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Questionnaire PLD-complaint-specific assessment identifies need for therapy in polycystic liver disease: A multi-centric prospective study

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Abstract

Background and Aims: Polycystic liver disease (PLD) can lead to extensive hepatomegaly. Symptom relief is the primary goal of the treatment. The role of the recently developed disease-specific questionnaires for identification of the thresholds and the assessment of therapy needs further investigation.

Methods: A five-year prospective multi-centric observational study in 21 hospitals in Belgium gathered a study population of 198 symptomatic PLD-patients of whom the disease-specific symptom questionnaire PLD-complaint-specific assessment (POLCA) scores were calculated. The thresholds of the POLCA score for the need for volume reduction therapy were analyzed.

Results: The study group consisted of mostly (82.8%) women with baseline mean age of 54.4 years ±11.2, median liver volume expressed as height-adjusted total

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liver volume(htLV) of 1994 mL (interquartile range [IQR] 1275; 3150) and median growth of the liver of +74 mL/year (IQR +3; +230). Volume reduction therapy was needed in 71 patients (35.9%). A POLCA severity score (SPI) ≥ 14 predicted the need for therapy both in the derivation ($n = 63$) and the validation cohort ($n = 126$). The thresholds to start somatostatin analogues ($n = 55$) or to consider liver transplantation ($n = 18$) were SPI scores of ≥14 and ≥ 18 and the corresponding mean htLVs were 2902 mL (IQR 1908; 3964) and 3607 mL (IQR 2901; 4337), respectively. Somatostatin analogues treatment resulted in a decrease in the SPI score −6.0 versus + 4.5 in patients without somatostatin analogues ($p < 0.01$). Changes in the SPI score were significantly different between the liver transplantation group and no liver transplantation group, +4.3 ± 7.1 versus −1.6 ± 4.9, respectively, ($p < 0.01$). **Conclusion:** A polycystic liver disease-specific questionnaire can be used as a guide on when to start a volume reduction therapy and to assess the effect of treatment.

KEYWORDS
health-related quality of life, liver transplantation, liver volume, polycystic liver disease, somatostatin analogues

INTRODUCTION

Polycystic liver disease (PLD) is a rare inherited disease in which numerous fluid-filled cysts are spread throughout the liver parenchyma. Two different phenotypes are described: autosomal dominant polycystic kidney disease (ADPKD) with the co-existence of renal and hepatic cysts and the isolated form where only the liver is affected (autosomal dominant polycystic liver disease or ADPLD).[1–3] Most patients with PLD remain asymptomatic. However, especially women before menopause may develop rapid progressive disease. It is estimated that 20% of ADPKD patients will eventually develop symptomatic PLD. On the other hand, a stabilization or reduction of liver volume has been reported in post-menopausal women.[4–7]

Symptoms in PLD are caused by massive hepatomegaly and the most frequently reported symptoms are abdominal distension, early satiety, and abdominal pain, resulting in a decreased quality of life.[8,9] Patients reduce their meal size because of early satiety and malnutrition can develop with loss of muscle mass and sarcopenia.[10,11] Also, local cyst complications can occur (cyst infection, cyst hemorrhage, hepatic venous outflow obstruction, and portal hypertension) but these are rather infrequent.[12]

Symptom relief is the primary goal of the treatment of patients with PLD, and this can be obtained using volume reduction therapies.[13] Current treatments are somatostatin analogues (SA) and surgical procedures (aspiration sclerotherapy, cyst fenestration, or resection), although the latter are only appropriate in localized disease.[3,14–18] Ultimately, liver transplantation (LT) is indicated in patients with severe complaints that lead to a seriously decreased quality of life and malnutrition.[19,20]

The need for medical or surgical treatment and even the decision to LT is often determined by subjective, patient-reported symptoms. Therefore, it is crucial that these hepatomegaly-related complaints can be assessed in a standardized and validated way. Generic quality-of-life questionnaires lack specificity to capture PLD-related symptoms, which was the reason why in the initial trials with SA no significant effect was seen on the quality of life.[14] For that reason, disease-specific symptom severity questionnaires were developed. The PLD-Q is a valid, reproducible, and sensitive disease-specific questionnaire that has been validated both in European and American cohorts.[21] In 2014, the PLD-complaint-specific assessment (POLCA) score was developed as a self-report instrument to objectively capture the presence and severity of disease-specific complaints.[8] Limitations of this study were its partially retrospective setting and single center enrollment of highly symptomatic patients predominantly referred for LT.[8] The thresholds of the recently developed disease-specific questionnaire scores to select patients for volume-reducing therapy need further investigation.[3] Several studies

Key Summary

Summarize the established knowledge on this subject

- Patients with polycystic liver disease can develop hepatomegaly, which is mostly the cause of symptoms and complaints.
- The need for volume reduction therapy depends on the severity of the complaints.

