequence ascites.[31]

KNOWLEDGE GAPS

Hepatic cyst infections

Previous studies showed a high tissue penetration of ciprofloxacin in resected polycystic liver tissue.[25] In contrast, poor tissue penetration of cefazolin into hepatic cysts was seen *in vivo* after cyst aspiration.[32] These findings suggests that pharmacokinetics are potentially an important limiting factor in antibiotic treatment of hepatic cyst infections and require further investigation.

Some patients present with monthly or yearly recurrence of hepatic cyst infection, resulting in repeated hospital admissions, prolonged antibiotic use and a subsequent decrease of quality of life.[26] In these cases, there is an unmet need for comprehensive secondary prophylaxis that is able to prevent recurrent infections. Selective decontamination of the digestive tract (SDD) is sometimes used to prevent infectious complications in intensive care patients, and could provide a benefit.[33,34] However, no previous studies have assessed the effectiveness of SDD on hepatic cyst infection incidence.

Portal hypertension

Studies on treatment options for portal hypertension and ascites – other than liver transplantation – are limited to case reports and small case series, but the literature is scarce on when and how these options come into play. To our knowledge, no pertinent guidelines for clinical care are available.

Surgery

Laparoscopic fenestration is the least invasive surgical option for PLD. A recent clinical guideline proposes laparoscopic fenestration as first-line therapy with the restriction of low quality of evidence as most previous studies consist of case series and cohort studies.[35] To our knowledge,

a comprehensive synthesis of the literature in the form of a meta-analysis has not been previously performed and could be used to systematically grade the available evidence in its entirety.

Currently, large liver volume reduction in PLD can only be achieved by combined partial hepatectomy and cyst fenestration (PHCF).[19] A large retrospective study reported a median liver volume reduction of 61% after PHCF that was durable up to 20 years.[15] This establishes PHCF as an effective volume-reducing procedure. However, despite being the primary goal of treatment, the effectiveness of PHCF on symptom relief and quality of life has not been aptly assessed.

Estrogen

Based on the available evidence, counseling advice in the outpatient clinic includes discouragement of any exogenous estrogen therapy.[1] However, it is unclear whether these data also hold for the population of premenopausal patients with PLD, as recently published cohort studies suggested that exposure to estrogen-containing oral contraceptives is not correlated with total liver volume.[7,8] These data raise the question whether the advice to discontinue estrogen-containing oral contraceptives in premenopausal patients with PLD is valid.

RESEARCH AIMS

This thesis comprises four general aims: treatment of hepatic cyst infections, treatment of portal hypertension, surgical treatment and the risk of estrogens. The specific aims per chapter are described below. In addition, Table 1 summarizes the research questions, including study design and outcome measures.

RESEARCH AIM 1: TO EVALUATE EFFECTIVENESS AND SAFETY OF TREATMENT OPTIONS FOR RARE COMPLICATIONS OF PLD

In chapter 2, we present the rationale and design of a currently ongoing randomized pharmacokinetic study and provide an interim report of study conductance. In this study, we aim to measure ciprofloxacin, cotrimoxazole, doxycycline and piperacillin/tazobactam concentrations in cyst fluid and blood in patients undergoing aspiration sclerotherapy.

In chapter 3, we aimed to assess the hepatic cyst infection incidence before and after use of SDD in patients with recurrent hepatic cyst infections in a retrospective, multicenter cohort study.

In chapter 4a, we aimed to summarize all the available data on portal hypertension and ascites in PLD. In a narrative review, the various causes, epidemiology, clinical presentation, diagnostics and treatment options are discussed.

In chapter 4b, we describe the use of a venous stent for refractory ascites caused by obstruction of hepatic veins in a patient with PLD. A case report was written to comment on the feasibility and effects in one patient.

Table 1. Summary of research questions and methodology of this thesis

#	Research Question	Study design	Measures
2	What is the tissue penetration of ciprofloxacin, piperacillin/ tazobactam, cotrimoxazole and doxycycline in non-infected large hepatic cysts?	Randomized controlled pharmacokinetic study	Concentration (mg/L)
3	Can selective decontamination of the digestive tract (SDD) prevent recurrent hepatic cyst infections?	Retrospective cohort study	Hepatic cyst infection incidence
4a	What is the effectiveness of treatment options for portal hypertension and ascites in PLD?	Narrative review	Evidence level (GRADE)
4b	What is the feasibility of venous stent placement for refractory ascites in PLD?	Case report	Feasibility
5	What is the clinical response after laparoscopic fenestration of symptomatic hepatic cysts.	Systematic review Meta-analysis	Symptomatic relief rate (%) Recurrence rate (%) Re-intervention rate (%)
6	How does symptom relief and quality of life improve after Combined PHCF in PLD?	Prospective cohort study	Patient-reported outcomes (PLD-Q, SF-12 and EQ-VAS)
7	Is use of estrogen-containing oral contraceptives associated with PLD severity?	Cross-sectional study	Height-adjusted liver volume (ml/m) Oral contraceptive use (years)

RESEARCH AIM 2: TO EVALUATE EFFECTIVENESS AND SAFETY OF SURGICAL TREATMENT OF SYMPTOMATIC HEPATIC CYSTS

In chapter 5, we aimed to assess symptomatic relief, symptomatic recurrence and re-intervention rate after laparoscopic fenestration for cystic liver diseases, including both PLD and solitary cysts. We made use of a broad literature search, systematic review and meta-analysis of prevalence numbers.

In chapter 6, we aimed to measure symptom scores and quality of life before and after PHCF with validated questionnaires in a prospective cohort study. All procedures were performed in an expert center in the USA.

1 RESEARCH AIM 3: TO EVALUATE THE EFFECT OF FEMALE HORMONES ON LIVER CYST GROWTH

In chapter 7, we aimed to assess the correlation between oral estrogen-containing contraceptive use with liver volume. We made use of large cross-sectional cohort including both ADPKD and ADPLD patients with a broad spectrum of PLD severity. Data on female hormonal history was collected with a regularly-used questionnaire. In addition, the correlation with cumulative pregnancy duration was also assessed.

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2

HEPATIC CYST TISSUE PENETRATION OF CIPROFLOXACIN, COTRIMOXAZOLE, DOXYCYCLINE AND PIPERACILLIN/ TAZOBACTAM IN PATIENTS RECEIVING ASPIRATION SCLEROTHERAPY (PENTAC-2): PROTOCOL AND INTERIM OVERVIEW OF STUDY CONDUCTANCE

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SUMMARY

Background

Spontaneous hepatic cyst infection is a severe complication frequently requiring hospitalization, long-term antibiotic treatment, or invasive therapies. There is an unmet need for an evidence-based antibiotic strategy. In this study we assess the hepatic cyst penetration of intravenously administered antibiotics (ciprofloxacin, co-trimoxazole, doxycycline and piperacillin/tazobactam) by comparing blood and cyst fluid concentrations.

Methods

We performed a single-center, randomized pharmacokinetics study. We aimed to enroll 20 patients eligible for elective drainage of non-infected, symptomatic hepatic cysts. Patients with renal failure or specific drug contra-indications were excluded. We randomized patients into two groups. Group 1 received intravenous ciprofloxacin (200mg, in 30 minutes) and intravenous piperacillin/tazobactam (4000mg/500mg, in 30 minutes) simultaneously. Group 2 received intravenous cotrimoxazole (960mg, in 30 minutes) and intravenous doxycycline (200mg, in 2-5 minutes) simultaneously. Three blood samples were taken: (a.) directly after antibiotic administration, (b.) during cyst drainage and (c.) six hours after the first blood sample. Antibiotics concentrations will be measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS). The assay is validated for the appropriate matrices. Statistical analysis, modelling and simulations will be performed using NONMEM.

Discussion

Between 8 February 2019 and 1 March 2020, we included 19 patients. Due to the COVID-19 pandemic the study was temporarily halted on 1 March 2020. At this time, we included 19 out of the prespecified 20 patients (95%). The majority of patients is female and had a solitary hepatic cyst. Hemocytometry and protein levels in blood were comparable. In contrast, laboratory values for cyst fluid showed a skewed distribution and several outliers for all measured values except for cyst fluid pH. The most important challenge of this study was of operational nature, as multiple departments were involved. We aim to complete final recruitment and all analyses in 2020.

Trial registration

This trial was registered in the European Union Drug Regulating Authorities Clinical Trials Database (date: 16-08-2018; ID: 2018-003262-13) and the Netherlands Trial Register (date: 25-09-2018; ID: NL7290). The study was approved by the Medical Research Ethics Committee of the region Arnhem-Nijmegen, the Netherlands (date: 15-01-2019; ID: 2018-4683).

BACKGROUND

Hepatic cysts are fluid-filled cavities lined with cholangiocytes that arise from malformations of the ductal plate during embryonic development.[1] Spontaneous bacterial infection of hepatic cyst is a severe complication, which is often difficult to treat and requires extensive antibiotic treatment. *Escherichia coli* is the foremost causative isolate found in cyst cultures, presumably resulting from translocated intestinal flora.[2] Failure of antibiotic treatment occurs in 50%, and recurrence has been reported in up to 20% of patients.[3] We hypothesize that the reason for this high failure rate is a low penetration of targeted tissue, leading to subtherapeutic intracystic concentrations.[4]

Four previous publications reported on hepatic cyst penetration of the antibiotics ciprofloxacin, meropenem and cefazolin.[5-8] Here, we calculated the mean cyst fluid to plasma concentration ratio (CR) based on these data:

Ciprofloxacin

A post-mortem case series and case report demonstrated that ciprofloxacin reaches high concentrations in infected and non-infected hepatic cysts with a CR of 214.1%.[5,6] Patients were treated with oral and/or intravenous ciprofloxacin before drainage. This supports the choice of selecting ciprofloxacin as a first-line treatment.[9] However, antibiotic resistance to ciprofloxacin is rising and no alternative antibiotic strategy, substantiated with pharmacokinetic evidence, is available.[10]

Meropenem

In a prospective observational study, intravenously administered meropenem showed poor penetration in 12 infected hepatic cysts with a mean CR of 9.5%.[7] Two renal cysts in the original article were excluded to calculate this CR. There are some limitations to the study; blood samples were only collected just after completion of intravenous administration. Moreover, all patients had renal failure and received hemodialysis which altered the pharmacokinetic profile of these patients and limits generalizability to patients with intact renal function.

Cefazolin

In the PENTAC-1 trial, a prospective observational study in our center, the tissue penetration of pre-procedurally administered intravenous cefazolin was measured in non-infected hepatic cysts. The median CR of cefazolin was 1.8% after administration of a single intravenous dose.[8]

The antibiotics co-trimoxazole, doxycycline and piperacillin/tazobactam are all chemically effective against the pathogens most often implicated in hepatic cyst infections.[9] To evaluate their site-specific tissue penetration, we have updated our previously reported human *in vivo* study model to assess hepatic cyst penetration (PENTAC-1),[8] and focused on improving research methodology in collaboration with experts from the Departments of Microbiology and Pharmacy. This model makes use of patients scheduled to undergo percutaneous aspiration sclerotherapy of symptomatic, non-infected, non-neoplastic hepatic cysts.[11] Ciprofloxacin was also included as

a positive control and to compare the *in vivo* model to previously published results in non-infected and infected hepatic cysts.

Our primary aim was to evaluate tissue penetration into non-infected hepatic cysts by measurement of blood and cyst fluid levels after intravenous administration of the antibiotics ciprofloxacin, co-trimoxazole, doxycycline and piperacillin/tazobactam.

METHODS/DESIGN

The study was approved by the Medical Research Ethics Committee of the region Arnhem-Nijmegen (#2018-4683, approval date: January 15th, 2019). The study was conducted in accordance with the Declaration of Helsinki. All data was safely stored in Castor (Castor EDC, Amsterdam, the Netherlands). The trial was registered in the Netherlands Trial Register (ID: NL7290, www.trialregister.nl/trial/7290). All investigational products were ordered, prepared, labelled (according to GMP annex 13), stored and delivered by the Clinical Trials Unit of the Radboudumc Pharmacy department.

Study design and participants

This randomized, single-center, pharmacokinetic trial was carried out in the Radboudumc, Nijmegen, the Netherlands (Figure 1). Patient inclusion started in February 2019. Patients were identified in the outpatient clinic by the treating gastroenterologist. Written informed consent was obtained from all patients before inclusion in the trial. All adult (≥18 years) patients who were diagnosed with a symptomatic hepatic cyst and indication for aspiration sclerotherapy were suitable for inclusion.[11] Exclusion criteria were: allergy or hypersensitivity to the included antibiotics; use of other drugs with a contra-indication for antibiotic use; impossibility for placement of an intravenous cannula for administration of antibiotics and vena puncture on the other arm; severe renal impairment with an estimated glomerular filtration rated (eGFR) < 30ml/min/1,73m2 (CKD stage 4 or 5), and (planned) use of antibiotics in the seven days before aspiration sclerotherapy.

Study procedures

Antibiotics

Included patients were randomized into two groups. Group 1 received intravenous ciprofloxacin (200mg, in 30 minutes) and intravenous piperacillin/tazobactam (4000mg/500mg, in 30 minutes) simultaneously. Group 2 received intravenous cotrimoxazole (960mg, in 30 minutes) and intravenous doxycycline (200mg, in >2 minutes) simultaneously. Antibiotics were administered preceding the cyst drainage procedure. Combinations were defined on the absence of pharmacokinetic drug interactions at the level of phase I and phase II enzyme systems as well as transporter affinities.

Random allocation was performed by block randomization, without stratification, in a 1:1 allocation ratio, with block sizes of 4 and 2, resulting in a maximum of 10 patients per group. Allocation was performed with Castor (Castor EDC, Amsterdam, the Netherlands). Assignment

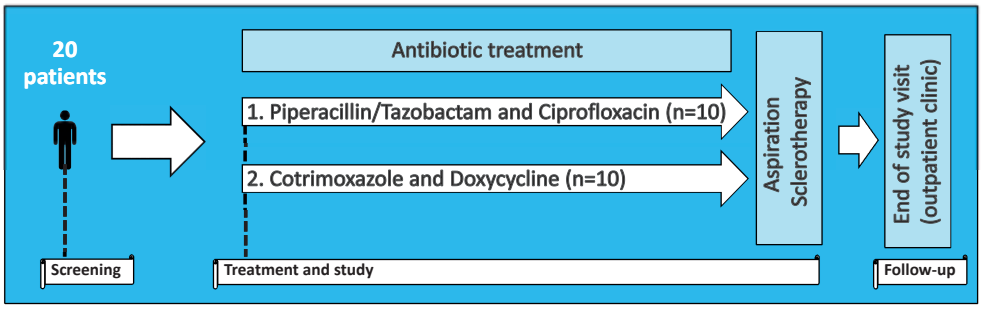

Figure 1. Study design. Twenty patients were planned to be randomized in two groups with different investigational products. Cyst drainage is performed according to standard clinical practice.[12]

to time of administration was carried out by the investigators based on planning and timing of the procedure at the radiology department. Antibiotics were administered sequentially by a registered nurse.

Sampling

For the purposes of the study, blood was drawn from the patient at three separate timepoints by vena punctures (thus not obtained from the intravenous cannula which was used for antibiotic administration) by a trained nurse or physician. We obtained the first blood sample directly after completing antibiotics administration (mg/L). During the moment of hepatic cyst fluid drainage as part of aspiration sclerotherapy, the second blood sample was drawn to calculate the ratio (%) of antibiotic penetration. Before hospital discharge but within the dosing interval, the final blood sample was obtained. Typically, this was approximately six hours after first sample. The exact time and duration of infusion (minutes), timing of blood sample withdrawals and cyst fluid collection were recorded (hh:mm). All samples were collected on ice and stored in a fridge (max. 6°C) for up to 24 hours to ensure stability of antibiotic molecules. After centrifuging blood samples (5 min at 1900 g) plasma and cyst fluid samples were stored at −80°C.

Aspiration Sclerotherapy

All patients received aspiration sclerotherapy with or without use of propofol as procedural sedation at the department of interventional radiology. Guided by ultrasound, the interventional radiologist inserts a 5 French pigtail catheter (Cook Medical, Bloomington, IL, USA) in the cyst and performs fluid drainage until collapse of the cyst and subsequent collection of uncontaminated cyst fluid. Thereafter, connection of the cyst with the biliary tree or leakage into the abdominal cavity is ruled out by instillation of contrast medium (Iomeron 300, Bracco Imaging, Konstanz, Germany, up to 20 ml). This is followed by sclerotherapy by instilling 100% ethanol in a 10% ratio of the aspirated cyst volume (up to 50 ml) into the aspirated hepatic cyst, and is left for 10 minutes before re-aspirating the instilled ethanol (Figure 2).

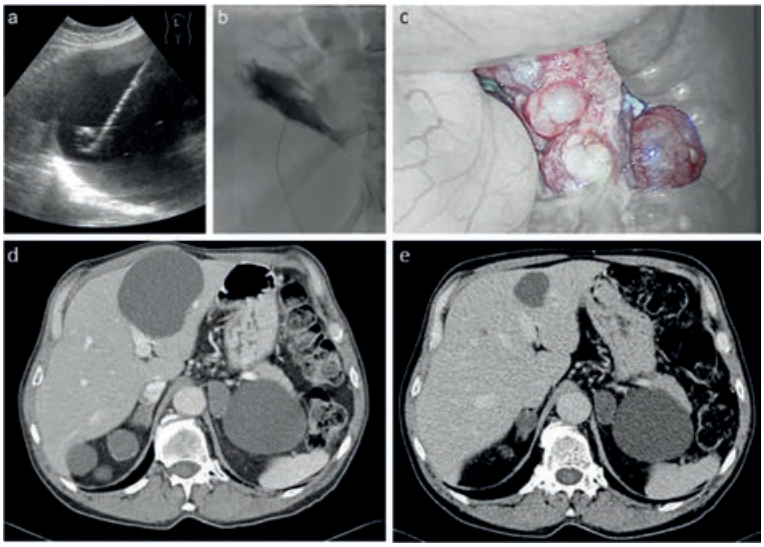

Figure 2. Aspiration sclerotherapy overview. (a.) ultrasound image of intracystic catheter. (b.) x-ray image of intracystic contrast medium; no leakage is revealed. (c.) photo of a sclerosed cyst during laparoscopy, other tissues in grayscale for clarity. Notice the irregularities due to scarring. (d.) CT-scan image of a hepatic cyst before and (e.) after aspiration sclerotherapy.

Outcome measures

Our primary outcome was hepatic cyst penetration of administered antibiotics, expressed as the ratio (%) of unbound concentration in hepatic cyst fluid to plasma (both in mg/L). Secondary study parameters included clinical characteristics (age, gender, body weight, body length, cyst location in the liver and estimated cyst volume determined with ultrasonography during screening).

Furthermore, we analyzed the following blood parameters: hemoglobin, white blood cell (WBC) count (10^9/L), creatinine (µmol/L), CKD-EPI estimated GFR (ml/min/1,73m^2), total protein (g/L), and International Normalized Ration (INR). Cyst fluid was analyzed for erythrocyte count (10^9/L), WBC count (10^9/L), total protein (g/L), and pH. Finally, we monitored all adverse events during hospital admission.

Quantification of antibiotic concentrations

Analysis of total plasma and cyst fluid concentrations will be performed with liquid chromatography-tandem mass spectrometry (LC-MS/MS). All samples of one included patient will be measured in one run. Plasma concentrations will be reported in mg/L and rounded to two decimal places. For group 1, piperacillin, tazobactam and ciprofloxacin concentrations will be measured. For group 2, sulfamethoxazole, N-acetyl sulfamethoxazole, trimethoprim and doxycycline concentrations will be measured. The assay has been validated according to the latest guidance documents from the EMA.

Validation has been done for all matrices including cyst fluid.

Pharmacokinetic modelling

A pharmacokinetic model will be fitted to the data from all individuals simultaneously. Data will be analyzed using non-linear mixed effects modeling NONMEM 7.3 (ICON Development Solutions, Hanover, USA), Pearl-speaks-NONMEM (PsN) 4.6.0 and visualized using Pirana 2.9.7 (Pirana Software & Consulting BV), R 3.4.4. Data will be co-modelled with existing data from previous studies conducted in ICU patients

Multiple compartment models with first-order or saturable elimination will be tested. Between-subject variability and, when applicable, between-occasion variability will be included on all pharmacokinetic parameters. Residual unexplained variability will be estimated with additive or proportional error models. The first-order conditional estimation method with interaction will be used, other estimation methods of non-parametric methods may be investigated. After selection of the final model, a simulation study is performed using this model to assess exposure and probability of target attainment following various dosing regimens. Probability of target attainment following different dosing regimens will be assessed.

Statistical analysis

All analyses for this protocol report were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL). Descriptive variables are expressed as percentage (%) and number of patients (n), or median and interquartile range (IQR). Due to the nature of this study, we did not perform a power calculation. Our sample size is in line with similar pharmacokinetic studies.[8,13]

DISCUSSION

Patient inclusion

Between 8 February 2019 and 1 March 2020, a total of 29/31 (94%) patients were eligible for inclusion, one patient was excluded based on other medical conditions, and one because of a history of difficulty with blood sampling. Finally, 19/29 (66%) were willing to participate (Figure 3). One patient remains to be included. In 17/19 (89%) patients all samples were taken and stored, in patient 5 and 8 one blood sample is missing due to logistical reasons, which does not preclude inclusion in pharmacokinetic analyses (Figure 4).

Baseline characteristics

Baseline characteristics are presented in Table 1. The majority of patients was female and had a solitary hepatic cyst. There was a numerical difference in cyst etiology, with more solitary cysts in group 1 and more ADPLD patients in group 2. Importantly, aspirated cyst volume was similar between groups.

Laboratory values for blood and cyst fluid are presented in Table 2. Hemocytometry and protein levels in blood showed little variation between patients. In contrast, laboratory values for cyst fluid showed a skewed distribution and high outliers for all values except pH. There were no relevant differences between group 1 and 2. These factors will be included in the modelling studies.

Safety

There were no adverse events related to the administration of investigational products. There were no severe adverse events during the study.

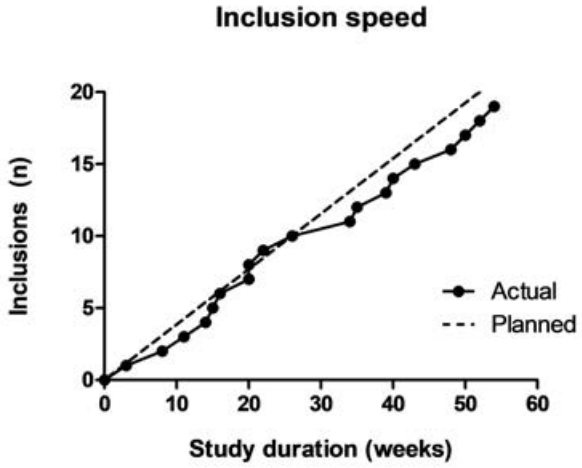

Figure 3. Inclusions over time. Cumulative inclusion number on the Y-axis. Study duration in weeks on the X-axis. Dashed line represents the planned inclusion period (52 weeks for 20 patients).

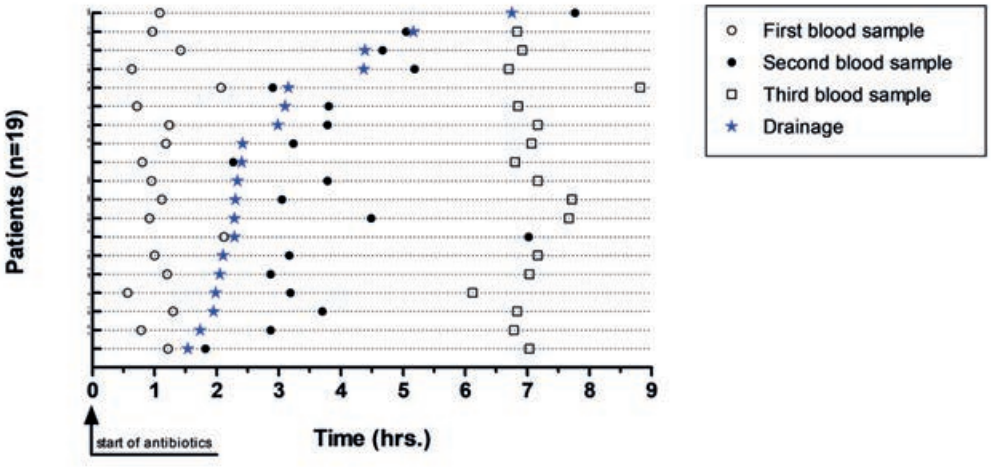

Figure 4. Overview of sampling timepoints per patient. First, second and third blood sampling, and time of cyst drainage are shown for individual patients, sorted by time of drainage. Time after start of the first antibiotic infusion in hours (hrs.) is shown on the X-axis.

Table 1. Baseline characteristics

Characteristic	Total group (n=19)	Group 1: Ciprofloxacin & Piperacillin/tazobactam (n=9)	Group 2: Cotrimoxazole & doxycycline (n=10)
Age (years), median (IQR)	61 (55 – 68)	56 (42 – 66)	63 (55 – 72)
Female, n (%)	17 (89%)	8 (89%)	9 (90%)
Etiology, n (%)			
Solitary cyst	11 (58%)	7 (78%)	4 (40%)
ADPLD	6 (32%)	1 (11%)	5 (50%)
ADPKD	2 (11%)	1 (11%)	1 (10%)
Length (m), median (IQR)	1.68 (1.63 – 1.79)	1.70 (1.64 – 1.85)	1.66 (1.62 – 1.80)
Weight (kg), median (IQR)	71.8 (59.0 – 98.0)	74.0 (56.7 – 113.8)	66.4 (59.0 – 80.2)
BMI (kg/m^2), median (IQR)	24.0 (20.2 – 30.4)	25.6 (20.1 – 36.4)	23.7 (21.8 – 27.7)
Renal dysfunction (eGFR), n (%)			
Normal (≥90)	8 (42%)	5 (56%)	3 (30%)
Mild (60-89)	10 (53%)	3 (33%)	7 (70%)
Moderate (30-59)	1 (5%)	1 (11%)	0 (0%)
Aspirated cyst volume (ml), median (IQR)	700 (350 – 1300)	700 (435 – 950)	800 (288 – 2525)
Cyst fluid appearance, n (%)			
Clear	12 (63%)	6 (67%)	6 (67%)
Bile-stained	1 (5%)	1 (11%)	0
Blood-stained	1 (5%)	1 (11%)	0
Brown (turbid)	4 (21%)	1 (11%)	3 (33%)

Abbreviations: BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate based on CKD-EPI equation in ml/min/1,73m2.

Table 2. Laboratory values

Characteristic	Total group (n=19)	Group 1: Ciprofloxacin & Piperacillin/ tazobactam (n=9)	Group 2: Cotrimoxazole & doxycycline (n=10)
Blood:			
Hemoglobin (mmol/l)	8.1 (7.5 – 8.7)	8.4 (7.5 – 8.8)	8.0 (7.4 – 8.8)
White blood cell count (10^9/l)	6.0 (5.0 – 7.1)	5.8 (4.8 – 7.6)	6.2 (5.4 – 6.7)
Protein (g/l)	73.5 (71.0 – 76.3)	73.5 (71.3 – 75.8)	73.5 (70.8 – 77.3)
Creatinine (µmol/l)	69.0 (61.0 – 78.0)	67.0 (56.0 – 70.5	76.5 (64.0 – 81.3)
eGFR (ml/min/1,73m^2)	86 (67 – ≥90)	>90 (81 – ≥90)	80 (64 – ≥90)
Cyst fluid:			
Erythrocytes (10^9/l)	1.0 (0.0 – 19.0)	1.0 (0.0 – 23.0)	2.0 (0.0 – 54.5)
White blood cell count (10^9/l)	0.0 (0.0 – 0.6)	0.1 (0.0 – 12.1)	0.0 (0.0 – 0.6)
Protein (g/l)	9.9 (5.1 – 23.2)	9.9 (6.5 – 23.4)	10.5 (5.0 – 28.7)
pH	7.6 (7.5 – 7.7)	7.6 (7.5 – 7.7)	7.6 (7.5 – 7.7)

Legend: All values are median (IQR). Abbreviations: eGFR = estimated glomerular filtration rate (CKD-EPI formula).

Challenges

We encountered several practical and operational issues while performing the study. While participation (66%) was higher than the anticipated 50%, the number of procedures was lower than the expected 40-50 per year. Together, inclusion speed did not differ significantly from planning. Most patients who were unwilling to participate either had an aversion to use of antibiotics or did not want additional voluntary procedures.

The most important challenge of this study was operational, as multiple departments were involved. First, patients were included at the gastroenterology outpatient clinic. For treatment, patients are admitted to either the short-stay unit (SSU) or gastroenterology ward, which had both just moved from another building before start of the study, with different teams of nurses who are not necessarily accustomed to assisting with research. Aspiration sclerotherapy is performed at the department of interventional radiology, or incidentally in the operating rooms. In addition, three laboratories were involved with the studies. Cyst fluid samples were prepared in the gastroenterology laboratory and stored in the biobank, biochemical analyses were performed in the clinical diagnostics laboratory, and samples were stored in the clinical pharmacy laboratory where all measurements will take place. Taking a blood sample during cyst aspiration proved to be more difficult than anticipated. When patients undergo aspiration sclerotherapy with sedation, this was easily done. However, many patients only had a local anesthetic. In these patients, a blood sample was taken shortly after the procedure (Figure 4).

Future perspectives

Since most bacterial infections occur outside the bloodstream, antibiotic site-specific tissue concentrations are of significant relevance to optimize treatment.[14] However, a recent review has highlighted that before tissue penetration is to serve as a basis for the design of optimal strategies for drug and dose selection, more reliable information is absolutely necessary as there is a critical lack of robust data.[15] The PENTAC-2 trial accounts for that by using a prospective design, ensuring rigorous data collection, while leaving room for variation of measurement timing. By including two randomized groups and four antibiotics, it is possible to accurately compare tissue penetration between different antibiotics and between patients. We think that this trial will lead to better selection of medication and more optimal dosing, which will help patients and could prevent antibiotic resistance in the future.

The PENTAC-1 and PENTAC-2 trials have resulted in increased collaboration between the departments of gastroenterology, intervention radiology, microbiology and pharmacy. The availability of tissue and/or fluid samples in combination with state-of-the-art quantification and pharmacokinetic modelling will lead to further research on antibiotic tissue penetration.

TRIAL STATUS

This publication is based on the most recent protocol (version 3.0; 07-01-2019). Recruitment began 8 February 2019. The first patient was included on 7 March 2019. As of now 19 out of 20 patients have

been included. Due to the COVID-19 pandemic the study was temporarily halted March 2020. We aim to complete all analyses in 2020.

DECLARATIONS

This study was internally funded by the Gastroenterology & Hepatology and Clinical Pharmacy departments of the Radboudumc. We have no conflicts of interest to disclose.

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3

EFFICACY AND SAFETY OF SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT (SDD) TO PREVENT RECURRENT HEPATIC CYST INFECTIONS IN POLYCYSTIC LIVER DISEASE: A RETROSPECTIVE CASE SERIES

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ABSTRACT

Background

Hepatic cyst infection is a complication of polycystic liver disease (PLD) that causes substantial morbidity. Repetitive infection is frequent and is increasingly difficult to treat. As translocated gut bacteria are considered the cause, we hypothesize that selective decontamination of the digestive tract (SDD) reduces recurrence of hepatic cyst infection.

Methods

We performed a retrospective, observational study in two referral centers. All patients with PLD, treated with SDD for hepatic cyst infection were included. Efficacy was determined by calculating the infection incidence (hepatic cyst infections per month) before and during SDD therapy. Adverse events were scored according to the Common Terminology Criteria for Adverse Events (CTCAE).

Results

We identified eight patients who received SDD (88% female, 88% polycystic kidney disease). Median age was 65 years (IQR 51–74). SDD lowered median incidence from 0.09 episodes per month (IQR: 0.06–0.25) to 0.01 episodes per month (IQR: 0.00–0.05) (p=0.12). Discontinuation of SDD led to rapid recurrence of cyst infection (71% within six weeks). SDD consisted of polymyxins with/without aminoglycosides. Median SDD treatment duration was 20 months (range: 3–89 months). Six patients (75%) developed adverse events, CTCAE grade 1 (gastrointestinal: n=3) or grade 3 (ototoxicity: n=1; fungal infection: n=1), mostly attributable to aminoglycosides. One patient developed polymyxin E resistance.

Conclusions

SDD prophylaxis provides a novel strategy for limiting recurrent hepatic cyst infection in PLD patients. However, adverse events are frequent and curtail its use. As most were attributable to aminoglycosides, Polymyxin E is considered the preferred therapy.

INTRODUCTION

Hepatic cyst infection is a severe complication of polycystic liver disease (PLD).[1, 2] PLD can be present in context of either autosomal dominant polycystic liver disease (ADPLD) or autosomal dominant polycystic kidney disease (ADPKD).[3, 4] *Escherichia coli* (*E.coli*) is the most frequent isolate in patients with hepatic cyst infections, fuelling the concept of bacterial translocation from the gut as root cause.[5, 6] Failure of antibiotic treatment occurs in 50%, and recurrence has been reported in up to 20%.[1, 2, 5] Recurrent infections may further compromise quality of life.[1, 7] This signals that there is an unmet need for comprehensive antibiotic prophylaxis that is able to prevent recurrent hepatic cyst infection.

Selective decontamination of the digestive tract (SDD) controls overgrowth of potential pathogens in the gut and is intended to prevent opportunistic infections in at-risk patients.[8] This led us to hypothesize that SDD may reduce infection rates in patients with recurrent cyst infections. Our aim was to explore the efficacy and safety of SDD as secondary prophylaxis in PLD.

PATIENTS AND METHODS

Ethics

This study was approved by the Institutional Ethical Review Board of the Radboudumc (reference: 2019-6062) and LUMC (reference: 2019.057). We obtained informed consent from study participants.

Study design, setting and participants

Our retrospective, observational cohort study was executed in two referral centers for ADPKD/ADPLD (Radboudumc, Nijmegen, and LUMC, Leiden, the Netherlands). We considered PLD patients (≥18 years), with history of multiple (>2) hepatic cyst infections and who received at least one SDD dose as prophylaxis (polymyxins, neomycin and/or tobramycin; all oral use in tablet form). We reviewed all electronic patient records for these criteria using search engine CTCUE (CTcue B.V., Amsterdam, the Netherlands) and asked all physicians involved in care for PLD patients to provide cases. Renal cyst infection patients were excluded. This study is reported according to STROBE.[9]

Outcome measures

Patient demographics and clinical course were extracted from electronic records. We recorded every diagnosis of hepatic cyst infection during follow-up. Diagnosis was made by the treating physician involved, based on clinical, biochemical, microbiological and imaging criteria, in addition to response to antimicrobial treatment.[10] When hepatic cyst infection occurred within 1 month following end-of-treatment of previous cyst infection, it was defined as: (A) persistence of the same infection when cultured pathogen and resistance pattern matched with findings from earlier infection, or (B) as a new episode when different pathogens or distinct resistance patterns were found. Only (B) was included in analyses.

An adverse event was defined as any unfavorable and unintended sign, symptom or disease temporally associated with SDD use that may or may not be considered related to SDD. Adverse

events were scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 by the authors. Severity is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death (Grade 5).[11] Beyond the scope of CTCAE, confirmed antimicrobial resistance following SDD was included separately.

Statistical methods

We calculated hepatic cyst infection incidence by dividing number of episodes by months of follow-up before and during SDD. To limit bias, the first episode during follow-up prior to SDD was omitted, as follow-up started with a hepatic cyst infection in all cases. Hepatic cyst infections occurring after (temporary) discontinuation of SDD were excluded.

Descriptive variables are expressed as number (%), or median and IQR. Pre and post SDD incidence was compared using the Related-Samples Wilcoxon signed-rank test for nonparametric distributions. Analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL).

Literature review

To investigate previously reported use of SDD to prevent recurrent hepatic cyst infection, we performed a literature search. We systematically searched PubMed (MEDLINE) and Ovid (Embase) from inception to 23 March 2020 (Table S1).

RESULTS

We identified eight PLD patients with a history of hepatic cyst infection who were exposed to SDD. Patient characteristics are described in Table 1. SDD regimens differed between patients (Table 1). Median SDD treatment duration was 20 months (range: 3–89 months). Individual case descriptions are shown below and summarized in Figure 1.

Case descriptions

Case 1: A female patient (ADPKD, CKD-3b, renal transplantation [RTx]) had a history of four hepatic cyst infections in 120 months. The last episode, with negative cultures, but confirmed with ^{18}F-FDG PET/CT, was treated with meropenem and subsequently ciprofloxacin. As repeated ^{18}F-FDG PET/CT showed no sign of infection, ciprofloxacin was stopped after four weeks and SDD prophylaxis with polymyxin B/neomycin sulfate 1ME/250mg four times daily was initiated. Patient suffered from recurrent oral and vaginal candida infections for which she received anti-fungal treatment and nystatin prophylaxis (grade 3, severe). After 43 months, patient presented with abdominal pain and fever, suspected to be either diverticulitis or a recurrent hepatic cyst infection. Blood cultures were negative, and imaging was not performed because of a lack of therapeutic consequences. Oral ciprofloxacin was initiated for two weeks. There were no new episodes of hepatic cyst infection while on SDD in the following ten months. Ultimately, because of unbearable suffering due to multiple chronic physical complaints, patient requested euthanasia.

