ORIGINAL ARTICLE

Center is an important indicator for choice of invasive therapy in polycystic liver disease

Hedwig M. A. D'Agnolo[1], Wietske Kievit[2], Kim N. van Munster[1], Jouke J. H. van der Laan[1], Frederik Nevens[3] & Joost P. H. Drenth[1]

1 Department of Gastroenterology and Hepatology, Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands
2 Radboud Institute for Health Sciences, Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands
3 Department of Gastroenterology and Hepatology, University Hospital Leuven, Leuven, Belgium

Correspondence
Hedwig M. A. D'Agnolo MD, Department Gastroenterology and Hepatology, Radboud University Medical Center Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
Tel.: 31 24 361 9190;
fax: 31 24 354 0103;
e-mail: hedwig.dagnolo@radboudumc.nl

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SUMMARY

Polycystic liver disease (PLD) is a rare genetic disorder with progressive cyst growth as the primary phenotype. Therapy consists of volume reduction through invasive surgical or radiological procedures. To understand the process of treatment decision, our aim was to identify factors that increased the likelihood of treatment. We performed a cross-sectional study using an international population of patients with PLD. We collected data on the following therapies: liver transplantation, resection, fenestration, and aspiration sclerotherapy. Data on the potential determinants, sex, center, autosomal dominant polycystic kidney disease (ADPKD), autosomal dominant polycystic liver disease (ADPLD), age at diagnosis, symptoms, and phenotype, were included. We corrected for follow-up time. We included 578 patients in our study, and 35% underwent invasive therapy. Multivariate regression analysis showed that number of symptoms and age at diagnosis of PLD increased the likelihood of treatment (respectively, RR: 1.4, $P < 0.001$ and RR = 1.4, $P = 0.03$). The choice for liver transplantation or aspiration sclerotherapy was center dependent (RR: 0.7, $P < 0.001$ and RR: 1.1, $P = 0.03$, respectively). The results of our international cross-sectional study suggest that a higher number of symptoms and every 10 years of PLD diagnosis increase the risk to undergo treatment by 40%. The choice to elect a particular modality is center dependent.

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Key words
autosomal dominant polycystic kidney disease, autosomal dominant polycystic liver disease, polycystic liver disease, surgery, treatment

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Introduction

Polycystic liver disease (PLD) is a condition characterized by progressive liver cyst growth [1]. PLD is part of the phenotype of two genetically distinct disorders. It is presented as a primary phenotype in autosomal dominant polycystic liver disease (ADPLD), and it is the most common extra-renal manifestation in autosomal dominant polycystic kidney disease (ADPKD) [2–4]. Isolated PLD is rare with a prevalence of 1 in 158 000, which contrasts that of ADPKD which has a higher prevalence (1:400–1000 individuals) [5,6]. The vast majority of patients with ADPKD (94%) >35 years of age possess hepatic cysts [4].

Although PLD is often asymptomatic, patients who progress to severe hepatomegaly have a decreased health-related quality of life and are often in need of therapy [7,8]. Risk factors for progressive disease are

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age, female sex, estrogen use, and pregnancies [4,8–10]. The concept central to PLD therapy is downsizing liver volume as this leads to improvement of symptoms [3]. Currently, the mainstay of therapies includes invasive surgical and radiological procedures such as, liver transplantation, the only curative treatment, resection, fenestration, and aspiration sclerotherapy [2,11]. Treatment is indicated in patients who suffer from symptomatic hepatomegaly, and the choice for a specific therapy mainly depends on the presence and location of dominant cysts [2,3,12]. Clear guidelines about timing and choice of therapy are lacking. This might be explained by a lack of evidence generated by clinical trials comparing efficacy of invasive treatment strategies for PLD. In addition, there are no standardized outcome measures to assess treatment success in clinical practice, which hampers the building of an evidence base.

To guide physicians on therapy, it is necessary to explore factors involved in the process of treatment decision. To this end, we aimed to delineate patient characteristics and disease-specific factors that trigger therapy. Our secondary aim was to identify determinants that increased the likelihood of a specific invasive therapy for PLD.