What are the significant and/or new findings of this study?

- This study demonstrates that a disease-specific questionnaire reveals the thresholds when therapy might be necessary and is able to assess the effect of the therapy.

have demonstrated that liver volume measured by Computed Tomography (CT) or Magnetic Resonance Imaging can be measured in an accurate and highly reproducible way.[22,23]

The aim of our study was to investigate the threshold scores of a disease-specific questionnaire when volume reduction therapy became necessary and whether this score is able to assess the effect of therapy.

METHODS

Aim of the study

The primary aim of the study was to investigate the thresholds of the disease-specific questionnaire POLCA severity scores (SPI) in patients who received volume reduction therapy. The secondary aims which were explored were the changes in POLCA severity of perceived illness score (POLCA SPI) score in patients who received SA, the evolution of the SPI score in patients with or without LT, and in a subset of patients the threshold of liver volumes in patients treated with volume reduction therapy (SA and LT).

Study population and design

Patient data were obtained from the PLD-Registry, a prospective multi-centric study in 21 Belgian hospitals from 2014 until 2019, gathering a cohort of 266 patients with PLD. The study had an observational design: participating centers were invited to include patients to collect prospective data of all PLD-patients with new diagnosis or in regular follow up. Informed consent was obtained from each patient and the local ethics committee in the participating centers approved this study. Eligible patients were symptomatic PLD patients aged 18 years or older and diagnosed with either ADPKD or ADPLD. Polycystic liver disease was defined as having >10 liver cysts.[3] Patients on hormonal replacement therapy or hormonal contraception were excluded as this therapy could alter the natural evolution of the disease. Menopause was defined as 52 years of age or more.[5] Patients who did not complete the POLCA questionnaire appropriately ($n = 42$) or who received a volume reduction therapy before the start of the prospective follow up ($n = 26$) were excluded. After taking in consideration of all inclusion and exclusion criteria, the total study group finally consisted of 198 patients (Supplement Figure 1). Patients who suffered from severe renal impairment (renal replacement therapy or creatinine clearance <30 mL/min/1.73 m2) or received a combined liver-kidney transplantation (LKT) ($n = 9$) were not used for analysis of the validation of the POLCA score since this degree of renal impairment could influence the quality of life score irrespectively of the hepatomegaly related complaints. However, their volumetry data were used to study the natural evolution of the disease.

Patients were asked to complete the POLCA score at baseline and during follow-up, unaware of the results of liver volume analysis at that very moment. Participants were asked to follow the patients biannually with POLCA and yearly with liver volumetry if available. The scores were analyzed at the end of the study by N.V. The POLCA questionnaire (as available online: https://www.uzleuven.be/nl/polca) consists of 16 items (each scored 0–5) in which 4 subscales are recognized: severity of perceived illness (SPI) (score range, 0–35; 7 items); gastroesophageal reflux disease–related complaints (score range, 0–20; 4 items); impact on food intake (score range, 0–10; 2 items); and perception of enlarged liver volume (score range, 0–15; 3 items).[8]

In a subset of patients, liver volumes could be calculated. Liver volume was expressed as height-adjusted total liver volume (htLV) = LV (imaging)/height in ml.[24] CT scans were performed on different multidetector scanners as available at the participating centers and later sent to the coordinating center for calculation of LV. All calculations of LV were performed blindly in the principal investigating center (by W.C.), unaware of the clinical situation. CT-volume analysis of the liver was performed using the "Volume" tool from Siemens MMWP (multi-modality work place—Siemens Healthineers AG, Erlangen, Germany). Not all CT scans could be read by this program and finally accurate measurements of liver volumes were available in 96 patients.

Lower mid-upper arm circumference of the non-dominant arm (MUAC) was used as a marker of malnutrition[25] and was measured by the investigator at each study site unaware of the POLCA score and volumetric analysis at that moment.