Case 2: A female patient (ADPKD, CKD-4, RTx, history of six hepatic cyst infections in 18 months) suffered from recurrent cyst infections with different pathogens (*E. coli, Enterococcus faecium* and *Klebsiella* species). The most recent episode included a ciprofloxacin-resistant *E. coli* bacteremia and was treated with intravenous cefuroxime for two weeks. Four days later, patient presented with recurrent bacteremia with an identical *E. coli* strain and cefuroxime was reinitiated (six weeks). SDD prophylaxis with polymyxin B/neomycin sulfate (1ME/250mg four times daily) was commenced one week before discontinuing cefuroxime. Two and half months later, patient was admitted with hepatic cyst infection (*Klebsiella oxytoca* bacteremia) and ciprofloxacin was initiated for two weeks. Eighteen months later, SDD was discontinued while she suffered from a urinary tract infection. One and a half months after stopping SDD, patient was admitted for a hepatic cyst infection, which was treated with ciprofloxacin. Subsequently, polymyxin B and neomycin were restarted. Twenty-five months after reinitiating, SDD was stopped to evaluate whether prophylaxis was no longer required. Ten days later, patient was admitted with a hepatic cyst infection (*Klebsiella pneumoniae* bacteremia). We initiated ciprofloxacin treatment for six months, and SDD prophylaxis was restarted. Thirty-eight months later, she was admitted three times in five months' time with recurrent hepatic cyst infections. Different species were cultured (*Klebsiella pneumoniae, E. coli*), and ^{18}F-FDG PET/CT showed FDG-uptake in hepatic cysts in multiple liver segments. SDD prophylaxis was continued. Six months after the last episode, patient was admitted twice in two months' time with a recurrent *E. coli* bacteremia due to a hepatic cyst infection, treated with cotrimoxazole for six weeks. SDD was continued. There were no cyst infections in the following five months, and no adverse events during SDD treatment. Patient has been screened for liver transplantation because of the previous recurrent infections, despite SDD, but this is tentatively postponed because of the current episode-free period

Case 3: A male patient (ADPKD, CKD-4, naïve kidney) gave a history of five cyst infections in 37 months. Patient suffered from recurrent *E. coli* bacteremia with different resistance patterns at each episode. The most recent episode was treated with ciprofloxacin for six weeks. SDD prophylaxis with polymyxin B/neomycin (1ME/250mg four times daily) was started. On SDD therapy, there were no cyst infections or admissions in the following 19 months. Patient suffered from progressive, irreversible perceptive hearing loss, possibly related to neomycin-induced ototoxicity (grade 3, severe). Polymyxin B and neomycin were discontinued and low-dose cotrimoxazole (480mg one daily) was started as alternative prophylaxis. Two weeks after stopping SDD, patient was admitted twice in six weeks' time with a recurrent hepatic cyst infection, confirmed by ^{18}F-FDG PET/CT. During the last episode two weeks ago, ceftazidime was initiated for six weeks and polymyxin monotherapy will be subsequently considered.

Case 4: A female patient (ADPKD, CKD-2, RTx, history of 11 hepatic cyst infections in 66 months, ciprofloxacin allergy) suffered from recurring hepatic cyst infections with different pathogens (*Klebsiella pneumoniae, E. coli*). The most recent episode was one month before referral and was treated with meropenem for six weeks based on previous cultures that grew a multi-resistant *E. coli*. Polymyxin E 95mg once daily was started, while neomycin was withheld because of observed adverse events in other patients. She stopped polymyxin E after two months because of diarrhea (grade 1, mild). One month later, she was admitted with a recurrent hepatic cyst infection and was

treated with meropenem upon admission. One week later, ^{18}F-FDG PET/CT showed FDG-uptake in multiple hepatic cysts and patient was treated with meropenem for another week. Two months later, patient was admitted with a recurrent hepatic cyst infection, confirmed by ^{18}F-FDG PET/CT. Patient was treated with a 3 months course of intravenous ceftriaxone while polymyxin E was added to the regimen. Under polymyxin E monotherapy, there were no hepatic cyst infections, adverse events and admissions in the following 12 months.

Case 5: A female patient (ADPKD, CKD-3a, RTx) with a history of eight hepatic cyst infections in 132 months) was referred because of recurrent hepatic cyst infections. The most recent episode was three months before the initial visit, confirmed by ^{18}F-FDG PET/CT and treated with ciprofloxacin for six weeks because of an amoxicillin- and cotrimoxazole-resistant *E. coli* bacteremia. We commenced neomycin 375 mg and polymyxin E 95 mg once daily as prophylaxis. During 21 months of follow-up, no hepatic cyst infections occurred. Neomycin was then stopped because the drug was not locally available and polymyxin E was continued as monotherapy.

Case 6: A female patient (ADPKD, CKD-3, naïve kidney) had a history of five hepatic cyst infections in 12 months. She suffered from recurrent cyst infections with different pathogens (*E. coli, Enterococcus faecium* and *Streptococcus* species). The most recent episode was one month prior to referral, was confirmed by ^{18}F-FDG PET/CT and treated with ciprofloxacin and amoxicillin. We continued this regimen for three months, and introduced polymyxin E (95mg once daily) as SDD. After six months, polymyxin E was discontinued because of diarrhea (grade 1, mild). In the subsequent two months, she was free of hepatic cyst infections.

Case 7: A female patient (ADPKD, CKD-2, naïve kidney) had a history of eight hepatic cyst infections in 108 months. The most recent episode (ciprofloxacin-resistant *E. coli* bacteremia) was treated with amoxicillin/clavulanate, and subsequently with cotrimoxazole (total 12 weeks). We prescribed a suspension of tobramycin 160 mg and polymyxin E 200 mg once daily as SDD. The malodorous suspension abhorred the patient, which was the reason to switch to tablets (neomycin 375 mg and polymyxin E 95 mg once daily) after 2 months. Five months later, patient was admitted with a hepatic cyst infection (*E. coli* bacteremia). She was treated with intravenous ceftriaxone and subsequently oral ciprofloxacin for six weeks. SDD was temporarily stopped for two weeks during treatment. The patient was advised to use ciprofloxacin for one week every time she had a suspicion of a hepatic cyst infection (e.g. fever, pain). Six months after discharge, SDD was switched to polymyxin E 95mg monotherapy as neomycin caused nausea and diarrhea (grade 1, mild). In the subsequent two years of follow-up, patient had fever for which she took ciprofloxacin eight times (without requiring hospital admission). Thereafter she stopped polymyxin E and was admitted for the 10th hepatic cyst infection three weeks later. Patient was treated with ciprofloxacin and cotrimoxazole for six weeks. Polymyxin E monotherapy was resumed after release from the hospital. Patient was admitted for hepatic cyst infection nine months later. Polymyxin E was stopped during admission. Patient was treated with ciprofloxacin during admission. Oral medication with cotrimoxazole was commenced and continued for six weeks after release from hospital. Subsequently, polymyxin E monotherapy was restarted.

Case 8: A female patient (ADPLD, no kidney damage, naïve kidneys) with a history of two hepatic cyst infections in 15 months had the most recent episode of hepatic cyst infection three months

before referral. This infection was confirmed using ^{18}F-FDG PET/CT. Seven months thereafter she developed her third cyst infection. Polymyxin E 95mg once daily was commenced 8 months later. Three months later, she had a hepatic cyst infection, which was treated with piperacillin/tazobactam, and was switched to intravenous amoxicillin after culture of an amoxicillin-sensitive E. coli. Because the cultured E. coli was resistant to polymyxin E, SDD was stopped.

Hepatic cyst infections

Benefit from treatment was evident in 75% (n=6) of patients; 50% (n=4) did not have any hepatic cyst infections during SDD treatment (Figure 1). In three cases, the episode-free period after introducing SDD was limited to six months, but during follow-up these cases had a numerically reduced frequency of infections. SDD was (temporarily) stopped seven times in six patients, because of adverse events (n=3), development of antimicrobial resistance (n=1) or as an experiment to validate continued effectiveness (n=3). After cessation of SDD, five out of seven times (71%) a hepatic cyst infection developed shortly after discontinuation (median: 3 weeks, range: 1.5–6 weeks). SDD was reinitiated by the treating physician in three cases and is under consideration in another.

Cyst infections over time are shown in Figure 1. Median incidence before SDD was 0.09 episodes per month (IQR: 0.06–0.25). Incidence during treatment was reduced to 0.01 episodes per month (IQR: 0.00–0.05). This 89% reduction was not significant (p=0.12).

Adverse events

In total, 75% (n=6) suffered from adverse events probably SDD related (Figure 1). These were mild (grade 1) in three, and consisted of diarrhea and/or nausea. Severe (grade 3) adverse events

Table 1. Baseline characteristics

Characteristic	Outcome (n=8)
Age, median (IQR)	65 (51-74)
Center, n (%):	
Radboudumc	5 (63%)
LUMC	3 (37%)
Female, n (%)	7 (88%)
ADPKD, n (%)	7 (88%)
Renal transplant , n (%)	4 (50%)
CKD stage >3, n (%)	5 (63%)
Initial SDD regimen, n (%):	
Polymyxin B/neomycin; 1ME/250mg 4x/day	3 (38%)
Polymyxin E/neomycin; 95/375 mg 1x/day	1 (13%)
Polymyxin E/tobramycin; 200/160mg 1x/day	1 (13%)
Polymyxin E; 95mg 1x/day	3 (38%)

Abbreviations: ADPKD = autosomal dominant polycystic kidney disease; CKD = Chronic Kidney Disease; SDD = selective decontamination of the digestive tract.

occurred in two and consisted of: (1) recurrent oral/vaginal candida infections requiring anti-fungal treatment and addition of nystatin (2) severe progressive, irreversible perceptive hearing loss probably related to neomycin-induced ototoxicity. In one, antibiotic resistance to polymyxin E in blood culture isolates of *E. coli* was documented during SDD use. In another patient, loss-of-response after years of SDD use suggests development of antibiotic resistance, but this was not confirmed by microbiological testing.

Literature search

Our systematic search yielded 56 articles in PubMed and 114 in Embase. After screening of title and abstracts, no relevant publications were found (Table S1).

DISCUSSION

Our observational data suggest that SDD reduces incidence of recurrent hepatic cyst infection and show that recurrence occurs shortly after SDD discontinuation.

However, adverse events deemed related to SDD occurred in 75% of patients. Two events were graded severe, whereof one was irreversible hearing loss due to aminoglycoside ototoxicity.[12]

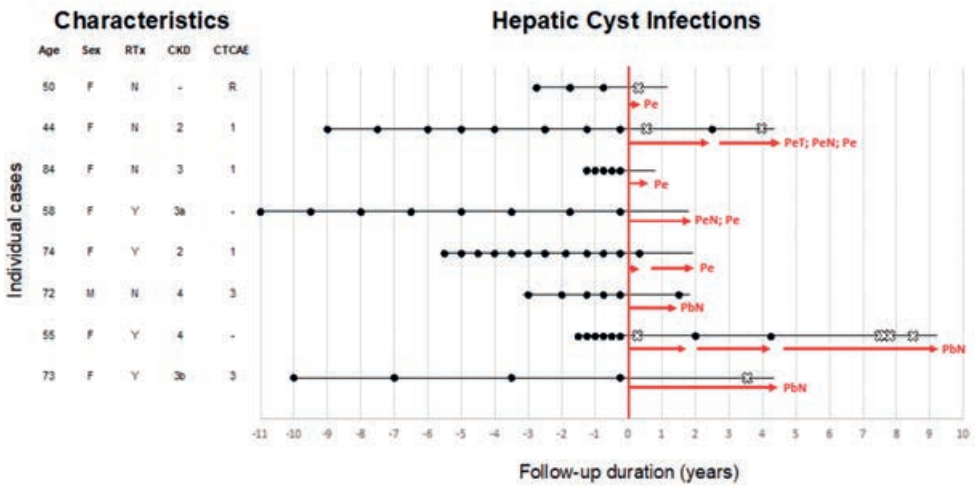

Figure 1. Hepatic cyst infections before treatment and during follow-up. Individual cases on the Y-axis. Table: Age at start of SDD. Sex (F/M) = sex (female/male); RTx (Y/N) = renal transplantation (yes/no); CKDs = Chronic Kidney Disease stage; CTCAE = Common Terminology Criteria for Adverse Events. Graph: Follow-up duration in years on the X-axis, follow-up per patient is represented by the black line, starting from the first known cyst infection. Start of Selective Decontamination of the Digestive tract (SDD) is centered at T=0, and treatment duration is represented as red arrows below the patient data. Type or combinations of SDD used are abbreviated in red (Pe = polymyxin E; Pb = polymyxin B; N = neomycin; T = tobramycin). Each dot (•) represents a hepatic cyst infection when no SDD was given. Crosses (x) represent a hepatic cyst infection during SDD treatment. When exact dates of cyst infection before SDD were not available, events were dispersed evenly (patients 2, 4, 5 and 8).

This complication occurs principally with parenteral administration, although a combination of prolonged oral administration and deficient clearance because of renal impairment may lead to systemic complications.[13, 14] In light of adverse events of aminoglycosides in an ADPKD population with impaired renal function, polymyxin E should be considered the preferred SDD therapy. In those with preserved renal function, a combination of polymyxin and neomycin is suggested to increase its antimicrobial coverage.

One case had proven resistance to polymyxin E, and another was suspected because of loss-of-response. As patients were not regularly screened for antimicrobial resistance, total prevalence and impact remains unknown. Resistance to SDD usually does not influence future therapy as polymyxins and aminoglycosides are rarely used as therapeutic systemic antimicrobials in these patients.

Antimicrobial resistance and recurrence after cessation of SDD have been reported previously.[15] A prospective study showed that post-intensive care unit (ICU) incidences of hospital acquired infections tended to be higher in patients that had received SDD, which may be related to changes in gut colonization.[16] This was supported by the finding that rebound of antibiotic resistance occurred upon withdrawal of SDD.[17] By contrast, a meta-analysis did not show increase in resistance with SDD in ICUs.[18] These conflicting results may stem from highly individualized effects on the gut resistome.[19] Nevertheless, the societal impact of potential increased antimicrobial resistance should be considered before initiating SDD. In clinical practice, periodic surveillance of antimicrobial resistance should be considered for long-term SDD, especially for monotherapy.

We describe the experience in two Dutch referral centers, limiting generalizability. Several factors could have led to over- or underestimation of infection incidence. First, data may have been collected directly from patients by their physician. Second, some episodes were diagnosed as probable hepatic cyst infection without systematically excluding other causes of infection. We decided to use the treating physician's diagnosis. Third, we used resistance patterns to distinguish rapidly succeeding infection from persistent infections, as specific pathogen typing was not available. Fourth, the post-SDD incidence may be underestimated because the recurrence free-episode period until present was included. All microbiological diagnostic procedures performed in Dutch clinical microbiology laboratories follow standardized procedures and have set performance standards for antimicrobial susceptibility tests. However, in view of the retrospective nature of this study variations in pathogen identification and susceptibility testing between laboratories cannot be excluded.

Future studies are needed to corroborate these preliminary results. As there are only few patients, conducting a randomized trial is not feasible. While crossover may reduce sample size, stopping SDD early may pose a serious risk of recurrence. Therefore, a study with fixed investigational products, a set follow-up duration before and after start of SDD, with prospective assessment of efficacy, safety and antimicrobial resistance is paramount.

To conclude, this proof-of-concept retrospective study shows a potential benefit of SDD prophylaxis in PLD patients suffering from recurring hepatic cyst infections. Despite that SDD is associated with potentially severe adverse events, we recommend considering SDD in management of recurrent cyst infection in these patients.

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TRANSPARENCY DECLARATION

None to declare.

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4a

MANAGEMENT OF PORTAL HYPERTENSION AND ASCITES IN POLYCYSTIC LIVER DISEASE

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ABSTRACT

Patients suffering from polycystic liver disease may develop Hepatic Venous Outflow Obstruction, Portal Vein Obstruction and/or Inferior Caval Vein Syndrome due to cystic mass effect. This can cause portal hypertension, leading to ascites, variceal hemorrhage or splenomegaly. For this review, we evaluate the evidence to provide clinical guidance for physicians faced with this complication. Diagnosis is made with imaging such as ultrasound, CT or MRI. Therapy includes conventional therapy with diuretics and paracentesis, and medical therapy using somatostatin analogues. Based on disease phenotype various (non-)surgical liver-volume reducing therapies, hepatic or portal venous stenting, transjugular intrahepatic portosystemic shunts and liver transplantation may be considered. Due to complicated anatomy, use of high-risk interventions and lack of empirical evidence, patients should be treated in expert centers.

KEY POINTS

- Portal hypertension is a rare but severe complication of polycystic liver disease
- Patients may suffer from obstruction of hepatic, portal or caval veins
- Diagnostics should focus on imaging techniques
- Treatment should be tailored to each individual patient's symptoms
- Interventional treatment should be performed in specialist centers

INTRODUCTION

Polycystic liver disease (PLD) is characterized by the presence of numerous fluid-filled cysts in the liver. PLD occurs in two distinct genetic disorders, associated with autosomal dominant polycystic kidney disease (ADPKD) or in absence of renal cysts as autosomal dominant polycystic liver disease (ADPLD).[1] PLD is a hereditary condition that results in progressive hepatomegaly in a proportion of patients with subsequent displacement of adjacent organs and symptoms such as pain, dyspnea, early satiety, hepatic cyst infections and the development of portal hypertension.[1,2] Disease severity is classified as mild when height-adjusted liver volume (hTLV) is below 1600 ml/m, moderate between 1600 and 3200 ml/m, and severe above 3200 ml/m.[3] PLD may result in clinically significant portal hypertension through various mechanisms with variable treatment options. However, literature is scarce on when and how these options come into play. We aim to review the literature on portal hypertension in PLD and discuss management of related complications. Portal hypertension in context of autosomal recessive polycystic kidney disease (ARPKD) with congenital hepatic fibrosis is not within the scope of this review.[4]

Causes of portal hypertension in PLD

Clinically significant portal hypertension is a clinical syndrome characterized by splenomegaly, ascites, gastrointestinal varices, and encephalopathy and is defined by an increased hepatic venous pressure gradient (HVPG).[5] Although portal hypertension is mostly associated with cirrhosis, it can also occur in advanced cases of PLD. Patients may be confronted with three typical types of vascular obstruction: (1) Hepatic Venous Outflow Obstruction (HVOO), (2) Portal Vein Obstruction (PVO) and/or (3) inferior caval vein syndrome (ICVS) due to cystic mass effect or unfavorably located cysts. These conditions can lead to non-cirrhotic portal hypertension.[6] An anatomical representation of the three vascular obstruction types is presented in Figure 1.

HVOO is characterized by reduction of the outflow of venous blood from the liver into the caval vein (Figure 2). HVOO is a rare condition, which can either be caused by (I) hepatic vein thrombosis in Budd-Chiari Syndrome (BCS), (II) external compression by tumor, cyst or abscess, or (III) after liver transplantation.[7,8]

PVO is characterized by obstruction of inflow from the portal venous system into the liver. This may be due to external compression, but also by portal vein thrombosis induced by disruption of portal vein inflow and stagnant blood flow due to mechanical effects from compression.[9]

Finally, the polycystic liver can become so large that it will cause compression of the inferior caval vein (ICV), resulting in ICVS. Edema of both lower extremities can be the presenting symptom in case of ICVS.[10]

Incidence of portal hypertension in PLD

There is limited data on incidence of portal hypertension in PLD and these few reports are restricted to small cohorts which are heterogeneous or highly selected. In a retrospective study of 125 ADPLD patients, 6% developed portal hypertension during follow-up.[11] A single-center retrospective study

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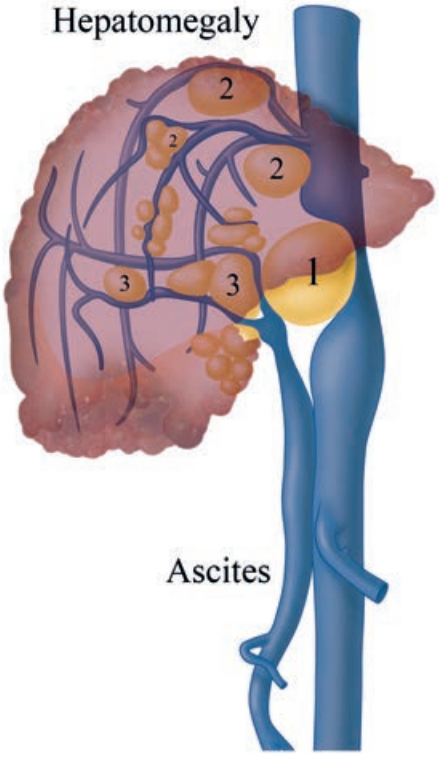

Figure 1. Causes of portal hypertension in PLD are shown: 1. inferior caval vein syndrome (ICVS); 2. hepatic venous outflow obstruction (HVOO); 3. portal vein obstruction (PVO).

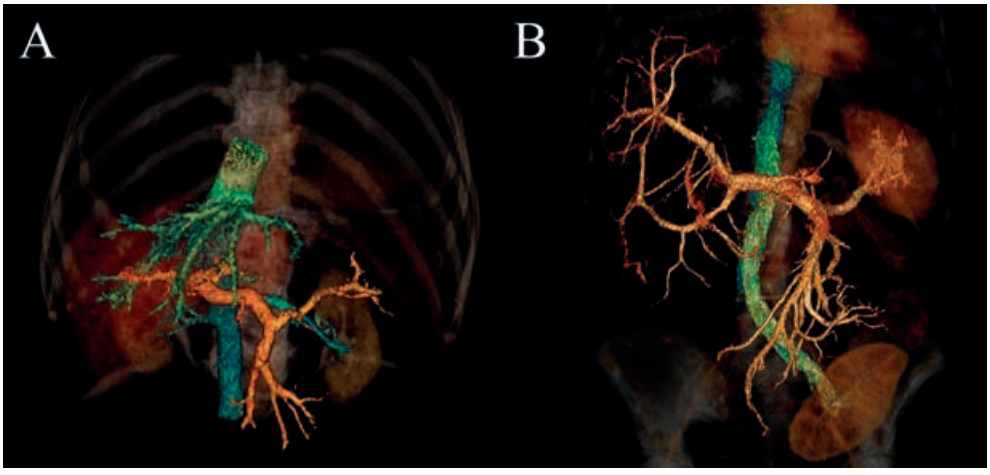

Figure 2. 3D-reconstruction of intravenous contrast, the portal venous system is colored orange and the caval venous system is colored cyan. Panel A: healthy control. Panel B: patient with polycystic liver disease and hepatic venous outflow obstruction. No hepatic veins are visible due to external compression by cystic liver tissue. Renal transplant is also visible.

from the United Kingdom found that of 47 PLD patients listed for liver transplantation, 40% had portal hypertension.[12]

The largest cause of portal hypertension in PLD patients is HVOO. The incidence has been investigated in a recent cohort study of pre-operative imaging for 45 PLD patients undergoing liver resections. The study demonstrated that, based on a semiquantitative score, 78% of PLD-patients had moderate stenosis while 22% had severe hepatic vein stenosis. Venous collaterals were present in the majority of patients.[9] In addition to obstruction at the level of hepatic veins, the non-cystic liver parenchyma of these patients may show so-called 'HVOO lesions' at the level of the sinusoidal endothelium or terminal hepatic vein. These lesions (sinusoidal distension, congestion, peliosis and regenerative nodular hyperplasia) are seen in non-cystic parenchyma in 92% of PLD patients and are also encountered in other diseases with HVOO.[9,13]

In addition, the cohort study documented that liver biopsy findings were compatible with abnormal portal spaces in 67% of patients and portal vein dilation was present in 7% of patients.[9] However, the incidence of clinically relevant PVO and ICVS is probably rare as the literature is limited to a few case reports.[10,14-17] Interestingly, both presentations may be caused by a single, strategically located (very) large cyst.[10,18]

Clinical symptoms of portal hypertension in PLD

The most common clinical symptom of portal hypertension in PLD is ascites. The accumulation of fluid within the peritoneal cavity further increases intra-abdominal pressure leading to pressure-related symptoms such as dyspnea, abdominal distension, abdominal pain, increased weight and decreased quality of life of the polycystic patient.[15,19] As these overlap with symptoms caused by hepatomegaly in PLD, it can be challenging to discriminate between liver growth and ascites.[19,20]

Cross-sectional data show that 5% of ADPLD patients developed ascites during follow-up.[11] In a retrospective study of 461 ADPKD patients from South Korea, prevalence of ascites on imaging was 16.6% for the whole group. Importantly, presence of ascites was strongly correlated with liver volume, and more than half of severely affected PLD patients (hTLV ≥ 3200) were affected.[3] In another study with PLD patients with portal hypertension that were listed for liver transplantation, nearly 58% had ascites.[12]

Besides liver volume, another important risk factor for the occurrence of ascites is abdominal surgery such as liver resections, laparoscopic fenestration or nephrectomy.[15,21-24] For most patients, post-operative ascites is transient and usually responds to medical management with diuretics, low salt diet and repeat paracenteses.[14] After liver resection, 42% of patients had post-operative ascites.[25] Persistent and massive ascites was seen in 18%.[25] In another study, refractory ascites after liver resection occurred in 9%.[14] After laparoscopic fenestration, transient ascites occurred in 46% in one study, but was absent in other cohorts.[26-28] We were unable to find data on refractory ascites after laparoscopic fenestration.

Finally, cyst rupture, a very rare complication of PLD, can also be the cause of transient ascites and is often accompanied by severe abdominal pain.[1]

Case reports have highlighted HVOO and refractory ascites as a complication of nephrectomy in ADPKD patients.[15,21,22] In this respect , it is relevant to weigh the risks and benefits of nephrectomy,

as the merits of nephrectomy and patient selection are uncertain.[29] A 2015 guideline suggests that polycystic kidneys should not be routinely removed prior to transplantation, as it is associated with significant morbidity and mortality.[30] Pre-transplant nephrectomy is reserved for patients with a history of severe or recurrent cyst infections or bleeding, symptomatic nephrolithiasis, intractable pain and space restriction prior to transplantation.[30] Post-transplant unilateral nephrectomy appears to have fewer complications, but is also not without significant risks.[31]

It is not to be expected that etiology of polycystic disease forms an important risk factor. Unpublished data from our center show that prevalence of ascites was evenly distributed among ADPKD (4%) en ADPLD patients (5%). In another cohort study there were no differences in ascites prevalence between patients listed for liver transplantation or combined liver-kidney transplantation.[12]

The presence of varices and variceal hemorrhage is rare in PLD. In a retrospective study of 125 ADPLD patients, two (2%) patients had varices during follow-up.[11] The prevalence of varices was also 2% in patients listed for liver transplantation.[12] Variceal hemorrhage has been described in only six cases.[32-37] For management of varices, we refer to the relevant guidelines.[38,39]

DIAGNOSIS OF PORTAL HYPERTENSION IN PLD

Imaging

Both hepatic cysts and ascites can be clearly distinguished with ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) (Figure 3).[40,41] In PLD-patients presenting with increased abdominal swelling, ultrasound can be used to promptly distinguish between liver growth and accumulation of ascites. Splenomegaly can also be assessed with all three imaging modalities.[12] Contrasted multiphasic CT or MRI can be used to show compression of the portal vein, hepatic veins and the inferior caval vein , while Doppler ultrasound is able to measure flow.[42]

Paracentesis

The role of paracentesis as a diagnostic tool is debated. Some suggest that initial workup in polycystic patients should include routine analysis of ascitic fluid to rule out infections.[42] The discriminatory capacity beyond diagnosis of infectious processes is questionable. Ascites due to PLD can be both transudative[42-45] and exudative.[12,18,44] Transudates result from increased fluid pressures in the plasma. Exudates can occur due to high permeability to proteins of the dilated sinusoidal walls in HVOO.[44] As paracentesis does not distinguish between types of vascular obstruction, its merit only lies in the diagnosis of infected ascites.

Hepatic Venous Pressure Gradient (HVPG)

Even though HVPG is mandatory according to the definition of (clinically significant) portal hypertension, it is not universally performed in a standard fashion when evaluating cirrhotic patients.[46] Furthermore, measurement of HVPG can be particularly technically challenging in patients with PLD due to the distorted anatomy.[12] With lack of reporting of HVPG measurements in the literature, its use for PLD patients requires further clarification and validation in future studies.

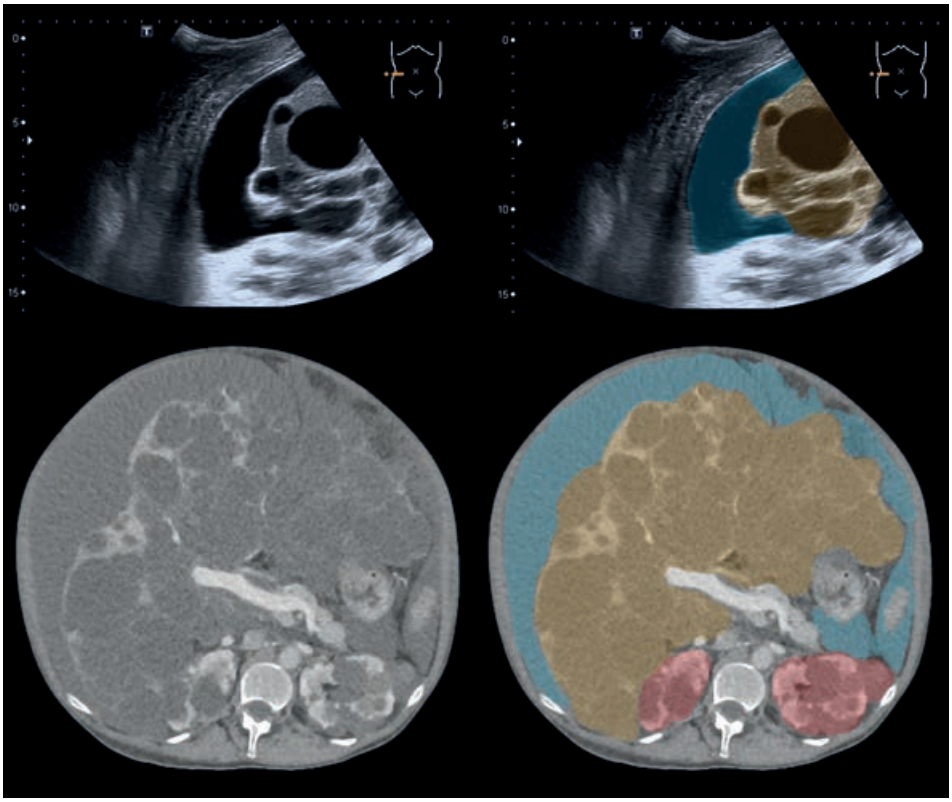

Figure 3. Imaging with ultrasound and transversal computed tomography (CT) of ascites in a polycystic liver disease patient with hepatic venous outflow obstruction. Ascites is colored blue, polycystic liver tissue is colored orange, polycystic kidney tissue is colored red.

MANAGEMENT OF PORTAL HYPERTENSION IN PLD

Reduction of portal pressure is achieved by decrease of portal flow by splanchnic vasodilation. Beta blockers are the cornerstone of treatment of portal hypertension, however, there is no literature that documents the benefit of propranolol or carvedilol in context of PLD.[38] Somatostatin analogues (SSA), such as octreotide or lanreotide, also reduce hepatic blood flow and portal pressure and are often used in PLD patients due to the ability to reduce liver volume.[1] However, the reported effects on lowering portal pressure have been variable with a majority of studies in general cirrhotic patients reporting little to no effect.[47] Octreotide is only recommended in case of variceal bleeding.[38]

This review on the management of portal hypertension in PLD focusses on (1) the management of ascites by SSA, diuretics and paracentesis, (2) the percutaneous or surgical reduction of liver volume (3) the restoration of flow in the liver vasculature by stents and shunts. Finally, liver transplantation will be discussed. It is important to consider liver transplantation assessment in an early stage, and should be performed in parallel to the management options described below.

Management of ascites

While the effect of SSA on abdominal complaints and liver volume has been studied in PLD, little research has been done to study the merits of therapy for ascites. One study described two cases of PLD-associated ascites that were successfully treated with SSA. In both patients, this resulted in a dramatic clinical improvement, disappearance of ascites and a decrease of liver volume, without the need for interventional treatment.[48] As side effects of SSA are usually mild and diminish over time, they can be used as a valid alternative to more invasive procedures in PLD.[1] Some authors have proposed treatment with SSA in combination with ranitidine after fenestration surgery to minimize development of ascites through the surface of the exposed cyst remnants, but more research is needed to support this strategy.[49]

Ursodeoxycholic acid (UDCA) has also been proposed as medical therapy for PLD, as it inhibits cholangiocyte proliferation in vitro and in murine models.[50,51] However, a phase-2 randomized controlled trial showed no benefit on growth of total liver volume.[52] We were unable to find any data on the effect of UDCA on ascites or portal hypertension in PLD.

As with ascites in decompensated cirrhotic patients, diuretics are used to decrease production of ascites. Although sodium restriction has not been studied in PLD-patients, it seems reasonable to advocate this practice in line with guidelines for other causes of ascites.[38,53] Spironolactone and furosemide are indicated in cirrhosis as the Renin-Angiotensin-Aldosteron-System (RAAS) is markedly upregulated and patients develop a hyperdynamic circulatory syndrome.[54,55] However, this is not necessarily the case for PLD-related ascites. We could not identify studies that investigated RAAS in PLD, but the mechanisms of HVOO in PLD are likely to be comparable to BCS. One study found that hemodynamics are markedly different between BCS patients and matched decompensated cirrhosis patients. Patients with BCS had normal cardiopulmonary hemodynamics, and most of them did not exhibit systemic vasodilation, but nonetheless had a marked activation of neurohumoral vasoactive systems (such as RAAS).[54] In addition, patients with ADPKD are predisposed to early onset hypertension, which has been attributed, among other factors, to activation of RAAS by the enlargement of renal cysts. [56] Since RAAS upregulation and the resulting hyperaldosteronism also seem to play a pivotal role in hepatic vein obstructions, spironolactone should typically be the first-line diuretic. Chlorothiazide or furosemide can be added, which can provide synergy and avoid hyperkalemia.[38]

Vaptans are selective antagonists of the vasopressin 2 (V2) receptors in the principal cells of the collecting ducts that enhance solute-free water excretion and thus raise serum sodium levels.[53] For example, tolvaptan has been shown to have a survival-benefit compared to control.[57] Additionally, a phase 2 trial has shown that tolvaptan significantly reduced the body weight and abdominal circumference compared to placebo in patients with liver cirrhosis-associated ascites.[58] Another randomized trial showed that a combination of conventional natriuretic drugs and tolvaptan was superior to conventional therapy alone in cirrhosis-associated ascites.[59]

Two recent case reports have suggested that tolvaptan may also reduce liver volume.[60,61] The potential effect was corroborated by an *in vitro* study that showed involvement of vasopressin in liver cyst growth.[62] The effect of tolvaptan on liver volume in PLD is currently being investigated

in larger cohorts. Tolvaptan is also effectively used in ADPKD patients with rapidly progressive disease to slow deterioration of renal function.[63] So in theory, ADPKD patients with PLD-related portal hypertension could benefit particularly from tolvaptan treatment.

It is important to note that the safety of vaptans for cirrhotic patients has only been established for short-term treatments lasting from one week to one month.[38] Thus, at present, the use of vaptans for portal hypertension is limited to controlled clinical studies.[38] As liver function is preserved in PLD patients, we hypothesize that the risks of vaptans is lower in this group and its use for PLD-related portal hypertension needs further investigation. However, the high cost of tolvaptan, which ranges between € 15,000 and € 30,000 per year, is a major barrier for widespread use.[64-66]

Lastly, large volume paracentesis (with or without albumin replacement) under radiological guidance should be used to achieve symptomatic relief, reduce fluid burden and alleviate abdominal distension.[15,45] The presence of spontaneous bacterial peritonitis, although infrequent, should be considered.[38] We were unable to find data on the prevalence of peritonitis in PLD patients.

Reduction of liver volume

Liver-volume reducing therapy is the mainstay of treatment for PLD. Current guidelines advocate the use of SSA for this purpose.[1] Multiple studies have shown that SSA reduce liver volume by 3 to 8% compared to an increase in liver volume in the control group of 1 to 8%.[1] Besides medical treatment with SSA, several percutaneous (sclerotherapy and embolization) and surgical (fenestration and resection) interventions are used.[1] In specific cases, these interventions can also be used to treat strategically located cysts or reduce mass effect. Subsequent improvement of hepatic blood flow reduces portal hypertension.

Percutaneous aspiration sclerotherapy is a valid strategy for treatment of large symptomatic hepatic cysts. A pigtail catheter is positioned in the cyst cavity to evacuate the fluid. Next, a sclerosing agent (e.g. ethanol, tetracycline, polidocanol) is injected, which damages the inner epithelial lining resulting in regression of the cyst.[67] A recent systematic review found that aspiration sclerotherapy reduces proportional cyst volume by 76-100%.[68] Aspiration sclerotherapy comes with complications such as pain, ethanol intoxication, cyst bleeding and rarely cyst infections.[68] Because of its minimally invasive nature and potency to achieve cyst volume reduction, aspiration sclerotherapy can be used to treat strategically located cysts that are the cause of portal hypertension. In a case report, in one patient with ascites and massive edema of the lower extremities, three strategically located cysts were aspirated to relieve caval pressure. Additionally, ascites was drained, diuretics and somatostatin analogue were started and the patient recovered,[10] highlighting that a combination of conventional and interventional treatment is often necessary. In a second patient with portal hypertension, a large gastro-renal shunt and liver dysfunction, a total of 13 aspiration sclerotherapy procedures were used to reduce liver volume. Afterwards, balloon-occluded retrograde transvenous obliteration of the shunt and partial splenic embolization were performed to increase portal blood flow, which resulted in restoration of liver function.[69]

A novel intervention to reduce liver volume is transcatheter arterial embolization (TAE). Therapy comprises placement of microcoils in hepatic artery branches and may be an option for

treatment of patients in poor functional status with symptomatic polycystic liver disease.[70] TAE was first described in 2004. In this case report, two TAE procedures were performed in a patient with massive ascites who needed therapeutic paracentesis every two weeks. The need for any paracenteses subsided after the second intervention. Liver volume was reduced by 54% after two years of follow-up.[71] TAE may be an alternative to liver resection, however, only retrospective studies have been performed and very few centers are experienced with this procedure.