Materials and methods

Study design and subjects

We performed a cross-sectional study that included patients with PLD coming from two independent PLD registries. Both registries were developed at two nationwide referral hospitals for PLD, Radboud University Medical Center Nijmegen in the Netherlands (center 1) and University Hospital of Leuven in Belgium (center 2) [13]. Both hospitals are national referral centers for clinical evaluation and treatment of PLD. The Dutch registry contains all patients with PLD who have visited the outpatient clinic of the Department of Hepatology of the Radboud University Medical Center between January 2008 and February 2015. Patients with ADPKD who had visited the Department of Nephrology between January 2008 and December 2014 were included, if PLD was present. The Belgium registry includes all patients with PLD who had visited the outpatient clinic of the Department of Hepatology of the University Hospital of Leuven, from January 2008 to July 2015. According to the Dutch and Belgium regulations, these registries do not need formal ethical approval as this was an observational study.

The inclusion criterium for this analysis was a diagnosis of PLD as documented by patients' physician where diagnosis of PLD had literally to be written down in the medical file of patients, or as shown on radiological imaging by the presence of ≥20 hepatic cyst larger than 0.5 cm. Underlying diagnosis of ADPKD or ADPLD was a requirement. ADPKD diagnosis was based upon modified Ravine criteria [14], and ADPLD diagnosis was based on the presence of ≥20 liver cysts, in the absence of renal cysts. If renal cysts were present in patients with ADPLD, the Ravine criteria should not be met [15]. Patients with hepatic cysts due to other diseases (e.g., Caroli's disease, autosomal resistant polycystic kidney disease) were excluded.

Potential determinants for treatment

We selected the following patient characteristics and disease-specific factors as potential determinants for treatment: sex, age at PLD diagnosis, phenotype, underlying diagnosis of PLD (ADPKD or ADPLD), number of symptoms, total liver volume (TLV), height-adjusted TLV (hTLV), estrogen use, and history of pregnancy. Center was also added as a factor determining choice of treatment. Parameters that pertained treatment decision were chosen on the basis of expert opinion, and evidence coming from studies on risk factors for severe PLD [4,5,9,10].

Data collection

Data were retrospectively collected from medical charts of patients. We included information on the following invasive treatment modalities: liver transplantation (combined with or without renal transplantation), resection, fenestration, and aspiration sclerotherapy. Experimental therapies such as somatostatin analogues were excluded as these drugs are mainly used in clinical trial settings. We reviewed medical charts for demographics, underlying diagnosis of PLD, age at diagnosis of PLD, TLV, hTLV, estrogen use, and pregnancies. We used the most recent value for TLV that was available. Liver volumes had been calculated in the past by 3D measurements of CT scans. This included manually outlining of the liver every 9 mm with interpolation of intermediate slices and calculation of TLV. We also collected data on hepatic cyst phenotype by assessing MRI, CT, ultrasound images, or reviewing imaging reports. We have distinguished between a phenotype with either the presence or absence of one or more dominant cysts (≥8 cm). Finally, we collected data on the presence of

the following symptoms in medical records of patients: abdominal discomfort, feeling full, abdominal pain, tiredness, pain in the rib cage, and pain in the side. These symptoms were selected as they were overrepresented in a Dutch population of patients with symptomatic PLD [16].

Statistical analysis

We performed descriptive statistical analyses to summarize population characteristics. Baseline continuous variables were expressed in mean [standard deviation (SD)] for normally distributed data or median [interquartile range (IQR)] for non-normally distributed data. Dichotomous outcomes were expressed as % (*n*/*n* total).

For our primary and secondary aims, we used multivariate logarithmic linked modified Poisson regression analysis to generate risk ratios (RRs) for determinants associated with, respectively, treatment and specific treatment modalities [17,18]. Risk ratios >1 and <1 were interpreted as, respectively, increasing and decreasing the likelihood of treatment or a specific therapy, while a risk ratio equal to 1 with a 95% CI smaller than 1 indicates no association. We included a potential determinant in the regression model only if at least 10 patients (1.7% of 578 patients) were exposed to the determinant to guarantee adequate statistical power. For the primary analysis, the dependent variable was specified as treatment or no treatment, whereas treatment was defined as patients who underwent surgical or radiological therapy, at least once. Independent variables included sex, center, age at diagnosis of PLD (defined as age at diagnosis of PLD divided by 10 years), phenotype, underlying diagnosis (ADPKD or ADPLD), number of symptoms, TLV, hTLV, estrogen use, and pregnancy in history. We added the variable follow-up, defined as interval from diagnosis to inclusion in the study divided by 10 years to the model to correct for follow-up period.

