

Understanding and Assessing the Patient Experience of Symptoms for Polycystic Liver Disease: Development of a New Disease-specific Symptom Patient-reported Outcome Measure

Brod M¹, Pfeiffer KM¹, Waldman LT^{1*}, Olevik A², Axling U², Johnsson M²

¹The Brod Group, Mill Valley, CA United States; ²Camurus AB, Lund, Sweden

*LTW was an employee of The Brod Group at time of work

camurus®

BACKGROUND

- Polycystic Liver Disease (PLD) is a rare genetic condition in which multiple cysts develop in the liver. PLD may occur as a standalone condition (autosomal dominant PLD (ADPLD)) or more commonly, with autosomal dominant polycystic kidney disease (ADPKD).
- ADPLD is rarer with an estimated prevalence of <1/10,000 to <1/100,000 individuals^{1,2} and ADPKD is more common with an estimated prevalence of <5/10,000 individuals.³⁻⁴
- Approximately 20% of patients diagnosed with PLD experience high symptom burden.⁵⁻⁹
- PLD is more prevalent and severe in women, who are estimated to constitute up to 80% of symptomatic cases.^{2,6,10-11}
- There is currently no PLD disease-specific, patient-reported outcome measure (PROM) that includes direct patient input, i.e., concept elicitation and cognitive debriefing interviews, and comprehensively incorporates all key symptoms associated with this condition.
- The study objective was to develop a disease-specific PROM to assess the symptoms of PLD named the Polycystic Liver Disease Symptom (PLD-S) Measure.

METHODS

CONCEPT ELICITATION

- The PLD-S was developed based on the United States (US) Food and Drug Administration¹² and European Medicines Agency¹³ guidelines, and best practices for PROM development.¹⁴⁻¹⁷
- Concept elicitation data were collected iteratively through individual telephone interviews with 4 clinical experts and 30 adults diagnosed with PLD following semi-structured interview guides. Interviews were audio-recorded and transcribed verbatim.
- Inclusion criteria for clinical expert interviews included being a physician, nurse, or nurse practitioner; currently providing clinical care to adult patients aged 18 or older in the US or United Kingdom (UK); patient load of at least 50 unique adult patients with PLD; spending at least 50% of time in clinical practice; at least 5 years' experience providing clinical care to adult patients with PLD; and Hepatology board certification if a physician with MD degree.
- Eligible patient participants had to be at least 18 years old; able to read, write, and speak English; living in the US or UK; diagnosed with moderate or severe PLD; and currently experiencing at least one symptom associated with PLD.
- Participants were recruited through a professional market research organization that identified patients via physician-referral, advocacy organizations, or social media outreach, and screened them to confirm eligibility. Participants not recruited via physician-referral were required to provide confirmation of diagnosis, such as a physician's letter or medical records.

QUALITATIVE DATA ANALYSIS

- Qualitative methods were then used to analyze the concept elicitation interviews, utilizing an adapted grounded theory approach that focused on iteratively reviewing the data to identify and explore concepts that emerged from the research to develop a theoretical framework inductively.¹⁸ Dedoose qualitative software (www.dedoose.com) was used to code participant and clinician transcripts for thematic content. Each transcript was initially reviewed, coded, and then re-reviewed multiple times.
- Subgroup analyses were conducted to identify potential differences in PLD experiences based on country, gender, age, disease severity, having PLD with vs. without polycystic kidney disease (PKD), work status, and treatment status (has vs. has not ever received treatment for PLD). Differences of at least 20% in the proportions of participant endorsement rates between subgroups were considered potentially meaningful.

ITEM GENERATION

- During an item generation meeting, the research team evaluated the concepts reported by participants and determined which were major and should be included in the measure and which were minor and not to be included.
- The criteria for identifying a symptom as major were:
 - Endorsement by at least 40% of patient participants, or endorsement of 35-39% if determined to be of conceptual importance by the research team
 - Associated with PLD by participants
 - Considered bothersome by most participants
 - Experienced at least once a week by most participants
 - Potentially responsive to treatment
 - Proximal symptom of PLD
- Symptoms were categorized as minor if endorsed by at least 10% of participants and proximal in nature with the remainder categorized as either health consequences or distal impacts of PLD.