An alternative to the percutaneous approach is laparoscopic fenestration, sometimes also called deroofing. It combines cyst fluid aspiration and surgical excision of extra-hepatic cyst wall in a single laparoscopic procedure. A recent systematic review reported the effectiveness for solitary cysts and polycystic liver disease patients. The recurrence rate (34%) and complication rate (29%) in PLD patients was high. An estimated 7% of PLD-patients undergoing laparoscopic fenestration suffered major complications.[23] Laparoscopic fenestration is also a risk factor for ascites. Aspiration sclerotherapy and laparoscopic fenestration have never been compared head-to-head in a formal clinical trial. Indications, techniques and follow-up vary between centers and studies, so it is difficult to compare the volume-reducing ability of the procedures. In our center, there is a preference for aspiration sclerotherapy as it is less invasive and carries a lower complication rate.[72] Laparoscopic fenestration is used after second recurrence of cyst growth or if more than two large cysts need to be treated for a relevant effect. Specialized hepatologists, surgeons and interventional radiologists should make a comparative assessment on gains and risks for the individual patient. The effectiveness of laparoscopic fenestration for treatment-resistant ascites has not been described in the literature.

Beyond laparoscopic fenestration, there is more extensive surgery that can be applied to PLD. Liver resection consists of resection of multiple liver segments and is often combined with cyst fenestration of the remnant liver. Liver resection is the only therapy that guarantees a large reduction of liver volume.[24] However, major morbidity occurs in 21% of patients and operative mortality is 3%. Importantly, liver resection was the cause of treatment-resistant HVOO that required vascular intervention in 5% of patients.[24] A few published cases (one with PVO and three with ICVS) underline the potential of (extended) liver resection for ascites in PLD.[10,15]

Two classifications that guide decision-making for surgical therapy in PLD have been proposed. The Gigot classification (type I, II & III)[73] and Mayo classification (type A, B, C & D)[74] both categorize patients based on number, size and location of hepatic cysts. Observation or medical therapy is advised for type A patients. Cyst fenestration is recommended for type B or type I/II patients. Combined partial hepatectomy and cyst fenestration is performed in type C or type III patients. Liver transplantation can be considered for type D patients. However, the classifications have not been tailored to PLD patients suffering from portal hypertension or ascites due to liver cysts.

Restoration of flow

In a number of PLD patients, conventional therapy for portal hypertension is insufficient, refractory ascites has ensued, and the limits of volume-reducing therapy have been reached and preclude repeat operative intervention. Also, imaging of the portal and hepatic veins or ICV may have identified a focal point of compression/stenosis leading to venous obstruction. These clinical

settings should prompt the consideration of intravascular stenting. In addition, the use of surgical portocaval or percutaneous peritoneovenous shunt creation is discussed.

In case of ICVS and/or HVOO, patients may be treated with percutaneous venous stenting to relieve venous obstruction. One retrospective study found seven patients that were treated with ICV stenting and two patients had concomitant right hepatic vein stenting. All patients presented with refractory ascites. Five (71%) of patients had maintained clinical improvement after a mean follow-up of 12 months. In the two non-responders, surgical peritoneovenous shunt creation was necessary.[14]

Only two case reports describe the use of hepatic vein stenting without ICV stenting. Both patients presented with intractable ascites due to HVOO and were treated with self-expanding metal stents. The first patient had normal caliber left and right hepatic veins and stenosis of the middle hepatic vein due to multiple cysts, which was treated with stent placement. The second patient had absence of contrast enhancement in the left and middle hepatic veins, and only minor flow in the right hepatic vein. In this case, only canalization of the right hepatic vein could be established to facilitate stent placement. In both patients the pressure gradient restored to normal values after stent placement and patients showed a swift recovery with disappearance of ascites.[45,75]

Literature on stent placement for PVO is limited to one report. This describes a PLD patient with recurrent variceal hemorrhage due to portal vein stricture, that was treated with balloon dilation and placement of a 14mm Wallstent in the portal vein. In addition, gastric and esophageal varices were embolized.[32]

These results suggest that venous stent placement is safe and effective in select patients and should be considered as a possible intervention in the treatment of medically intractable ascites.

Transjugular intrahepatic portosystemic shunts (TIPS) decompresses the portal system by shunting the portal system into a hepatic vein. The clinical effects of TIPS for decompensated cirrhotic patients have been confirmed in prospective randomized controlled trials and meta-analyses have concluded that TIPS controls ascites better than large-volume paracentesis.[38] However, presence of PLD has been described as an contra-indication for the use of TIPS for portal hypertension as the creation of an intrahepatic tract may involve traversal of a cyst.[76] The potential consequences of cyst puncture may include (severe) hemorrhage, and instability if the stent bridges a cyst cavity rather than parenchyma. In addition, the effect of contact between the stent and cyst fluid, or a blood-filled cyst cavity, on shunt patency is unknown.[77,78]

In contrast, some authors have questioned this contra-indication.[76] The use of TIPS for PLD is limited to a few case reports, and has been described as successful.[76,78-82] However, complications such as intracystic hemorrhage, spontaneous bacterial peritonitis and encephalopathy have also been reported.[82] The use of a hybrid 2D/3D imaging instruments or intravascular US guidance can be used to increase safety of TIPS placement in the setting of PLD.[78,80,82] Thus, TIPS placement in context of PLD should be approached with caution. There are risks and technical challenges, and evidence of feasibility is based on a limited number of case reports. When TIPS is considered it should be preferably performed in expert centers with experienced teams and advanced imaging-guidance systems.

The more widespread use of liver transplantation and TIPS has superseded the use of surgical portocaval shunts, which consist of surgical stent graft placement between the portal and caval venous systems.[83] The decline is explained by the high mortality rate of 20 to 50%,[84] which may be even higher in the present due to a world-wide decline of experience with these procedures. The placement of a surgical mesocaval and portocaval shunt has been reported for PLD, with no procedure-related mortality and disappearance of ascites. However, no long-term follow-up was described.[15,44] Mesocaval shunts can also be placed percutaneously by an interventional radiologist.[84] But to our knowledge, this procedure has not been used for PLD patients as of yet.

The use of peritoneovenous shunts for decompensated cirrhotic patients with refractory ascites was popularized in the 1970s, but has been largely abandoned in recent years due to poor long-term results and excessive complications.[53] According to the American Association for the Study of Liver Diseases guideline, peritoneovenous shunting is reserved for diuretic-resistant decompensated cirrhosis patients who are not candidates for transplant or TIPS.[53] One case report, published in 1986, describes a patient with PLD and renal cysts. Symptoms and ascites resolved after peritoneovenous shunt placement and renal function had also improved at 14 months follow-up.[85]

In our opinion, performing surgical shunts is only indicated in severely affected PLD patients that are not eligible for liver transplantation. Potential benefits and risk should be carefully considered. Surgery should be performed in centers with extensive expertise in vascular surgery and surgical graft placement.

Liver transplantation in PLD

Liver transplantation is the only curative treatment option for PLD. As liver function is preserved in almost all patients, exception criteria have been formulated: transplantation is indicated in case of massive hepatomegaly and poor quality of life, in combination with a complication that is likely to resolve after liver transplantation. Specified complications include severe malnutrition, cachexia, biliary obstruction, cholestasis, recurrent cyst infections, and importantly: refractory ascites, portal hypertension, variceal bleeding or HVOO.[86] Data from the European Liver Transplantation Registry show a high five-year graft survival (88%) and patient survival rate (92%) for transplanted PLD patients.[87]

Liver transplantation should be considered in patients with refractory ascites, that is not amenable to treatment with conventional measures, liver-volume reducing therapy and vascular stenting or shunting. We advise to refer patients promptly for assessment for liver transplantation to prevent any delays. Combined liver-kidney transplantation in ADPKD patients with severe renal impairment should also be considered.[1]

CONCLUSION

The evidence base supporting treatment options for portal hypertension and ascites in PLD is limited, and primarily consists of case reports. Thus, all recommendations have an evidence level of D according to the GRADE criteria, and should be read as an expert opinion.[88] The use of liver transplantation in PLD has been studied in large cohort studies, resulting in moderate quality of

evidence (grade B). It is important to consider liver transplantation assessment in parallel to alternative treatment options for ascites and portal hypertension.

We propose the following algorithm for treatment of portal hypertension in PLD (Figure 4). When ascites is present, first treatment should consist of conventional therapy with diuretics. Large-volume paracentesis can be performed to provide symptomatic relief. When this is insufficient, patients are suffering from therapy-resistant and/or refractory ascites. In this case, further diagnostics are warranted and could consist of US, CT or MRI imaging. Depending on the presence of PVO, HVOO, ICVS or a combination, treatment should be tailored to the individual patient. When somatostatin analogues, percutaneous interventions, surgery, venous stenting and TIPS are not possible or not efficacious, liver transplantation should be performed, which is also curative therapy. If patients are not eligible for liver transplantation, surgical shunt placement might be an alternative, but has a serious morbidity and mortality rate, especially in less experienced hands.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

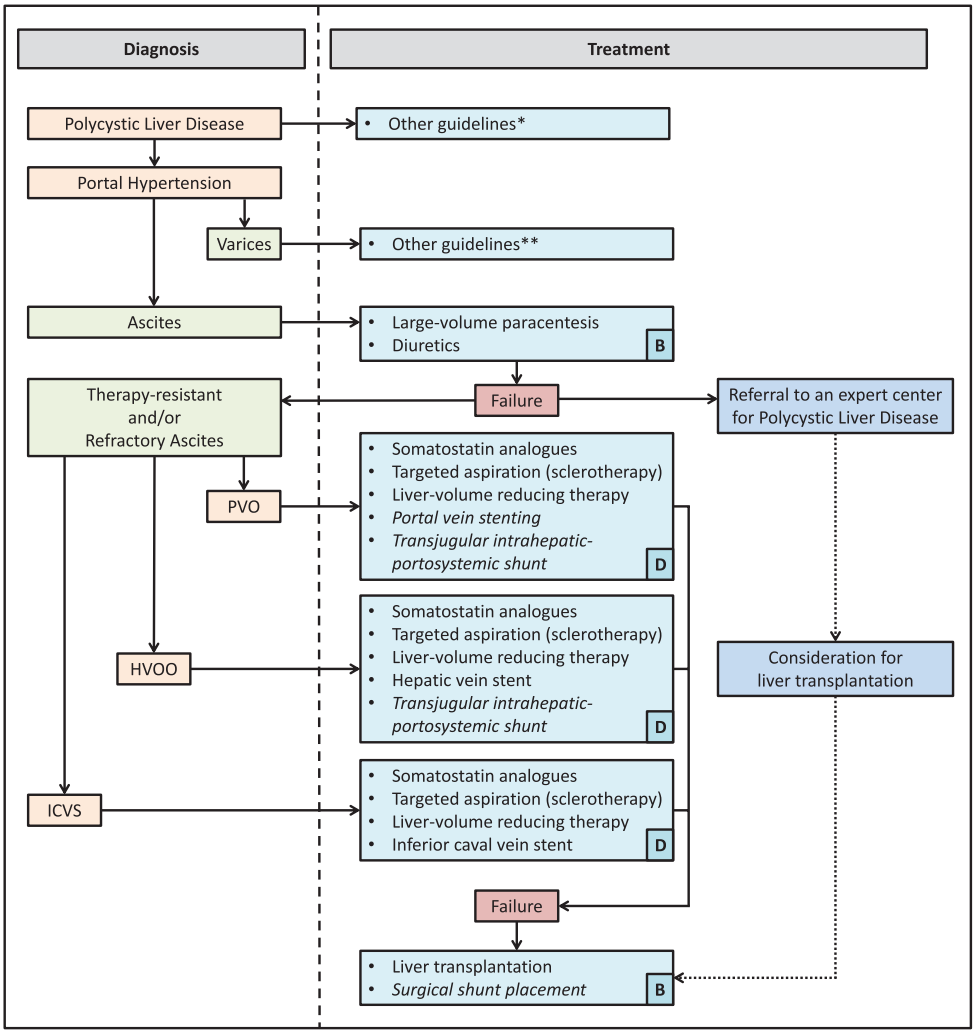

Figure 4. Treatment flowchart. Diagnoses are marked in orange, symptoms in green, treatment options in blue, failure of therapy in red. Treatment options are italicized as a caution when caveats apply. Assessments for liver transplantation should be performed in parallel to other therapies. Level of evidence is shown in the lower right corner according to the GRADE criteria (A=high, B=moderate, C=low, D=very low). Abbreviations: PVO = portal vein obstruction, HVOO = hepatic venous outflow obstruction, ICVS = inferior caval vein syndrome. Asterisks: *: See reference 1. **: See references 38 and 39.

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4b

VENOUS STENT PLACEMENT FOR REFRACTORY ASCITES DUE TO HEPATIC VENOUS OUTFLOW OBSTRUCTION IN POLYCYSTIC LIVER DISEASE – A CASE REPORT

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CASE REPORT

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by growth of fluid-filled cysts in the kidneys and liver, leading to hepatomegaly in a proportion of patients. In advanced polycystic liver disease (PLD), patients may develop hepatic venous outflow obstruction (HVOO) due to strategically located hepatic cysts. The ensuing portal hypertension results in ascites, variceal hemorrhage, splenomegaly and abnormal liver- and kidney function.[1] A recent imaging study in severe PLD revealed that hepatic venous stenosis was present in 78% of patients, while venous collaterals were present in 89%.[2] Hepatic vein stent placement has become standard practice for HVOO after liver transplantation, with patency rates of 80% after 3-years of follow-up.[3] A literature search failed to identify descriptions on hepatic venous stent placement in PLD. A patient with severe PLD complicated by HVOO who developed ascites that was resistant to pharmacological therapy was treated with a hepatic venous stent.

The Institutional Review Board did not require approval for publication. A 67-year-old female with ADPKD and extensive PLD (liver volume: 5036 mL, left kidney volume: 499 mL, right kidney volume: 638 mL, total volume: 6173 mL) was admitted for an elective left side nephrectomy because of abdominal pain, early satiety and bladder prolaps. The patient underwent kidney transplantation 15 years prior to admission. Pre-operative analysis revealed creatinine of 156 µmol/L, eGFR of 29 mL/min consistent with Chronic Kidney Disease (CKD) grade 4. An overview of therapeutic interventions is presented in Figure 1.

In the hours following nephrectomy, she developed hypoxia (oxygen saturation: 88%), right-sided dullness to percussion and auscultatory absent breath sounds. Chest-radiography showed right-sided pleural effusion with mediastinal shift. A thoracic drain was inserted with removal of 2 liters of transudative pleural fluid. A CT-scan showed multiple cysts <5 cm in diameter in the left liver lobe, and transudative ascites (serum-ascites albumin gradient of 17 to 19). Markers of cholestasis and hepatic metabolic function (ALT 49 U/L; AST 50 U/L; GGT 569 U/L; AP 338 U/L; bilirubin 24 µmol/L; prothrombin time 16 seconds) were elevated, and albumin was decreased (28.1 g/L). In absence of congestive heart failure, this suggested portal hypertension as cause of the ascites and pleural effusion. Pleurodesis was performed and furosemide (40mg/day) and spironolactone (100 mg/day) were started. This was ineffective to curtail fluid production. Because creatinine rose from 95 to 166 µmol/L (eGFR from 51 to 27 mL/min), diuretic treatment was discontinued and renal function improved within 4 days (creatinine 103 µmol/L, eGFR 46 mL/min). Intravenous octreotide, 50µg/hour was commenced, but a 10 day-course did not affect ascites production. An ascites drain was inserted, which produced 6 liters of ascites per day.

CT-angiography showed normal contrast enhancement of portal veins and compression of the caval vein from hepatic cysts. Contrast enhancement was absent in the left and middle hepatic vein and minor in the right hepatic vein (Figure 2). Duplex ultrasonography detected only a minor Doppler signal over the right hepatic vein. This suggested HVOO, with complete obstruction of the middle and left hepatic veins and partial obstruction of the right hepatic vein, as cause for ascites and pleural effusion in this patient.

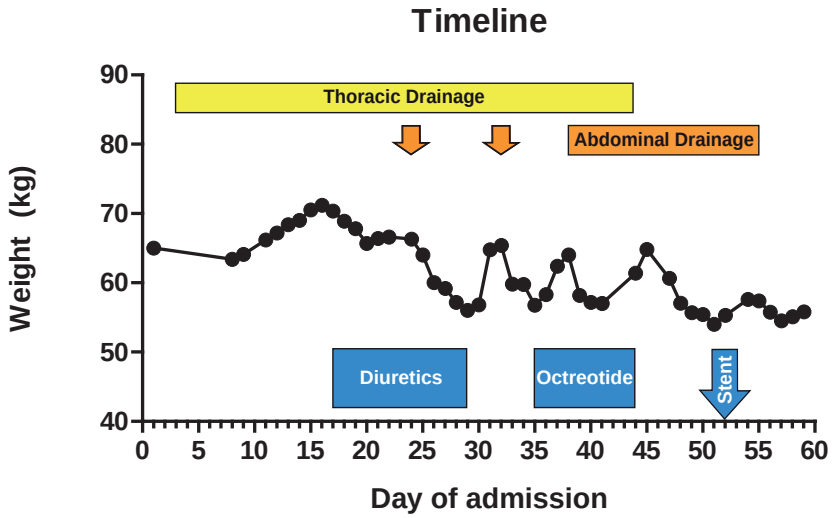
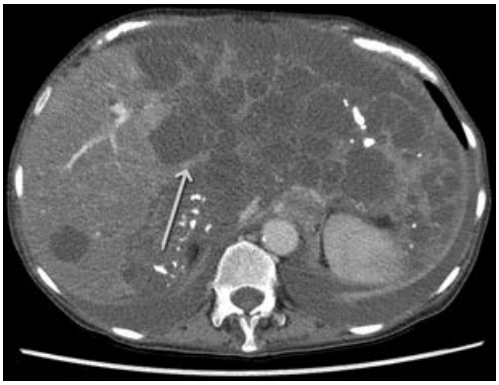


Figure 1. Timeline of hospital stay. Day of admission is plotted on the X-axis; Nephrectomy took place on day 1 and patient was released on day 59. Weight (kg) as a marker for excess fluid is plotted on the Y-axis. Fluid drainage is shown in orange bars for continuous ascites drainage and orange arrows for paracentesis. Yellow bars represent continuous drainage of pleural effusion. Treatment strategy is presented in blue bars or arrows.

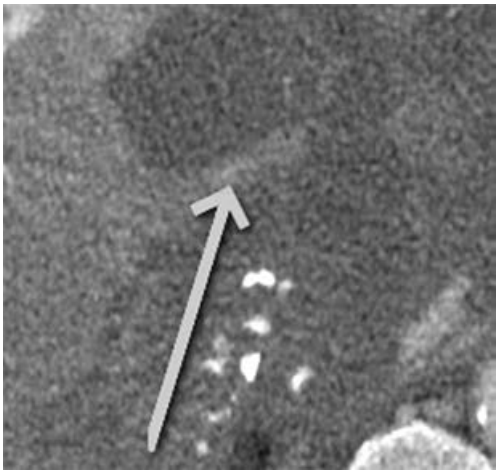
As no cysts were suitable for treatment with aspiration sclerotherapy, placement of a right hepatic vein stent was considered. After ultrasound-guided antegrade puncture of the right internal jugular vein, introduction with an 8-FR sheath and a 4-FR catheter through the stenosis in the right hepatic vein was successful (Figure 3A). Pre-stenotic peripheral pressure as well as right hepatic vein wedge pressure was 33 mmHg, right atrium pressure 7 mmHg, resulting in a 26 mmHg pressure gradient across the stenosis. An open-cell, nitinol, self-expanding stent (VENOVO Venous Stent, 10 mm in diameter x 6 cm long, Bard Medical, Covington, GA, USA) was centrally placed in the right hepatic vein partially extending into the suprahepatic caval vein (Figure 3B). Right hepatic vein pressure was 20 mmHg and right atrium pressure 19 mmHg. Production of ascites decreased rapidly and subsided 3 days after stent placement. She was discharged and three weeks after stent placement liver function tests were: ALT 62 U/L; GGT 651 U/L; AP 403 U/L; Bilirubin 19 µmol/L. Follow-up four months after stent placement showed no recurrence of ascites or pleural effusion on ultrasound and a normal ALT value (28 U/L). Renal function was unchanged creatinine: 97 µmol/L, eGFR: 49 mL/min, CKD g3a.

In summary, hepatic venous stent placement was effective to treat HVOO in context of PLD as it resulted in a drop of pressure gradient from 26 mmHg to 1 mmHg with disappearance of ascites. It is likely that the nephrectomy in the patient triggered tilting of the liver causing kinking and acute obstruction of the middle and left hepatic vein. Alternatively, a pre-existent splenorenal shunt relieving the portal pressure from HVOO might have been severed with nephrectomy. This could not be assessed on pre-operative imaging.

A)



B)



C)

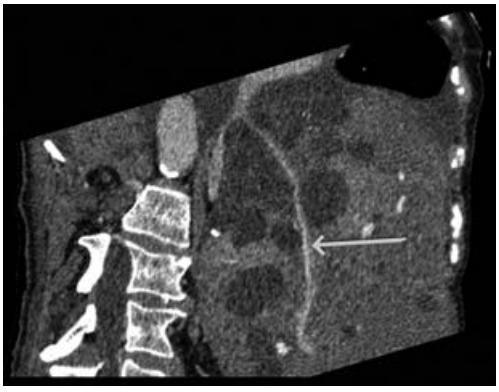


Figure 2. Panel A: CT-scan of chest and abdomen with intravenous contrast (transverse plane). **Panel B:** Magnification of the image in panel A. **Panel C:** In this more detailed reconstruction, the scan is centered on the right hepatic vein (arrow) with other structures warped around it. This shows that there was still some residual blood flow in the right hepatic vein, draining into the inferior caval vein.

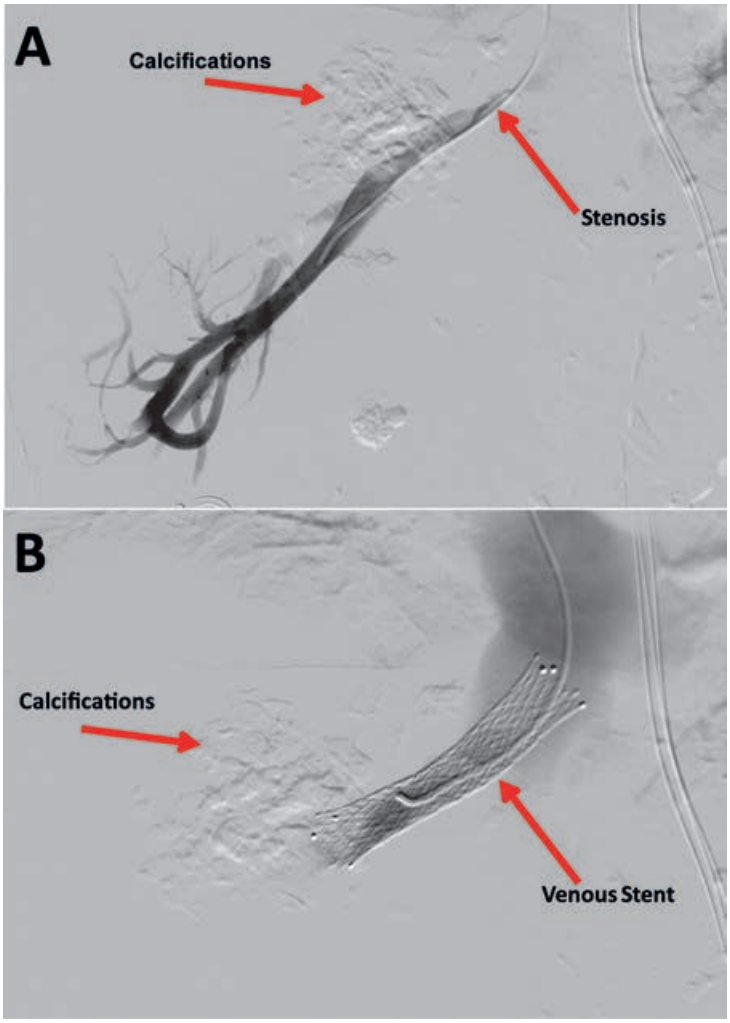


Figure 3. **Panel A:** Pre-stent placement angiography. Angiogram shows very little antegrade flow, minimal passage past the stenosis in the hepatic vein ostium and hepatic vein collaterality. **Panel B:** Post-stent placement angiography. Angiogram shows the venous stent and antegrade flow into the caval vein.

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5

CLINICAL RESPONSE AFTER LAPAROSCOPIC FENESTRATION OF SYMPTOMATIC HEPATIC CYSTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background

Laparoscopic fenestration is one of the treatment options for symptomatic hepatic cysts, either solitary or in context of polycystic liver disease (PLD), but indications, efficacy and surgical techniques are under debate.

Methods

A systematic literature search (1950-2017) of PubMed, Embase, Web of Science and the Cochrane Library was performed (CRD42017071305). Studies assessing symptomatic relief or symptomatic recurrence after laparoscopic fenestration in patients with symptomatic, non-parasitic, hepatic cysts were included. Complications were scored according to Clavien-Dindo. Methodological quality was assessed by Newcastle-Ottawa scale (NOS) for cohort studies. Pooled estimates were calculated using a random effects model for meta-analysis.

Results

Out of 5277 citations, 62 studies with a total of 1314 patients were included. Median NOS-score was 6 out of 9. Median follow-up duration was 30 months. Symptomatic relief after laparoscopic fenestration was 90.2% (95%-CI: 84.3-94.9). Symptomatic recurrence was 9.6% (95%-CI: 6.9-12.8) and re-intervention rate was 7.1% (95%-CI: 5.0-9.4). Post-operative complications occurred in 10.8% (95%-CI: 8.1-13.9) and major complications in 3.3% (95%-CI: 2.1-4.7) of patients. Procedure-related mortality was 1.0% (95%-CI: 0.5-1.6). In a subgroup analysis of PLD patients (n=146), symptomatic recurrence and re-intervention rates were significantly higher with respective rates of 33.7% (95%-CI: 18.7-50.4) and 26.4% (95%-CI: 12.6-43.0). Complications were more frequent in PLD patients, with a rate of 29.3% (95%-CI: 16.0-44.5).

Conclusions

Laparoscopic fenestration is an effective procedure for treatment of symptomatic hepatic cysts with a low symptomatic recurrence rate. The symptomatic recurrence rate and risk of complications are significantly higher in PLD patients.

INTRODUCTION

Simple hepatic cysts are fluid-filled cavities that arise from malformations of the ductal plate during embryonic development. Simple hepatic cysts are a relatively common finding as it is estimated to be present in 2.5 – 18% of the general population.[1, 2] The presence of multiple cysts, arbitrarily >10, is defined as polycystic liver disease (PLD) [3] and is usually part of the phenotype of two inherited disorders: autosomal dominant polycystic kidney disease (ADPKD) or autosomal dominant polycystic liver disease (ADPLD). Regardless of underlying pathology these patients are at risk to develop large cysts, arbitrarily defined as >5 cm in diameter. Large cysts may cause symptoms such as pain, loss of appetite, early satiety, nausea or dyspnea, sometimes causing a considerable decrease in quality of life.[3, 4] As such, treatment of large symptomatic cysts is indicated. Treatment options for large cysts comprise laparoscopic fenestration, also termed laparoscopic deroofing or unroofing, and percutaneous aspiration sclerotherapy.[5]

Laparoscopic fenestration combines cyst fluid aspiration, followed by excision of extra-hepatic cyst wall in a single laparoscopic procedure. The surgical approach of large hepatic cysts has gained popularity since the 1990s, especially after the introduction of laparoscopy. As usual in surgical practice, operative treatment has been gradually adopted in routine clinical care without valid comparison. Multiple cohort studies, however, suggest that laparoscopic fenestration is effective and safe in selected populations. Some surgeons routinely apply omentopexy (also termed omentoplasty, omental transposition or greater omentum flap), a procedure that applies omental tissue in the residual cyst cavity to prevent symptomatic recurrence. The merits and risks of omentopexy over and beyond mere laparoscopic fenestration are unexplored.

Percutaneous aspiration sclerotherapy is an alternative approach that percutaneously places a pigtail catheter in the cyst cavity to evacuate hepatic cyst fluid. After complete drainage, a sclerosing agent (e.g. ethanol, tetracycline, polidocanol) is injected in the cyst which destroys the inner epithelial lining resulting in regression of the cyst. A recent clinical guideline suggests that symptomatic simple hepatic cysts may better be managed with laparoscopic fenestration rather than percutaneous aspiration sclerotherapy with the restriction of low quality of evidence.[6] It is imperative to quantify the benefits and risks of laparoscopic fenestration and to grade the evidence on this topic.

The purpose of this study was therefore to assess the efficacy and safety of laparoscopic fenestration using a systematic review of the literature. The primary goal of treatment is alleviation of clinical symptoms, hence our focus on cohort studies and clinical trials that assessed symptomatic relief or symptomatic recurrence. We aim to give a comprehensive summary of reported efficacy and safety rates of laparoscopic fenestration to aid in clinical decision-making when faced with symptomatic hepatic cysts.

MATERIALS AND METHODS

We conducted a systematic review of studies that evaluated the efficacy of laparoscopic fenestration for symptomatic simple hepatic cysts. This study was reported according to the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist[8] (Supplementary File 1). The study protocol was registered in the Prospero database of systematic reviews (CRD42017071305) on 10 July 2017.

Eligibility criteria

We included cohort studies and clinical trials of adult patients with one or more simple (non-parasitic, non-neoplastic) and symptomatic hepatic cysts (excluding choledochal cysts or hepatic foregut cysts), either solitary or in context of PLD, that underwent laparoscopic surgery with minimal resection of healthy liver parenchyma (e.g. fenestration, deroofing, unroofing). We included studies that assessed symptomatic relief and/or symptomatic recurrence. We excluded case reports, overlapping datasets, reviews, unpublished data and conference abstracts. We excluded studies with a mean or median follow-up <6 months. For practical reasons, only articles in the following languages were included: Dutch, English, French, German, Italian and Spanish.

Literature search strategy

We systematically searched the electronic databases of PubMed MEDLINE, Embase, Web of Science and the Cochrane Library from inception to 18 July 2017, without any restrictions. The search strategy combined terms related to hepatic cysts and laparoscopic interventions. The search terms were composed in collaboration with an experienced medical librarian. Exact search terms are presented in Supplementary File 2. If no full-text article was available, the original authors were emailed in order to gain access. References of included studies were checked for additional studies missed in the primary search. All identified records were exported to citation management program EndNote X8 (Clarivate Analytics, Philadelphia, PA, USA) for deduplication, which was performed according to a published protocol.[9] After deduplication, all records were exported to the browser-based systematic review management program Covidence (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). First, two investigators (LB and SE) independently screened title and abstract to determine the eligibility of each study. Second, the full-text of all included abstracts was independently assessed by the same investigators. Disagreements in both screening phases were resolved through discussion between the two investigators. Any remaining disagreement between reviewers was resolved through discussion with a third reviewer (CR, JD).

Data extraction

All data were extracted using standardized forms by one investigator (LB). Cases of uncertainty about data extraction were resolved through discussion between two investigators. Original data of four studies was requested by email. One author was able to send the additional data required for inclusion.[10] Data extraction was checked for errors by random sampling of 10% of included studies by a second investigator (SE), which did not show any errors. Our primary outcomes were symptomatic relief (i.e. full or partial symptomatic relief) directly after surgery and symptomatic recurrence (recurrent symptoms with refilling or recurrent symptoms without confirmation of

refilling on imaging) during long-term follow-up. Secondary outcomes were study characteristics, patient characteristics, re-intervention rates, operative time, hospital stay, conversion to laparotomy and surgical technique. Reported rates of procedure-related complications and mortality were extracted. Reported post-operative complications were scored according to the Clavien-Dindo classification[11] by one investigator (LB). Grade I and II were regarded as minor complications; grade III, IV and V as major complications.

Risk of bias assessment

We used the Newcastle-Ottawa scale for cohort studies to assess the risk of bias within individual studies. Adaptations were made *a priori* to make the scale more specific for our research question (Supplementary File 3). Using this scale, studies were scored on selection of study groups, the inclusion of a control group, the comparability of groups and the ascertainment of outcome of interest. Studies were independently scored by two investigators (LB, SE). Disagreements were resolved through discussion between two investigators.

Data synthesis and analysis

For meta-analysis of reported rates, pooled estimates and 95% confidence intervals (CI) were calculated using a random effects model for meta-analysis of prevalence, using MetaXL 5.2 (Epigear, Sunrise Beach, Australia. Available at www.epigear.com). When comparing means, not overlapping 95% CI were considered significant. When comparing medians, P-value was calculated with Mann Whitney test in GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA), $P<0.05$ was considered significant.

Heterogeneity for pooled estimates was assessed using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. As we included a large number of studies, Cochran's Q and P-values are less practical for assessing heterogeneity.[12] Low, moderate and high heterogeneity was defined as an I^2 value above 25%, 50% or 75%, respectively.[12] All I^2 values were calculated with MetaXL.

Publication bias was assessed by generating funnel plots, where the standard error is plotted against the double arcsine transformed prevalence estimates of individual studies. Likelihood of publication bias was quantified using the Luis Furuya-Kanamori asymmetry index (LFK-index). An LFK-index within 1 or -1 indicates no asymmetry. An LFK-index exceeding 1 or -1 but within 2 or -2 indicates minor asymmetry. An LFK-index exceeding 2 or -2 indicates major asymmetry.[13] LFK-indices and funnel plots were generated with MetaXL.

Subgroup analyses

Potential causes of heterogeneity, as such influences on pooled estimates, were investigated by performing pre-specified subgroup analyses of underlying disease, different surgical techniques, study design, publication date and follow-up duration. Subgroups of non-categorical parameters were made by splitting included studies into two groups; 1: equal or below the median and 2: above the median.

All figures were made with Microsoft PowerPoint 2007 (Microsoft Corporation, Redmond, WA, USA) and GraphPad Prism 5.

RESULTS

Systematic search

The systematic search identified 5278 citations. Ultimately, 62 studies were included for this systematic review (Fig. 1A). Citations are presented in the supplementary files.

Study characteristics

The 62 included studies comprise a total of 1314 patients (Table 1). Studies from 5 different continents were included and most included studies were performed in Europe (Fig. 1B). The median number of patients per study was 17 (total range: 3 – 66). Of all included studies, 5 were prospective cohort studies, 10 were retrospective analyses of prospectively collected data, 28 were retrospective cohort studies and 19 studies did not give an explicit statement on data collection. Publication dates ranged from 1994 to 2017. Study periods ranged between 1982 and 2015 (Fig. 2G). Median follow-up duration was 30 months (IQR: 19 – 48) (Fig. 2A).

Of all included patients, 74% was female and 33% had PLD. Median age at time of operation was 58.7 years (IQR: 54.5 – 62.0) (Fig. 2B). Average pre-operative cyst diameter was 11.9 cm (95% CI: 11.1 – 12.7) (Fig. 2C). In 10 studies that did not exclusively operate on solitary cysts, median number of treated cysts was 1.4 (IQR: 1.3 – 2.0; total range: 1.2 – 37.7). Individual study results are presented in Supplementary File 4A-B.

Efficacy

There were 27 studies that reported the proportion of patients with full or partial symptomatic relief after surgery. Symptomatic relief was based on clinical follow-up data in 25 studies, on a structured telephone interview in one study[14] and on a specific questionnaire in another study.[15] Pooled symptomatic relief was 90.2% (95% CI: 84.3 – 94.9). Symptomatic recurrence during follow-up was 9.6% (95% CI: 6.9 – 12.8). The rate of re-intervention for the same cyst was 7.1% (95% CI: 5.0 – 9.4) (Table 2). Mean time until symptomatic recurrence was 16.1 months in 10 patients. Mean time until re-intervention was 22.1 months in 13 patients.