For our secondary analysis, liver transplantation, resection, fenestration, and aspiration sclerotherapy were included as dependent variables. In this analysis, the same independent variables as for the primary analysis were included. Unpaired Student's *t*-test or chi-square test was used to compare patient characteristics or disease characteristics between specific treatment modalities. In addition, a subgroup analysis of hepatic phenotype and treatment strategy between patients with ADPKD and ADPLD was performed. Finally, we tested whether patients who underwent aspiration sclerotherapy or fenestration differed on sex, center, age at diagnosis of PLD, phenotype, and underlying diagnosis of PLD. If patients underwent aspiration sclerotherapy and fenestration, the first treatment that was given was used for this analysis. A *P*-value of <0.05 was considered statistical significant. Data were analyzed using SPSS 22.0 (SPSS Statistics Inc., Chicago, IL, USA).

Results

Characterization of the study population

We included 578 patients in our study population, and 200 (35%) underwent invasive therapy (Fig. 1). The large majority of patients were female (81%) and 383 (66%) had an underlying diagnosis of ADPKD (Table 1). A total of 421 patients showed a phenotype without dominant cysts while a phenotype with concomitant dominant cysts was present in 54 patients. Liver phenotype significantly differed between patients with ADPKD and ADPLD (Fig. 2). Patients with ADPLD possessed dominant cysts on radiological

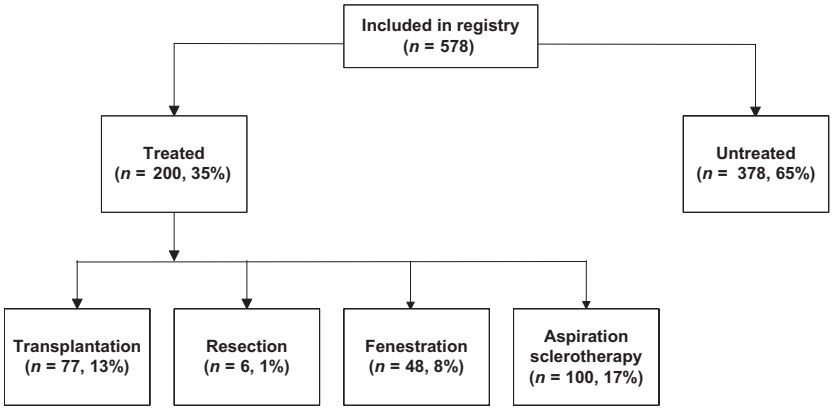

Figure 1 Overview of the study population. A total of 578 patients were included, and 35% (*n* = 200) received therapy. A number of patients received ≥1 treatment modality.

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Table 1. Characteristics of the study population.

	Complete population (n = 578)	
Female	468	81%
ADPKD	383	66%
Age diagnosis PLD	45	±13
Center 1	380	66%
Volumetry*		
TLV (ml)	4093	[2717–6066]
hTLV (ml/m)	2639	[1669–3840]
Phenotype*		
≥20 cysts + ≥1 dominant cyst	54	11%
≥20 cysts	421	89%
Symptoms		
Abdominal tension	225	39%
Feeling full	210	36%
Abdominal pain	141	24%
Tiredness	129	22%
Pain rib cage	120	21%
Pain side	78	14%
No. of symptoms	1	[1–3]

ADPKD, autosomal dominant polycystic kidney disease; hTLV, height-adjusted total liver volume; PLD, polycystic liver disease; TLV, total liver volume.

Date are in number and percentage (%), mean ± standard deviation, or median and interquartile range [IQR].

Center 1 = Radboud University Medical Center Nijmegen, the Netherlands; center 2 = University Hospital of Leuven, Belgium.

*Data were missing in, respectively, 56%, 72%, and 18% of patients for TLV, hTLV, and phenotype.