COGNITIVE DEBRIEFING

- Cognitive debriefing was conducted by telephone in an independent sample of 12 adults with PLD recruited via the same process as concept elicitation sample. Eligibility criteria were the same as the concept elicitation sample.
- The interviews were conducted with a semi-structured interview guide employing a "think aloud" method, in conjunction with "verbal probing" as appropriate.¹⁹⁻²⁰

REFERENCES

- Sawabe T, Chamberlain AM, Killian JM, et al. Epidemiology of autosomal-dominant polycystic liver disease in Olmsted county. *JHEP Rep.* 2020;2(6):100166. Epub 2020/11/05.
- Van Keimpema L, De Koning DR, Van Hoek B, et al. Patients with isolated polycystic liver disease referred to liver centres: clinical characterization of 137 cases. *Liver Int.* 2011;31(3):32-8.
- Willey C, Kamat S, Stellhorn R, et al. Analysis of nationwide data to determine the incidence and diagnosed prevalence of autosomal dominant polycystic kidney disease in the USA-2013-2015. *Kidney Dis (Basel).* 2019;5(2):107-17. Epub 2019/04/26.
- Willey C, Bass D, Hall NK, et al. Prevalence of autosomal dominant polycystic kidney disease in the European Union. *Nephrol Dial Transplant.* 2017;32(8):1356-63. Epub 2016/06/22.
- Alba-Wael B, Walsh C, Keough V, et al. Pathophysiology, epidemiology, classification and treatment options for polycystic liver diseases. *World J Gastroenterol.* 2013;19(35):5775-86. Epub 2013/10/15.
- Van Aerts RMM, Van De Laarschot LFM, Banalles JM, et al. Clinical management of polycystic liver disease. *J Hepatol.* 2018;68(4):827-37. Epub 2017/11/28.
- Neijzenhuis MK, Gevers TJ, Hogan MC, et al. Development and validation of a disease-specific questionnaire to assess patient-reported symptoms in polycystic liver disease. *Hepatology.* 2016;64(1):151-60. Epub 2016/03/13.

- Concept elicitation participant demographic and health characteristics are presented in Table 1.