Safety

Conversion from laparoscopic to open surgery during the procedure was necessary in 4.5% (95% CI: 3.2 – 6.0), typically because of intra-operative bleeding, difficult positioning or extensive adhesions. Median hospital stay was 5.0 days (IQR: 3.7 – 6.0) (Fig. 2D). Post-operative complication rate was 10.8% (95% CI: 8.1 – 13.9), generally consisting of either bile leakage, ascites, pleural effusion or infections. Out of 136 reported post-operative complications, 115 could be scored according to the Clavien-Dindo classification (Fig. 2F). Of scored complications, 71.3% were minor and 28.7% were major. Overall, the pooled estimate of having a major complication after surgery was 3.3%

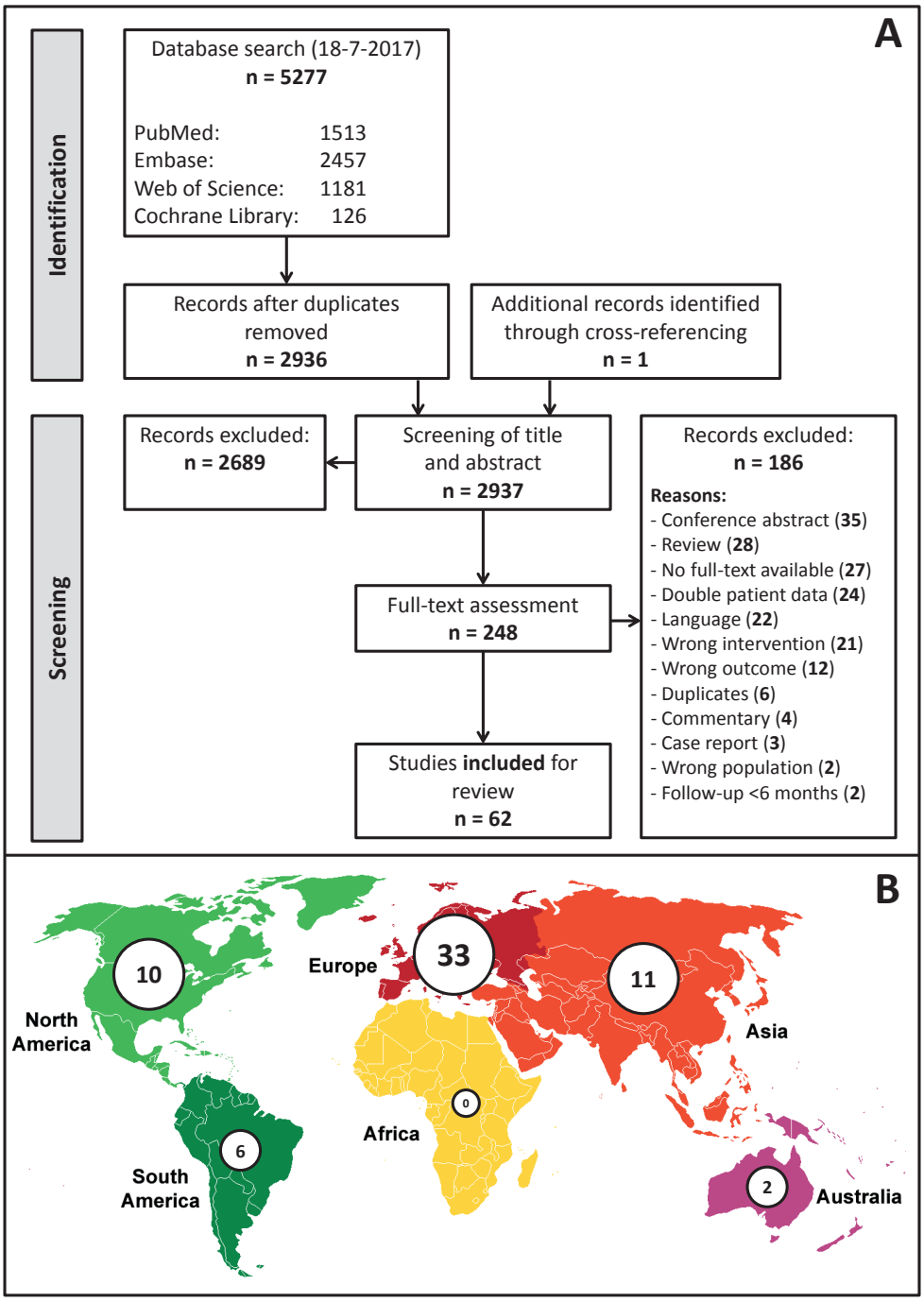

Figure 1. Panel A: PRISMA diagram. Flow chart representing literature search and elements of systematic review (identification and screening). **Panel B:** Illustrative schematic of country of origin of included studies. The number of inclusions per continent is shown.

Table 1. Summary of included studies

#	First Author	Year	N_p	#	First Author	Year	N_p
1	Ammori	2002	3	32	Lee	2014	29
2	Andriani	2000	17	33	Lolle Noerregaard	2014	29
3	Ardito	2013	47	34	Manterola	2016	41
4	Bai	2007	44	35	Marks	1998	17
5	Caetano	2006	12	36	Martin	1998	20
6	Cappellani	2002	9	37	Martinez-Perez	2016	12
7	De Reuver	2017	35	38	Maruyama	2013	16
8	Debs	2016	27	39	Mazoch	2011	15
9	Descottes	2000	15	40	Mazza	2009	66
10	Diez	1998	10	41	Morino	1994	11
11	Emmermann	1997	18	42	Neri	2006	15
12	Fabiani	2005	26	43	Palanivelu	2006	27
13	Faulds	2010	5	44	Pante	2014	7
14	Fiamingo	2003	15	45	Petri	2002	34
15	Gall	2009	61	46	Regev	2001	18
16	Gamblin	2008	46	47	Robinson	2005	11
17	Gigot	2001	19	48	Roesch Dietlen	1999	7
18	Gocho	2013	6	49	Sasi Szabo	2006	25
19	Hansen	1997	19	50	Schachter	2001	14
20	Hansman	2001	6	51	Scheuerlein	2013	47
21	Heintz	1995	3	52	Sendt	2009	27
22	Hsu	2005	5	53	Tagaya	2003	5
23	Kabbej	1996	13	54	Tan	2005	10
24	Kamphues	2011	43	55	Tocchi	2002	8
25	Katkhouda	2000	25	56	Torices	2004	21
26	Kisiel	2017	48	57	Torres	2009	13
27	Koea	2008	24	58	Treckmann	2010	42
28	Konstadoulakis	2005	9	59	Van Keimpema	2008	12
29	Koperna	1997	10	60	Wahba	2011	23
30	Kornprat	2004	21	61	Wu	2014	30
31	Kwon	2003	14	62	Zacherl	2000	7
					Total:	1994-2017	1314

Legend: Last name of first author, year of publication, N_p: number of included patients per study.

(95% CI: 2.1 – 4.7). The pooled estimate of procedure-related mortality was 1.0% (95% CI: 0.5 – 1.6) (Table 2). This was based on a single patient from a series of 9 patients.[16] The patient presented with severe PLD symptoms. After an uneventful in-hospital stay, acute renal insufficiency ensued 20 days after discharge, followed by hepatorenal failure. The patient succumbed 15 days later. Other studies showed no procedure-related mortality.

Operative technique

Median operative time was 83.5 minutes (IQR: 72 – 120) (Fig. 2E). The use of omentopexy was explicitly mentioned in 31 studies that included a total of 824 patients. The pooled estimate for use

Table 2. Overall versus PLD outcomes

	Overall:					PLD:					
Outcome	N_s	N_p	PE (%)	95% CI	I^2 (%)	N_s	N_p	PE (%)	95% CI	I^2 (%)	
Recurrence	62	1314	9.6	6.9 – 12.8	68	15	146	33.7	18.7 – 50.4	76	*
Re-intervention	56	1176	7.1	5.0 – 9.4	50	10	109	26.4	12.6 – 43.0	69	*
Complications	60	1276	10.8	8.1 – 13.9	62	13	129	29.3	16.0 – 44.5	69	*
Major	56	1106	3.3	2.2 – 4.7	27	13	129	7.2	2.1 – 14.6	46	
Conversions	44	889	4.5	3.2 – 6.0	0	9	83	8.2	3.2 – 15.0	0	
Mortality	60	1271	1.0	0.5 – 1.6	0	13	135	2.3	0.4 – 5.6	0	

Legend: asterisk (*): statistically significant difference. Abbreviations: PLD: polycystic liver disease. N_s: number of studies. N_p: number of patients. PE: pooled estimate, CI: confidence interval.

of omentopexy was 14.8% (95% CI: 5.8 – 26.6), with a total range from 0% to 100% between studies. The use of concomitant cholecystectomy was mentioned in 37 studies that included a total of 822 patients. In 21.5% (95% CI: 15.8 – 27.8) of patients concomitant cholecystectomy was performed, cited reasons were gall stones on image studies or cyst location adjacent to the gallbladder

Risk of bias

An evaluation of the quality of individual studies is presented in Table 3, which provides details of risk of bias within studies, as reflected by adjusted Newcastle-Ottawa Scale (NOS) scoring. Overall, median score for 'selection of study groups' was 3 out of 4; median score for 'comparability of groups' was 0 out of 2 and median score for 'ascertainment of outcome of interest' was 3 out of 3. Median of the total NOS-score was 6 out of 9.

Heterogeneity

Pooled estimates of outcomes were assessed for heterogeneity and publication bias. The I^2 value for symptomatic relief was 72%, for symptomatic recurrence 68%, for re-intervention 50%, for complications 62%, indicating moderate heterogeneity. The I^2 value for intra-operative conversions and for mortality was 0%, indicating negligible heterogeneity.

Publication bias

LFK-index for re-intervention was 0.91, for complications 0.42 and for intra-operative conversions 0.19, indicating no asymmetry. LFK-index for symptomatic relief was -1.09, for symptomatic recurrence 1.11, indicating minor asymmetry. LFK-index for mortality was 2.87, indicating major asymmetry. Funnel plots are shown in Figure 3.

Subgroup analyses

Polycystic liver disease

We performed a subgroup analysis of 15 studies that included only PLD patients or reported outcomes of PLD patients separately and compared these to the overall results (Table 2).

Table 3. Risk of bias assessment (NOS). Color coding: 0 1 2 3 4

Author	S. 0-4	C. 0-2	O. 0-3	Score 0-9	Author	S. 0-4	C. 0-2	O. 0-3	Score 0-9
Ammori	3	0	3	6	Lee	3	0	3	6
Andriani	3	0	2	5	Lolle Noerregaard	3	0	2	5
Ardito	2	0	3	5	Manterola	2	0	3	5
Bai	3	0	2	5	Marks	3	0	1	4
Caetano	3	0	2	5	Martin	3	0	3	6
Cappellani	3	0	3	6	Martinez-Perez	3	0	3	6
De Reuver	3	2	3	8	Maruyama	2	0	3	5
Debs	3	0	2	5	Mazoch	3	0	2	5
Descottes	2	0	3	5	Mazza	3	0	3	6
Diez	3	0	2	5	Morino	3	0	2	5
Emmermann	3	0	3	6	Ner	3	0	3	6
Fabiani	3	0	2	5	Palanivelu	3	0	3	6
Faulds	3	0	2	5	Pante	2	0	3	5
Fiamingo	3	0	3	6	Petri	2	0	2	4
Gall	3	0	1	4	Regev	2	0	3	5
Gamblin	3	0	3	6	Robinson	3	0	3	6
Gigot	3	0	3	6	Roesch Dietle	3	0	3	6
Gocho	3	0	3	6	Sasi Szabo	3	0	3	6
Hansen	3	0	3	6	Schachter	3	0	2	5
Hansman	2	0	2	4	Scheuerlein	3	0	3	6
Heintz	3	0	2	5	Sendt	3	0	3	6
Hsu	3	0	2	5	Tagaya	3	0	3	6
Kabbej	3	0	3	6	Tan	3	0	3	6
Kamphues	3	0	2	5	Tocchi	3	0	3	6
Katkhouda	3	0	3	6	Torices	3	0	3	6
Kisiel	3	0	1	4	Torres	3	0	3	6
Koea	3	0	3	6	Treckmann	3	0	2	5
Konstadoulakis	3	0	3	6	Van Keimpema	3	0	2	5
Koperna	3	0	3	6	Wahba	3	0	2	5
Kornprat	3	0	3	6	Wu	2	0	3	5
Kwon	3	0	3	6	Zacherl	3	0	3	6
					Median:	3	0	3	6

Legend: NOS: Newcastle-Ottawa Scale. S.: selection of the study groups. C.: the comparability of the groups. O.: ascertainment of outcome of interest. Score: Total NOS-Score.

Symptomatic recurrence and re-intervention rates were significantly higher with respective rates of 33.7% (95% CI: 18.7 – 50.4) and 26.4% (95% CI: 12.6 – 43.0). Post-operative complications were more frequent in PLD patients with a pooled estimate of 29.3% (95% CI: 16.0 – 44.5) (Fig. 4A). Out of 37 reported post-operative complications, all could be scored according to Clavien-Dindo. Of scored complications, 70.3% were minor and 29.7% were major. Overall, the pooled estimate of having a major complication after surgery was 7.2% (95% CI: 2.1 – 14.6). Conversion rate and procedure-related mortality did not differ significantly from overall results. Data was insufficient to analyze symptomatic relief in the PLD subgroup.

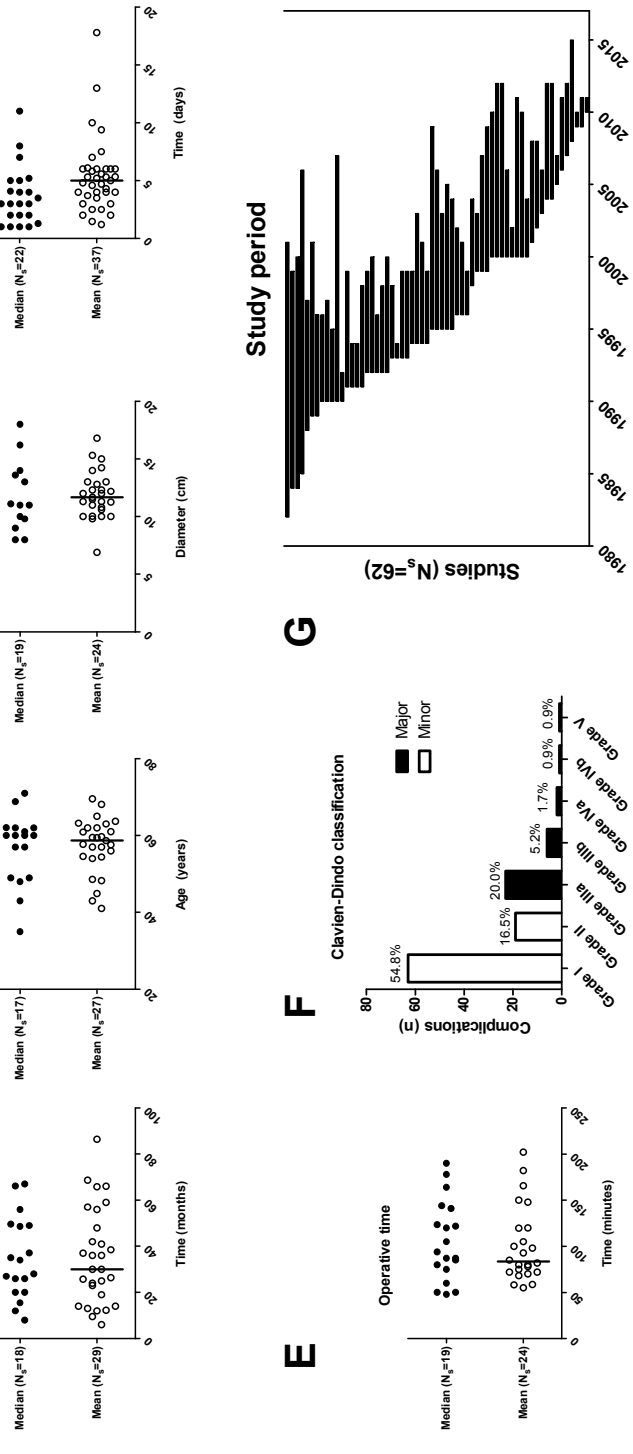

Figure 2. Panels A-E: Analysis of continuous data: reported medians and means, N_s = number of studies. For reported means, the vertical line represents the median of means **C:** Preoperative cyst size, diameter in centimetres. **Panel F:** Scoring of post-operative complications according to Clavien-Dindo. **Panel G:** Timeframes wherein patients were included (study periods) are shown per study, sorted chronologically on first inclusion.

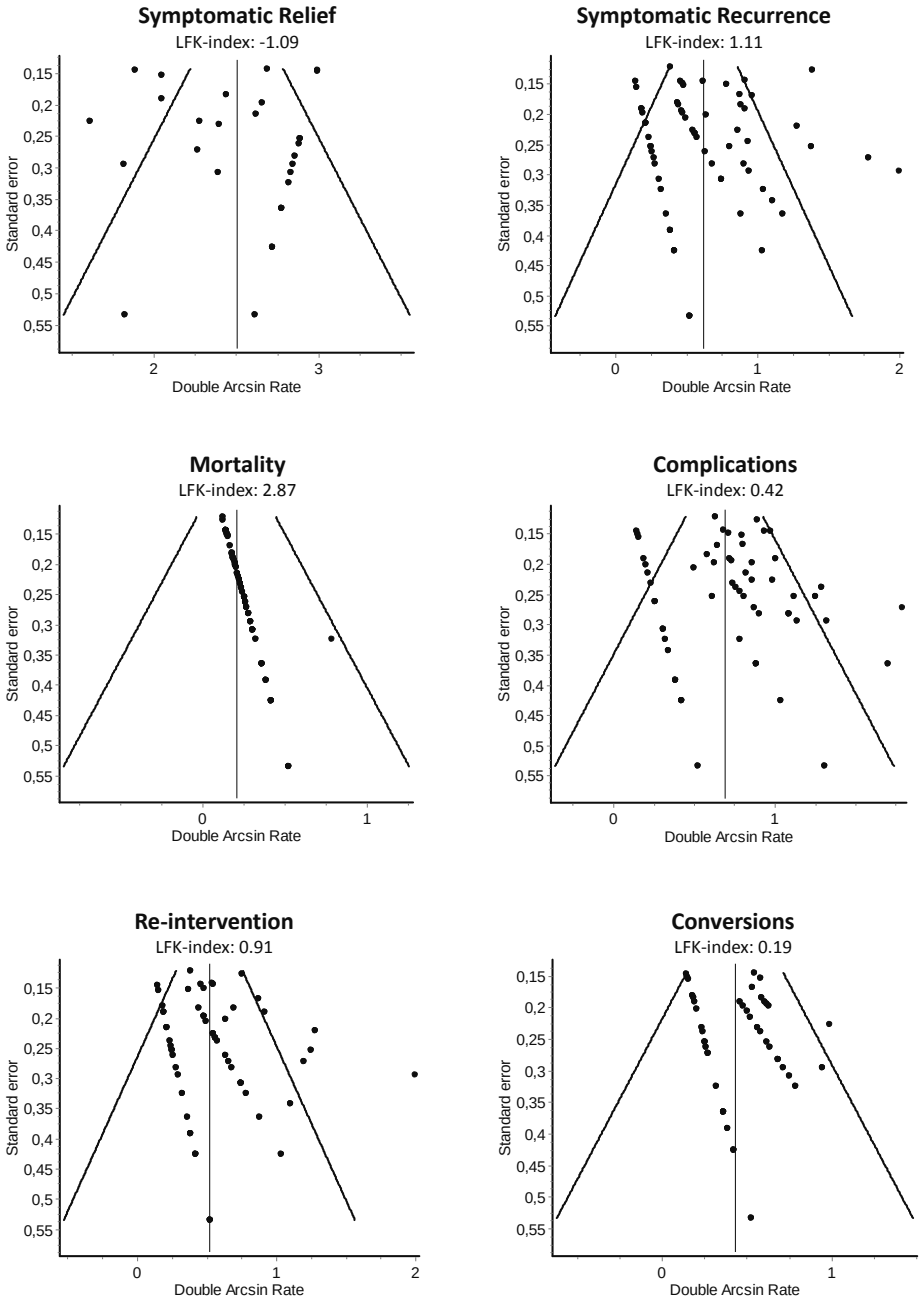

Figure 3. Funnel plots of meta-analysis outcomes. The modelled standard error is plotted against the double arcsine transformed estimates of individual studies. Luis Furuya-Kanamori asymmetry index (LFK-index) is also shown.

Omentopexy

For analysis of the effect of omentopexy on symptomatic recurrence rates, 31 studies that specified the use of omentopexy were split into two groups. As the median of additional omentopexy was 0%, studies were split accordingly. Group 1: no omentopexy performed. Group 2: omentopexy performed in 1 or more patients (total range: 11% – 100%). For group 1, pooled symptomatic recurrence was 8.7% (95% CI: 3.4 – 16.0). For group 2 it was 5.7% (95% CI: 3.0 – 9.3). In addition, we assessed the effect of omentopexy on post-operative complication rates in the same groups. For group 1, pooled complication rate was 8.4% (95% CI: 5.2 – 12.2). For group 2, it was 11.0% (95% CI: 5.8 – 17.5). In summary, there were no significant differences in pooled estimates of symptomatic recurrence rates and complication rates between groups. Data was insufficient to correct for cyst location and cyst size. (Fig. 4B-D).

Concomitant cholecystectomy

For analysis of the effect of concomitant cholecystectomy on symptomatic recurrence rates, 37 studies that specified the use of cholecystectomy were split into two groups. As the median proportion of patients that underwent additional cholecystectomy was 18.2%, studies were divided accordingly. Group A: cholecystectomy in 18.2% of patients or less (total range: 0% – 18.2%). Group B: cholecystectomy in more than 18.2% of patients (total range: 21% – 80%). For group A, pooled symptomatic recurrence was 9.3% (95% CI: 6.0 – 13.3). For group B, it was 7.3% (95% CI: 3.0 – 13.3). Next, we focused on the effect of concomitant cholecystectomy on post-operative complication rates in the same groups. For group A, pooled complication rate was 9.1% (95% CI: 5.0 – 14.2). For group B, it was 7.6% (95% CI: 3.5 – 12.9). These data are consistent with the absence of significant differences in pooled estimates of symptomatic recurrence rates and complication rates between groups (Fig. 4F-H).

Follow-up duration

We were interested in the effect of prolonged follow-up on symptomatic recurrence rates. To this end we selected 27 studies that specified mean follow-up and distinguished into two groups. The median of reported mean follow-up duration was 30 months, and we categorized studies in two groups accordingly. Group I: mean follow-up duration of 30 months or less (total range: 6 – 30 months). Group II: mean follow-up duration of more than 30 months (total range: 36 – 86.4). For group I, pooled symptomatic recurrence was 11.5% (95% CI: 5.2 – 19.7). For group II, it was 6.8% (95% CI: 1.9 – 13.9). Thus, there was no significant effect of length of follow-up after six months on reported symptomatic recurrence rates (Fig. 4E).

Publication date

Publication dates ranged between 1994 and 2017, with the year 2005 as the median. Pooled symptomatic relief for studies published from 1994 to 2005 was 90.4% (95% CI: 84.0 – 95.4) and for studies published from 2006 to 2017 it was 92.2% (95% CI: 82.0 – 98.7). Symptomatic recurrence for studies published from 1994 to 2005 was 9.8% (95% CI: 5.9 – 14.6) and for studies published from

2006 to 2017 it was 9.1% (95% CI: 4.4 – 13.5). Next, we assessed the effect of publication date on conversion rates. In studies published from 1994 to 2005 the pooled conversion rate was 6.8% (95% CI: 4.3 – 9.8) and for studies published from 2006 to 2017 it was 3.4% (95% CI: 2.1 – 5.0). It must be noted that there were four studies with a conversion rate of 10% or higher and all were published before 2006.[16-19] In studies published from 1994 to 2005 the pooled complication rate was 12.4% (95% CI: 8.2 – 17.4) and for studies published from 2006 to 2017 it was 9.9% (95% CI: 6.4 – 14.1). In studies published from 1994 to 2005, the median hospital stay was 5.3 days (IQR: 4.0 – 6.3). In studies published from 2006 to 2017, the median hospital stay was 4.7 days (IQR: 3.5 – 5.7), medians were not significantly different (P=0.23). We can conclude that there were no significant effects of publication date on outcomes (Fig. 4I-L).

Data collection

To assess the effect of original study design on our primary outcomes we performed a subgroup analysis on 15 studies that performed data collection prospectively and 27 studies that did retrospectively. In the prospective subgroup, symptomatic relief was 95.3% (95% CI: 86.8 – 100.0%), symptomatic recurrence was 7.9% (95% CI: 3.0 – 14.8) and complication rate was 6.9% (95% CI: 3.0 – 12.2). In the retrospective subgroup, symptomatic relief was 88.9% (95% CI: 79.1 – 96.1), symptomatic recurrence was 12.5% (95% CI: 8.3 – 17.4) and complication rate was 9.6% (95% CI: 6.8 – 12.9). We can state that there were no significant effects of data collection on outcomes (Fig. 4M-O).

DISCUSSION

Efficacy & safety

This systematic review describes the safety and efficacy of laparoscopic fenestration in 1314 patients reported in 62 individual studies. We document that laparoscopic fenestration of large, symptomatic cysts is effective and results in symptomatic relief in the large majority of patients. Symptomatic recurrence after fenestration is low (9.6%) as is the re-intervention rate for the same cyst (7.1%). Omentopexy after cyst fenestration did not improve efficacy, but also was not associated with a higher complication rate.

Laparoscopic fenestration appears to be a safe procedure and while procedure-related complications do occur in 11% of patients, scoring according to Clavien-Dindo shows that these are mostly minor and amenable to treatment. We were unable to assess the relation between pre-surgical cyst size, complication rate and recurrence rate. Concomitant cholecystectomy is feasible, but does not contribute to the overall success of the procedure but similarly does not result in a higher complication rate.

The average interval between surgery and symptomatic recurrence was 16 months, and mean time until re-intervention was 22 months. This interval should be interpreted very carefully because of the small sample size, but underscores the need for long-term follow-up when investigating cyst recurrence in future studies.

Patients with PLD may possess one or more large cysts against the background of multiple smaller cysts in surrounding liver. Symptoms in PLD may be attributed to these large cysts and it

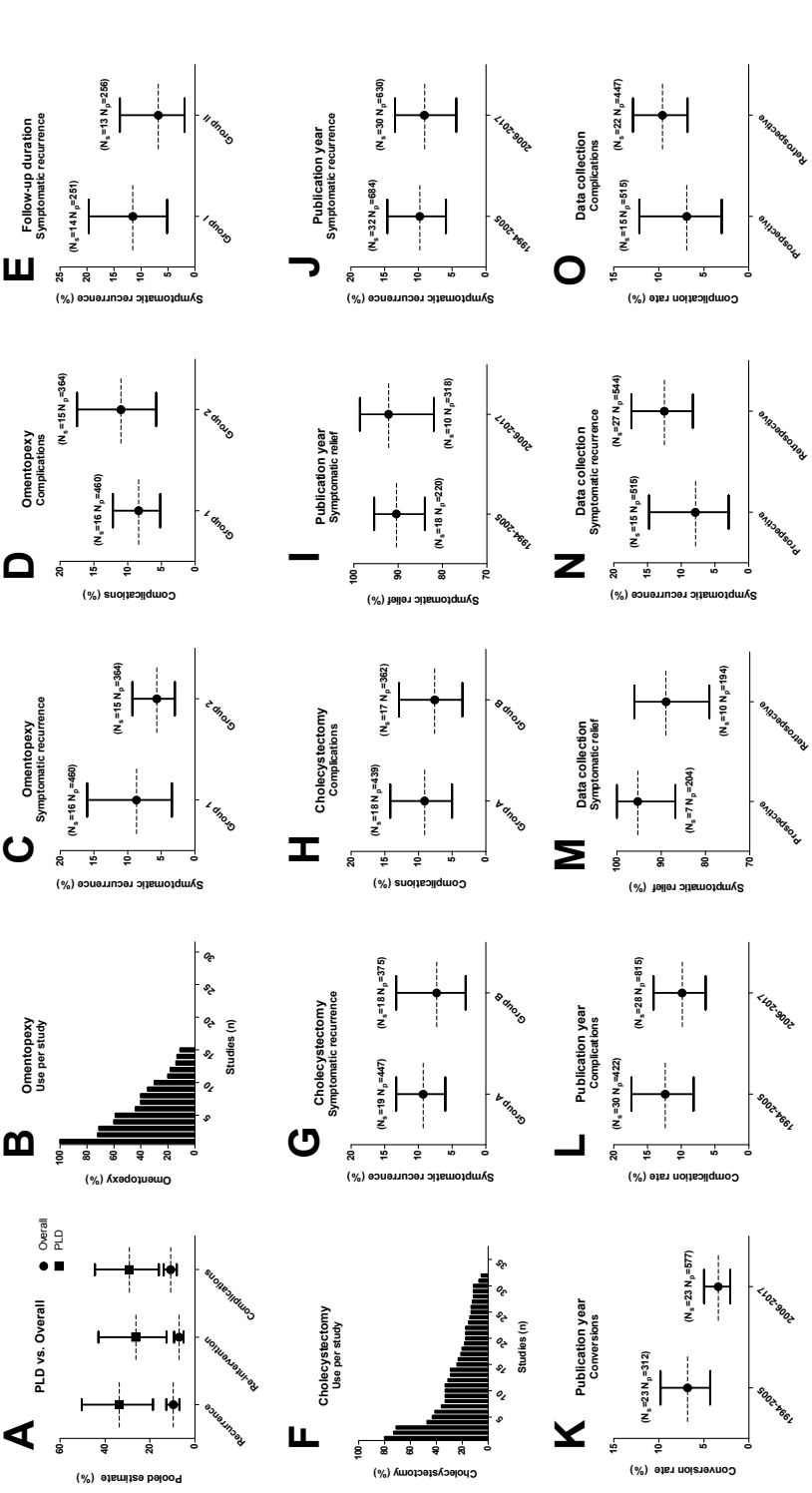

Figure 4. Subgroup analyses. N_s: number of studies. N_p: number of patients. Interrupted lines: pooled estimates. Error bars: 95% confidence intervals. **Panel A:** outcomes for the polycystic liver disease (PLD) subgroup and overall results. **B:** percentage of patients that underwent omentopexy per included cohort. **C-D:** outcomes for omentopexy subgroups (Group 1: no omentopexy, Group 2: omentopexy). **E:** outcomes for mean follow-up subgroups (Group I: ≤38 months, Group II: >38 months). **F:** percentage of patients that underwent concomitant cholecystectomy per included cohort. **G-H:** outcomes for concomitant cholecystectomy subgroups (Group A: ≤21.5%, Group B: >21.5%). **I-L:** outcomes for publication year subgroups (1994-2005 and 2006-2017). **M-O:** outcomes for data collection subgroups (prospective and retrospective).

may be tempting to perform laparoscopic fenestration here. We found that this subgroup is at a high risk for complications and that long-term symptomatic relief is less well achieved. Potential causes of the elevated risk of complications are the changes in hepatic anatomy in PLD and the use of extensive fenestration, with some studies fenestrating over 30 cysts per patient.[16, 20] The elevated recurrence rate is probably related to the different natural history of PLD and large solitary cysts. Hepatic cysts, regardless whether they are solitary or multiple, arise as a result from inactivation of 2 alleles from PLD genes. PLD is a genetic disorder and patients have a germline mutation in one of the PLD genes and must acquire only one additional somatic mutation to develop cysts. Patients with solitary large cysts need to acquire somatic mutations on 2 PLD genes to develop the phenotype.[3] Thus, the risk for recurrence is low in these patients. This contrasts with the situation in PLD where the liver volume increases with 1.8% every 6-12 months. As a consequence, the natural growth of PLD will rapidly overtake the potential volume-curtailing effect of laparoscopic fenestration of a single, albeit large, cyst. The implication is that the threshold for laparoscopic fenestration in PLD must be high in view of the limited long-term efficacy and higher risks.

Percutaneous aspiration sclerotherapy is a valid alternative strategy for large simple hepatic cysts. A recent systematic review found that aspiration sclerotherapy reduces symptoms in 72-100% while symptoms disappeared in 56-100% of patients. Aspiration sclerotherapy comes with complications such as pain, ethanol intoxication, cyst bleeding and rarely cyst infections.[21] It is essential to understand the dynamics of fluid reaccumulation and disappearance after aspiration sclerotherapy to appreciate the merits of the procedure. Within days after complete evacuation of the cyst using aspiration sclerotherapy, cyst fluid reaccumulates only to disappear slowly over (at least) 26 weeks.[22] As a corollary, aspiration sclerotherapy takes months to achieve its full effect, compared to the immediate effect of fenestration. Despite these differences it still needs to be determined which treatment is superior or which patient subgroup has the most benefit from either procedure. As percutaneous aspiration sclerotherapy and laparoscopic fenestration have never been compared directly in a controlled setting, we believe that a randomized trial that focuses primarily on symptomatic relief and symptomatic recurrence should be conducted. Subgroup analyses might elucidate patient-related factors that make either procedure better suited.

Surgical technique

The question here is whether the evolution of laparoscopic fenestration is complete. In our dataset we did not find a significant change in rates of efficacy, complications, conversions to laparotomy or length of hospital stay over time. Although conversion rates above 10% only occurred before 2006. The basic surgical technique used is straightforward and entails laparoscopy, aspiration of cyst fluid first and finally wide deroofing of the cyst wall (near the transition zone between cyst wall and normal hepatic parenchyma). There are innovations such as the use of robot-assisted laparoscopic fenestration for giant hepatic cysts,[23] single incision laparoscopic surgery[24-30] or 3D-vision supported surgery.[31] In addition, the use of indocyanine green fluorescent imaging intra-operatively may facilitate better assessment of bile duct communication or identification of bile duct injuries.[32-36] However, the additive value of these techniques for cyst fenestration remains unclear.

Cyst recurrence is an issue and is thought to result from incomplete deroofing or development of a false lumen by adjacent tissues.[37, 38] To reduce recurrence risk, omentopexy is advocated in view of the hypothesis that omental tissue resorbs fluid and keeps the residual cavity open. Some authors cite specific indications to perform omentopexy such as a small exposed cyst wall, intrahepatic cysts, cyst size >10 cm, cysts located posteriorly or in segment 7 and 8, or if <50% of cyst wall can be resected.[15, 39-45] Other researchers refrain from omentopexy because of questionable evidence, similar recurrence rates without omentopexy, additional complications (e.g. omental bleeding) or extension of operating time.[16, 46-49]

Our systematic review did not identify advantages or disadvantages of omentopexy as adjunct to the surgical procedure. One caveat is that the data was limited and no correction for cyst size and cyst location could be made. We included only studies that explicitly mentioned omentopexy in the subgroup analysis and it is possible that we missed data from studies that used the procedure but did not report that. Randomized clinical trial data are lacking but a single retrospective study compared fenestration with or without omentopexy and did not report a significant benefit.[49] In view of the limited benefit, the customary use of omentopexy with laparoscopic fenestration is questionable. Other options are in development to curtail cyst recurrence after deroofing such as ethanol sclerotherapy,[50-53] argon beam coagulation[54, 55] or wide electrocoagulation,[56] but evidence to support their use is limited and the provided data was not sufficient to perform a subgroup analysis of these techniques.

Strengths and limitations of the study

There are a number of strengths and limitations that result of the very nature of a systematic review. The compliance with the recommendations of the PRISMA and MOOSE guidelines is a major strength of our systematic review. This included a pre-published protocol, an up-to-date extensive literature search, independent screening of all references by two authors and independent risk of bias assessment of included studies by two authors. Data extraction was checked for errors by random sampling of 6 studies by a second investigator and was found 100% accurate. Contact with the corresponding authors of the included studies for additional information provided an extra inclusion. We excluded studies with a mean or median follow-up less than 6 months to reduce biases in reported recurrence rates. Selection bias was reduced by excluding case series and all articles were methodically checked for presence of duplicate datasets. A limitation of our review is that we could not include some studies because of language restrictions and unavailable full-text articles. This resulted in exclusion of some substantial Russian,[57, 58] Ukrainian,[59] Romanian,[60] Hungarian,[61] and Chinese[62, 63] cohorts, which is a possible source of bias and may result in lower generalizability in other countries. In addition, an important question is if the location of the treated hepatic cyst correlates with a different clinical response. It has been reported that unfavorably located cysts have a higher tendency for recurrence. [17] Unfortunately, the provided data was not sufficient to analyze this question in a subgroup analysis.

In our risk of bias assessment, studies scored well on selection of the study groups and ascertainment of outcome of interest. However, studies scored very low on comparability of groups, as most studies did not include a control group. The implication is that the data collection

resulted in a robust data set but that comparison to untreated patients and correction for center-dependent biases is not possible.

We observed moderate heterogeneity for the outcomes symptomatic relief, symptomatic recurrence, re-intervention and complication rate. This is in part attributable to the diverse patient populations (PLD, solitary cysts or both). Our subgroup analyses established that omentopexy, cholecystectomy, follow-up duration, publication date and data collection did not significantly affect the results and are an improbable cause of heterogeneity. Remaining causes of heterogeneity, that could not be assessed, are clinical diversity (e.g. center, surgical expertise) and methodological diversity (e.g. study design, reporting).

Most outcomes had an LFK-index demonstrating minor or no asymmetry in the publication bias assessment, except for mortality. In theory, this could indicate that studies with high mortality were less likely to be published. However, as most studies had a prevalence of 0% and the one reported procedure-related death occurred in a small cohort, the pooled mortality rate and LFK-index are probably overestimated.

No randomized controlled trials were included, and most included studies used patient records or prospective databases. Only few studies used a validated questionnaire to assess symptoms and none used specific questionnaires such as the PLD-Q or POLCA.[3] In addition, not all studies had a clear definition of symptomatic recurrence and it is unclear if imaging had been performed for all patients during follow-up. In order to address this issue we pooled patients with recurrent symptoms with evidence of radiological recurrence and patients with recurrent symptoms. By pooling both categories it is possible that we included patients with recurrent symptoms without radiological recurrence. This could have affected our results. However, in included studies only 3 out of 1203 patients had recurrent symptoms without radiological recurrence. We suggest that any future studies use validated questionnaires and standard imaging techniques at pre-set time points.

CONCLUSIONS

In conclusion, this systematic review provides evidence that laparoscopic fenestration is an effective treatment for symptomatic simple hepatic cysts with a low symptomatic recurrence rate. The symptomatic recurrence rate and risk of complications are significantly higher in PLD patients.

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DISCLOSURES

Drs. Lucas H.P. Bernts, Sebastiaan G. Echternach, Wietske Kievit, Camiel Rosman and Joost P.H. Drenth have no conflicts of interest or financial ties to disclose.