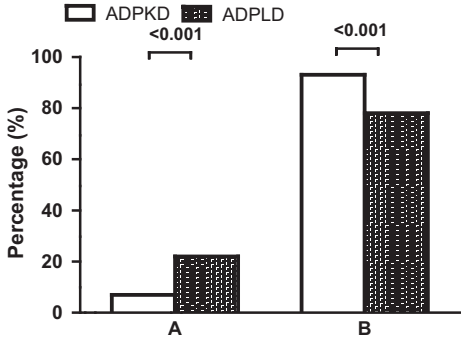

Figure 2 Liver cyst phenotype in patients with autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (ADPLD). (a) A phenotype with dominant cysts (≥8 cm) was significantly more present in ADPLD patients compared with ADPKD patients (22% vs. 7%, $P < 0.001$). (b) A phenotype without dominant cysts was more often present in ADPKD (93% vs. 78%, $P < 0.001$).

imaging in 34 patients (22%) whereas this was the case in only 21 of patients with ADPKD (7%) ($P < 0.001$).

Most patients were Dutch (66%, n = 380), and stratification of patients by center demonstrated that populations from both centers were comparable with respect to sex, TLV, and hTLV (Table S1). Dutch patients had more symptoms, were more often diagnosed with ADPLD, were diagnosed at a later age, and more often possessed a phenotype without dominant cysts. The follow-up of patients at the University Hospital of Leuven in Belgium was significantly longer than the follow-up of patients at the Radboudumc in the Netherlands (18 vs. 7 years, $P < 0.001$). Therefore, all analysis was corrected for follow-up time by including this in the multivariate model.

Determinants that trigger treatment

Liver transplantation, resection, fenestration, and aspiration sclerotherapy were performed in, respectively, 13%, 1%, 8%, and 17% of patients (Fig. 1). Multivariate regression analysis revealed that patients who suffer from more symptoms have a 40% higher likelihood (CI: 1.17–1.60, $P < 0.001$) to receive treatment (Fig. 3, Table S2.). Every 10 years of diagnosis of PLD was also significantly associated with a 40% increased risk of treatment (CI: 1.04–1.88, P = 0.03). TLV, hTLV, estrogen use, and pregnancy in history were not included in the regression analyses as data were missing in, respectively, 56%, 72%, 54% (women only), and 49% (women only) of patients.

Characterization of patient undergoing invasive therapy

Table S3 provides an overview of patient and disease characteristics of individuals who underwent, respectively, transplantation, resection, fenestration, and aspiration sclerotherapy. Liver transplantation was carried out at a median age of 53 ± 10 years in a total of 77 patients of whom 69 were diagnosed with ADPKD. In 43% (n = 33) of patients, this was combined with a renal transplantation and radiological imaging showed a median TLV of 4271 ml [IQR 3438–6243 ml] in these patients. Resection was carried out in six patients (1%), and most patients underwent other treatment modalities as well. Interestingly, a total of 27 patients received >1 different treatment modality. A combination of fenestration and aspiration sclerotherapy was most common (9%, n = 17). Only a small proportion of the total study population underwent fenestration (8%, n = 48), and a minority of them had ADPKD (38%, n = 18). Patients who underwent fenestration or

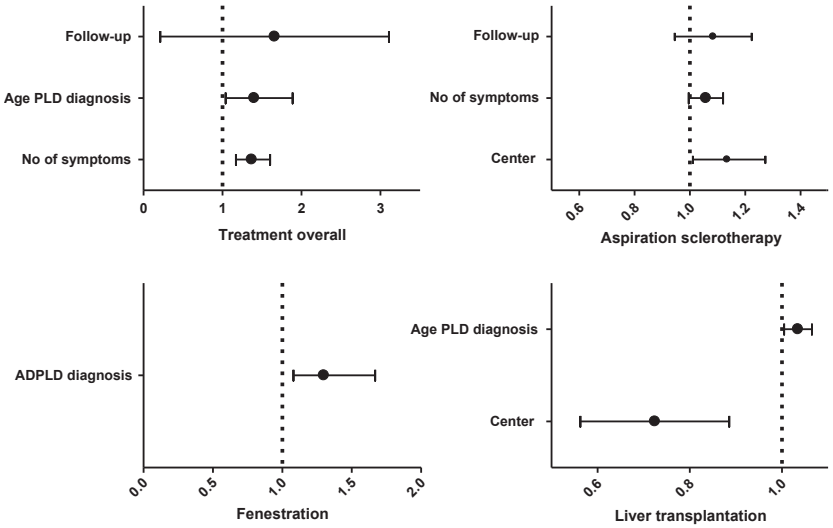

Figure 3 Forest plots showing risk ratios with 95% confidence intervals for, respectively, treatment in general, liver transplantation, fenestration, and aspiration sclerotherapy. Risk ratios were calculated by multivariate regression analyses. A risk ratio of <1 represents a decreased risk and >1 increased risk for treatment. A risk ratio of 1 (dotted line) indicates no association.