All volume reducing therapies were recorded in the registry. Medical treatment with SA (somatuline autogel 120 mg every 4 weeks) could be initiated at the discretion of the treating physician and the effect was assessed by the POLCA score after 6 months and 1 year and liver volumetry if available. The indication for surgical therapy or LT was discussed in a multidisciplinary setting by physicians who were unaware of the POLCA score at that moment.

All data regarding patient characteristics, POLCA scores, liver volumetric analyses, MUAC measurements and volume reduction therapy (medical, surgical, transplantation) were collected prospectively at the principal study site in an anonymous electronic Case Report Form for analysis later on.

Statistical analysis

GraphPad Prism version 9.3.1 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis. Continuous variables are presented as mean ± standard deviation or median (interquartile range (IQR)) for non-normally distributed values. The Kolmogorov-Smirnov test was used to test for normality. Categorical variables are presented as proportions and percentages. Differences in characteristics between groups were analyzed using an independent *t* test (two tailed) or Mann-Whitney *U* test, where appropriate. To describe correlations, non-parametric testing by Spearman was performed. To assess the diagnostic accuracy of the POLCA SPI score, receiver operating characteristic (ROC) curves were constructed and

the areas under the ROC curves (AUROC) were calculated. Sensitivity, specificity and positive likelihood ratio were determined from the ROC curves and optimal cut-off values were based on the product method (maximum product of sensitivity and specificity). The cohort was separated into a training and a validation cohort in a 1:2 random manner. The last POLCA score before the start of therapy was used for AUROC analysis. Statistical significance was set at a 2-sided *p*-value of <0.05.

RESULTS

Baseline characteristics and natural history

The characteristics of the study population (n = 198) are shown in Table 1. The study group consisted of mostly women (82.8%) with a mean age at baseline of 54.1 year ±11.3 and predominantly ADPKD (62.6%). The median htLV at baseline was 1994 mL (IQR 1275; 3150) and premenopausal women (n = 36) had significantly higher htLV: 2600 mL (IQR 1681; 3742) versus 1679 mL (IQR 1117; 2744) in postmenopausal women (n = 46); p = 0.011. Median time of follow-up was 48 months (range 1–61). The median growth of the liver was +74 mL/y (IQR +3; +230) and was significantly higher in premenopausal women (n = 20) than in postmenopausal women (n = 14): +152 mL/y (IQR +3; +356) versus−6 mL/y (IQR −61; +80); $p < 0.001$ (Supplement Figure 2).

Liver volumetry was available in 96 patients and 61 patients had at least one follow-up volumetry. In the SA-treated cohort and in the liver transplantation cohort, 38 and 14 patients had repetitive liver volumetry, respectively. Overall, patients who had minor complaints did not have several liver volume measurements. Of the study population, 118 patients were followed in 6 academic centers and 80 patients in 15 non-tertiary centers. Liver transplantation was performed in 3 academic centers and SA was given in 4 centers.

Volume reduction therapy was needed in 71 patients (35.9%) of which 55 patients (27.8%) received SA. Furthermore, 3 patients received a cyst fenestration, 3 patients a cyst resection and 1 patient underwent a cyst aspiration sclerotherapy. Finally, 18 patients (9.1%) received an LT and 9 patients (4.5%) received a combined LKT; however, the latter were excluded from analysis of the thresholds of the POLCA score. Of these transplant patients, 9 underwent primary transplantation (6LT and 3LKT) without previous volume reducing therapy.

Threshold for treatment

The number of patients included, the wide range of liver volumes and the number of patients with volume reduction therapies allowed us to analyze the POLCA score in a derivation cohort and a validation cohort. The characteristics of both cohorts are shown in Table 1 and were similar. In the training cohort (n = 63) ROC analysis showed that the accuracy of the POLCA SPI score in predicting the need for therapy was 80.0% (69.1%–90.0%) (Figure 1a). The optimal cut-off was SPI score ≥14 and this predicted the need for therapy with a sensitivity of 60.0% (38.7%–78.1%) and a specificity of 79.1% (64.8%–88.6%) and a likelihood of 2.9. The characteristics of the validation cohort (n = 126) are shown in Table 1. Receiver operating characteristic analysis showed that the accuracy of the POLCA SPI score in predicting the need for therapy was 87.0% (80.8%–93.3%) (Figure 1b) and a SPI score ≥14 predicted the need for therapy with a sensitivity of 78.6% (64.1%–88.3%) and a specificity of 79.8%

TABLE 1 Patient characteristics.