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SUPPLEMENTARY FILES

Supplementary file 1. MOOSE checklist. From: Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283(15):2008-12.

Section/Topic	Brief description of how the criteria were handled in the meta-analysis
Background	
Problem definition	Laparoscopic fenestration is one of the treatment options for symptomatic simple hepatic cysts, either solitary or in context of polycystic liver disease (PLD), but indications, effect size and surgical techniques are under debate.
Hypothesis statement	Laparoscopic fenestration is effective and safe in selected populations.
Description of study outcomes	Symptomatic relief or symptomatic recurrence
Type of exposure or intervention used	Laparoscopic fenestration combines cyst fluid aspiration, followed by excision of extra-hepatic cyst wall in a single laparoscopic procedure
Type of study designs used	Cohort studies and clinical trials
Study population	Adults with large, symptomatic, simple hepatic cysts
Search strategy	
Qualifications of searchers (eg, librarians and investigators)	The credentials of the three investigators are indicated in the authors list and the librarian who performed the study is mentioned in the acknowledgements section.
Search strategy, including time period included in the synthesis and keywords	See methods for search strategy. Period: inception to 18 July 2017, without any restrictions.
Effort to include all available studies, including contact with authors	Authors were emailed.
Databases and registries searched	MEDLINE, Embase, Web of Science and the Cochrane Library
Search software used, name and version, including special features used (eg, explosion)	PubMed. OvidSP.

Supplementary file 1. (continued)

Section/Topic	Brief description of how the criteria were handled in the meta-analysis
Use of hand searching (eg, reference lists of obtained articles)	Bibliographies of included articles were hand searched for additional references.
List of citations located and those excluded, including justification)	Details of the literature search process are outlined in the PRISMA flow chart. The citation list of excluded articles is available upon request.
Method of addressing articles published in languages other than English	Articles in the following languages were included: Dutch, English, French, German, Italian and Spanish.
Method of handling abstracts and unpublished studies	Abstracts and unpublished studies were excluded.
Description of any contact with authors	When full-text could not be obtained, we contacted authors via email. When additional data was necessary, we contacted authors via email.
Methods	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the methods section of the article.
Rationale for the selection and coding of data (eg sound clinical principles or convenience)	Data extraction sheets were developed (available on request). Extracted data was related to bibliographic details of included studies, patient characteristics, relevant outcomes, study design and quality assessment
Documentation of how data were classified and coded (multiple raters, blinding and inter-rater reliability)	Detailed documentation can be found in the methods section of the article.
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Confounders were searched for with pre-specified subgroup analyses
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results.	We used the Newcastle-Ottawa scale to assess quality
Assessment of heterogeneity	We used the I^2 value to assess heterogeneity

Supplementary file 1. (continued)

Section/Topic	Brief description of how the criteria were handled in the meta-analysis
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results) in sufficient detail to be replicated	Pooled estimates and 95% confidence intervals were calculated with a random effects model). Detailed documentation can be found in the methods section of the article.
Provision of appropriate tables and graphics	PRISMA flow chart is presented in article. Table 1 summarizes included articles.
Results	
Graphic summarizing individual study estimates and overall estimate	Individual study results are added as supplementary files. Overall estimates are presented in the Results section.
Table giving descriptive information for each study included	Table 1 and supplementary files.
Results of sensitivity testing (eg, subgroup analysis)	Subgroup analyses can be found in Figure 4, detailed descriptions are presented in Results section of the article.
Indication of statistical uncertainty of findings	For pooled estimates, 95% confidence intervals are presented together with I^2 values. For medians, IQR and/or total range is presented.
Discussion	
Quantitative assessment of bias (eg, publication bias)	Results of subgroup analyses are discussed in the results and discussion section. Risk of publication bias is described in results section and funnel plots are shown in Figure 3.
Justification for exclusion (eg, exclusion of non-English-language citations)	Detailed documentation can be found in the Methods section of the article.
Assessment of quality of included studies	NOS scores for individual studies are shown in Table 3. Implications are described in the discussion section of the article.
Conclusions	
Consideration of alternative explanations for observed results	Confounders and biases are described in the discussion section of the article.

Supplementary file 1. (continued)

Section/Topic	Brief description of how the criteria were handled in the meta-analysis
Generalization of the conclusions (ie, appropriate data presented and within the domain of the literature review)	Generalizability is described in the discussion section of the article.
Guidelines for future research	We suggest that any future studies use validated questionnaires and standard imaging techniques at pre-set time points. We propose a randomized clinical trial comparing percutaneous aspiration sclerotherapy and laparoscopic fenestration
Disclosure of funding source	No financial disclosures

W

Supplementary file 2. Search terms

PICO format	No.	Search terms
Pubmed MEDLINE		
1. Patient	#1	("Liver diseases"[MeSH] AND "Cysts"[MeSH Terms]) OR "Polycystic liver disease"[Supplementary Concept]
	#2	((hepatic[tiab] OR liver[tiab] OR livers[tiab]) AND (cyst[tiab] OR cysts[tiab] OR cystic[tiab])) OR polycystic liver[tiab] OR liver polycystic[tiab] OR PCLD[tiab]
	#3	#1 OR #2
2. Intervention	#4	"Laparoscopy"[Mesh] OR "Video-Assisted Surgery"[Mesh:NoExp] OR "Minimally Invasive Surgical Procedures"[Mesh:NoExp]
	#5	Fenestration*[tiab] OR deroofing*[tiab] OR de-roofing*[tiab] OR marsupialisation*[tiab] OR marsupialization*[tiab] OR minimally invasive surg*[tiab] OR minimally invasive procedure*[tiab] OR minimally invasive technique*[tiab] OR minimally invasive method*[tiab] OR laparoscop*[tiab] OR video assisted surger*[tiab] OR video assisted procedure*[tiab] OR videolaparoscop*[tiab] OR laparoendoscopic[tiab]
	#6	#4 OR #5
3. Comparator		*Not specified*
4. Outcome		*Not specified*
5. PICO	#7	#3 AND #6
OvidSP Embase		
1. Patient	#1	liver cyst/ OR liver polycystic disease/
	#2	(((hepatic OR liver OR livers) AND (Cyst OR cysts OR cystic))OR Polycystic liver OR liver polycystic OR PCLD).ti,ab,kw.
	#3	#1 OR #2
2. Intervention	#4	laparoscopy/ OR hand assisted laparoscopy/ OR laparoendoscopic single site surgery/ OR laparoscopic surgery/ OR exp minimally invasive procedure/
	#5	(Fenestration* OR deroofing* OR de-roofing* OR marsupialisation* OR marsupialization* OR minimally invasive surg* OR minimally invasive procedure* OR minimally invasive technique* OR minimally invasive method* OR laparoscop* OR video assisted surger* OR video assisted procedure* OR videolaparoscop* OR laparoendoscopic).ti,ab,kw.
	#6	#4 OR #5
3. Comparator		*Not specified*
4. Outcome		*Not specified*
5. PICO	#7	#3 AND #6
Cochrane Library & Web of Science		
1. Patient	#1	((hepatic OR liver OR livers) AND (cyst OR cysts OR cystic)) OR "polycystic liver" OR "liver polycystic" OR PCLD
2. Intervention	#2	fenestration* OR deroofing* OR "de-roofing*" OR marsupialisation* OR marsupialization* OR "minimally invasive surg*" OR "minimally invasive procedure*" OR "minimally invasive technique*" OR "minimally invasive method*" OR laparoscop* OR "video assisted surger*" OR "video assisted procedure*" OR videolaparoscop* OR laparoendoscopic
3. Comparator		*Not specified*
4. Outcome		*Not specified*
5. PICO	#3	#1 AND #2

Supplementary File 3. Adjusted Newcastle-Ottawa scale for cohort studies

Selection (0-4)

1) Representativeness of the exposed cohort

a) truly representative of the average community (1 point)

b) somewhat representative of the average community (1 point)

c) selected group of users e.g. nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort (1 point)

b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

d) not applicable

3) Ascertainment of exposure

a) secure record (e.g. surgical records) (1 point)

b) structured interview (1 point)

c) written self-report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes (symptomatic patients) (1 point)

b) no (asymptomatic patients)

c) no description

Comparability (0-2)

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for median cyst size (1 point, max. 2)

b) study controls for cyst location (1 point, max. 2)

c) symptomatic patients (1 point, max. 2)

c) not applicable

Outcome (0-3)

1) Assessment of outcome

a) independent blind assessment OR conformation by secure records (1 point)

b) record linkage (1 point)

c) self-report

d) no description

2) Was follow-up long enough for outcomes to occur

a) >12 months (1 point)

b) > 6 months

3) Adequacy of follow-up of cohorts

a) complete follow-up - all subjects accounted for (1 point)

b) >80% follow-up, or description provided of those lost

c) follow-up rate < 80% and no description of those lost

d) no statement

Supplementary File 4A. Individual study results (characteristics)

Study (subgroups)	Year	Design	Study period	Location	N_p	PLD (n)	Female (n)	Age (years)	Cyst diameter (cm)	Operated cysts (N_p)	Follow-up (months)
Ammori[1]	2002	RCS	1992-1999	UK	3	1	NS	NS	NS	NS	NS
Andriani[2]	2000	RCS	1993-1998	Argentina	17	0	11	NS	Mean 9.8 cm (5-30cm)	Total 24	Mean 23
Ardito[3]	2013	RAPCD	2000-2010	Italy	47	19	10	Mean 57.6	Mean 13 cm (5-22)	Total 96	Median 67
Bai[4]	2007	RCS	1998-2004	China	44	10	30	Mean 57	Mean 12.3 (6-23)	NS	Mean 57
Caetano[5]	2006	NS	1994-1999	Brazil	12	3	12	Mean 56	Median 9.8 (6-15)	NS	NS
Cappellani[6]	2002	NS	1992-2000	Italy	9	1	9	NS	Mean 11.5 (8-16)	NS	Mean 42
Debs[7]	2016	RCS	2000-2012	France	27	NS	NS	NS	NS	NS	Mean 24
Descottes[8]	2000	RCS	1991-1999	France	15	4	14	Mean 54	15.7 (8.3-23)	NS	Mean 14
De Reuver[9]	2017	RAPCD	2000-2013	Australia	35	2	30	Mean 63.7	Mean 14 cm. Median 12 cm.	NS	Median 49,64. Mean 65,79
Diez[10]	1998	NS	1992-1996	Argentina	10	1	NS	Mean 43	NS	NS	NS
Emmermann[11]	1997	NS	1991-1994	Germany	18	0	18	Mean 57	Mean 12 (9-18)	18	Mean 19
Fabiani[12]	2005	RCS	1989-2001	France	26	0	35	Median 68.8	Mean 11 (5.5-20)	NS	Mean 68,7
Faulds[13]	2010	PCS	2009-2010	Canada	5	NS	6	Mean 63.2	Mean 11.3 (7-16)	NS	Mean 9,6
Fiamingo[14]	2003	RCS	1996-2002	Italy	15	6	13	Median 57	Median 9 (7-13) in No PLD Median 11 (10-13) in PLD	Total 18	Median 34
Gall (PLD)[15]	2009	RAPCD	1985-2006	UK	13	13	NS	Median 49	Median 10 (4-18)	NS	NS
Gall (No PLD)[15]	2009	RAPCD	1985-2006	UK	48	0	NS	Median 60	Median 11 (2-30)	NS	NS
Gamblin[16]	2008	RAPCD	2001-2008	USA	46	45	40	Median 60	Median 13 (2-21)	NS	Mean 13
Gigot[17]	2001	NS	1984-1999	Belgium	19	2	18	Median 57	Mean 13 (8-30)	NS	Mean 38,5
Gocho[18]	2013	NS	2010-2011	Japan	6	NS	6	Median 60	Median 11.1 (10.0-15.2)	NS	Median 15,5
Hansen[19]	1997	PCS	1990-1996	USA	19	2	16	Mean 65	Mean 15 (7-25) in No PLD Mean 9 (6-16) in multiple cysts	NS	Mean 30
Hansman[20]	2001	RCS	1984-2000	USA	6	0	NS	NS	NS	NS	NS

Supplementary File 4A. (continued)

Study (subgroups)	Year	Design	Study period	Location	N_p	PLD (n)	Female (n)	Age (years)	Cyst diameter (cm)	Operated cysts (N_p)	Follow-up (months)
Heintz[21]	1995	NS	1993-1994	Germany	3	NS	3	Mean 59.7	Mean 12.3 (8-16)	NS	Median 8 Mean 6
Hsu[22]	2005	NS	1996-2001	Taiwan	5	NS	6	Mean 59.5	Mean 16.8 (10-20)		Mean 48
Kabbej[23]	1996	NS	1991-1994	France	13	13	NS	Median 49	NS	Median 32 (range 18-58)	Median 26
Kamphues[24]	2011	RAPCD	2002-2008	Germany	43	7	41	Median 48	Median 8 (2-27)	Median 1 (range 1-7)	Median 49
Katkhouda (PLD)[25]	2000	NS	1990-1997	USA	9	9	6	Median 43	Median 8 (4-16)	NS	NS
Katkhouda (No PLD)[25]	2000	NS	1990-1997	USA	16	0	12	Median 35	Median 14 (7-22)	16	NS
Kisiel[26]	2017	RAPCD	2000-2012	UK	48	NS	39	Median 71	NS	NS	Median 66,2
Koea (PLD)[27]	2008	RAPCD	2000-2006	New Zealand	12	12	12	Median 62	NS	NS	Median 26
Koea (No PLD)[27]	2008	RAPCD	2000-2006	New Zealand	12	0	11	Median 62	Median 18 (11-52)	12	Median 20
Konstadoulakis[28]	2005	RCS	2000-2002	Greece	9	9	9	Mean 69.6	NS	Mean 37,7 (range 18-64)	Mean 25,8
Koperna[29]	1997	RCS	1990-1995	Austria	10	5	NS	NS	NS	NS	NS
Kornprat[30]	2004	NS	1994-2003	Austria	21	8	NS	NS	NS	NS	Median 27
Kwon[31]	2003	NS	1994-2001	Japan	14	NS	10	Mean 62	NS	Total 19	Median 56
Lee[32]	2014	RCS	2004-2012	South Korea	29	NS	NS	NS	NS	NS	NS
Lolle Noerregaard[33]	2014	RCS	2007-2012	Denmark	29	NS	NS	Median 61	NS	NS	Median 28
Manterola[34]	2016	PCS	2008-2015	Chile	41	NS	31	NS	Mean 10 (6-21)	Total 52	Median 35
Marks[35]	1998	NS	1989-1996	France	17	NS	NS	NS	NS	NS	NS
Martin (PLD)[36]	1998	RCS	1988-1997	UK	7	7	NS	NS	NS	NS	Mean 37
Martin (No PLD)[36]	1998	RCS	1988-1997	UK	13	0	NS	NS	NS	NS	Mean 25
Martinez-Perez[37]	2016	RCS	2004-2012	Spain	12	12	NS	NS	NS	NS	NS
Maruyama[38]	2013	RCS	2000-2011	Japan	16	0	NS	NS	NS	16	NS
Mazoch[39]	2011	RCS	1995-2009	USA	15	0	NS	NS	Mean 15.32 (6-26)	15	NS
Mazza (PLD)[40]	2009	RAPCD	1990-2007	Argentina	20	20	NS	NS	NS	NS	NS

Supplementary File 4A. (continued)

Study (subgroups)	Year	Design	Study period	Location	N_p	PLD (n)	Female (n)	Age (years)	Cyst diameter (cm)	Operated cysts (N_p)	Follow-up (months)
Mazza (No PLD)[40]	2009	RAPCD	1990-2007	Argentina	46	0	NS	NS	NS	NS	NS
Morino (PLD)[41]	1994	NS	1990-1992	Italy	7	7	NS	Mean 54.57	NS	NS	NS
Morino (No PLD)[41]	1994	NS	1990-1992	Italy	4	0	2	Mean 57.75	Mean 14.25 (9-14)	4	NS
Neri (PLD)[42]	2006	NS	1999-2003	Italy	3	3	NS	NS	NS	NS	NS
Neri (No PLD)[42]	2006	NS	1999-2003	Italy	12	0	NS	NS	NS	NS	NS
Palanivelu[43]	2006	PCS	1995-2006	India	27	0	5	Mean 48.6	Median 16.2 (5.4-42.6)	Total 27	Mean 86,4
Pante[44]	2014	NS	2006-2011	Italy	7	7	5	Mean 59.4	NS	NS	NS
Petri[45]	2002	RCS	1982-2001	Hungary	34	NS	NS	NS	Mean 10.03 ± 3	NS	Mean 12
Regev[46]	2001	RCS	1993-1999	USA	18	NS	NS	NS	NS	NS	NS
Robinson[47]	2005	RCS	1995-2003	USA	11	11	10	Mean 41 ± 7	(1-10)	NS	Mean 41
Roesch Dietlen[48]	1999	RCS	1992-1998	Mexico	7	0	5	Mean 61	(12-18)	7	Mean 26,4
Sasi Szabo[49]	2006	NS	1995-2005	Hungary	25	4	16	Mean 54.4	Mean 6.9 (3.5-20)	NS	Median 48,7
Schachter[50]	2001	RAPCD	1996-1999	Israel	14	2	NS	NS	NS	NS	Mean 30
Scheuerlein[51]	2013	RCS	2000-2010	Germany	47	NS	NS	NS	NS	Mean 2 (range 1-9)	NS
Sendt[52]	2009	RAPCD	1995-2004	Germany	27	4	24	Median 60	Mean 10 (6-20)	Mean 1,3 (range 1-5)	Mean 56
Tagaya[53]	2003	NS	1993-1999	Japan	5	0	1	Mean 63	Mean 10 (7-18)	5	Mean 66
Tan[54]	2005	RCS	1992-2000	Singapore	10	0	NS	NS	Mean 12.8 (6-18)	10	Median 20
Tocchi[55]	2002	RCS	1994-1999	Italy	8	0	NS	NS	NS	8	NS
Torices[56]	2004	RCS	2000-2004	Mexico	21	NS	15	Mean 62	Mean 12 (8-15)	NS	Mean 36
Torres[57]	2009	NS	2003-2006	Brazil	13	2	11	Mean 48.3	Mean 11.3 (9.5-17) in No PLD Mean 10.6 (9.2-12.1) in PLD	NS	Mean 36
Treckmann[58]	2010	RCS	1999-2007	Germany	42	4	NS	NS	Mean 10.8 (6-18)	NS	NS
Van Keimpema[59]	2008	PCS	2005-2007	Netherlands	12	12	12	Mean 44.9	NS	NS	Median 12
Wahba[60]	2011	RCS	1999-2009	Germany	23	NS	19	Mean 68.09	Mean 12.2 ± 3.2	NS	Mean 59

Supplementary File 4A. (continued)

Study (subgroups)	Year	Design	Study period	Location	N_p	PLD (n)	Female (n)	Age (years)	Cyst diameter (cm)	Operated cysts (N_p)	Follow-up (months)
Wu (SILS)[61]	2014	RCS	2009-2011	China	15	NS	8	Mean 60.93	Mean 11.67 ± 3.66	NS	Mean 12,26
Wu (standard)[61]	2014	RCS	2009-2011	China	15	NS	9	Mean 58.67	Mean 11.27 ± 2.22	NS	Mean 14
Zacherl[62]	2000	NS	1991-1998	Austria	7	NS	NS	Median 62.1	Median 13.6	NS	Median 37,2

Legend: When not specified otherwise, means are presented with standard deviations (±) or 95%-CI. Medians are presented with IQR. **Abbreviations**: N_p: number of patients. PLD: polycystic liver disease. PCS: prospective cohort study. RAPCD: retrospective analysis of prospectively collected data. RCS: retrospective cohort study. NS: no statement.

Supplementary File 4B. Individual study results (outcomes)

Study (subgroups)	Recurrence (N_p)	Relief (N_p)	Re-intervention (N_p)	Complications (N_p)	Conversion (N_p)	Mortality (N_p)	Operative time (minutes)	Hospital stay (days)
Ammori[1]	0	2	0	1	NS	0	NS	NS
Andriani[2]	1	NS	1	2	0	0	NS	Mean 2 (1-5)
Ardito[3]	2	47	2	0	NS	0	Median 164 (50-240)	Median 5,2 (2-12)
Bai[4]	2	NS	NS	5	NS	0	NS	Mean 4
Caetano[5]	0	NS	0	3	1	0	Mean 105 (60-180)	Median 4.1 (3-8)
Cappellani[6]	0	NS	0	0	0	0	NS	NS
Debs[7]	6	NS	6	5	2	NS	NS	NS
Descottes[8]	5	NS	5	0	1	0	NS	NS
De Reuver[9]	6	20	5	1	0	0	NS	Mean 7,5 (1-12)
Diez[10]	0	10	1	0	NS	0	NS	Mean 4 (3-6)
Emmermann[11]	1	16	1	2	1	0	Mean 100 (50-150)	Mean 5 (2-14)
Fabiani[12]	1	NS	NS	3	2	0	Mean 82 (15-210)	Mean 5,3 (2-12)
Faulds[13]	0	5	0	1	0	0	NS	Mean 1,2 (0-4)
Fiamingo[14]	2	15	NS	4	1	0	Median 80 (45-120)	Median 8 (6-12)
Gall (PLD)[15]	11	NS	6	4	NS	0	Median 105 (40-180)	Median 4
Gall (No PLD)[15]	14	NS	2	7	NS	0	Median 75 (40-170)	Median 3
Gamblin[16]	0	46	0	9	0	0	Median 178 (54-380	Median 2 (1-11)
Gigot[17]	1	10	1	4	4	0	NS	Mean 6,1 (3-17)
Gocho[18]	0	NS	0	0	0	0	Median 144 (100-210)	3
Hansen[19]	3	16	1	3	NS	0	Mean 150 (90-253)	Mean 2,5 (1-8)
Hansman[20]	0	NS	0	0	NS	0	NS	NS
Heintz[21]	0	3	0	0	0	0	Mean 68,33 (55-90)	Mean 5,33 (5-6)
Hsu[22]	0	5	0	0	NS	0	Mean 148 (110-215)	Mean 4,3 (3-5)
Kabbej[23]	8	11	4	8	0	0	Median 190 (95-330)	Median 11 (3-30)
Kamphues[24]	6	NS	2	0	0	0	Median 94 (30-195)	Median 5 (2-8)
Katkhouda (PLD)[25]	0	8	1	3	1	0	Median 141 (94-165)	Median 3 (2-7)
Katkhouda (No PLD)[25]	0	16	0	1	0	0	Median 48 (45-56)	Median 1,3 (1-3)

Supplementary File 4B. (continued)

Study (subgroups)	Recurrence (N_p)	Relief (N_p)	Re-intervention (N_p)	Complications (N_p)	Conversion (N_p)	Mortality (N_p)	Operative time (minutes)	Hospital stay (days)
Kisiel[26]	9	46	3	5	0	0	NS	Median 2 (1-7)
Koea (PLD)[27]	2	NS	2	0	0	0	Median 87 (63-130)	Median 2 (2-7)
Koea (No PLD)[27]	0	12	0	0	0	0	Median 50 (27-67)	Median 1
Konstadoulakis[28]	2	9	1	1	1	1	Mean 119,6 (55-179)	Mean 4,6 (2-6)
Koperna[29]	1	9	1	NS	1	0	NS	NS
Kornprat[30]	0	NS	0	3	1	0	Mean 100 (70-120)	Mean 10 (8-14)
Kwon[31]	0	14	0	0	0	0	Mean 93 (40-170)	Median 7,0 (6-10)
Lee[32]	1	NS	1	?	0	0	NS	NS
Lolle Noerregaard[33]	5	26	3	2	2	0	NS	Median 1 (1-14)
Manterola[34]	0	NS	0	0	0	0	Median 50 (35-90)	Median 1 (1)
Marks[35]	0	NS	0	6	1	0	NS	NS
Martin (PLD)[36]	5	NS	5	2 out of 5	NS	0	Median 120 (75-180)	Median 3 (1-7)
Martin (No PLD)[36]	2	NS	2	3 out of 5	NS	0	Median 60 (45-155)	Median 3 (1-10)
Martinez-Perez[37]	2	NS	1	2	1	0	Median 122 (60-210) *	Mean 3,7 (1-7) *
Maruyama[38]	3	NS	0	2	NS	0	Mean 165,8 (90-270)	Mean 17,8 (10-38)
Mazoch[39]	0	NS	0	2	NS	0	NS	Mean 5,57
Mazza (PLD)[40]	1	NS	1	5	NS	0	NS	Mean 3 (1-6)
Mazza (No PLD)[40]	1	NS	1	1	NS	0	NS	Mean 1,47 (1-3)
Morino (PLD)[41]	2	5	NS	4	2	0	Mean 202 (149-295)	Mean 13 (4-25)
Morino (No PLD)[41]	0	4	0	0	0	0	Mean 80 (40-135)	Mean 4 (2-6)
Neri (PLD)[42]	0	3	0	3	0	0	Mean 120 (80-150)	Mean 6 (4-14)
Neri (No PLD)[42]	0	12	0	2	0	0	Mean 55 (40-90)	Mean 6 (4-14)
Palanivelu[43]	0	NS	0	3	0	0	Mean 72 (55-104)	Median 4
Pante[44]	2	NS	NS	4	0	0	Mean 98 (75-130)	Mean 6 (3-13)
Petri[45]	7	NS	NS	3	NS	0	NS	7
Regev[46]	1	NS	1	0	0	0	NS	NS
Robinson[47]	8	11	8	3	1	0	Mean 75 ± 17	Median 1 (0-7)

Supplementary File 4B. (continued)

Study (subgroups)	Recurrence (N_p)	Relief (N_p)	Re-intervention (N_p)	Complications (N_p)	Conversion (N_p)	Mortality (N_p)	Operative time (minutes)	Hospital stay (days)
Roesch Dietlen[48]	0	7	0	1	0	0	Mean 72 (40-110)	Mean 2 (1-3)
Sasi Szabo[49]	1	NS	1	2	2	0	NS	Mean 4,7 (3-37)
Schachter[50]	1	NS	1	0	1	0	NS	Mean 5,8 (3-10)
Scheuerlein[51]	0	NS	0	6	2	0	NS	Mean 4 (1-18)
Sendt[52]	1	NS	1	0	0	0	Mean 182 (72-270)	Mean 9,4 (7-12)
Tagaya[53]	1	NS	1	0	NS	0	Mean 70 (60-225)	Mean/Median 6
Tan[54]	2	NS	2	NS	NS	NS	Mean 78 ± 20	Mean 6,0 ± 5,0
Tocchi[55]	0	20	0	0	NS	0	NS	Mean 2-3
Torices[56]	0	NS	1	2	0	0	Mean 85 (53-110)	Mean 3,5 (2-9)
Torres[57]	2	31	1	6	3	0	Median 85 (30-145)	Median 5 (2-29)
Treckmann[58]	1	NS	NS	3	NS	0	Median 123,5 (50-318)	Median 3,5 (1-8)
Van Keimpema[59]	1	NS	1	1	1	0	NS	NS
Wahba[60]	1	NS	NS	NS	0	0	58,3 ± 7,43	4,8 ± 0,44
Wu (SILS)[61]	0	NS	0	NS	0	0	58,7 ± 6,14	5,2 ± 0,56
Wu (standard)[61]	1	7	1	1	0	0	Median 87 (30-180)	NS
Zacherl[62]	1	7	1	1	0	0	Median 87 (30-180)	NS

Legend: When not specified otherwise, means are presented with standard deviations (±) or 95%-CI. Medians are presented with IQR. **Abbreviations**: N_p: number of patients. NS: no statement.

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6

SYMPTOM RELIEF AND QUALITY OF LIFE AFTER COMBINED PARTIAL HEPATECTOMY AND CYST FENESTRATION IN HIGHLY SYMPTOMATIC POLYCYSTIC LIVER DISEASE

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ABSTRACT

Background

Polycystic liver disease (PLD) can cause severe symptomatic hepatomegaly. Combined partial hepatectomy and cyst fenestration (PHCF) can be performed to reduce liver volume and symptom burden. We aimed to assess change in symptom relief and quality of life six months after PHCF in PLD patients.

Method

We established a prospective cohort between 2014 and 2018 at a referral center in the United States. Patients who underwent PHCF for volume-related symptoms were included. Primary outcome was change in PLD-related symptoms, measured with PLD Questionnaire (PLD-Q). Secondary outcomes were change in liver volume (CT/MRI) and change in quality of life, measured with the 12-Item Short Form Survey (SF-12) and the EuroQoL Visual Analogue Scale (EQ-VAS). Questionnaire scores range from 0 to 100 and were assessed before and six months after PHCF. Surgical complications were scored according to Clavien-Dindo (grade 1 to 5).

Results

We included 18 patients (mean age 52 years, 82% female). PHCF reduced median liver volume (4917 to 2120 ml). Symptoms, measured with PLD-Q, decreased (76.9 to 34.8 points; $p<0.001$) six months after surgery; 15/16 symptoms declined after treatment, with most impact seen on early satiety and dyspnea. Quality of life also improved after surgery: median physical and mental component scales of the SF-12 and EQ-VAS increased (24.9 to 45.7, $p=0.004$; 40.5 to 55.4, $p=0.02$; and 40.0 to 72.5, $p=0.003$). Major complications (grade 4) occurred in two patients. There was no procedure-related mortality.

Conclusion

PHCF substantially improves symptom burden and quality of life in highly symptomatic PLD patients.

INTRODUCTION

Polycystic liver disease (PLD) is a rare hereditary condition that results in progressive hepatomegaly in a proportion of patients.[1] It is associated with autosomal dominant polycystic kidney disease (ADPKD), and occurs less commonly without renal cysts in autosomal dominant polycystic liver disease (ADPLD).[2] The enlarged cystic liver may cause compression of adjacent abdominal structures and organs, leading to symptoms and a compromised quality of life.[3] This underscores the need for volume-reducing therapies that improve patient-reported outcomes.

There are limited therapeutic options for patients with severe polycystic liver disease. Except for liver transplantation, there is no curative treatment available yet. However, PLD patients usually require exception points for transplantation, since liver function remains preserved.[4] Aspiration sclerotherapy and laparoscopic fenestration are limited to patients with superficial large cysts, and while reduction of symptoms and improvement of quality of life can be achieved, the rate of recurrent symptoms and need for re-intervention is high.[5-7] For diffuse cystic involvement, transcatheter arterial embolization (TAE) is a novel intervention to reduce cyst volume, but more experience by Western groups is needed to confirm the safety and efficacy of this procedure.[8, 9] Somatostatin analogues curtail liver cyst growth in clinical trials and improve quality of life, but the proportional reduction in liver volume is limited to 5% after one year.[10, 11]

Currently, large liver volume reduction in PLD can only be achieved by combined partial hepatectomy and cyst fenestration (PHCF).[12] A large retrospective study (n=186) reported a median liver volume reduction of 61% after PHCF that was durable up to 20 years.[13] This establishes PHCF as an effective volume-reducing procedure. Despite being the primary goal of treatment, the effectiveness of PHCF on symptom relief and quality of life remains to be elucidated.

Results from a single study suggested that quality of life after PHCF is comparable to that of healthy controls after a mean follow-up of 9 years.[12] However, baseline scores were missing, no validated symptom questionnaire was used and follow-up duration varied between patients.[12] Furthermore, it should be investigated whether this procedure leads to a clinically relevant change in symptoms and quality of life that outweighs the risk of surgery.

The aim of this study was to prospectively investigate symptom relief and improvement of quality of life using validated questionnaires in a cohort of PLD-patients six months after PHCF. Our secondary aim was to identify the threshold for minimal clinically important differences in PLD-related symptoms and to explore potential predictors for clinically relevant improvement.

METHODS

Study design and setting

We performed a prospective cohort study at the Mayo Clinic, Rochester MN, United States (US) between November 2014 and May 2018. Patients received a questionnaire set before surgery and six months after surgery. Non-responders received a reminder call after 2 weeks. Patients that did not respond on paper were asked to complete a phone interview 4 weeks after the initial follow-up survey was sent. This study was approved by the Mayo Clinic Rochester Institutional Review Board

(IRB# 14-003832) and informed consent was obtained from all study participants. This study is reported in compliance with the STROBE guidelines for cohort studies (Supplementary Table 1).[14]

Procedure

PHCF consists of (extended) hemihepatectomy or multiple segmentectomies, in combination with fenestration of remnant cysts.[12] It is often combined with cholecystectomy for technical reasons.[15] Sometimes PHCF is combined with renal surgery in ADPKD patients (e.g. nephrectomy) for additional cyst volume reduction. All procedures were performed by open approach by two surgeons (RLS, DMN). Preoperative evaluation and surgical technique have been detailed previously.[12, 13, 15]

Participants

We included patients who underwent PHCF for massive and symptomatic PLD. Patients were selected for surgery by their treating surgeon independent of this study. PHCF was only offered if one or more hepatic sections (sector) were relatively spared of cysts, with preservation of the majority of parenchyma, if afferent and efferent sectoral hepatic vasculature was patent, and liver function was maintained (Figure 1).[12, 13]

Patients who underwent PHCF for reasons other than control of volume-related symptoms and patients that were predisposed to unreliable questionnaire responses due to mental illness or insufficient knowledge of the English language were excluded.

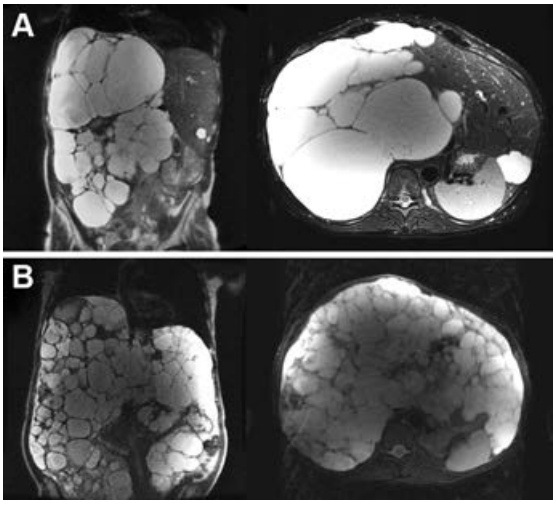

Figure 1. Magnetic resonance imaging for polycystic liver disease patients. **Panel A:** Coronal and axial cross section of a patient that was eligible for partial hepatectomy and cyst fenestration (PHCF). **Panel B:** Coronal and axial cross section of a patient that was not eligible for PHCF as there were no areas of relatively normal liver parenchyma.

Outcome measures

Baseline characteristics

We collected baseline demographic variables (patient characteristics, laboratory and treatment variables), and surgery-related parameters (indication for surgery, operating surgeon, perioperative blood loss, duration of surgery, concomitant cholecystectomy, concomitant hernia repair, ICU admission, total duration of admission and rate of any complications) from patient records. All complications were scored according to the Clavien-Dindo classification.[16] Type of surgery was defined using the Brisbane 2000 Nomenclature of Hepatic Anatomy and Resections, however exact classification of the resected segments is not always possible due to the disturbed anatomy in polycystic liver disease.[17]

Total liver and kidney volume

All patients underwent magnetic resonance imaging (MRI) or computed tomography (CT) as part of the preoperative evaluation. When follow-up imaging was available, change in liver volume was measured. No standardized imaging measurement method was used as symptoms and quality of life were our primary outcomes, and the large reduction of liver volume after partial hepatectomy surpasses the possible measurement errors.[18] A blinded investigator (M.E.) measured total liver volume (TLV), pre- and post-surgery, using Analyze software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN).[19] In patients with polycystic kidney disease, we also measured total kidney volume (TKV). Disease severity was calculated by dividing total liver volume by height in meters. PLD was classified as mild (<1600 ml/m), moderate (1600 – 3200 ml/m) or severe (>3200 ml/m) based on previously published cut-off values.[20]

Symptoms and quality of life

We used a questionnaire set, consisting of the disease-specific Polycystic Liver Disease Questionnaire (PLD-Q)[21] (primary outcome), and two general quality of life questionnaires: 12-Item Short Form Survey (SF-12)[22], and the EuroQoL Visual Analogue Scale (EQ-VAS)[23] (secondary outcomes).

The PLD-Q was extensively validated in cohort of PLD patients in the USA and the Netherlands.[21] PLD-Q scores the frequency (6-point Likert scale ranging from 1= never to 6= always) and burden (5-point Likert scale ranging from 0=not at all to 5= a lot) of PLD-related symptoms; abdominal fullness, lack of appetite, early satiety, acid reflux, nausea, pain in rib cage, side, abdomen and back, dyspnea after exertion, limited mobility, tiredness, anxiety about the future, concerns for growing liver, dissatisfaction of the size of abdomen and discomfort with intercourse. It is able to distinguish symptoms from polycystic liver disease and polycystic kidney disease.[21] A total score can be generated by adding the score of the frequency and burden of all symptoms. This score can be transformed to a score ranging from 0-100 and a higher score indicates a higher symptom burden. The total PLD—Q score was not calculated if >1 question score was missing. The general reference population in the US scored a median of 13 points (IQR: 7 – 22).[21]

Overall quality of life was measured with the frequently used SF-12, a shorter version of the SF-36. In validation studies, the SF-12 provides reproducible results of the summarizing physical

component score (PCS) and a mental component scores (MCS) compared to the SF-36.[24-26] Scores range from 0-100 and a higher component score implicates a better physical or mental quality of life. PCS and MCS were only calculated if no question score was missing. Results are compared to norm scores, derived from an age-matched (45 – 54 years) female general reference population from the US, as PLD occurs predominantly in females.[1] This reference population scored a median PCS of 51.61 points and median MCS of 53.48 points.[27]

The EQ-VAS records patients' self-rated overall quality of life on a vertical 0-100 scale ('best imaginable health state' - 'worst imaginable health state').[23] A higher score implicates a better overall quality of life. Results are compared to a norm score, derived from an age-matched (45 – 54) general reference population from the US, as sex-matched scores were not available. The general reference population scored 79.2 points on average.[28]

Sensitivity analyses of quality of life analyses were performed by excluding patients with major complications (Clavien-Dindo grade 4), renal transplant recipients and concomitant renal surgery.