Table 1. Concept Elicitation Participant Demographic and Health Characteristics

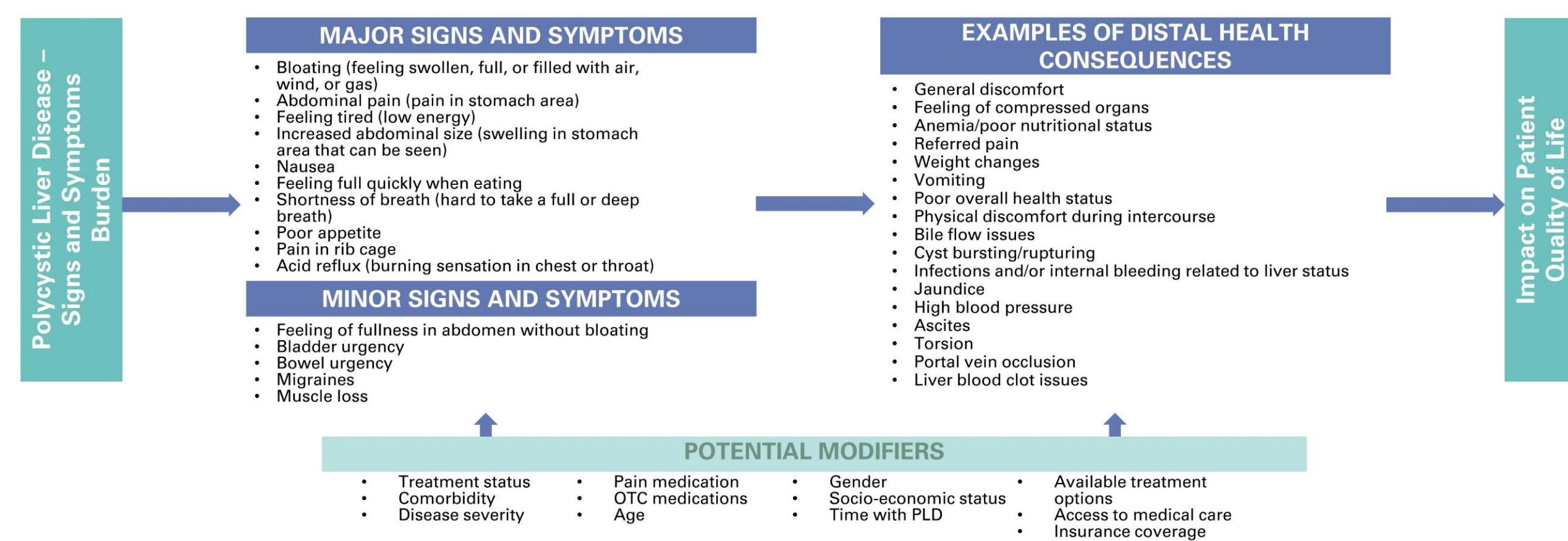
Demographic and Health Characteristics	UK (n=15)	US (n=15)	Total (n=30)
Gender, n (%) female	14 (93.3)	9 (60.0)	23 (76.7)
Age in years, mean (SD)	53.9 (8.8)	48.5 (9.9)	51.2 (9.6)
Range	42-72	32-63	32-72
Racial/ethnicity, n (%)			
Latino/Hispanic	0 (0.0)	4 (26.7)	4 (13.3)
White	14 (93.3)	7 (46.7)	21 (70.0)
Other	1 (6.7)	3 (20.0)	4 (13.3)
Decline to answer	0 (0.0)	1 (6.7)	1 (3.3)
Work status, n (%)			
Full time	7 (46.7)	6 (40.0)	13 (43.3)
Part time	3 (20.0)	1 (6.7)	4 (13.3)
Retired	2 (13.3)	3 (20.0)	5 (16.7)
Student	0 (0.0)	1 (6.7)	1 (3.3)
On medial leave	1 (6.7)	0 (0.0)	1 (3.3)
Disabled	0 (0.0)	1 (6.7)	1 (3.3)
Not working (other)	2 (13.3)	3 (20.0)	5 (16.7)
Educational status (UK only), n (%)			
Secondary School (GCSE's/O'Levels) or less	1 (6.7)	-	-
Further education/A-levels	4 (26.7)	-	-
University (BA/BSc/HND, etc.)	3 (20.0)	-	-
Post-Graduate Qualification (MA/PHD, etc.)	7 (46.7)	-	-
Educational status (US only), n (%)			
High school or equivalent	-	1 (6.7)	-
Vocational or technical school	-	2 (13.3)	-
College or University degree	-	11 (73.3)	-
Post-graduate or Degree	-	1 (6.7)	-
General health, n (%)			
Very Good	2 (13.3)	0 (0.0)	2 (6.7)
Good	5 (33.3)	7 (46.7)	12 (40.0)
Fair	6 (40.0)	6 (40.0)	12 (40.0)
Poor	2 (13.3)	2 (13.3)	4 (13.3)
Self-reported PLD severity, n (%)			
Moderate	7 (46.7)	12 (80.0)	19 (63.3)
Severe	8 (53.3)	3 (20.0)	11 (36.7)
Time to diagnosis (in years), mean (SD)	13.2 (6.8)	4.4 (3.3)	8.8 (6.9)
Range	1.6-25.0	0.75-11.0	0.75-25.0
Diagnosed with PKD, n (%) yes	13 (86.7)	7 (46.7)	20 (66.7)
Self-reported comorbidities, n (%) yes			
Kidney disease, urinary conditions (including PKD)	13 (86.7)	8 (53.3)	21 (70.0)
Heart disease, cardiovascular conditions (including hypertension)	7 (46.7)	1 (6.7)	8 (26.7)
Lung disease, respiratory conditions (including allergies, asthma)	2 (13.3)	3 (20.0)	5 (16.7)
Stroke, neurological conditions (including migraines)	1 (6.7)	4 (26.7)	5 (16.7)
Ever received treatment for PLD, n (%) yes	4 (26.7)	13 (86.7)	17 (56.7)
Treatment(s) received, n (%) yes			
Cyst aspiration	1 (6.7)	10 (66.7)	11 (36.7)
Fenestration	2 (13.3)	6 (40.0)	8 (26.7)
Hepatic resection	1 (6.7)	0 (0.0)	1 (3.3)
Somatostatin analogues	2 (13.3)	0 (0.0)	2 (6.7)