	Study population (n = 198)	Training cohort[a] (n = 63)	Validation cohort[a] (n = 126)
ADPKD/ADPLD (n)	124/74	34/29	81/45
Female/Male (n)	164/34	53/10	104/22
Age (year mean ± SD)	54.4 ± 11.2	54.4 ± 11.5	54.4–5±11.6
Female	54.1 ± 11.3		
Male	55.7 ± 12.0		
Follow up (months) median (range)	48 (1–61)	48 (1–61)	48 (1–61)
htLV at baseline (ml) (n = 96)	1994 (1275; 3150)	1762 (1312; 2978)	2015 (1188; 3552)
Patients in need for therapy (n):	71 (35.9%)	20 (30.8%)	42 (33.9%)
Somatostatin analogue	55	17	33
Surgical (fenestration/resection/sclerotherapy)	7 (3/3/1)	2	5
Liver transplantation	18	6	12
Liver-kidney transplantation[a]	9		

Note: Data presented as median (IQR) where appropriate.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; hTLV, height-adjusted total liver volume.

[a]Liver kidney transplant patients (n = 9) were excluded in the analysis of the POLCA score.

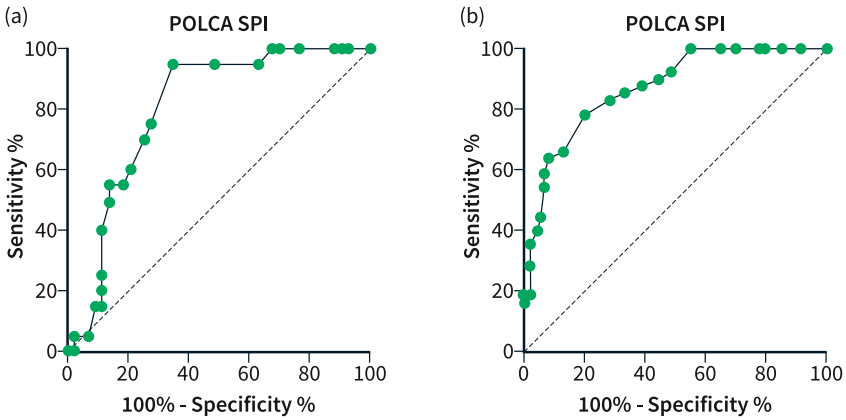

FIGURE 1 (a) Receiver operating characteristic (ROC) curve of the POLCA severity of perceived illness score (POLCA SPI) score and the need for volume reducing therapy in the training cohort ($n = 63$). (b) ROC curve of the POLCA SPI score and the need for volume reducing therapy in the validation cohort ($n = 126$). In (a) ROC analysis showed that the accuracy of the POLCA SPI score in predicting the need for therapy was 80.0% (69.1%–90.0%). In (b) ROC analysis showed that the accuracy of the POLCA SPI score in predicting the need for therapy was 87.0% (80.8%–93.3%).

(70.0%–87.0%) and a likelihood of 3.9. No patients with a POLCA SPI score of seven or lower needed volume reducing therapy.

Somatostatin analogues

Patients who received SA were mostly female, were younger, 51.2 ± 10.2 years versus 55.9 ± 11,6years ($p = 0.003$) and had lower MUAC, 24.6 ± 2.4 cm versus 26.2 ± 3.2 cm ($p = 0.012$). Moreover, their htLV was higher: 2902 mL (IQR 1908; 3964) versus 1625 mL (IQR 1097; 2506) ($p < 0.001$).

POLCA severity of perceived illness score scores were significantly higher in patients treated with SA than those without SA treatment, with median values of 18.0 (IQR 14.0; 22.0) versus 9.0 (IQR 5.0; 13.0) ($p < 0.001$) respectively (Table 2). Receiver operating characteristic analysis showed a likelihood ratio of 3.2; the POLCA SPI score predicting the need for SA was 83.7% (78.1%–89.2%) (Figure 2) and a SPI score ≥14 predicted the need for SA with a sensitivity of 78.2% (65.6%–87.1%) and a specificity of 75.5% (67.8%–81.8%).