Clinical relevance

A statistically significant change in symptom score after surgery does not necessarily implicate a clinically relevant improvement for individual patients. Previous literature has shown that half the standard deviation of score changes (change between baseline and follow-up score) is equivalent to the Minimal Clinically Important Difference (MCID).[29] Subsequently, the proportion of patients with a change in PLD-Q score (primary outcome) after six months that exceeded the MCID was calculated. Subsequently, baseline characteristics (age, liver volume, change in liver volume, pre-surgical PLD-Q, PCS, MCS, EQ-VAS score, diagnosis, ASA status, previous abdominal surgery, Clavien-Dindo complication grade ≥2) and individual PLD-Q symptom score changes of patients with or without a clinically relevant response were compared in an exploratory analysis to find potential response predicting factors.[29]

In addition, we calculated the effect size of differences six months after therapy for PLD-Q, SF-12 and EQ-VAS scores. Overall effect size is defined as the change in mean quality of life score, divided by the standard deviation of score changes. Overall effect size was assessed by calculating Cohen's d for paired-samples, d > 0.2 – 0.5 is defined as a small, d > 0.5 – 0.8 as a medium and d > 0.8 as a large effect size.[30]

Statistical methods

As literature on change in symptoms and quality of life is lacking, no formal a-priori power analysis was performed. We aimed to include 20 patients because of the rarity of this condition and as large differences after surgery were expected. Descriptive variables are expressed as mean (standard deviation [SD]) for normally distributed data, or median (interquartile range [IQR]) for skewed data. We compared pre- and postoperative values of liver volume, PLD-Q total and individual symptom scores, PCS, MCS and EQ-VAS scores, using the Related-Samples Wilcoxon signed-rank test for non-normally distributed continuous data. A one-sample Wilcoxon signed-rank test was used to determine whether median quality of life scores of patients were different from general reference population norm scores before and after surgery. For responder vs. non-responder

subgroup analyses, we used the Independent-Samples Mann-Whitney U test for continuous data or the Chi-squared test for categorical data. P-values are two-tailed and a p-value <0.05 is considered statistically significant. In case of missing data, subjects were only excluded from that particular analysis. All analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL).

RESULTS

Of 22 eligible patients, 18 were included in the study (Figure 2). After enrollment, one patient was excluded from analysis because no baseline data were available. Response rate per questionnaire, per timepoint ranged between 76% and 94%. Baseline and follow-up questionnaires were completed in full in 13/17 (76%) patients for PLD-Q, 14/17 (82%) for SF-12 and 12/17 (71%) for EQ-VAS (Supplementary Table 2). Median time to return the questionnaire set was six months after surgery.

Baseline characteristics

Baseline characteristics are presented in Table 1. The included patients had a mean age of 52 years and 82% were female. Included patients had moderate (53%) or severe (47%) PLD, with a median TLV before surgery of 5141.8 ml (IQR: 3773.6 – 7374.2). Included patients with polycystic kidney disease had a median TKV of 452.5 ml (IQR: 337.2 – 1032.3) and no patients were on dialysis. Patients were classified as ASA II (59%) or ASA III (41%) before surgery. Indications for surgery were abdominal discomfort or fullness in 88% of patients; 76% pain, 65% early satiety, 35% fatigue and 24% dyspnea.

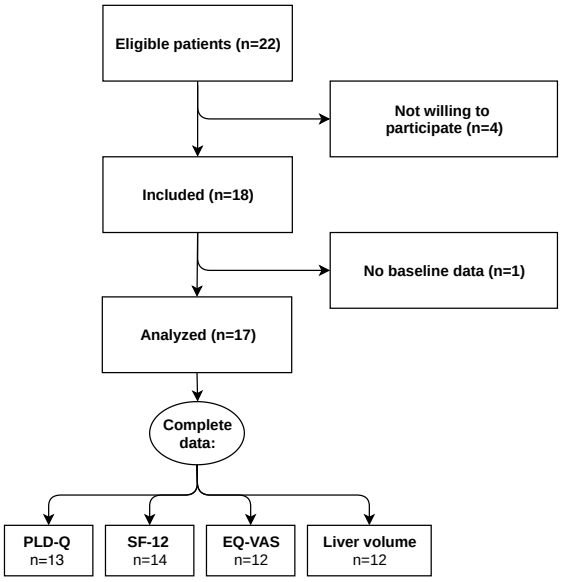

Figure 2. Study flow chart. Small boxes at the bottom show the number of patients with complete data (baseline and follow-up data) for a specific outcome.

Abbreviations: PLD-Q: Polycystic Liver Disease Questionnaire. SF-12: 12-Item Short Form Survey. EQ-VAS: EuroQoL Visual Analogue Scale.

Table 1. Baseline characteristics

Baseline characteristics:	n=17
Age (years), mean ± SD	52.0 ± 9.2
Female sex, n (%)	14 (82%)
Race, n (%)	
White	15 (88%)
Asian	1 (6%)
Hispanic	1 (6%)
Diagnosis, n (%)	
ADPKD	14 (82%)
ADPLD	3 (18%)
ASA status, n (%)	
ASA II	10 (59%)
ASA III	7 (41%)
Previous abdominal surgery, n (%)	
All	12 (71%z)
Hernia repair	4 (24%)
Gynecological surgery	4 (24%)
Kidney transplant	3 (18%)
Liver cyst fenestration	2 (12%)
Bilateral nephrectomy	2 (12%)
Height (cm), median (IQR)	171 (162 – 174)
Weight (kg), median (IQR)	67.6 (60.2 – 73.7)
BMI (kg/m^2), median (IQR)	23.7 (22.7 – 25.8)
Total liver volume (ml), median (IQR)	5142 (3774 – 7374)
Total kidney volume (ml), median (IQR)	453 (337 – 1032)
eGFR (ml/min/1,73m^2), n (%)	
≥60	12 (71%)
45 – 59	3 (18%)
30 – 44	1 (6%)
Surgery characteristics:	
Estimated blood loss (ml), n (%)	
1 – 500	11 (65%)
501 – 1000	4 (24%)
1001 – 2000	1 (6%)
>2000	1 (6%)
Received packed cells, n (%)	6 (35%)
Number of packed cells*, median (IQR)	2.0 (1.0 – 4.5)
Complications (Clavien-Dindo), n (%)	
None	6 (35%)
Grade 1	4 (24%)
Grade 2	5 (29%)
Grade 3	0 (0%)
Grade 4	2 (12%)
Grade 5	0 (0%)

Baseline characteristics for 17 included patients. *: only patients who received ≥1 packed cells (n=6). ADPLD: autosomal dominant polycystic liver disease. ASA: American Society of Anesthesiologists. BMI: body-mass index. eGFR: estimated glomerular filtration rate.

Surgery characteristics

A detailed surgery description per patient is presented in Supplementary Table 3. Concomitant cholecystectomy was performed in 13/17 (76%) patients and hernia repair in 3/17 (18%). Median duration of surgery was 167 minutes (IQR: 143.5 – 209.0) and mean hospital stay was 8.4 days (SD: 3.3). Perioperative blood loss and complications are presented in Table 1. Post-operative complications occurred in 11/17 patients (65%) and most complications were minor (Grade I or II).

However, two patients (12%) had to be admitted to the ICU (grade IV). The first patient with a history of abdominal surgeries had extensive abdominal adhesions and developed complications consisting of biliary leakage which required stent placement in the common bile duct, pneumonia, delirium and bilateral lower extremity deep venous thrombosis. The second patient underwent concomitant renal cyst fenestration and developed a wound infection, acute kidney injury and a right ureteric leak which required ureteric stenting. None of the patients had persistent ascites after surgery. There were no patients with post-operative liver failure.

Change in liver volume

Follow-up imaging was available in 13/17 patients. In some patients, follow up was done by their referring physician. In four of them, no postoperative imaging was performed. Median liver volume was reduced from 4781 ml (IQR: 3303 – 6228) to 2110 ml (IQR: 1589 – 2532) (p=0.001), which translates to a median reduction of 57% (IQR: 45 – 67%). Median baseline liver volume of non-analyzed patients (n=4) was 7185 ml (IQR: 6211 – 9340). Median time between surgery and follow-up scan was 3 months (IQR: 1 – 7.5).

Quality of life

PLD-Q

After surgery, PLD-symptoms decreased (p<0.001). Median total PLD-Q score fell from 76.9 points (IQR: 41.0 – 83.0) at baseline to 34.8 points (IQR: 17.0 – 43.8) six months after surgery (Figure 3A). The effect size was large (d=1.42). Patients had a significantly higher PLD-Q score compared to the general reference population, both before (76.9 vs. 13.0, p=0.001) and after surgery (34.8 vs. 13.0, p=0.001). An overview of baseline symptom severity derived from the PLD-Q is presented in Supplementary Figure 1.

The MCID of the PLD-Q was -11.2 points in this cohort, which results in a clinically relevant difference in 10/13 (77%) patients (Figure 4). Only one patient had an increase in PLD-score (+4.2 points), this ASA III patient, with a history of multiple abdominal surgeries and renal transplant, had severe complications after surgery (Grade IV). Characteristics of patients that did (n=10) or did not (n=3) show clinically relevant response are shown in Table 2. Non-responders had a lower symptom burden and a better health state before surgery compared to responders (PLD-Q: 40.3 vs 79.2, p=0.03; EQ-VAS 55.0 vs 40.0, p=0.04). There were more ASA III patients in the non-responders subgroup (p=0.01).The factors age (p=0.1), baseline liver volume (p=0.6), change in liver volume (p=1.0), baseline scores for PCS and MCS (p=0.2; p=0.4), diagnosis (p=0.4), previous abdominal

surgery (p=0.2), and perioperative complications grade ≥2 (p=0.4) were not correlated with clinically relevant response.

Nearly all individual symptoms of the PLD-Q declined after treatment (Figure 5). Only change in 'abdominal pain' was not statistically significant (p=0.07). This can be explained by an increase of abdominal pain in four patients, which was not associated with major complications or kidney volume change. Early satiety and shortness of breath showed the largest decrease, with a reduction of median score of 6 points. Changes in individual symptom scores for response subgroups are shown in Supplementary Figure 2.

SF-12

Quality of life as assessed by the SF-12 questionnaire improved significantly after surgery. Median PCS increased (p=0.004) from 24.9 points (IQR: 17.4 – 26.5) to 45.7 points (IQR: 34.6 – 55.3) (Figure 3B). Median MCS increased (p=0.02) from 40.5 points (IQR: 25.9 – 59.0) to 55.4 points (IQR: 50.8 – 58.9) (Figure 3C). The effect size was large for increase of PCS (d=0.93) and medium for MCS (d=0.79). Patients had a worse PCS score before surgery compared to the general reference population (24.9 vs. 51.61, p=0.001), while no significant difference remained after surgery (45.7 vs. 51.61, p=0.07). Median MCS was also significantly lower before surgery (40.5 vs. 53.48, p=0.05) and was comparable to the general reference population after surgery (55.4 vs.53.48, p=0.4). Score changes per individual patient are shown in Figure 4. The MCID of the PCS and MCS was +8.4 and +7.6 points in this cohort, respectively. This results in a clinically relevant improvement of physical and mental quality of life in 9/14 (69%) and 8/14 (57%) patients (Figure 4).

EQ-VAS

On a visual analogue scale of quality of life, patients scored a median of 40.0 (IQR: 36.8 – 48.8) before surgery. Six months after surgery, patients scored a median of 72.5 (IQR: 63.3 – 92.3) which was a significant improvement (p=0.003) (Figure 3D, Figure 4). The effect size was large (d=1.89). Patients scored worse before surgery compared to the general reference population (40.0 vs. 79.2, p=0.002) and had a comparable score after surgery (72.5 vs. 79.2, p=0.6). The MCID of the EQ-VAS was +6.9 points, therefore 12/12 (100%) patients had a relevant improvement of health state.

Sensitivity analyses

When excluding patients that suffered major complications (n=2), there were no clinically relevant differences in PLD-Q, PCS, MCS and EQ-VAS score changes (p=0.002, p=0.01, p= 0.04, p=0.003, respectively). Also, results did not change significantly after excluding renal transplant recipients (n=3; p=0.005, p=0.03, p=0.05, and p=0.008, respectively) and patients that had concomitant renal surgery (n=2; p=0.003, p=0.01, p=0.02, and p=0.003, respectively).

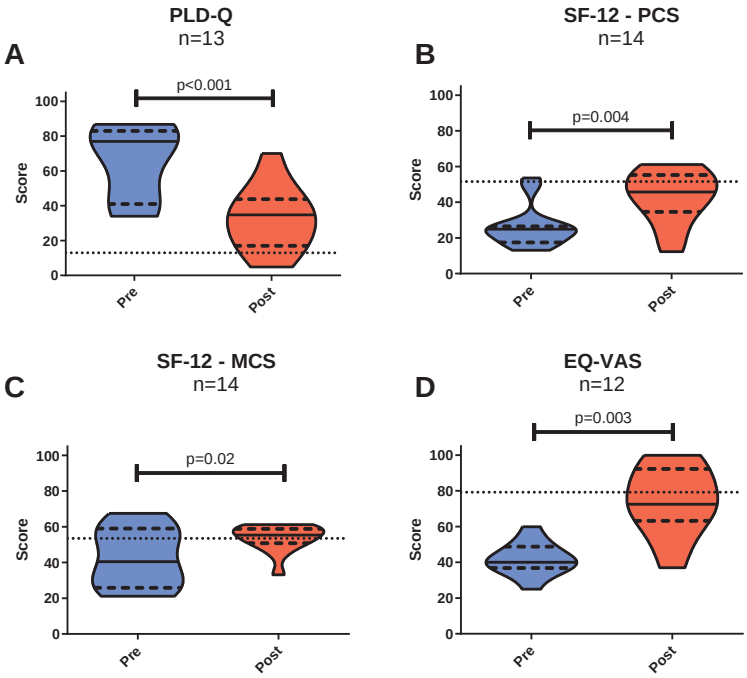

Figure 3. Patient-reported outcomes pre-surgery (blue) and six months post-surgery (red). Violin plots show the distribution of scores, median (solid line) and interquartile range (dashed lines) are superimposed. Dotted lines represent the general reference population score.
Abbreviations. PLD-Q: Polycystic Liver Disease Questionnaire. SF-12: 12-Item Short Form Survey. PCS: Physical Component Scale. MCS: Mental Component Scale. EQ-VAS: EuroQoL Visual Analogue Scale.

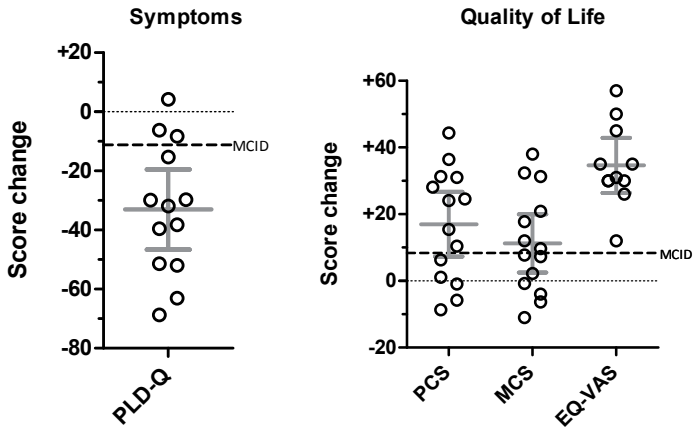

Figure 4. Score change per patient per questionnaire score. Polycystic liver disease questionnaire (PLD-Q) score, Physical Component Scale (PCS) and Mental Component Scale (MCS) of the SF-12 questionnaire and EuroQoL-Visual Analogue Scale (EQ-VAS) are presented. Individual patient results are shown; mean and 95% confidence interval are superimposed. For PLD-Q, the Minimal Clinically Important Difference (MCID) is shown at -16.5 points.

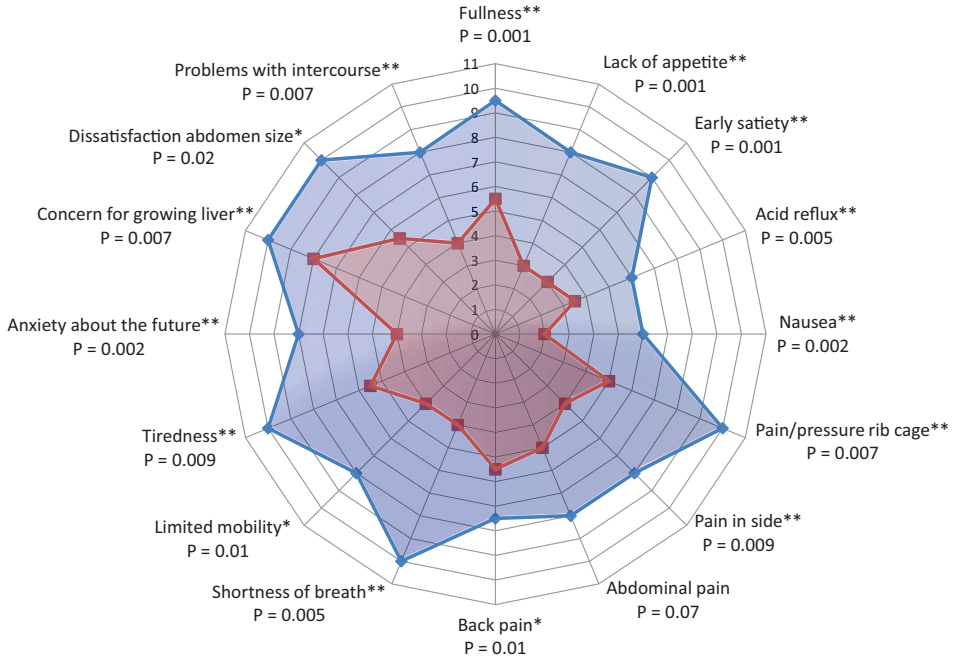

Figure 5. Radar chart of median individual symptom scores of the Polycystic Liver Disease Questionnaire, pre-surgery (blue) and six months post-surgery (red). *: p<0.05; **: p<0.01

Table 2. Responder subgroup analysis

Characteristic:	Responders (n=10) Median (IQR)	Non-responders (n=3) Median (range)[a]	P-value
Age (years)	48 (44 – 57)	60 (52 – 71)	0.1
Liver volume pre-surgery (mL)	5098 (4436 – 7049)	6571 (3961 – 10556)	0.6
Change in liver volume (mL)	2794 (2306 – 5444)	2944 (1427 – 4462)	1.0
PLD-Q pre-surgery (score)	79.2 (64.3 – 84.4)	40.3 (34.0 – 41.7)	**0.03**
PCS pre-surgery (score)	22.1 (16.8 – 25.8)	25.7 (24.8 – 48.7)	0.2
MCS pre-surgery (score)	40.5 (25.8 – 57.1)	60.2 (22.7 – 67.6)	0.4
EQ-VAS pre-surgery (score)	40.0 (35.5 – 42.5)	55.0 (50.0 – 60.0)	**0.04**
	N (%)	N (%)	
Diagnosis (% ADPKD)	8 (80%)	3 (100%)	0.4
ASA status (ASA II : III)	8:2	0:3	**0.01**
Previous abdominal surgery (% yes)	6 (60%)	3 (100%)	0.2
Clavien-Dindo complication grade ≥2 (%)	4 (40%)	2 (67%)	0.4

Comparison of responders and non-responders based on a minimal clinically important difference of -11.2 points for the PLD-Q. (a.) Total range, as only 3 values were available.

Abbreviations: IQR: interquartile range, PLD-Q: polycystic liver disease questionnaire, PCS: physical component scale. MCS: mental component scale. EQ-VAS: EuroQoL-Visual Analogue Scale. ASA: American Society of Anesthesiologists. ADPKD: autosomal dominant polycystic kidney disease.

DISCUSSION

PHCF significantly improves both symptom burden and quality of life in moderate and severe PLD patients with relative sectorial sparing. Based on our primary outcome (PLD-Q), the majority of patients (77%) met the threshold of a clinically relevant response six months after treatment.

A large treatment effect was detected using the PLD-Q, reflected by improved quality of life scores. At baseline, the included patients presented with very high symptom scores (PLD-Q: 76.9). By comparison, moderate and severe PLD patients with an equivalent median liver volume (5001 mL) in a previously published cross-sectional study (n=56) had a median PLD-Q of 42.6 (IQR: 30.1 – 48.7).[3]

In addition to high symptom burden, patients also had a profoundly impaired quality of life (PCS: 24.9, MCS: 40.5). To compare, quality of life of these patients is worse than that of hemodialysis patients (PCS: 33.3, MCS: 47.5) or cirrhotics (PCS: 34, MCS: 44).[31, 32] After surgery, there were no relevant differences in quality of life between patients and the general reference population for PCS, MCS and EQ-VAS scores, confirming that PHCF achieves a large improvement in this population. Quality of life after PHCF has been previously assessed with SF-36 questionnaire in 69 patients, on average nine years after surgery. Compared to our cohort, PCS was equivalent (45 vs. 45.7) and MCS was higher (50 vs. 55.4) at long-term follow-up.[12]

Three patients (23%) did not achieve clinically relevant improvement after surgery. Our results suggest that the risk of non-response after surgery increases in patients with lower symptoms scores before surgery and with a higher pre-surgical ASA classification. The lower baseline PLD-Q and EQ-VAS score of the non-responders (based on MCID) shows that only highly symptomatic patients should be treated with PHCF, but this cohort is too small to define strict cut-off criteria based on patient-reported outcome measures. We did not see a correlation between change in liver volume and clinical response, but this could be underestimated due to the exclusion of four patients with relatively high baseline liver volume that did not have follow-up imaging.

When looking at individual symptoms of the PLD-Q, only abdominal pain did not significantly improve after surgery. Although it can be caused by a lack of statistical power, it may suggest that abdominal pain in these patients is multifactorial and not only associated with liver volume.

Major complications occurred without mortality in 12% of included patients, which is comparable to previous studies. Two retrospective studies (n=186; n=45) also scored complications after PHCF according to Clavien-Dindo and respectively reported major complications in 21% and 13% of patients and mortality in 3% and 0%.[13, 33] The relatively higher rate of complications in the first study may be due to general reduction of operative risk since 1985.[34] Sensitivity analysis showed that the overall improvement on quality of life was not significantly impacted by the patients with major complications.

An alternative to PHCF in PLD patients with severe hepatomegaly is liver transplantation. In one cohort (n=36), 91% of patients felt better or much better after a mean follow-up time of 62 months.[35] Specifically, the symptoms fatigue, physical fitness, loss of appetite and vomiting showed significant improvement.[35] The 5-year overall survival (92%) and graft survival (88%) after liver transplantation in PLD patients are high.[36] In contrast to symptomatic benefit and good long-term

results, perioperative mortality in PLD varies between 4 and 17%, which is higher than in liver transplantation for other indications.[36, 37] In light of the scarcity of available grafts, the necessity for long-term immunosuppressive medication and high post-operative mortality in a benign disease, PHCF is often preferred.[37] Additionally, combined liver-kidney transplantation can be performed in PLD patients with concomitant renal failure.[38, 39] Although there are some studies with favorable effect of TAE on liver volume, the effect on symptoms and quality of life remains to be elucidated.

The main limitation of this study was the small sample size. This is inevitable for a surgical procedure that is infrequently performed, even in an international referral center. In addition, change in scores could be calculated in 71% to 82% of the cohort despite a high response rate per timepoint. Nonetheless, as the improvement in quality of life after surgery is large, even this small sample size has adequate power to achieve statistically significant and clinically relevant results for our primary and secondary outcomes.

No long-term data on symptom reduction and quality of life is available for our cohort yet. We have chosen a six month follow up as quality of life during postoperative recovery usually normalizes within three to six months after hemihepatectomy.[40, 41] Although liver volume and symptoms have no linear relationship, we do not expect that quality of life will decline notably over time due to liver growth.[3] While recurrence of cysts is common after fenestration, a previous study showed lasting reduction of liver volume after PHCF for up to 20 years.[13] In addition, equivalent SF-36 scores measured nine years after PHCF, corroborate this.[12]

This study was performed in a referral center that is specialized in treatment of polycystic liver disease, with experienced operating teams. Therefore, the generalizability of these results to other centers may be limited. However, PHCF is an infrequently used and complex surgical procedure due to the altered anatomy and consequently, centralization of this procedure is necessary to achieve the best outcome for the patient.

We calculated the MCID with a distribution-based method based on the standard deviation. Another viable option would have been to calculate the MCID through an anchor-based method. This method uses an additional patient-reported question after the procedure to assess whether the patient thinks a clinically relevant improvement has been achieved.[42] The PLD-Q does not include a question that could be used to accurately calculate an anchor-based MCID six months after surgery in our cohort. However, as it has been previously shown that half the standard deviation of score changes is equivalent to the MCID, both methods provide an accurate representation of clinically relevant improvement.[29]

Strengths of this study are that we conducted a prospective study with reliable, responsive and reproducible questionnaires to accurately assess the course of symptoms and quality of life after surgery. In addition, follow-up measurements were performed at predetermined timepoints. Besides statistical significance, we also tested the clinical relevance of our results.

In conclusion, PHCF provides a reduction of symptoms and increase in quality of life in the majority of patients, with values similar to a healthy reference population six months after surgery. However, 23% of patients did not have a clinically relevant improvement of symptoms, despite a decrease in liver volume. In light of potential major complications, careful selection of

patients and managing patients' expectations is important. We confirm that PHCF can be effective for selected patients with moderate or severe PLD and a high symptom burden.

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SUPPLEMENTARY DATA

Supplementary Table 1. Strobe checklist
STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant paragraph from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2	Prospective cohort study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4	'Introduction'
Objectives	3	State specific objectives, including any prespecified hypotheses	4	'Introduction'
Methods				
Study design	4	Present key elements of study design early in the paper	4	Methods (study design and setting)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	Methods (study design and setting)
Participants	6	*Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5	Methods (study design and setting, procedure, participants)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6	Methods (Outcome measures)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6	Methods (Outcome measures)

Supplementary Table 1. (continued)

	Item No.	Recommendation	Page No.	Relevant paragraph from manuscript
Bias	9	Describe any efforts to address potential sources of bias	5	Patients who underwent PHCF for reasons other than control of volume-related symptoms and patients that were predisposed to unreliable questionnaire responses due to mental illness or insufficient knowledge of the English language were excluded.
Study size	10	Explain how the study size was arrived at	4	Methods (study design and setting)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8	Methods (outcome measures, clinical relevance, statistical methods)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8	Methods (clinical relevance, statistical methods)
		(*b*) Describe any methods used to examine subgroups and interactions	7-8	Methods (clinical relevance, statistical methods)
		(c) Explain how missing data were addressed	8	In case of missing data, subjects were only excluded from that particular analysis.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	8	In case of missing data, subjects were only excluded from that particular analysis.
		(e) Describe any sensitivity analyses		n/a
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	Results

Supplementary Table 1. (continued)

	Item No.	Recommendation	Page No.	Relevant paragraph from manuscript
		(b) Give reasons for non-participation at each stage	8	Results
		(c) Consider use of a flow diagram		Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9	Results (baseline characteristics, surgery characteristics)
		(b) Indicate number of participants with missing data for each variable of interest	8	Results & Figure 2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8	Median time to return the questionnaire set was six months after surgery.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-10	Results (Change in liver volume, Quality of life)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		No confounders were analyzed.
		(b) Report category boundaries when continuous variables were categorized	5-7	Category boundaries were described in the methods section.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10	Responder vs non-responder subgroups. Individual symptom score analysis.
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12	Discussion

Supplementary Table 1. (continued)

	Item No.	Recommendation	Page No.	Relevant paragraph from manuscript
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	13	This study was performed in a referral center that is specialized in treatment of polycystic liver disease, with experienced operating teams. The generalizability of these results to other centers may be limited. However, PHCF is an infrequently used and complex surgery due to the altered anatomy and consequently, centralization of this procedure is necessary to achieve the best outcome for the patient.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14	Acknowledgements

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplementary table 2. Missing questionnaire scores per patient.

#	PLD-Q Baseline	PLD-Q Follow-up	Change PLD-Q	PCS Baseline	PCS Follow-up	Change PCS	MCS Baseline	MCS Follow-up	Change MCS	EQ-VAS Baseline	EQ-VAS Follow-up	Change EQ-VAS	Missing values per patient: n (%)
1			-29,7			10,46			7,76			31,00	**0**
2			-31,89			44,38			-,80			45,00	**0**
3			-63,03			31,02			31,27			57,00	**0**
4		MISSING	n/a		MISSING	n/a		MISSING	n/a		MISSING	n/a	**4 (50%)**
5			-38,19			28,09			38,03			30,00	**0**
6			4,17			24,56			9,72			30,00	**0**
7			-51,39			15,41			17,78			26,00	**0**
8			-29,86			-5,75			-3,95	MISSING		n/a	**1 (13%)**
9			-8,33			24,13			-6,31			50,00	**0**
10			-51,99			6,28			7,32			35,00	**0**
11			-68,75			36,42			32,34			35,00	**0**
12	MISSING		n/a	MISSING		n/a	MISSING		n/a	MISSING		n/a	**4 (50%)**
13			-39,58			31,28			2,24			30,00	**0**
14			-15,28			-,87			12,01			12,00	**0**
15			-6,25			-8,66			-10,99	MISSING		n/a	**1 (13%)**
16	MISSING		n/a			1,09			20,88	MISSING		n/a	**2 (25%)**
17		MISSING	n/a		MISSING	n/a		MISSING	n/a			10,00	**3 (38%)**
Missing values per timepoint: n (%)	**2 (12%)**	**2 (12%)**	**4 (24%)**	**1 (6%)**	**2 (12%)**	**3 (18%)**	**1 (6%)**	**2 (12%)**	**3 (18%)**	**4 (24%)**	**1 (6%)**	**5 (29%)**	

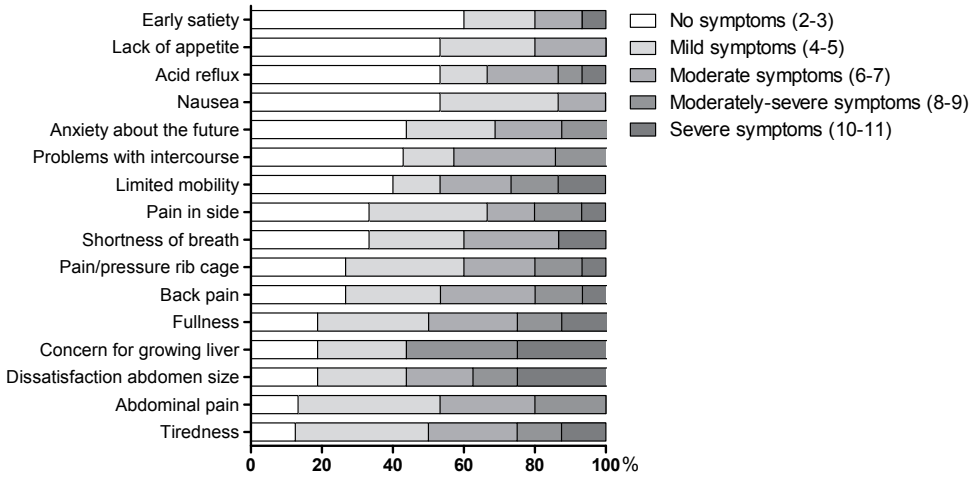
Abbreviations: PLD-Q: polycystic liver disease questionnaire. PCS: physical component scale. MCS: mental component scale. EQ-VAS: EuroQoL-Visual Analogue Scale.

Supplementary table 3. Individual Patient Characteristics

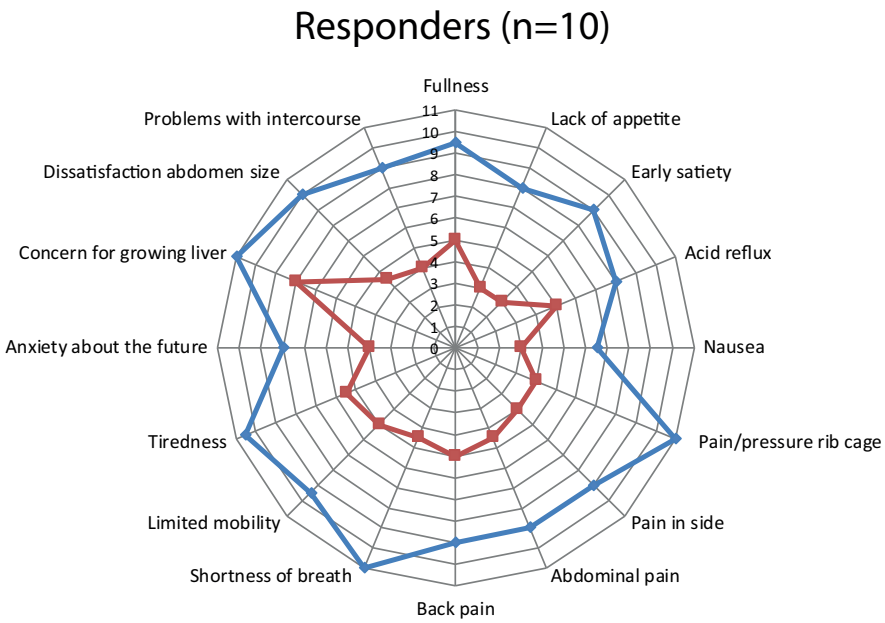
#	Age	Gender	ASA	Type of surgery	Cholecyst-ectomy	Hernia repair
1	62	Male	II	Right hepatectomy, left fenestration	Yes	Yes
2	51	Female	II	Segmentectomy (VII and VIII), left fenestration	Yes	No
3	55	Female	II	Right hepatectomy, partial segmentectomy (IV), left fenestration	Yes	No
4	49	Female	II	Bisegmentectomy (VII and VIII), fenestration (I and VI)	Yes	No
5	46	Female	III	Extended right hepatectomy, left fenestration	Yes	No
6	60	Male	III	Right hepatectomy, left fenestration	Yes	No
7	61	Female	III	Right hepatectomy, right fenestration.	No	Yes
8	39	Female	II	Right hepatectomy, left fenestration	Yes	No
9	71	Female	III	Laparoscopic hand-assisted left lateral hepatectomy and sectorectomy, combined with nephrectomy	No	No
10	45	Female	II	Left hepatectomy, subsegmentectomy (V and VI), right fenestration	No	No
11	35	Female	II	left hepatectomy, right fenestration	Yes	No
12	63	Male	II	Subsegmental resection (IVB and V), fenestration, combined with fenestration of bilateral renal cysts	Yes	No
13	49	Female	II	Right hepatectomy, excision of caudate lobe, left fenestration	No	No
14	47	Female	II	Left lateral sectorectomy, subsegmentectomy VIII, right fenestration, combined with hysterectomy and bilateral salpingectomy with ovarian preservation	Yes	No
15	52	Female	III	Right hepatectomy	Yes	No
16	46	Female	III	Left hepatectomy, fenestration	Yes	Yes
17	53	Female	III	Right Hepatectomy, fenestration	Yes	No

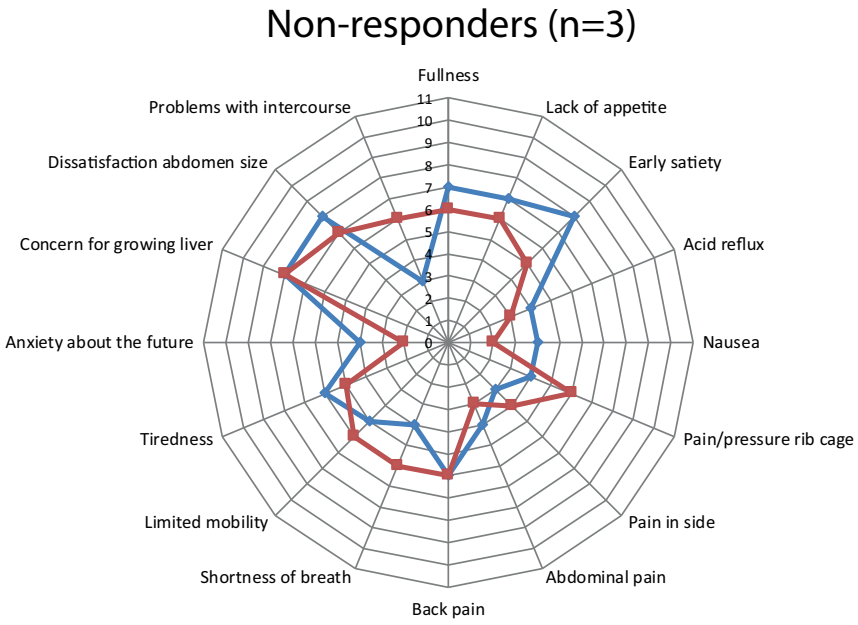
Abbreviations: ASA: American Society of Anesthesiologists status. LV: total liver volume. ICU: intensive care unit. PLD-Q: polycystic liver disease questionnaire. n/a: not available. Change in PLD-Q score is marked green if the decrease is more than the MCID of 16.5 (responder) and marked red if it is less (non-responder).