PLD polycystic liver disease; PKD polycystic kidney disease; SD standard deviation; UK United Kingdom; US United States

PRELIMINARY THEORETICAL MODEL

- Based on the analysis, a theoretical model of PLD symptoms (major, minor, modifiers) was developed (Figure 1).

Fig. 1 Preliminary Theoretical Model of the Symptom Burden of Illness for Adult Patients with Polycystic Liver Disease



RESULTS

CONCEPT ELICITATION FINDINGS

- Conceptual saturation, the point when no additional important or meaningful concepts emerged, was assessed for the 30 patient participant interviews in chronological order. Forty symptoms of PLD emerged, 78% of them by the 12th interview, and 95% by the 19th interview.
- In total, participants and clinicians combined identified 43 signs and symptoms, which they associated with PLD (Table 2).
- Subgroup analyses showed higher symptom endorsement rates among participants from the UK (vs. US), women (vs. men), participants with severe PLD (vs. moderate PLD), participants who had not received PLD treatment (vs. those who had), and participants with PKD (vs. those without).

Table 2. Patient- and Clinician-reported Signs and Symptoms of PLD

Signs/Symptoms, n (%)	Patients (n=30)	Clinicians (n=4)
Bloating (feeling swollen, full, and/or filled with air, wind, or gas)	27 (90)	4 (100)
Abdominal/stomach pain	26 (87)	4 (100)
Tired/low energy	25 (83)	3 (75)
Abdominal/stomach increase	25 (83)	0 (0)
Visible abdominal swelling/distension	23 (77)	3 (75)
Nausea	22 (73)	0 (0)
Loss or lack of appetite	21 (70)	1 (25)
Getting/feeling full quickly when eating	20 (67)	1 (25)
Pain in side	20 (67)	0 (0)
Shortness of breath/breathlessness	20 (67)	4 (100)
Pain or pressure in rib cage	18 (60)	0 (0)
Acid reflux	17 (57)	2 (50)
Pain in back	12 (40)	2 (50)
Vomiting	11 (37)	0 (0)
Feeling of fullness in abdomen without bloating	11 (37)	3 (75)
Weight gain	10 (33)	0 (0)
Weight loss	9 (30)	1 (25)
Physical discomfort during sexual intercourse	9 (30)	1 (25)
Feels sick	5 (17)	0 (0)
Compression symptoms	5 (17)	1 (25)
Referred pain	4 (13)	0 (0)
Bladder urgency	4 (13)	0 (0)
Bowel urgency	4 (13)	0 (0)
Cyst bursting/rupturing	3 (10)	0 (0)
Migraines	3 (10)	0 (0)
Muscle loss	3 (10)	0 (0)
Anemia	2 (7)	0 (0)
General discomfort	2 (7)	4 (100)
Infections	2 (7)	4 (100)
Bile flow issues	2 (7)	3 (75)
Itching	2 (7)	0 (0)
Indigestion	2 (7)	1 (25)
Diarrhea	2 (7)	0 (0)
Internal bleeding	1 (3)	3 (75)
Jaundice	0 (0)	3 (75)
High blood pressure	0 (0)	2 (50)