Liver transplantation

Patients who received a LT ($n = 18$) were younger (46.2 ± 9.6 years vs. 55.2 ± 11.2 years; $p < 0.01$), more often treated with SA (61.0% vs. 26.9%), had lower MUAC (24.1 ± 2.4 cm vs. 25.9 ± 3.0 cm; $p = 0.037$) and they had more enlarged livers [htLV 3607 mL (IQR 2901; 4337) versus 1707 mL (IQR 1173; 2690); $p < 0.001$)].

Liver transplant patients had significantly higher scores on all POLCA subscales (Table 3): POLCA SPI (23.5 vs. 10; $p<0.001$); reflux-related complaints (7 vs. 2; $p < 0.001$); impact on food intake (6 vs. 2; $p = 0.001$); and perception of enlarged liver volume (10 vs. 6; $p<0.001$).

TABLE 2 Comparison of POLCA severity of perceived illness score (POLCA SPI) score and liver volume between patients who received somatostatin analogue or not.

POLCA	SA ($n = 55$)	No SA ($n = 143$)	p value[a]
SPI score	18.0 (14.0; 22.0)	9.0 (5.0; 13.0)	<0.001
	SA ($n = 41$)	**No SA ($n = 55$)**	**p value[a]**
htLV, ml	2902 (1908; 3964)	1625 (1097; 2506)	<0.001

Note: Data presented as median (IQR) where appropriate.
Abbreviations: hTLV, height-adjusted total liver volume; LV, liver volume; SA, somatostatin analogues; SPI: Severity of perceived illness.
[a]Mann–Whitney *U* test.

Receiver operating characteristic analysis showed that the AUROC of the POLCA SPI score for predicting the need for LT was 86.0% (76.7%–95.3%) (Figure 2) and a SPI score ≥18 predicted the need of LT with a sensitivity of 83.3% (60.8%–94.2%) and a specificity of 83.0% (76.7%–87.9%) and a likelihood ratio of 4.9. No patients with a POLCA SPI score of seven or lower needed liver transplantation.

Changes in PLD-complaint-specific assessment score

Before volume reduction therapy

The number of patients who had several POLCA measurements before the start of SA was too low to make conclusions but in case of liver transplantation, changes in POLCA SPI score were significantly different between the LT group and no LT group, +4.3 ± 7.1 versus −1.6 ± 4.9 respectively ($p < 0.01$). Patients needing LT had rapidly increasing htLV with a median increase of +329 mL/y (IQR +29; +518) versus +16 mL/y (IQR −47; +100) in patients who did not need a LT ($p = 0.002$) (Supplement Figure 2).

During somatostatin analogues

Women treated with SA had a median decrease in htLV of −120 mL/y (IQR: −233; +6), whereas women not receiving treatment had a median increase in htLV of +74 mL/y (IQR −18; +230). SA resulted in a decrease in SPI score (−6.0 vs. + 4.5) ($p < 0.01$) when a htLV reduction of 80 mL was achieved.