aspiration sclerotherapy did not significantly differ on sex, diagnosis, age at diagnosis, and phenotype (Table S4). We found that the choice for fenestration or aspiration sclerotherapy was mainly center dependent ($P < 0.001$). Aspiration sclerotherapy was most frequently performed with a total of 197 procedures in 100 patients. Half of patients (49%, $n = 97$) had >1 procedure (range 1–15 procedures), and the majority of patients were diagnosed with ADPLD (65%, $n = 65$).

Determinants associated with invasive therapies

We tested the association of six potential determinants with the likelihood to undergo either liver transplantation, fenestration, or aspiration sclerotherapy (Fig. 3, Table S5). Determinants associated with hepatic resection were not analyzed as only seven patients (1%) underwent this procedure and a minimum of 10 patients was required. Patients from center 2 had a 30% higher likelihood ($P < 0.001$) to receive a liver transplantation compared with patients from center 1 (Table S5). The likelihood to undergo a liver transplantation increased by 4% with every 10 years of PLD diagnosis (RR: 1.035, CI: 1.005–1.065). Multivariate analysis revealed that a diagnosis of ADPLD increased the likelihood to undergo fenestration by 30% ($P < 0.05$). The number of symptoms was associated with a higher likelihood to undergo aspiration sclerotherapy (RR: 1.1, $P < 0.001$). The likelihood to be subjected to aspiration sclerotherapy was center dependent (RR: 1.1, $P = 0.03$) and increased by follow-up time (RR = 1.1, $P = 0.002$).

Therapy differs between patients with ADPKD and ADPLD

We subsequently explored whether treatment strategies differed between patients with ADPKD and ADPLD. Fenestration and aspiration sclerotherapy was significantly more often performed in patients with ADPLD than in patients with ADPKD (15% vs. 5% and 33% vs. 9%, both $P < 0.001$) (Fig. 4). By contrast, patients with ADPKD more frequently underwent liver

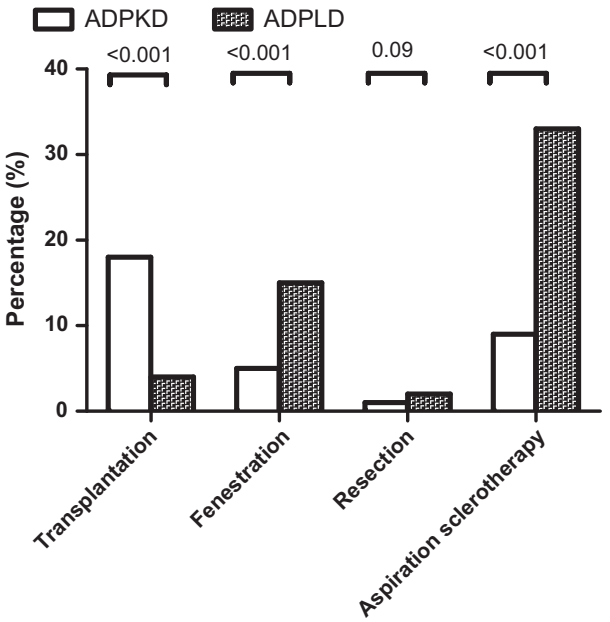

Figure 4 Treatment strategies for polycystic liver disease (PLD) in autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (ADPLD). Liver transplantation was more often carried out in patients with ADPKD whereas fenestration and aspiration sclerotherapy favored patients with ADPLD.

transplantation (18% vs. 4%, $P < 0.001$). In a total of 33 patients undergoing liver transplantation, this was combined with a renal transplantation on the same day.

Discussion

The results of our large cross-sectional study demonstrate that number of symptoms and age at diagnosis of PLD increased the likelihood to receive treatment for PLD. The choice for either liver transplantation or aspiration sclerotherapy was center dependent. This underscores a certain arbitrariness, probably due to a lack of evidence that supports any of the available treatment options.