Liver volume baseline (ml)	Liver volume follow-up (ml)	Duration surgery (min.)	Days in ICU	Clavien-Dindo classification	Admission (days)	Change PLD-Q
10979	3421	207	0	Grade I	8	-29,7
3021	1698	109	0	Grade 2	8	-31,89
9886	1481	155	0	None	4	-63,03
2644	1434	101	0	Grade I	4	n/a
10556	n/a	153	0	Grade 2	9	-38,19
6104	n/a	222	4	Grade 4b	13	+4,17
5054	1991	150	0	None	8	-51,39
4781	2530	184	0	Grade I	6	-29,86
3961	2534	148	0	None	3	-8,33
5142	2505	167	0	None	5	-51,99
5885	2555	211	0	Grade 2	11	-68,75
2929	2130	139	3	Grade 4a	16	n/a
3586	1225	128	0	Grade I	6	-39,58
4719	1925	273	0	Grade 2	11	-15,28
6571	2110	362	0	Grade 2	10	-6,25
6247	n/a	185	0	None	8	n/a
8123	n/a	167	0	None	8	n/a



Supplementary Figure 1. Severity of individual symptoms (%) as scored on the polycystic liver disease questionnaire in the study population before surgery. Scores range from 2 to 11 and are grouped according to severity.





Supplementary Figure 2. Radar chart of median individual symptom scores of the polycystic liver disease questionnaire (PLD-Q), pre-surgery (blue) and six months post-surgery (red) for responder and non-responder subgroups.

7

ESTROGEN-CONTAINING ORAL CONTRACEPTIVES ARE ASSOCIATED WITH POLYCYSTIC LIVER DISEASE SEVERITY IN PRE-MENOPAUSAL PATIENTS

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ABSTRACT

The association between estrogen-containing oral contraceptives and history of pregnancies with disease severity in females with polycystic liver disease (PLD) is unclear. We performed a cross-sectional cohort study to assess this association by selecting female PLD patients of which imaging was available prior to any liver volume reducing therapy. Patients received a questionnaire to collect detailed information on estrogen use and pregnancies. Preplanned subgroup analyses were performed on pre-menopausal and post-menopausal patients. The questionnaire was returned by 287 of 360 selected patients (80%). There was no significant association between estrogen-containing oral contraceptives and height-adjusted liver volume (hTLV) in the total group (P=0.06) and post-menopausal subgroup (P=0.7). By contrast, each year of exposure corresponds with a 1.45% higher hTLV (P=0.02) in the pre-menopausal subgroup, equivalent to a 15.5% higher hTLV for every 10 years of use. Pregnancy duration was not associated with hTLV. In conclusion, PLD patients should avoid exogenous estrogens.

7

STUDY HIGHLIGHTS

- **What is the current knowledge on the topic?**
  Female PLD patients are more at risk to develop severe hepatomegaly compared to males. It is thought that exposure to estrogen-containing oral contraceptives and a history of pregnancies influence the disease course in PLD. However the evidence in literature is contradicting.

- **What question did this study address?**
  We assessed whether estrogen-containing oral contraceptives and/or pregnancies are associated with PLD severity expressed as height-adjusted liver volume in pre- and post-menopausal patients.

- **What does this study add to our knowledge?**
  In this large cross-sectional cohort study we demonstrate that use of estrogen-containing oral contraceptives worsens PLD severity in pre-menopausal patients. Every year of exposure correlates with a 1.45% higher hTLV, which corresponds to a 15.5% higher hTLV for every 10 years of use, compared to unexposed females.

- **How might this change clinical pharmacology or translational science?**
  With these findings, we legitimize our current counseling advice in the outpatient clinic with evidence and underline the importance to avoid estrogen use in PLD patients. Clinicians should advise their patients to use non-hormonal contraceptives.

INTRODUCTION

Polycystic liver disease (PLD) is a progressive genetic disorder with a time-dependent increase of number and size of hepatic cysts.[1] In some cases this leads to hepatomegaly, pressure-related symptoms and reduced quality of life.[2, 3] PLD occurs in isolated form as autosomal dominant polycystic liver disease (ADPLD) or as a secondary manifestation in patients with autosomal dominant polycystic kidney disease (ADPKD). Risk factors for disease severity are ADPKD, age and gender.[4] PLD is particularly penetrant in females, and over 80% of patients from large cohort studies are female.[5] Endogenous estrogen production decreases after the menopause, which is defined as the time in a woman's life when menstruation periods cease permanently.[6] and literature suggests that liver volume increases in pre-menopausal patients, but stabilizes post-menopausally.[4, 7] These observations have led to the hypothesis that estrogen must be regarded as a trophic factor for PLD.

The concept that PLD severity is related to exposure to estrogen, either through use of estrogen-containing oral contraceptives or pregnancies, stems from a number of studies. The most robust evidence comes from a prospective study in 19 post-menopausal ADPKD patients, which showed that hormonal replacement therapy with estrogens was associated with a significant increase in total liver volume (TLV) compared to controls.[8] Based on this study, counseling advice in the outpatient clinic includes discouragement of exogenous estrogen therapy. However, it is unclear whether these data also hold for the population of pre-menopausal PLD patients, as recently published cohort studies suggested that exposure to estrogen is not correlated with TLV.[9, 10]

These data raise the question whether the advice to discontinue estrogen-containing oral contraceptives in pre-menopausal PLD patients is valid. Through the International PLD Registry, we were able to explore this controversy in a large cohort covering all stages of PLD.[4, 11] The goal of this cross-sectional study was to assess whether estrogen-containing oral contraceptives and/or pregnancies are associated with PLD severity at first presentation in pre- and post-menopausal patients. Our primary aim was to determine the correlation between cumulative exposure to estrogen-containing oral contraceptives in years and disease severity expressed as height-adjusted total liver volume (hTLV). Our secondary aim was to determine the correlation between cumulative months of pregnancy and hTLV.

METHODS

Study population and design

The International PLD Registry consists of patients with polycystic liver disease defined as having >10 liver cysts.[4, 11] For this study, patients from two referral centers (Radboud University Medical Center [Nijmegen, the Netherlands] and University Hospital Leuven [Leuven, Belgium]) were evaluated for inclusion. Patients were enrolled based on the following inclusion criteria: I) female gender; II) computed tomography (CT) or magnetic resonance imaging (MRI) was performed; III) imaging was performed prior to any liver volume reducing therapy (aspiration sclerotherapy, fenestration, hepatic resection, liver transplantation or treatment with somatostatin analogues);

IV) height-adjusted total liver volume was measured and available in the dataset; V) age between 18 and 75 years (a maximum age was chosen to minimize recall bias); VI) contact information was available. For all patients the first available type of imaging on which liver volume was measured was used for analysis.

Data collection

Data were extracted from the International PLD registry: age at imaging, diagnosis (ADPKD or ADPLD), total liver volume and height. Data on the female hormonal history were collected using a specific adapted questionnaire.[12] All selected patients received a questionnaire and a reminder two months later, if needed. Women were asked about age at menarche, regularity of menstruation cycle, exposure to estrogen-containing oral contraceptives (including temporary stops), use of non-estrogen containing contraceptives (e.g. intrauterine device), pregnancies and miscarriage, menopausal status and last menstruation, hormonal replacement therapy and history of hysterectomy and/or oophorectomy.

Based on this dataset, we calculated the total years of exposure to estrogen-containing oral contraceptives and the total months that patients were pregnant. For each live-born child a pregnancy duration of 9 months was assumed. In case a miscarriage was reported without information on duration of pregnancy, we assumed a pregnancy duration of three months as 80% of miscarriages occur in the first 12 weeks.[12] To determine whether patients were pre- or post-menopausal at time of imaging we used the age at last menstruation. Post-menopausal status was defined as the time after 12 consecutive months without menstruation. In some cases the menopausal status was uncertain because the patient underwent hysterectomy, used an intra-uterine device (IUD) or hormonal replacement therapy, or because data on the last menstruation was missing. In these cases, we imputed their menopausal status for our subgroup analyses. For this we used the average age of post-menopausal status (52 years) to classify them as pre- or post-menopausal accordingly.[13]

Measurement of liver volume

All imaging was performed from July 2000 until May 2018 as part of regular clinical care or because of participation in a clinical trial. Liver volume was measured by segmentation technique tracing the circumference of the liver. Volumetry on CT scans in the Netherlands was performed with *Pinnacle3* ® version 8.0 (Philips, Eindhoven, the Netherlands).[14, 15] For CT scans in Belgium we used *Volume* (Siemens, Erlangen, Germany).[16, 17] The volume on MRI scans was measured with *Analyze* 11 software (AnalyzeDirect Inc).[18] Previous studies have investigated inter-observer variability (-0.2 ± 2%) and agreement between different software programs.[15, 17] We divided liver volume by height in meters to obtain hTLV. Patients were classified in disease severity groups, as mild (hTLV < 1,600 mL/m), moderate (hTLV 1,600 to 3,200 mL/m) or severe (hTLV > 3,200 mL/m) PLD.[19]

Statistical analyses

Descriptive variables were expressed as mean (± standard deviation) or median (interquartile range [IQR]). Differences in baseline characteristics between pre- and post-menopausal females were tested with independent *t*-tests for normally distributed data or Mann-Whitney *U* test for non-normally distributed data. Chi-square tests were used to test differences between categorical variables.

We assessed the association between the total exposure of estrogen-containing oral contraceptive in years (main independent factor) and logarithmic transformed hTLV (dependent factor) using multiple linear regression models. Natural logarithmic (Ln) transformation of hTLV was used because of a non-normal distribution of hTLV. For ease of interpretation we back-transformed the unstandardized coefficients from all final models by exponentiation. Several potential confounders were defined based on an assumed association on both hTLV and the use of estrogen-containing oral contraception (treatment center, diagnosis [ADPKD/ADPLD], age at imaging, age at menarche, duration of pregnancy in months, duration of breastfeeding in months, fertility treatment [yes/no], hysterectomy [yes/no], menopausal status [yes/no/unclear], use of progestin-only contraceptives [yes/no], use of intrauterine device [yes/no]). Each potential confounder was added separately to our regression model. Confounders that had a relevant impact on the association, defined as >10% difference of the unstandardized coefficient (B) for the main independent factor, were included in our final model. In case of high collinearity (variance inflation factor >5) between confounders, the most significant confounder was selected.

It is hypothesized that liver volume increases in fertile women and stabilizes or even decreases after menopause.[7, 8] Therefore we a priori decided to repeat our model for the pre-menopausal and post-menopausal subgroup separately. Again, potential confounders were added to our regression model for each subgroup separately. Furthermore, we performed a sensitivity analysis in which we excluded all patients for which we had to impute their menopausal status based on average age at menopause (n=58).

The same method was used to determine the association between total months of pregnancy and Ln hTLV (secondary outcome) as well as between nulliparous/parous females and Ln hTLV.

In addition, we performed a post-hoc categorical analysis on disease severity groups based on hTLV. Mean duration of estrogen-containing oral contraceptive use was compared between groups and tested for statistical significance using an independent samples t-test.

Statistical analyses were performed with SPSS Statistics version 25 and statistical significance was defined as *P*-values <0.05, based on two-sided testing.

Ethical considerations

Concerning ethical approval of the PLD registry and thereby these analyses, formal evaluation was waived by the Institute Review Board Committee on Research Involving Human Subjects Arnhem-Nijmegen given the retrospective character of the data collection in the PLD Registry. The study was conducted in accordance with good clinical practice guidelines and the code of conduct for medical research (http://www.federa.org). Patients were informed about the intended

use of the questionnaire in an accompanying information letter. All patient data were entered in the database codified.[4] All questionnaires were coded before processing.

RESULTS

We identified 360 females that met the inclusion criteria for our study. Of all selected patients, a total of 287 (80%) patients returned the female hormonal status questionnaire (Radboudumc: 222, UK Leuven: 65) and were therefore eligible for analysis.

Baseline characteristics

Baseline characteristics for the whole group are presented in Table 1. Mean age at first available imaging was 50.2 years. Median hTLV was 2095 ml/m (IQR: 1419 – 3015), and patients were classified as mild (30%), moderate (48%) and severe PLD (21%). Baseline characteristics for pre-menopausal and post-menopausal subgroups are presented in Table 2. Patients with imaging in the pre-menopausal phase were taller and more frequently had breastfed compared to females who were included after menopause. Pre-menopausal women had significantly larger liver volumes. We were unable to use regularity of menstruation cycle as a potential confounder, due to missing data and unclear provided answers. Baseline characteristics of those who returned the questionnaire were not different compared to non-responders.

Estrogen-containing oral contraceptives

Patients who were exposed to estrogen-containing oral contraceptives had a higher Ln hTLV although this association did not reach statistical significance in an unadjusted linear regression analysis (B=0.0061; P=0.09) (Figure 1A and Table 3). Menopausal status was the only confounder that altered the effect of estrogen-containing oral contraceptives on Ln hTLV by more than 10%. After adjustment for this confounder, the correlation coefficient was 0.0068 (P=0.06). Based on our hypothesis that disease progression differs before and after the menopause we repeated our analysis for both subgroups independently.

Pre-menopausal

Unadjusted linear regression analysis showed an association (B=0.0156, P<0.01) between estrogen-containing oral contraceptives and Ln hTLV in pre-menopausal patients (Fig. 1B). Diagnosis, duration of breastfeeding and fertility treatment were identified as confounders as they changed the correlation coefficient by more than 10%. After adjustment for these confounders, the association between use of estrogen-containing oral contraceptives and Ln hTLV remained significant (B=0.0144, P=0.02) (Table 3). After back-transforming, this association can be interpreted as an estimated 1.45% higher hTLV per year of estrogen-containing oral contraceptive use compared to females who never used estrogen-containing oral contraceptives. We performed a sensitivity analysis using the same model, in which we excluded patients with imputed menopausal status. In 111 patients, the correlation coefficient remained unchanged (B=0.0143, P=0.05; 1.44% higher hTLV per year of estrogen-containing oral contraceptive use).

When dividing all pre-menopausal patients into disease severity groups, total years of estrogen-containing oral contraceptives use was significantly higher in the severe group when compared to the mild group (P=0.001) and significantly higher in the moderate group when compared to the mild group (P=0.02). There was no significant difference between the severe and moderate group (P=0.17) (Fig. 2A).

Table 1. Baseline characteristics

Characteristic	Patients n = 287
Age – yr	50.2 ± 9.3
Height – cm	167.8 ± 7.0
Center	
Radboud University Medical Center – n (%)	222 (77)
University Hospital Leuven – n (%)	65 (23)
Diagnosis	
ADPKD – n (%)	181 (63)
ADPLD – n (%)	106 (37)
Total liver volume – ml	3514 † (2400 – 4971)
Height adjusted total liver volume – ml/m	2095 † (1419 – 3015)
Severity classification: ‡	
Mild (<1600 ml/m) – n (%)	87 (30)
Moderate (1600-3200 ml/m) – n (%)	139 (48)
Severe (>3200 ml/m) – no. (%)	61 (21)
Ln hTLV – ml/m	7.66 ± 0.53
Age at menarche – yr	13.2 ± 1.5
Pregnancies – yes (%)	236 (82)
No. of pregnancies	2.6 ± 1.3
No. of months pregnant	20.5 ± 8.6
Breastfeeding – yes (%)	165 (70)
No. of months breastfeeding	10.1 ± 9.1
Fertility treatment – yes (%)	15 (5.2)
Estrogen-containing contraception – yes (%)	268 (93)
Estrogen-containing contraception – yr	14.1 ± 8.6
Progestin-only oral contraceptives – yes (%)	13 (5)
Intra-uterine device – yes (%)	65 (23)
Menopausal status:	
Pre-menopausal – n (%)	114 (40)
Post- menopausal – n (%)	115 (40)
Age at menopause	50.1 ± 4.5
Uncertain/unknown – n (%)	22 (8)
Hysterectomy / oophorectomy before scan – n (%)	36 (13)

Legend: Plus–minus values are means ± SD. † Non-parametric values expressed as median (IQR). ‡ Severity classification is based on height adjusted total liver volume (ml/m).Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; hTLV, height adjusted total liver volume; Ln, natural logarithm.

Table 2. Characteristics for menopausal status subgroups

Characteristic	Pre-menopausal (n=149)	Post-menopausal (n=138)	p-value
Age – yr	43.4 ± 6.4	57.5 ± 5.3	<0.001
Height – cm	169.2 ± 6.8	166.4 ± 6.9	0.001
Center			0.29 '
Radboud University Medical Center – n (%)	119 (80)	103 (75)	
University Hospital Leuven – n (%)	30 (20)	35 (25)	
Diagnosis			0.62 '
ADPKD – n (%)	96 (64)	85 (62)	
ADPLD – n (%)	53 (36)	53 (38)	
Total liver volume – ml	3968 (2741 – 5881)	3047 (2144– 4614)	0.001 †
Height adjusted total liver volume – ml/m	2340 (1616 – 3467)	1807 (1329 – 2755)	0.002 †
Severity classification: §			0.006 '
Mild (<1600) – no. (%)	37 (25)	50 (36)	-
Moderate (1600-3200) – no. (%)	70 (47)	69 (50)	-
Severe (>3200) – no. (%)	42 (28)	19 (14)	-
Ln hTLV – ml/m	7.76 ± 0.55	7.56 ± 0.50	0.002
Age at menarche – yr	13.0 ± 1.5	13.4 ± 1.5	0.071
Pregnancies – yes (%)	125 (85)	111 (80)	0.37
No. of pregnancies	2.6 ± 1.4	2.6 ± 1.2	0.86
No. of months pregnant	20.6 ± 9.1	20.4 ± 8.1	0.83
Breastfeeding – yes (%)	95 (76)	70 (64)	0.030
No. of months breastfeeding	11.5 ± 10.2	8.4 ± 7.2	0.034
Fertility treatment – yes (%)	7 (4.7)	8 (5.8)	0.72
Estrogen-containing contraception – yes (%)	140 (94)	128 (93)	0.68
Estrogen-containing contraception – yr	13.3 ± 7.2	14.9 ± 9.9	0.121

Legend: Plus–minus values are means ± SD and tested with Independent Samples T test. ' Mann-Whitney U for non-parametric values expressed as median (IQR). ' Fisher's Exact test. § Severity classification is based on height adjusted total liver volume (ml/m). Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; hTLV, height adjusted total liver volume; Ln, natural logarithm.

Post-menopausal

In post-menopausal females, cumulative exposure to estrogen-containing oral contraceptives was not correlated with Ln hTLV (B=0.0018, P=0.67) (Figure 1C). Center, age at menarche, breastfeeding duration, hysterectomy and IUD use were confounders as they changed the correlation coefficient by more than 10%. After adjustment for these confounders the association was not different (B=0.0017, P=0.70). Sensitivity analysis, excluding patients with imputed menopausal status, did not change results (B=-0.0012, P=0.80) (Table 3).

There were no differences in estrogen-containing oral contraceptives use between disease severity groups in post-menopausal females (Fig. 2B).

Table 3. Multiple Linear Regression Analysis (Ln hTLV)

Estrogen-containing oral contraceptives	N	B	%/year	P-value
Total group:				
Univariable	281	0.0061	0.61%	0.09
Adjusted [1]	281	0.0068	0.68%	0.06
Pre-menopausal				
Univariable	146	0.0156	1.57%	< 0.01
Adjusted [2]	142	0.0144	1.45%	0.02
Sensitivity analysis [2]	111	0.0143	1.44%	0.05
Post-menopausal				
Univariable	135	0.0018	0.18%	0.67
Adjusted [3]	131	0.0017	0.17%	0.70
Sensitivity analysis [4]	109	-0.0012	-0.12%	0.80
Pregnancy	**N**	**B**	**%/month**	**P-value**
Total group:				
Univariable	287	-0.0024	-0.24%	0.40
Adjusted [5]	285	-0.0011	-0.11%	0.69
Pre-menopausal				
Univariable	149	-0.0029	-0.29%	0.48
Adjusted [6]	149	-0.0026	-0.26%	0.54
Post-menopausal				
Univariable	138	-0.0027	-0.26%	0.50
Adjusted [7]	138	-0.0011	-0.10%	0.80

Legend: Included confounders are for **1:** menopausal status (yes/no/unclear); **2:** diagnosis (ADPKD/ADPLD), breastfeeding duration (in months), fertility treatment (yes/no); **3:** center (Radboud/Leuven), age of menarche (in years), breastfeeding duration (in months), hysterectomy (yes/no), IUD use (yes/no); **4:** see 3, excluding hysterectomy (yes/no); **5:** diagnosis (ADPKD/ADPLD), age at scan (in years), fertility treatment (yes/no), hysterectomy (yes/no); **6:** diagnosis (ADPKD/ADPLD), age at scan (in years), hysterectomy (yes/no); **7:** center (Radboud/Leuven), diagnosis (ADPKD/ADPLD), IUD use (yes/no). Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; IUD, intrauterine device.

Pregnancy

Pregnancy duration

Duration of pregnancy (in months) was not correlated with Ln hTLV in the univariable analysis (B=-0.0024, P=0.40) or after adjustment for the confounders diagnosis, age, fertility treatment and hysterectomy (B=-0.0011, P=0.69). Similar results were found in a subgroup analysis as no correlation was found in pre-menopausal (B=-0.0026, P=0.54) or post-menopausal females (B=-0.0011, P=0.80) (Table 3).

Parity

In an unadjusted analysis, nulliparous females (n=50) had a 3.19% higher hTLV compared to parous females (n=236, B=0.0314, P=0.71). After adjustment for center, diagnosis, age at scan, estrogen-containing oral contraceptive use, fertility treatment and hysterectomy, the difference was 4.97% (B=0.0485, P=0.56).

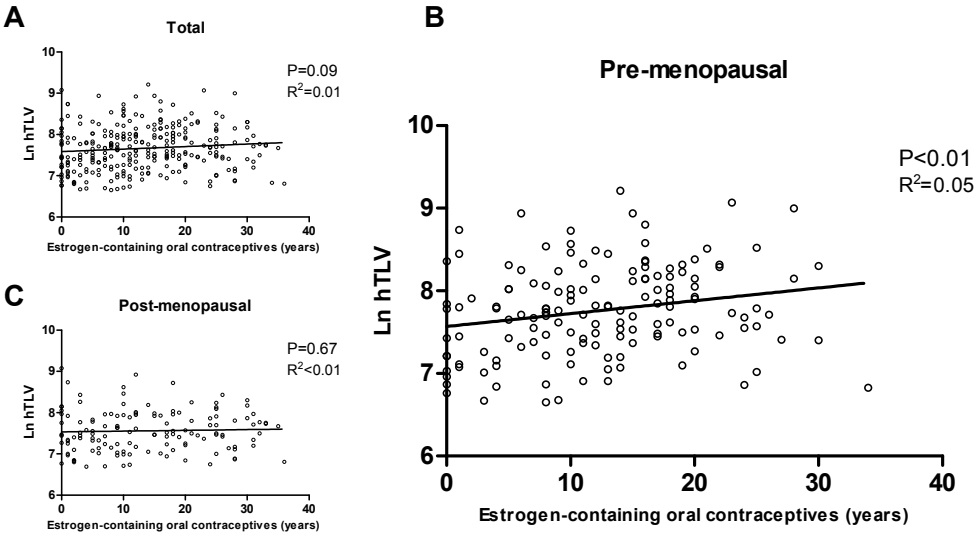

Figure 1. Scatter plots and unadjusted (univariable) regression lines for estrogen-containing oral contraceptives (years of use). Panel A shows the total group. Panel B shows the pre-menopausal and panel C the post-menopausal subgroup. All data points represent individual patients. Natural logarithmic transformed height-adjusted total liver volume is presented on the Y-axis. P-value and R^2 of the regression analysis are shown.

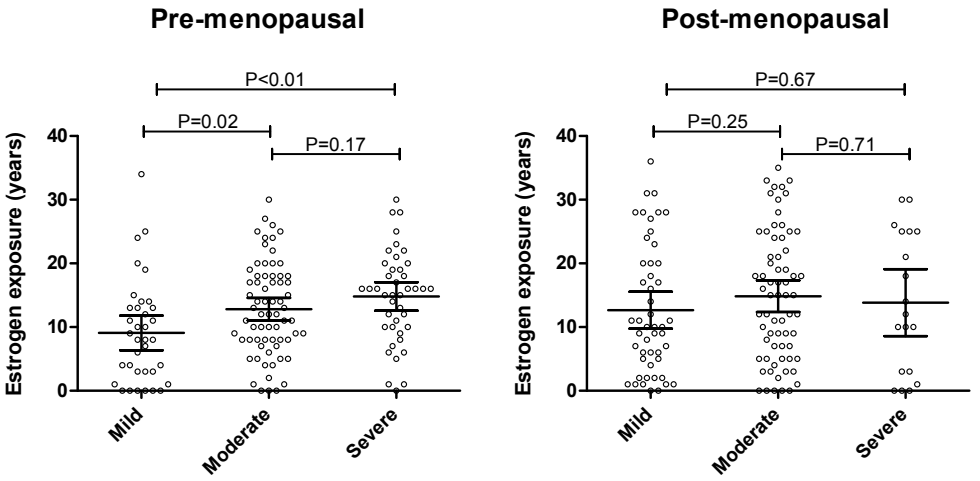

Figure 2. Categorical analysis for pre-menopausal (A) and post-menopausal subgroups (B)**:** Estrogen-containing oral contraceptives use (years) on the Y-axis and disease severity: mild (hTLV <1600 ml/m), moderate (hTLV 1600 – 3200 ml/m) and severe (>3200 ml/m) on the X-axis. All data points represent individual patients. Mean and 95% confidence interval are superimposed**.**

DISCUSSION

The main finding of this study is that a history of exposure to estrogen-containing oral contraceptives worsens PLD severity in pre-menopausal females. Every year of exposure correlates with a 1.45% higher hTLV, which corresponds to a 15.5% higher hTLV for every 10 years of use compared to unexposed females. This association was absent in post-menopausal PLD patients. PLD severity was independent of total duration and number of pregnancies.

The effect of estrogen and pregnancies on PLD has been the subject of several studies. A prospective study (n=19) found that one year of (post-menopausal) estrogen exposure resulted in a liver volume increase by 7% (SD: 12%). By contrast, liver volume decreased by 2% (SD: 8%) in controls ($P<0.03$).[8] There was no association between pregnancy and PLD severity in a cross-sectional analysis of 265 female ADPKD patients.[9] In a subgroup of 69 nulliparous females, no independent effect of estrogen use was found.[9] Another cross-sectional cohort study in 199 ADPKD patients found that nulliparous females had similar liver volume compared to patients with a history of pregnancy; the effect of estrogen exposure could not be analyzed because of missing data.[10]

In contrast to these studies, we established a firm association between the use of estrogen-containing oral contraceptives and liver volume in pre-menopausal females. The most important difference between our study and the aforementioned cohorts is that we have been able to include a broad spectrum of PLD severity, whereas other cohorts predominantly included patients with mild PLD.[9, 10] Another strength of our study is that we collected high-quality data on estrogen exposure by directly querying patients using a questionnaire. Compared to studies that retrieved data from patient charts, we were therefore able to minimize missing data and to determine the total exposure duration of estrogen-containing contraceptives use as accurately as possible. Furthermore, we obtained a high response rate, as 80% returned our questionnaire. There were no differences in baseline characteristics between responders and non-responders to the questionnaire, which minimizes response bias.

The association between estrogen-containing oral contraceptives use and hTLV was not detected in post-menopausal patients. This subgroup is relatively less affected, as the post-menopausal patients had lower hTLV at the time of first imaging in our hospitals (Table 2). There is epidemiological data to suggest that liver volume stabilizes or decreases after the menopause.[8] Thus, it is possible that post-menopausal patients in our study already had reduction in hTLV, which might cause dilution of the effect size of estrogen on liver volume. We were unable to explore the role of the interval period after discontinuation of estrogen-containing oral contraceptives due to the absence of longitudinal data.

Total months of pregnancy was not associated with hTLV in this cohort. This was unexpected, as endogenous estrogen levels increase considerably during pregnancy.[20] In addition, some patients remarked that they had experienced increased growth due to pregnancy. However, several studies report a prolonged reduction in endogenous estrogen exposure of up to 9 years after pregnancy, independent of having breastfed.[20-22] This might result in a similar or even lower lifetime estrogen exposure in parous females compared with their nulliparous counterparts, thereby negating the potential proliferative effect of pregnancy in cross-sectional and long-term studies.

Our data raise the question as to how estrogens influence cyst growth. The genes implicated in PLD encode proteins that act in concert to ensure quality control and proper folding of glycoproteins (e.g. polycystin-1). Experimental studies suggest that polycystin-1 expression is decreased in PLD. Together with PRKCSH or SEC63 inactivation it provides the trigger for cyst formation.[23, 24] Estrogens affect expression of many genes and a comprehensive DNA microarray analysis found that PRKCSH is suppressed more than twofold after exposure to estrogen, contributing to an altered genetic balance.[25] In a murine model, estrogens stimulated proliferation of cholangiocytes, the cell type that covers the inner lining of hepatic cysts.[26] These data are consistent with the notion that estrogens possess an inherent trophic effect for cholangiocytes. Recent discovery of a G protein-coupled estrogen receptor, which uses signaling pathways which are also implicated in PLD (i.e. cyclic AMP and calcium), further supports a role of estrogens in cyst formation.[27] The important role of the various genetic backgrounds implicated in PLD and their potential effect on disease severity could not be explored in this study, as mutation analysis was not performed standardly.

This study comes with several limitations. First, the cross-sectional nature of this study complicates drawing firm conclusions on the true effect size of estrogen-containing oral contraceptives use on PLD severity. However, because of the growing body of evidence and the already widely accepted management advice, it is very unlikely that a prospective controlled trial will be conducted in the future. Second, we were not able to analyze the effect of different types of estrogen-containing oral contraceptives or dosage because of missing data and recall bias. Most patients reported using combined oral contraceptives (estrogen and progestin); therefore we cannot exclude a potential effect of progestins on liver volume. Third, we could not exclude selection bias as these findings are solely based on patients from national referral centers in which imaging was performed. Despite this limitation, we were able to collect data from a large, clinically representative cohort.

In conclusion, the use of estrogen-containing oral contraceptives is associated with a higher liver volume in pre-menopausal PLD patients. With these findings, we legitimize our current counseling advice in the outpatient clinic with evidence and underline the importance to avoid estrogen use in PLD patients. Clinicians should advise their patients to use non-hormonal contraceptives. We advise clinicians to counsel daughters of PLD patients to avoid exogenous estrogen exposure until it has been confirmed that they did not inherit the disease.

CONFLICTS OF INTEREST

We have no potential conflicts that are relevant to the manuscript. No funding was received for this research.

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8

GENERAL DISCUSSION

RESEARCH AIMS

The aim of this thesis was to provide more evidence for clinical management of polycystic liver disease (PLD) patients, with a focus on treatment options for rare complications, surgical management and discouragement of estrogens. In this chapter, we will explain the results and point out strengths and limitations of the studies, explore the clinical relevance, and identify the remaining gaps in knowledge to create a new research agenda. An overview of the aims, main findings and most important limitations of each chapter are provided in Table 1.

RESEARCH AIM 1: TO EVALUATE EFFECTIVENESS AND SAFETY OF TREATMENT OPTIONS FOR RARE COMPLICATIONS OF PLD.

Chapter 2: Therapeutic antibiotics

The problem: Pharmacokinetics and antibiotic tissue penetration are potentially important limiting factors in successfully treating hepatic cyst infections and require further investigation.

The result: In a previously published case report, we concluded that ciprofloxacin reaches high intracystic concentrations, supporting a similar observation in a post-mortem study.[1,2] We hypothesize this is due to active transport from the blood stream into the hepatic cyst by means of cholangiocyte-specific transporter-proteins.[3,4] Importantly, this finding supports the current empiric strategy to start ciprofloxacin in patients suffering from hepatic cyst infection.[5,6] However, antibiotic resistance to quinolones is rising.[6] These findings fueled the development of a randomized pharmacokinetic trial where patients who were eligible for aspiration sclerotherapy of a hepatic cyst received intravenous antibiotics (either piperacillin/tazobactam, ciprofloxacin, doxycycline or cotrimoxazole, Chapter 2). This *in vivo* pharmacokinetic study model was previously proven to be feasible.[7] The results of our trial will influence future choices for antimicrobial therapy.

*"Antibiotic resistance to ciprofloxacin is rising and no alternative antibiotic strategy, substantiated with pharmacokinetic evidence, is available." (page **21**)*

So what? Ciprofloxacin should be first-line therapy, patients should be preferably treated for 6 weeks to prevent treatment failure and infection flare-up.[5] However, as antimicrobial resistance to ciprofloxacin is high, other antibiotics that reach adequate intracystic concentrations are duly needed.[8]

Chapter 3: Prophylactic antibiotics

The problem: A select group of patients present with frequent recurrence of hepatic cyst infections, resulting in repeated hospital admissions, and prolonged antibiotic use.[1,5,6] To illustrate, one of our included patients was prescribed 6 months of daily meropenem, to be administered with

a central venous catheter at home. In such cases, there is an unmet need for secondary prophylaxis that is able to prevent recurrent infections.

The result: In our retrospective case series, selective decontamination of the digestive tract (SDD) appears to reduce hepatic cyst infection incidence in patients with frequent cyst infections, although its use is limited by a large number of side effects, some of which were severe (e.g. aminoglycoside-induced ototoxicity). Moreover, it is imperative to confirm our findings in a prospective study to investigate the true potential of SDD prophylaxis.

*"Despite that SDD is associated with potentially severe adverse events, we recommend considering SDD in management of recurrent cyst infection in these patients." (page **41**)*

So what? SDD is a novel treatment strategy that may be able to prevent recurrence of hepatic cyst infection, which would result in less admissions, less antibiotics, and an overall improvement of quality of life for patients. First, a prospective study should be performed to confirm the results. Second, off-label use could already be considered in dire circumstances, but patients have to be adequately informed about possible adverse events. Regular monitoring of antimicrobial resistance should be considered. There are different SDD regimens available. The Radboudumc is using polymyxin E monotherapy (dose: 95mg, once daily) as first-line therapy, and the LUMC is using polymyxin B/neomycin (dose: 1ME/250mg, 4 times daily). Importantly, in case of renal failure, long-term use of neomycin as SDD is contra-indicated due to the risk of severe side effects with prolonged use.[9,10]

Chapter 4: Portal hypertension

The problem: PLD can lead to non–cirrhotic portal hypertension, mostly related to hepatic venous outflow obstruction (HVOO), but evidence for treatment options other than liver transplantation is scattered across the literature in small case reports and series.

The result: We propose the first comprehensive treatment algorithm for portal hypertension in PLD, based on the currently available literature.

*"When somatostatin analogues, percutaneous interventions, surgery, venous stenting and TIPS are not possible or not efficacious, liver transplantation should be performed" (page **57**)*

So what? Even in the ward of an expert-center, we struggle with the complex issue of portal hypertension in PLD, especially regarding alternative management options besides liver transplantation. We have aimed to provide physicians with some clinical guidance for this complication. Diagnostics should focus on clearly mapping the anatomy of (aberrant) hepatic

vasculature, as it is important for choice of therapy. Treatment should focus on adequate management of ascites, reduction of liver volume and/or restoration of flow. We conclude that liver transplantation should not be first-line therapy in all cases; many patients have recovered or have had transplantation postponed because of alternative therapies (e.g. somatostatin analogues, surgery, stenting), which should at least be considered. It is still important to assess transplantation eligibility at an early stage, as these processes can move on parallel tracks.

RESEARCH AIM 2: TO EVALUATE EFFECTIVENESS AND SAFETY OF SURGICAL TREATMENT OF SYMPTOMATIC HEPATIC CYSTS

Chapter 5 & 6: Surgery

The problem: In our center, there has been a preference for less invasive therapeutic options in PLD, such as aspiration sclerotherapy or somatostatin analogues.[11] However, as the risk-benefit ratio of surgery has not been thoroughly assessed, this preference is predominantly experience-based and not evidence-based.

The result: For decades, surgery has been the mainstay of interventions for PLD.[12] Based on an extensive meta-analysis and a prospective cohort study, we can conclude that surgery results in significant improvement of symptoms and quality of life. However, some considerations do apply: (1) There is a relevant (severe) complication risk for PLD patients, and (2) on an individual patient level, not everyone shows clinically relevant improvement.

So what? Surgeons and hepatologists can take these numbers and discuss them with their patients to weigh the expected benefits and potential risks. Possible improvement of quality of life should always be counterbalanced against the possibility of complications. As such, surgery in PLD should consist of multidisciplinary, patient-centered care in expert-centers and shared-decision making. In our center, we have increased collaboration with hepatobiliary surgeons, which has resulted in more referrals for laparoscopic fenestration and sparked new ideas for research.

*"In light of potential major complications, careful selection of patients and managing patients' expectations is important." (page **126**)*

RESEARCH AIM 3: TO EVALUATE THE EFFECT OF FEMALE HORMONES ON LIVER CYST GROWTH

Chapter 7: Estrogen

The problem: Since 1997, all exogenous estrogens are discouraged in female PLD patients.[13] However, this was based on a prospective case-control study on hormonal replacement therapy with equine estrogens. Current estrogen-containing oral contraceptives contain different hormones, and dosages have been lowered over the years.

The result: Almost 25 years later, we now confirm that this advice still holds true for estrogen-containing oral contraceptives in use today.

So what? Our advice to patients remains the same: all exogenous estrogens should be stopped in female PLD patients if not medically necessary. We are currently working on laboratory experiments to further the knowledge of involved molecular mechanisms, receptors and pathways, which has provided us with a powerful therapeutic target: blockage of endogenous estrogens.[14,15] This is further discussed below in the 'Future perspectives' paragraph.