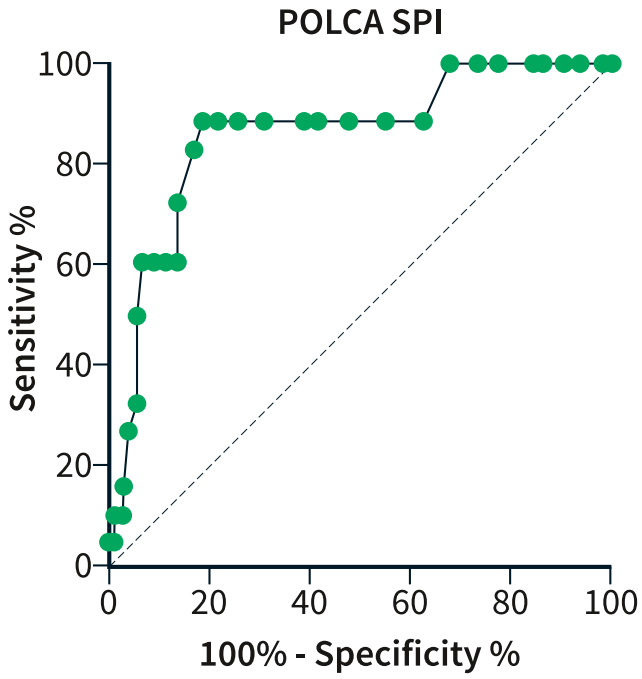

FIGURE 2 Receiver operating characteristic (ROC) curve of the POLCA severity of perceived illness score (POLCA SPI) score and the need for liver transplantation ($n = 18$). ROC analysis showed that the AUROC of the POLCA SPI score for predicting the need for liver transplantation (LT) was 86.0% (76.7%–95.3%) and a severity of perceived illness (SPI) score ≥18 predicted the need of LT with a sensitivity of 83.3% (60.8%–94.2%) and a specificity of 83.0% (76.7%–87.9%) and a likelihood ratio of 4.9.

Volume responsiveness in patients who had simultaneous PLD-complaint-specific assessment and volumetry measurements

A significant correlation was found between the POLCA SPI and htLV ($r = 0.48$; 0.30–0.63) ($n = 95$) and longitudinal data showed a significant correlation between the change in POLCA SPI score and the change in htLV ($r = 0.45$; 0.26–0.61) ($n = 38$) (Supplement Figure 3).

DISCUSSION

Polycystic liver disease can lead to extensive hepatomegaly and symptom relief is the primary goal of treatment.[3] Therefore, the decision to start therapy depends not only on the extent of the hepatomegaly but is predominantly based on the severity of complaints. For that reason, disease-specific questionnaires were developed such as the PLD-Q.[21] In this study we used the POLCA score (https://www.uzleuven.be/polca) that was developed in Belgium[8] and we investigated the natural history of patients both in tertiary as well as non-referral hospitals to avoid selection bias and to have a better understanding of the whole spectrum of the disease.

This prospective study revealed thresholds to guide management in patients with PLD. A POLCA SPI ≥14 predicted the need for therapy both in the derivation ($n = 63$) and the validation cohort ($n = 126$). No patients with an SPI score <7 needed liver transplantation or medical or surgical volume reduction therapy. The thresholds to start SA or to consider LT were SPI scores of ≥14 and ≥ 18 respectively. The corresponding htLV was 2.9 L for SA therapy and 3.6 L for liver transplantation.

In the present study, we found a significant correlation between the disease specific POLCA SPI score and htLV and also changes in htLV were significantly reflected in changes in POLCA SPI. In contrast to patients not in need of LT, patients who received an LT had a significant increase in POLCA SPI score, which corresponded with rapid

TABLE 3 Comparison of PLD-complaint-specific assessment (POLCA) subscales and liver volume between patients who received liver transplantation or not.

POLCA	**LT ($n = 18$)**	**No LT ($n = 171$)**	***p* value**[a]
Severity of perceived illness	23.5 (18; 26)	10.0 (6.0; 15.0)	<0.001
POLCA	**LT ($n = 17$)**[b]	**No LT ($n = 122$)**[b]	***p* value**[a]
GERD complaints	7.0 (4.5; 12.5)	2.0 (0.0; 5.0)	<0.001
Impact on food intake	6.0 (4.5; 9.0)	2.0 (0.0; 5.0)	<0.001
Perception of enlarged LV	10.0 (7.5; 12.0)	6.0 (3.0; 8.0)	<0.001
	LT ($n = 17$)	**No LT ($n = 71$)**	***p* value**[a]
htLV (ml)	3607 (2901; 4337)	1707 (1173; 2690)	<0.001

Note: Data presented as median (IQR) where appropriate.

Abbreviations: GERD, gastro-esophageal reflux disease; hTLV, height-adjusted total liver volume; LT, liver transplantation; LV, liver volume.

[a]Mann–Whitney *U* test.

[b]POLCA subscores of GERD related complaints, impact on food intake and perception of enlarged LV were not reported for all patients.

progression of liver volume of >300 mL per year. Therefore, these findings can be helpful in the initiation of medical therapy and in the selection of candidates for LT. However, decisions on therapeutic approach can definitely not be guided by volume-related complaints alone and other factors play an important role such as signs of malnutrition. We observed that patients in need of SA or liver transplantation had lower MUAC, which is used in some allocation organization as a marker of malnutrition in order to offer patients priority on the waiting list for LT.[26] However, this marker has never been validated for this purpose and has a high interobserver variability. Measurement of sarcopenia by CT scan offers a more objective measurement of malnutrition and should be further investigated for this purpose in this population of PLD patients as well.[25]

Several clinical trials have provided evidence that the somatostatin analogues lanreotide or octreotide can reduce the volume of the liver in PLD. The therapeutic efficacy was demonstrated in two pivotal placebo-controlled trials with lanreotide in 2009 and with octreotide in 2010, in one post hoc analysis and later on confirmed in other placebo controlled trials.[14–17,27–29] In this study, we observed a significant decrease in the POLCA SPI score, which suggests that this score can be used in the assessment of the success of a medical treatment.