A previous review suggests that the natural course of PLD in ADPLD and ADPKD is similar [3]. Our study suggests otherwise and demonstrates that patients with ADPLD more often possessed large dominant cysts, a phenotype that is amendable to treatment with fenestration or aspiration sclerotherapy [3]. The available therapies for patients without dominant cysts, most often patients with ADPKD, are resection or liver transplantation [2,3]. A resection is a high-risk procedure and not often performed in our population. Liver transplantation is a very invasive procedure, in particular for a disease that does not lead to liver failure or death. In view of a lack of donors, it is not offered widely [2,3]. These reasons probably explain why only 13% of this severe PLD population was transplanted while a higher percentage is in need of curative therapy. Interestingly, 90% of the transplanted patients were female. This might be explained by a more severe disease course in women, probably due to the effect of estrogen [9]. However, diagnosis was not significantly associated with any of the invasive therapies. These results are in contradiction with a cohort study showing that aspiration sclerotherapy was significantly more performed in patients with ADPLD, while patients with ADPKD were more often considered for liver transplantation [19].

About 14% of our treated study population underwent subsequent treatments. The combination of fenestration and aspiration sclerotherapy was the most frequently chosen option. In view of the comparable patients' characteristics, our data lend support to center-specific decision-making when it comes to the choice between both treatment modalities. These findings indicate that available expertise drives treatment while evidence that singles out the best treatment modality is lacking. A randomized controlled trial comparing effectiveness of fenestration and aspiration sclerotherapy is necessary to find out which treatment strategy is most effective. At the minimum, we should assess treatment outcomes in clinical care of PLD in an uniform fashion. Assessment of TLV, symptoms, and health-related quality of life before and after treatment should become standard of care and collected in a registry to build an evidence base of treatment efficacy [13]. In addition, our results demonstrated that liver transplantation was more frequently performed in Belgium while in the Netherlands there was a preference for aspiration sclerotherapy. Due to a different organ donor policy, Belgium has more donors available. This might lower the threshold for physicians to offer transplantation as a treatment option.

Our study also discovered that a large proportion of patients received treatment (35%), which is at odds with the literature that indicates that only a small subset of patients is symptomatic [2,3,11]. Our population consists of patients referred to two nationwide tertiary referral centers, which may have contributed to a selection of a population with more severe disease. This may overestimate the disease burden of PLD in this population as referral to these centers is often triggered by presence of symptoms. The threshold to treat patients with PLD is probably lower in tertiary centers because of wider experience with PLD and its treatment options.

The strength of our study was the large, international study population ($n = 578$) in view of the rarity of PLD. In addition, both patients with ADPKD and ADPLD were represented in this study as well as the most prevalent surgical therapies. Patients from all over the country are referred to one of both centers, and therefore, this study provides a good overview of the clinical profile of treated patients in both countries and made it possible to study the effect of center on treatment decision.

The main limitation of our study is the cross-sectional design. We were able to investigate factors involved in treatment decision, but it is impossible to infer causality. The retrospective data collection has led to missing data and therefore liver volume could not be included as potential determinant in our prediction model. Assessment of liver volume is time consuming, and trained staff and software are required. This might explain the amount of missing data for TLV. Although, it is questionable whether liver volume plays a major role in the treatment decision process as so little volumes were available in the medical charts. Therefore, this probably had no major impact on the primary outcome. This registry will continue in a prospective fashion including more patients worldwide with a long-term follow-up. A prospective nature will decrease the

number of missing data, and the long-term follow-up will support to learn more about the prognosis of PLD.

Conclusion

The results of our international cross-sectional study suggest that a higher number of symptoms and every 10 years of PLD diagnosis increase the likelihood to undergo treatment by 40%. The choice to elect a particular modality is center dependent. The major implication of these findings is that physicians should bear in mind that there is no evidence that favors either treatment option, and this contributes to center-specific preferences. Therefore, assessing efficacy of therapy by measuring liver volume and symptom burden is essential to gain evidence among the best treatment option. Future studies comparing efficacy of treatment modalities would be helpful to fill the gap of knowledge among the best treatment options.

Authorship

All authors have made substantive intellectual contributions to this manuscript and approved the final manuscript.

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Conflict of interest

No conflict of interests.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Characteristics of the study population split for center.

Table S2. Regression model including potential determinants of treatment.

Table S3. Treatment strategies in PLD patients.

Table S4. Comparison of patients who underwent aspiration sclerotherapy or Fenestration.

Table S5. Regression model showing factors associated with selection of treatment modality for PLD.

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