*"We legitimize our current counseling advice in the outpatient clinic with evidence and underline the importance to avoid estrogen use in PLD patients." (page **152**)*

LIMITATIONS AND STRENGTHS

An important limitation of this thesis is the small sample size in most studies, which decreases statistical power. As this is inevitable for rare outcomes in rare diseases, most studies on these topics have a retrospective design to achieve higher sample sizes within a short time-frame, with all its inherent biases.[16,17] We have tried to address these limitations in four ways: (1.) (inter)national collaboration for prospective studies, (2.) researching interventions with a large effect size, (3.) synthesis of case series in review papers, and (4.) using *in vivo* models. With this approach, we have aimed to answer clinically relevant questions. Strengths of this thesis are its focus on improvement of care, and the use of various robust methodologies, each tailored to a particular question. During the last three years, many research ideas were sparked by complex cases in our ward or legitimate questions in the outpatient clinic.

FUTURE PERSPECTIVES

As science usually raises more questions than answers, there are still many aspects of PLD and hepatic cystogenesis to explore. Future research should focus on the following topics.

Are we using the correct study models?

Previous trials have shown that with (inter)national collaboration, it is feasible to conduct large randomized controlled trials that target hepatomegaly in PLD.[18-20] However, most studies focus on liver volume. Whilst objective and independently measurable, it is not the primary goal of treatment of PLD. Future trials should focus more on patient-reported outcomes, and researchers should use validated methods such as in Chapter 6.[21]

Laboratory research for PLD is often performed in PKHD1-mutated rats or PRKCSH-knockout cholangiocytes. The differences between these *in vitro* models and the genetically heterogeneous patient population hamper the transition from bench to bedside. More widespread use of patient-derived hepatic cyst organoids could provide easier extrapolation of results.[22,23]

What are the areas of unmet need?

Rare complications

This thesis provides stepping stones for change of hepatic cyst infection management. If the study described in Chapter 2 provides reliable results, it would be a logical step to initiate follow-up studies with alternative antibiotics. As Chapter 3 has methodological limitations, it is vital to replicate the results in an international, prospective study. As this group of patients is limited in number and widely heterogeneous, significant confounding factors would pose a serious challenge for conducting a randomized trial. While a crossover design may reduce sample size, stopping SDD early may pose a serious risk of recurrence of infection. Therefore, we propose a prospective, multicenter, single-arm study with fixed investigational products, preferably colistin E monotherapy (95mg, once daily), three years of prospective follow-up after start of SDD, and detailed recording of three years of retrospective data (Figure 1). We deem this time-frame feasible for prospective follow-up, but it also ensures high-quality data for retrospective data collection. Efficacy, safety and occurrence of antimicrobial resistance should be regularly assessed. Our primary outcome will be the difference in hepatic cyst infection incidence before and after start of SDD therapy.

A limitation of most case reports and series included in the Chapter 4a review was a short follow-up duration. Clinical updates or correspondences on these patients are important for clinical decision making and could be easily synthesized with international collaboration. The same

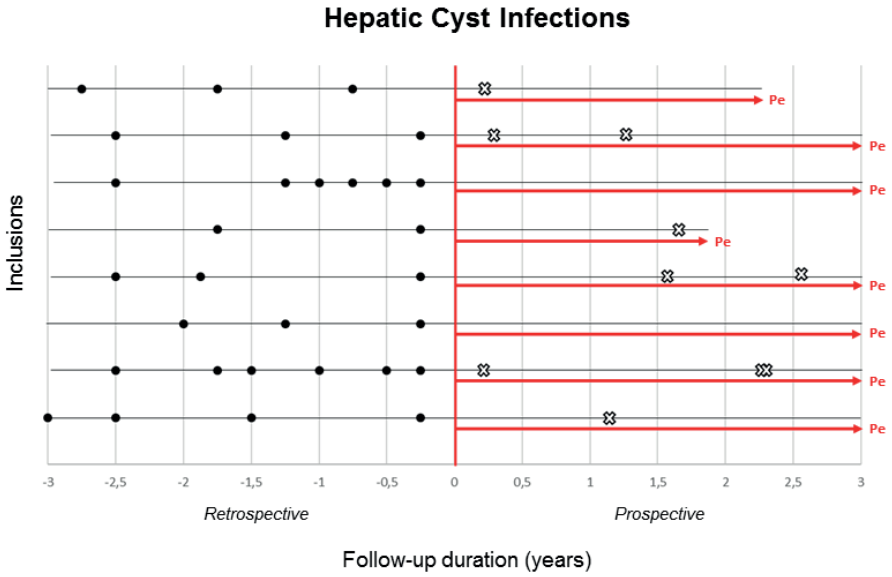

Figure 1. Hypothetical prospective study to assess efficacy of of SDD for hepatic cyst infections. This design ensures more conform data collection and less bias than our retrospective study (Chapter 3). Individual cases on the Y-axis. Follow-up duration in years on the X-axis, follow-up per patient is represented by the black line. Start of Selective Decontamination of the Digestive tract (SDD) and subsequent prospective follow-up is centered at T=0, and treatment duration is represented as red arrows below the patient data. Type of SDD is polymyxin E (Pe) for all patients. Each dot (•) represents a hepatic cyst infection when no SDD was given. Crosses (x) represent a hepatic cyst infection during SDD treatment.

holds true for our prospective study on partial hepatectomy and cyst fenestration (Chapter 6), we are planning to send a follow-up questionnaire to the same cohort ten years after surgery.

Besides infections and ascites there is another, presumably rare, complication of PLD that sees little scientific investigation: abdominal herniation and prolapse. In sharp contrast, many patients in the outpatient clinic present with issues related to herniation and surgical referrals are sometimes necessary. Future research should focus on (1.) estimating prevalence and severity of this problem in PLD patients, and (2.) provide evidence and guidance in surgical management of these patients, for example on the use of laparoscopy and mesh implants.

Surgery and other interventions

An innovative interventional therapy for treatment of PLD from Japan is Transcatheter Arterial Embolization (TAE).[24,25] It is reserved for patients who are not good candidates for surgery.[25] Hepatologists and interventional radiologists in expert centers should bring this promising technique to Europe and the USA and study the effects in our populations as well.

An important question that remains unanswered is the choice for aspiration sclerotherapy or laparoscopic fenestration. As this choice is center and physician dependent, there is clinical equipoise in certain patients, for example with large solitary hepatic cysts.[11] Because of the enormous selection bias in observational studies on this topic, a randomized controlled trial is necessary and should preferably focus on patient-reported outcomes. We are currently working on a grant proposal for such a study: *Assessment of Treatment with Laparoscopic fenestration or Aspiration Sclerotherapy for large symptomatic hepatic cysts (ATLAS trial)*. The primary outcome will be the Polycystic Liver Disease Questionnaire (PLD-Q) score, corrected for baseline score

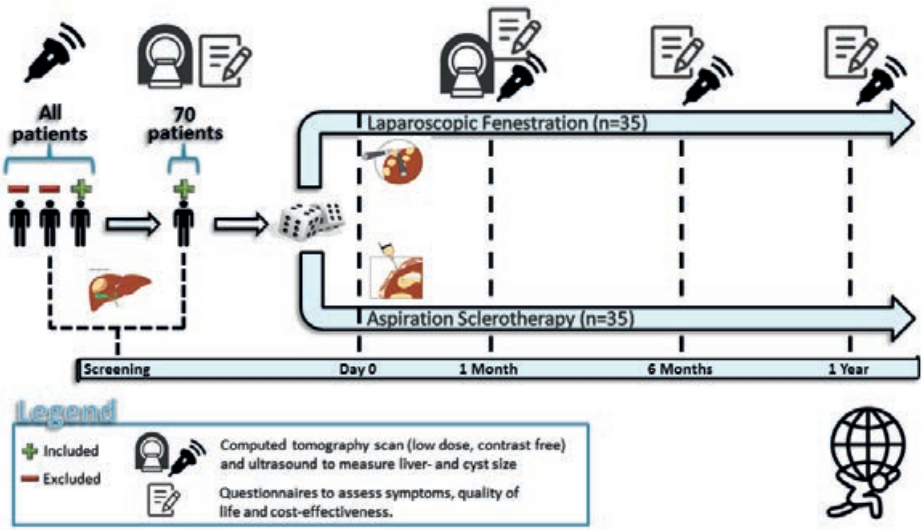

Figure 2. Study design of the ATLAS-trial. Overview of current study proposal. We aim to randomize 70 patients between aspiration sclerotherapy and laparoscopic fenestration. We will measure patient-reported outcomes, liver volume (CT-scans) and cyst size (ultrasound).

(Figure 2). One challenge of this trial is creating fair and sound inclusion criteria that reflect the clinical population, but do not result in excess harm. Cystic liver diseases comprise a vast spectrum of phenotypes, which often results in heterogeneous study populations, as seen in our meta-analysis (Chapter 5). For this trial, we aim to include patients with large simple hepatic cysts, that are symptomatic (defined as a PLD-Q score ≥20), while excluding patients with >20 cysts of >1.5 cm. We believe this will result in a study population with comparable risk-to-benefit ratios for both procedures.

Hormonal pathways

Only little research has been performed on the *in vitro* effects of estrogen on polycystic liver disease models and was exclusively performed on nuclear estrogen receptor 1 (ERα) and 2 (ERβ).[26] The recent discovery of the membrane-bound G-protein coupled estrogen receptor (GPER-1) provides a new therapeutic target (Figure 3).[14,27] Recently, we have confirmed the presence of GPER1 receptors on *in vitro* models and tissue samples of hepatic cysts.[15] We also saw that growth

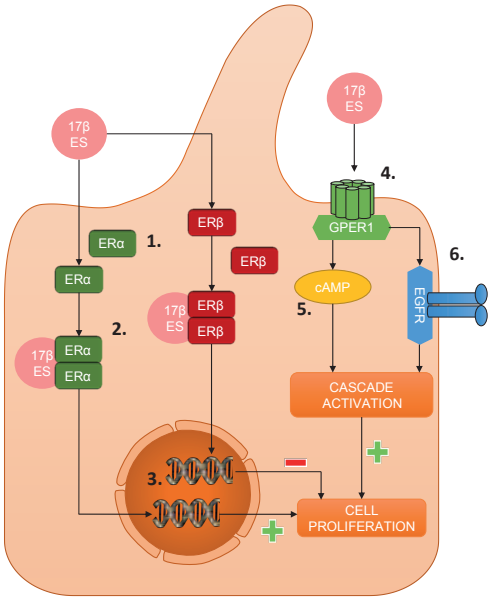

Figure 3. The estrogen pathway. Hypothesized and simplified estrogen-related proliferation pathways in affected cholangiocytes in PLD:

1. Nuclear receptors ERα and ERβ primarily bind estradiol (17βES) in the cytosol.
2. Nuclear receptor dimers are formed.
3. These dimers act as activated transcription factors in the nucleus, where ERα is proliferative and ERβ is anti-proliferative.
4. G protein-coupled estrogen receptor 1 (GPER1) is a membrane-bound receptor that is activated by 17βES.
5. GPER1 increases intracellular cyclic adenosine monophosphate (cAMP) levels, which in turn activate PLD-related proliferative pathways.
6. GPER1 stimulates PLD-related proliferative pathways through Epidermal growth factor receptor (EGFR).

of cell-lines and organoids was stimulated by estrogen as well as progesterone.[15] This suggests that a drug with anti-estrogen as well as anti-progesterone effects should be chosen for maximal effect.

The combination of clinical and laboratory confirmation of the importance of the hormonal pathways in PLD has led to more understanding and new research ideas. In collaboration with the University Medical Center Groningen (UMCG), we have submitted a grant proposal for a randomized clinical trial: *A GnRH Agonist IN pre-menopausal women STudy to treat severe Polycystic Liver Disease (AGAINST-PLD).*

The main objective of this study is to determine whether lowering estrogen and progesterone levels with the GnRH-agonist leuprorelin decreases liver growth rates in pre-menopausal women with severe PLD. We are hopeful that the trial will start in 2020 or 2021, as developing a novel and effective treatment would not only benefit individual patients and their families, but could also reduce healthcare costs, especially by preventing the need for a liver transplantation.

Our investigator-driven AGAINST-PLD study has a prospective, randomized, open-label design with blinded endpoint assessment (PROBE).[28] Patients will be randomized to direct or delayed start (18 months) of leuprorelin treatment (Figure 4). The primary analysis will compare growth of liver volume in these groups (Figure 4: b-c vs b-e). This is important to correct for a variable natural course of disease. Since the investigational treatment will induce menopause, blinding is not possible, and no placebo will be used in the delayed start group. The merits of the design were confirmed in a panel discussion with patients and reflect the perceived urgency. Some patients declared they would likely not participate in a trial if there would be a chance to be in a control group for a long time. A scientific benefit is the possibility for a prospective within-patient comparison (Figure 4: c-d vs b-c) as a secondary analysis.

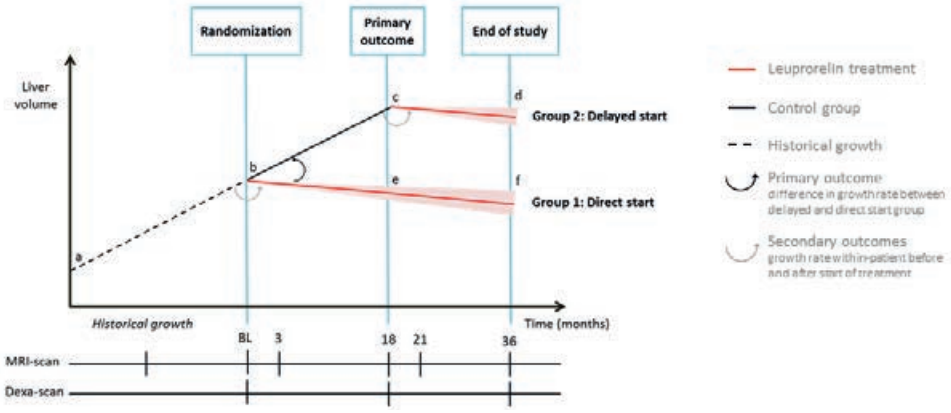

Figure 4. Study design of the AGAINST-PLD trial. Before start of study, liver growth needs to be confirmed and measured by at least one historical MRI or CT (dashed line). At baseline (BL) patients are randomized to direct start of leuprorelin (group 1) or delayed start after 18 months (group 2). Patients will undergo five MRI-scans for repeated measurement of liver volume. Measurements on a, b, c, d, e and f will be used for analysis. The primary outcome is b-c vs b-e. As a precaution, Dexa-scans will be regularly performed to assess bone mineral density. This figure was based on an illustration kindly provided by Sophie Aapkes (UMCG, Groningen, the Netherlands).

Based on our continued efforts on the estrogen-pathway in PLD, further experiments should be performed to explore the molecular mechanisms involved. We should study the effects of selective estrogen-receptor modulators/degraders on cholangiocyte proliferation, the effects of progesterone and testosterone on proliferation and receptor expression, and possible correlations between single nucleotide polymorphisms (SNPs) in sex-hormone-receptor genes and disease severity. As these developments will not necessarily help male patients, this 'forgotten group' would profit from more particular research into hormone levels, male disease progression and treatment response.

Weight and obesity may also be drivers for growth of liver volume, as adipose tissue is a possible cause of elevated estrogen levels.[29] However, body weight is not an accurate marker in severe PLD due to the weight of the liver. A better method might be automated body fat assessment of CT-scans, which could be conveniently used to study the correlation with disease severity.[30]

One of the patients that participated in our questionnaire study (Chapter 7) asked us an interesting question: if we had ever looked into phytoestrogens. They are a group of plant-derived substances that are structurally or functionally similar to estradiol.[31] As such, they could be positively or negatively associated with PLD severity. As the absence of specialized dieticians for PLD is often mentioned by patients as an important problem, we think that studying the effect of phytoestrogens may provide a fruitful first step towards collaboration between clinical and nutrition scientists, leading to more constructive advice on diet in PLD.

New tools for clinicians

There are several technological improvements that may assist clinicians and researchers alike. Firstly, most studies on PLD focus on liver volume or height-adjusted liver volume as primary outcomes. In the past this has been measured with manual tracing of CT or MRI images, but this is a very tedious and time-consuming approach. Recently, a neural network has been developed to perform fully automated segmentation and liver volume measurement on MRI scans, with accurate and reproducible outcomes.[32] However, as our cohort consists mostly of CT-scans, we are still bound to manual segmentation in our center. We are currently working on starting a validation study for similar software for CT-scans in our cohort, which is being developed in the ASEPOL study (NCT03960710). This program would make it possible to measure hundreds or thousands of scans in a short time, which would increase sample sizes by a large margin for future studies. To give a specific example, fully automated measurements would make the aforementioned study on adipose tissue in PLD feasible within weeks to months.

Secondly, a powerful tool for patients, clinicians and researchers would be a new classification model that can actually predict disease progression and clinical outcomes based on limited imaging. Previously proposed systems define disease severity by liver volume,[33] amount and distribution of cysts,[34] amount of cysts,[35] and symptoms in combination hepatic function.[36] A common trait of these classification systems is that they are used in already symptomatic patients and do not predict the natural course of cystic growth. A comparable classification for ADPKD makes use of height-adjusted renal volume and age at a certain time-point to predict renal function decline, this

can then be used to classify patients based on one scan.[37] As it is such a powerful tool, it is now proposed as one of the start criteria for medical therapy with tolvaptan.[38] A similar classification with liver volume will provide patients with evidence-based expectations at the moment of diagnosis, and could provide a starting point for composing criteria for starting and stopping somatostatin analogues.

Lastly, worth mentioning is the establishment of the European Reference Network for Rare Liver Disease (ERN RARE-LIVER). The ERN is focused on providing more equitable care across Europe and creates an interdisciplinary and international network which provides various convenient tools, such as an electronic 'clinical patient management system' and disease registries, elaborated on in two position papers.[39,40] We would like to stress that international collaboration is of the utmost importance for the advancement of clinical care for rare (liver) diseases.

Guideline

By answering more and more questions about PLD, saturation of the scientific literature should lead to the first comprehensive, evidence-based, European guideline on cystic liver diseases, preferably coauthored by the European Association for the Study of the Liver (EASL) and ERN RARE-LIVER.

Table 1. Overview of aims, main findings and limitations

Part	Chapter	Aim(s)	Main findings and conclusion	Limitations and comments
Hepatic cyst infection	2	To evaluate cyst penetration of ciprofloxacin, piperacillin, tazobactam, cotrimoxazole and doxycycline in non-infected large hepatic cysts	Conducting a randomized pharmacokinetic trial in aspiration sclerotherapy patients is feasible and the majority of patients are willing to participate	Measurements of antibiotics in cyst fluid and blood have not been performed as of yet
	3	To evaluate the efficacy and safety of selective decontamination of the digestive tract (SDD) to prevent recurrent hepatic cyst infections	Hepatic cyst infection incidence was reduced during SDD treatment After stopping SDD, recurrence within 6 weeks is common The majority of patients had adverse events, of which a third was rated severe Development of antimicrobial resistance may limit the long-term use of SDD	Retrospective, observational design Small sample size (n=8) Reduction was large and clinically relevant, but not statistically significant
Portal hypertension	4a	To give an overview of portal hypertension in PLD: Causes & anatomy Epidemiology Symptoms Diagnostics Management	Main cause is hepatic venous outflow obstruction (HVOO) and inferior caval vein syndrome (ICVS) When ascites is present, first treatment should consist of conventional therapy with diuretics Other treatment should be tailored to the individual patient It is important to consider liver transplantation assessment in parallel to alternative treatment options	Not systematically reviewed according to the PRISMA guidelines Most evidence GRADE D (very low)
	4b	To evaluate efficacy and safety of venous stent placement for HVOO in PLD	Venous stent placement was effective and safe to treat HVOO in PLD, both in pressure gradient as in Venous stent placement should be considered for HVOO with refractory ascites in PLD	Only one patient included No long-term follow-up There should be ≥1 patent hepatic vein(s) on imaging

Table 1. (continued)

Part	Chapter	Aim(s)	Main findings and conclusion	Limitations and comments
Surgery	5	To assess the efficacy and safety of laparoscopic fenestration for large hepatic cysts in the literature	Laparoscopic fenestration of large, symptomatic cysts is effective and results in symptomatic relief in the large majority of patients Procedure-related complications are mostly minor and amenable to treatment Outcomes were significantly worse for patients with PLD compared to solitary hepatic cyst	Exclusion of large studies based on language No control groups in included studies Only few included studies used patient-reported outcomes Variable follow-up duration
	6	To assess the efficacy and safety of partial hepatectomy and cyst fenestration (PHCF) in PLD	Overall, PHCF substantially improves symptom burden and quality of life in highly symptomatic PLD patients. A quarter of patients did not have clinically relevant improvement of symptoms Procedure-related complications are frequent (65%), severe complications in 12%, no procedure-related mortality	Small sample size (n-18) Missing data for change in scores. Only short follow-up Very specialized unit, so limited generalizability
Estrogen	7	To assess whether estrogen exposure and/or pregnancies are associated with PLD severity expressed as liver volume in pre- and postmenopausal patients	Every year of exogenous estrogen exposure is associated with a 1.45% higher hTLV in pre-menopausal women This corresponds to a 15.5% higher hTLV for every 10 years of us compared to unexposed females Total duration of pregnancies was not associated with PLD severity These findings legitimize current counseling advice to avoid estrogen-containing contraceptives. Clinicians should advise their patients to use non-hormonal contraceptives	Cross-sectional design Estrogen exposure calculated from patient-reported questionnaires (recall bias) Different types of contraceptives could not be analyzed

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9

SUMMARIES

ENGLISH SUMMARY

Polycystic liver disease (PLD) is characterized by the presence of numerous fluid-filled cysts in the liver. It is a genetic disease with an autosomal dominant inheritance pattern, which can result in progressive hepatomegaly with subsequent displacement of adjacent organs and symptoms such as pain, dyspnea, early satiety, hepatic cyst infections and portal hypertension.

Research aim 1: To evaluate effectiveness and safety of treatment options for rare complications of PLD

Chapter 2 outlines the protocol and provides an interim overview of study conductance of a randomized pharmacokinetic study, the PENTAC-2 trial. Its aim is to prospectively assess the intracystic concentrations of four antibiotics in a controlled setting.

In **Chapter 3**, we report a retrospective case series on a novel strategy to prevent recurrent hepatic cyst infections. Selective decontamination of the digestive tract (SDD) may provide benefit as secondary prophylaxis. However, adverse events are frequent and curtail its use. As most were attributable to aminoglycosides, Polymyxin E is considered the preferred therapy.

Chapter 4a is a narrative review on the topic of portal hypertension in PLD. Based on the available literature, we describe the etiology, epidemiology, clinical presentation, diagnostics and treatment of portal hypertension caused by PLD. In **Chapter 4b**, one alternative treatment option for portal hypertension in PLD is highlighted in a case report. In a patient suffering from refractory ascites caused by complete obstruction of the left and middle hepatic veins, and partial obstruction of the right hepatic vein. Hepatic venous stent placement of the latter was effective as it resulted in a drop of pressure gradient with subsequent disappearance of ascites.

Research aim 2: to evaluate effectiveness and safety of surgical treatment of symptomatic hepatic cysts

In **Chapter 5**, we have studied symptom relief and recurrence after laparoscopic fenestration surgery for large liver cysts. We have performed a systematic review of the literature and synthesized the data in a meta-analysis, a total of 62 studies were included. We found that laparoscopic fenestration is effective with a low symptomatic recurrence rate. However, the recurrence rate and risk of complications are significantly higher in PLD patients compared to solitary liver cysts.

We studied symptom relief and safety of another type of surgery – partial hepatectomy and cyst fenestration (PHCF) – in **Chapter 6**. A prospective questionnaire study was performed to assess patient-reported outcome measures before and after surgery. We conclude that PHCF provides a reduction of symptoms and increase in quality of life in the majority of patients, with values similar to a healthy reference population six months after surgery. In light of potential major complications, careful selection of patients and managing patients' expectations is important.

Research aim 3: to evaluate the effect of female hormones on liver cyst growth

In **Chapter 7**, our goal was to assess the influence of estrogen-containing oral contraceptives on PLD severity in a cross-sectional study. Our models showed that patients who were exposed to oral contraceptives for ten years had a 15.5% higher liver volume compared to females who were never exposed. With this finding, we further justify the current management advice to avoid exogenous estrogens in PLD patients.

In **conclusion**, this thesis paves the way for more evidence-based treatment of hepatic cyst infections, describes management of portal hypertension in PLD, provides more robust evidence on established surgical therapies and confirms that estrogen-containing oral contraceptives result in larger livers.

NEDERLANDSE SAMENVATTING

Polycysteuze leverziekte (PLD) wordt gekenmerkt door de aanwezigheid van talrijke, met vocht gevulde cysten in de lever. Het is een genetische ziekte, met een autosomaal dominant overervingspatroon. Door sterke groei van de cysten kan de lever ernstig vergroot raken (hepatomegalie). Aangrenzende organen kunnen hierdoor van hun plaats worden gedrukt. Dit kan zorgen voor klachten zoals pijn, kortademigheid, snel een volle maag, levercyste-infecties en verhoogde bloeddruk in de poortader, gelegen tussen darm en lever. Dit laatste staat bekend als portale hypertensie.

In dit proefschrift wordt onderzoek gepresenteerd, met betrekking tot drie verschillende doelen:

Onderzoeksdoel 1: het evalueren van de effectiviteit en veiligheid van behandelopties voor zeldzame complicaties van polycysteuze leverziekte (PLD)

Hoofdstuk 2 beschrijft het protocol van een nog lopende gerandomiseerde geneesmiddelenstudie, de PENTAC-2-trial. Het doel van deze studie is om van vier verschillende typen antibiotica de concentraties in bloed en in levercysten te bepalen. Hiermee kunnen we mogelijk de behandeling van levercyste-infecties verbeteren.

In **hoofdstuk 3** rapporteren we een klein retrospectief onderzoek van een nieuwe preventiestrategie om vaak terugkerende levercyste-infecties te voorkomen. De conclusie is dat Selectieve Darm Decontaminatie (SDD) mogelijk als preventiestrategie kan werken. Bijwerkingen komen echter vaak voor en beperken daarom het gebruik van deze strategie.

In **hoofdstuk 4a** beschrijven we op basis van de beschikbare literatuur de oorzaak, epidemiologie, klinische presentatie, diagnostiek en behandeling van portale hypertensie die specifiek wordt veroorzaakt door PLD. Een concreet voorbeeld van een van deze behandelingen wordt gepresenteerd in **hoofdstuk 4b**, namelijk de veneuze stentplaatsing.

Onderzoeksdoel 2: het evalueren van de effectiviteit en veiligheid van de chirurgische behandeling van levercysten

In **hoofdstuk 5** hebben we de effectiviteit bestudeerd van een minimaal-invasieve, laparoscopische operatie voor grote levercysten. We hebben daartoe een systematische literatuur-review uitgevoerd. Dit resulteerde in een selectie van 62 studies, waarvan we vervolgens de data hebben gecombineerd en geanalyseerd. Hierbij vonden we dat laparoscopische chirurgie voor grote levercysten effectief is en een lage kans op recidief van klachten en complicaties heeft. Echter, bij PLD-patiënten blijken de uitkomsten van de behandeling slechter dan bij patiënten met solitaire levercysten.

In **hoofdstuk 6** rapporteren we een evaluatie van een ander type operatie: de gedeeltelijke leverresectie. We hebben een prospectieve vragenlijststudie uitgevoerd om verschillende

uitkomstmaten voor en na de operatie te beoordelen. We concluderen dat de gedeeltelijke leverresectie bij de meeste patiënten de kwaliteit van leven verhoogt, met waarden die na de operatie vergelijkbaar zijn met een gezonde, vergelijkbare populatie. Zorgvuldige selectie van patiënten is bij deze zware operatie echter van vitaal belang, gezien het risico op ernstige complicaties.

Onderzoeksdoel 3: het evalueren van het effect van vrouwelijke hormonen op de groei van levercysten

In **hoofdstuk 7** wordt een cross-sectioneel onderzoek beschreven naar de invloed van oestrogeen bevattende orale anticonceptie ('de pil') op de ernst van PLD. We tonen aan dat patiënten die tien jaar lang de pil hebben genomen, gemiddeld een 15,5% hoger levervolume hebben in vergelijking met vrouwen die nooit dit middel hebben gebruikt. Met deze bevinding onderbouwen we het bestaande advies om medicijnen met oestrogenen bij vrouwelijke PLD-patiënten te vermijden.

Concluderend maakt dit proefschrift de weg vrij voor meer evidence-based behandeling van levercyste-infecties, beschrijft het de omgang met portale hypertensie bij PLD, biedt het grondiger bewijs voor gevestigde chirurgische therapieën en bevestigt het dat oestrogeen bevattende anticonceptie kan leiden tot grotere levercysten.

DEUTSCHE ZUSAMMENFASSUNG

Polyzystische Lebererkrankung (PLD) ist durch die Präsenz zahlreicher mit Flüssigkeit gefüllter Zysten in der Leber gekennzeichnet. PLD ist eine genetisch bedingte Krankheit mit einem autosomal-dominanten Vererbungsmuster. Aufgrund des starken Wachstums der Zysten kann sich die Leber stark vergrößern (Hepatomegalie). Benachbarte Organe können dadurch verdrängt werden. Dies kann zu Beschwerden wie Schmerzen, Kurzatmigkeit, schnellem Auffüllen, Leberzysteninfektionen und erhöhtem Blutdruck in der Pfortader, die zwischen Darm und Leber liegt, führen. Letzteres ist als portale Hypertonie bekannt.

In dieser Dissertation werden Forschungsarbeiten vorgestellt, die sich auf drei verschiedene Ziele beziehen:

Forschungsziel 1: Bewertung der Wirksamkeit und Sicherheit von Behandlungsoptionen für seltene Komplikationen der PLD

In **Kapitel 2** beschreiben wir das Protokoll einer laufenden randomisierten Medikament Studie, die PENTAC-2-Studie. Das Ziel dieser Studie ist es, die Konzentrationen von vier verschiedenen Arten von Antibiotika im Blut und in Leberzysten zu bestimmen. Dies könnte möglicherweise die Behandlung von Leberzysteninfektionen verbessern.

In **Kapitel 3** berichten wir über eine retrospektive Fallserie zu einer neuen Strategie zur Verhinderung wiederkehrender Leberzysteninfektionen. Daraus kann nun festgestellt werden, dass die selektive Darmdekontamination (SDD) möglicherweise als Präventionsstrategie funktionieren kann. Nebenwirkungen sind jedoch häufig und schränken daher den Einsatz dieser Strategie ein.

In **Kapitel 4a** beschreiben wir, basierend auf der verfügbaren Literatur, die Ursache, Epidemiologie, klinische Präsentation, Diagnose und Behandlung der portalen Hypertonie, die speziell durch PLD verursacht wird. Ein konkretes Beispiel für eine dieser Behandlungen wird in **Kapitel 4b** vorgestellt, nämlich die Platzierung eines venösen Stents.

Forschungsziel 2: Bewertung der Wirksamkeit und Sicherheit der chirurgischen Behandlung von Leberzysten

In **Kapitel 5** untersuchen wir die Wirksamkeit der minimal-invasiven, laparoskopischen Chirurgie bei großen Leberzysten. Zu diesem Zweck haben wir eine systematische Literaturrecherche durchgeführt. Dies führte zu einer Auswahl von 62 Studien, deren Daten wir dann zusammenführten und analysierten. Daraus lässt sich feststellen, dass laparoskopische Chirurgie bei großen Leberzysten effektiv ist und ein geringes Risiko für das Auftreten von Beschwerden und Komplikationen hat. Bei PLD-Patienten fielen die Behandlungsergebnisse jedoch schlechter aus als bei Patienten mit solitären Leberzysten.

In **Kapitel 6** berichten wir über eine Evaluierung einer anderen Operationsart: die Leberteilresektion. Wir haben eine prospektive Fragebogenstudie durchgeführt, um verschiedene Ergebnismaße vor und nach der Operation zu bewerten. Wir kommen zu dem Schluss, dass die Leberteilresektion bei den meisten Patienten die Lebensqualität erhöht, wobei die Werte mit einer gesunden, vergleichbaren Population vergleichbar sind. Angesichts des Risikos schwerwiegender Komplikationen ist bei dieser schweren Operation jedoch eine sorgfältige Patientenauswahl unerlässlich.

Forschungsziel 3: Bewertung der Wirkung weiblicher Hormone auf das Wachstum von Leberzysten

In **Kapitel 7** beschreiben wir eine Querschnittsstudie zum Einfluss östrogenhaltiger oraler Empfängnisverhütung ("die Pille") auf den Schweregrad der PLD. Wir zeigen, dass Patienten, die die Pille zehn Jahre lang eingenommen haben, im Durchschnitt ein um 15,5% höheres Lebervolumen haben als Frauen, die die Pille nie benutzt haben. Mit diesem Befund untermauern wir die bestehende Empfehlung zur Vermeidung von Medikamenten mit Östrogenen bei weiblichen PLD-Patientinnen.

Zusammenfassend zeigt diese Dissertation den Weg für eine mehr evidenzbasierte Behandlung von Leberzysteninfektionen auf, beschreibt die Behandlung der portalen Hypertonie bei PLD, liefert gründlichere Evidenz für etablierte chirurgische Therapien und bestätigt, dass östrogenhaltige Verhütungsmittel zu größeren Leberzysten führen können.

10

APPENDICES

DANKWOORD

Met het schrijven van dit laatste hoofdstuk komt er een einde van een geweldige tijd als arts-onderzoeker in het Radboudumc. Met dank aan alle hulp en steun van collega's, vrienden en familie is dit proefschrift, ondanks enkele flinke tegenslagen, tot stand gekomen.

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RIMLS PHD PORFOLIO

Name PhD candidate: LHP Bernts	PhD period: 15-06-2017 – 14-06-2020
Department: Gastroenterology	Promotor(s): prof. J.P.H. Drenth;
Graduate School: Radboud Institute for Molecular Life Sciences	prof. C. Rosman.
	Co-promotor(s): dr. M.A. Lantinga

	Year(s)	ECTS
TRAINING ACTIVITIES		
Courses & Workshops		
RIMLS introductory course 'In the Lead'	2017	1.5
BROK course	2017	1.5
NVH Ultrasound Course	2017	0.25
Feedback Course	2017, 2018	0.5
Scientific Integrity course	2018	1.0
Scientific writing course	2019	3.0
Seminars & lectures		
Radboud Research Rounds	2017-2020	1.0
Soeterbeeck Programme	2017-2020	1.0
GI-Hep meeting	2017-2020	1.0
Radboudumc Grand Round	2017-2020	1.0
Symposia & congresses		
Jubileumdag Nederlandse Vereniging voor Hepatologie	2017	0.5
Radboud Frontiers	2017	0.5
NVGE Digestive Disease Days	2017	0.5
EASL: ILC Paris (incl. poster)	2018	1.5
Radboud Frontiers	2018	0.5
PhD retreat (incl. poster)	2019	1.0
European ADPKD patient summit	2019	0.5
EASL: ILC Vienna (incl. two posters)	2019	2.0
UEGW (incl. poster)	2019	1.25
NVGE Digestive Disease Days (incl. two talks)	2019	1.5
PERFORMATION event	2020	0.25
Other		
Journal Club & Research meeting	2017-2020	12.0
PhD Council – Meet the Expert committee	2017-2019	1.5
PhD Council – Work stress committee	2019-2020	1.0
PhD Council – PhD retreat organization	2019-2020	2.0
Organizing 'MDL-Dinsdag-Werkbespreking'	2018-2020	1.5
Peer review scientific publications	2017-2020	0.5

RIMLS PhD porfolio (continued)

	Year(s)	ECTS
TEACHING ACTIVITIES		
Lecturing		
Bachelor Practicum spijsvertering en icterus	2018, 2019	1.0
Supervision of internships / other		
Student coaching	2017-2019	3.0
Clinical rotations: 'coassistenten'	2018-2019	0.5
TOTAL		44.75

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 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 2, 3, 6 and 7 is stored on the departments' shared drive: https://teamsites.radboudumc.nl/sites/mdl/ra/Onderzoekers/Afgeronde studies/PLD. All data from chapters 2 and 7 were anonymously collected and entered by use of Castor EDC (Amsterdam, The Netherlands). Data were later converted 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.

PUBLICATION LIST

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CURRICULUM VITAE

Lucas Hendrik Pieter Bernts werd op 13 april 1992 geboren in Nijmegen. In 2010 behaalde hij zijn VWO aan het Stedelijk Gymnasium te Nijmegen en startte daarna aan de Geneeskunde opleiding aan de Radboud Universiteit Nijmegen. In het derde jaar deed hij een wetenschappelijke stage in het gastro-enterologie laboratorium van de University of California, San Diego naar de genetische achtergrond van de ziekte van Crohn.

Na de reguliere coschappen, volgde hij in het laatste jaar van de opleiding een klinische stage op de afdeling Maag-, Darm- en Leverziekten van het Radboudumc, gevolgd door een stage op de afdeling Anesthesie en Intensive Care van het Evangelisches Krankenhaus Unna. Hij sloot de studie af met een wetenschappelijke stage naar het ontwikkelen van slokdarm organoïden in het laboratorium van de afdeling Maag-, Darm- en Leverziekten van het Radboudumc. In 2017 behaalde hij zijn artsexamen.

Na zijn afstuderen, startte hij in juni 2017 met zijn promotieonderzoek op de afdeling Maag-, Darm- en Leverziekten van het Radboudumc. Onder supervisie van prof. dr. J.P.H. Drenth, prof. dr. C. Rosman en dr. M.A. Lantinga deed hij onderzoek naar de behandeling van complicaties van polycysteuze leverziekte. Hij is per juni 2020 gestart als ANIOS Maag-, Darm- en Leverziekten in het Jeroen Bosch Ziekenhuis te 's-Hertogenbosch.

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