Signs/Symptoms reported by n=1 or less: Wind, Headaches/body aches, Dry mouth, Gallstones, Restless legs, Chills, Brain aneurysms

VALIDATION-READY PLD-S

- Eleven symptoms met the criteria for inclusion in the measure and were cognitive debriefed, which resulted in a 10-item validation ready PLD-S measure assessing the following: bloating (feeling swollen, full, or filled with air, wind, or gas); abdominal pain (pain in stomach area); feeling tired (low energy); abdomen (stomach area) looking bigger or enlarged; nausea; feeling full quickly when eating; shortness of breath (hard to take a full or deep breath); poor appetite; pain in or around your ribs; and acid reflux (burning sensation in chest or throat).
- Cognitive debriefing found all final items and instructions were relevant, understandable, and consistent with intended meaning.
- The PLD-S reflects one overall Symptom domain.
- Exemplary participant quotes by PLD-S item are presented below.

Bloating (feeling swollen, full, or filled with air, wind, or gas)

I felt like my stomach was bigger. I felt...just you felt fatter. I mean, you felt discomfort. You felt like your stomach shouldn't be this bloated from eating that much food. It felt foreign, like an alien in your stomach. Did you ever see that movie Alien? It kind of feels like that, a little bit, but obviously without the alien coming out, but it feel like somebody's inside your stomach making your stomach bigger. (US, male, age 47, moderate PLD, has received treatment)

Abdominal pain (pain in stomach area)

...stabbing pains in my, in my abdomen... it's like being stabbed with a needle or something...really sharp pain in, in your tummy. (UK, male, age 59, severe PLD with PKD)

Abdomen (stomach area) looking bigger or enlarged

Every afternoon, every evening, that happens by night-time; in the morning, my stomach's flat, but by the evening, I look like I'm pregnant. (US, female, age 64, moderate PLD)

Feeling tired (low energy)

I get tired doing stuff. I keep pretty busy and pretty active, but I have to sit down all the time, compared to most people I think I have to rest more. (US, female, age 64, moderate PLD)

Nausea

I feel sick, especially after eating and getting that bloated feeling, sometimes, with that. I feel like throwing up, or that feeling of stomach sickness. (US, male, age 36, severe PLD)

Feeling full quickly when eating

It's like having someone sitting on you almost and just a lot of pressure where you may be hungry, but you start to eat and you fill up rather quickly. I tend to kind of eat smaller meals and plan ahead. (US, female, age 53, severe PLD)

Shortness of breath (hard to take a full or deep breath)

It's like a shortness of breath. It comes and goes...You feel that you can't take enough air in your lungs. (US, female, age 63, moderate PLD with PKD, has received treatment)

Poor appetite

You're just not really interested in food, and I just mostly eat because I have to. (US, male, age 38, moderate PLD)

Pain in or around your ribs

...it's like pain and pressure at the top...right at the top of the ribcage. (UK, female, age 42, severe PLD with PKD)

Acid reflux (burning sensation in chest or throat)

It's a burning sensation. It's like a burning pain coming up to my ribcage, up to the top of my chest. Very uncomfortable. (UK, male, age 59, severe PLD with PKD)

DISCUSSION

- The findings indicate a high illness burden for this population with participants reporting a wide range of symptoms they associate with the condition.
- As a qualitative study, conclusions drawn from this analysis are suggestive and not definitive. However, for the purpose of this study, the respondent sample is more than adequate for exploring the experiences and burdens associated with PLD for adult patients in general.
- It is possible that the higher illness burden among UK vs. US participants may be due in part to differences in the health care systems, as suggested by the lower proportion of UK participants who reported receiving treatment for PLD. A higher proportion of UK participants also had a dual diagnosis of PKD, which may have potentially contributed to a higher symptom burden.

- Psychometric validation is now underway to confirm measurement properties of the PLD-S.

- Once validation is complete, the PLD-S should be a valuable tool for both researchers and clinicians to assess patient-reported symptom burden in this population.