This study confirms that the majority of patients with PLD do not require specific therapy. Moreover, this prospective study also confirms the differences in natural evolution of the disease in a subset of patients in which liver volumes were available Patients who had severe symptoms were mostly young women; and as was observed previously and in this group, a rapid progression in liver growth was seen. On the other hand, we also observed a spontaneous stabilization and even improvement of liver volume in postmenopausal women. These observations are of importance for power calculations and in the selection of patients for future clinical trials.

The prospective nature of the study also allows us to assess the need of the different treatment options in this large cohort. In this population with almost always numerous small to medium sized cysts throughout the liver, the indication for surgical intervention was limited: cyst fenestration, aspiration/sclerotherapy or resection were carried out in a very limited number of patients (4%). If therapy was needed, most often medical treatment with SA therapy was started (27.8%) and finally 9.1% of the patients needed LT and 4.5% needed combined LKT. However, the latter were excluded from analysis of the POLCA score in this study since the degree of renal impairment affects the quality of life of these patients irrespective of the size of the liver volume.

Grading of complaints is always subjective. In this study, patients were not aware of their liver volume when they filled in the questionnaire. Furthermore, the calculation of the POLCA score and the measurement of liver volume were performed by co-workers unaware of the clinical situation of the patients.

In the past, manual contouring of the liver by CT or NMR was the gold standard for liver volume measurements, but this is time-consuming because of the severely deformed liver anatomy in patients with PLD. Therefore, we validated in the past the "Volume" tool from Siemens MMWP (multi-modality work place—Siemens Healthineers AG, Erlangen, Germany). However, further work in the automatic segmentation of PLD livers should be performed so that this technology might find its way into clinical practice.[30]

The strengths of the current study are its sample size, prospective setting, and relatively long duration of follow-up. PLD remains a rare disease, making the gathering of a large cohort difficult. Of interest is that in this study also patients were included who were not referred to centers of expertise, which offered us a better idea of the natural history in the whole spectrum of the disease. Indeed, in our previous study, the conclusions were based on highly symptomatic patients predominantly referred for LT.[8]

A limitation of this study was that decisions on treatment were not centralized but were taken by experts at different centers. We are aware that the threshold to start therapy might be different between the participating centers based on local expertise. However for the indication of liver transplantation, the situation is different since the participating transplant units use the same criteria of the Eurotransplant allocation organization.

Although it was not the primary aim of the study, we recognize the limitation that liver volumetry was only available in about half of all patients. Not all raw imaging data that were sent to the principal investigating center could be interpreted by the "Volume" tool, leading to data loss. Another reason was that a CT scan was not mandatory during follow-up in the prospective observational registry. Threshold values of liver volumes when starting therapy needs further investigation.

No clinical data were available on cyst complications such as bleeding, infection, or rupture, as these events can cause an important temporary increase in complaints which could be missed in the recall time of the POLCA score. However, these symptoms are only temporary and acute cyst complications remain rare, as was demonstrated previously.[31] In patients with ADPKD, no information was available on the evolution of the kidney volume. However in previous studies kidney enlargement did not significantly influence volume related complaints, certainly since we excluded ADPKD patients with severe renal impairment which is commonly associated with large size kidney volumes.[21]

In conclusion, our findings highlight the potential of the POLCA score as a tool for longitudinal follow-up of PLD-patients as a guide for clinicians when evaluating the need for medical or surgical intervention and in the assessment of medical therapy.

AUTHOR CONTRIBUTION

Frederik Nevens, design, data acquisition, data analysis and interpretation, drafting manuscript; Antoon Billiet, data analysis and writing; Frederik Temmerman, study co-designer; Walter Coudyzer, liver volume measurements; Remaining authors: data acquisition, critical revision of the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Frederik Nevens: Research grant from Ipsen; all other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The dataset generated during this study is available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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