


ORIGINAL ARTICLE

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

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Abstract

Background and Aim: Polycystic liver disease (PLD) is related to hepatomegaly which causes an increased mechanical pressure on the abdominal wall. This may lead to abdominal wall herniation (AWH). We set out to establish the prevalence of AWH in PLD and explore risk factors.

Methods: In this cross-sectional cohort study, we assessed the presence of AWHs from PLD patients with at least 1 abdominal computed tomography or magnetic resonance imaging scan. AWH presence on imaging was independently evaluated by two researchers. Data on potential risk factors were extracted from clinical files.

Results: We included 484 patients of which 40.1% ($n = 194$) had an AWH. We found a clear predominance of umbilical hernias (25.8%, $n = 125$) while multiple hernias were present in 6.2% ($n = 30$). Using multivariate analysis, male sex (odds ratio [OR] 2.727 $p < .001$), abdominal surgery (OR 2.575, $p < .001$) and disease severity according to the Gigot classification (Type 3 OR 2.853, $p < .001$) were identified as risk factors. Height-adjusted total liver volume was an independent PLD-specific risk factor in the subgroup of patients with known total liver volume (OR 1.363, $p = .001$). Patients with multiple hernias were older (62.1 vs. 55.1, $p = .001$) and more frequently male (22.0% vs. 50.0%, $p = .001$).

Conclusion: AWHs occur frequently in PLD with a predominance of umbilical hernias. Hepatomegaly is a clear disease-specific risk factor.

KEYWORDS

abdominal wall hernia, hepatomegaly, polycystic liver disease

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; AWH, abdominal wall hernia; BMI, body mass index; CT, computed tomography; GCP, Good Clinical Practice; hTKV, height-adjusted total kidney volume; hTLV, height-adjusted total liver volume; IQR, interquartile range; MRI, magnetic resonance imaging; OR, Odds ratio; PLD, polycystic liver disease; SPSS, Statistical Package for the Social Sciences.

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1 | INTRODUCTION

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

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

We hypothesize that patients with PLD have an increased risk for AWH as PLD is related to hepatomegaly⁵ which exerts a permanent increase in mechanical pressure on the abdominal wall.⁶ In addition, hepatomegaly can lead to malnutrition and in severe cases to sarcopenia.⁷ Sarcopenia is thought to affect the integrity of the abdominal wall and may as such increase the risk for AWH.^{8,9} Together these two disease-specific factors could contribute to an increased rate of AWHs in PLD. AWHs are subgrouped according to location: inguinal, femoral, umbilical, paraumbilical, parastomal, cicatricial, Spigelian and epigastric. We hypothesize that the increased hernia risk is most evident for umbilical hernias, in view of the local pressure by the liver on the abdominal wall.

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

2 | METHODS

2.1 | Study design and patient population

Adult patients from the Radboud University Medical Center, a tertiary referral centre for PLD, participating in the international PLD registry were included in this study.¹⁰ The international PLD registry is a prospective cohort and currently holds data from 1825 patients with >10 hepatic cysts. Diagnosis of ADPLD was made in the presence of >10 isolated hepatic cysts, ADPKD was diagnosed using the Ravine Criteria.¹¹ Radboudumc is currently one of the largest contributors to this registry with 641 (35.1%)

Key points

1. Abdominal wall hernias (AWHs) occur frequently in polycystic liver disease (PLD) with a predominance of umbilical hernias. Hepatomegaly is an important disease-specific risk factor.
2. Physicians should pay special attention to AWHs in PLD patients, especially in severe cases. Hernia repair might be complicated in this patient population.

of the patients. The following inclusion criteria were used: (i) age ≥ 18 years and (ii) availability of an abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) scan that captured the entire abdominal wall. For all patients, the most recent scan was used.

2.2 | Data collection

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

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

their hernia is considered complex. If a patient had undergone hernia repair surgery before imaging, this patient was also considered to have a hernia.

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

2.3 | Statistical analyses

Baseline variables were noted as mean (SD) or median (interquartile range [IQR]) for continuous variables where appropriate and *n* (%) for nominal variables. Missing data were imputed using multiple imputations where possible. Multiple imputations were not used in case of >40% missing values, if data were not missing at random or if no reliable imputations could be made (e.g. because of the scarcity of the event). Baseline characteristics were compared using independent *t*-tests and Mann-Whitney *U* tests for continuous variables and chi-squared tests for nominal variables. Subsequently, univariate binary logistic regression analyses were performed to identify potential risk factors for AWHs. Variables with a *p* ≤ .2 were included in the multivariate binary logistic regression models. For the multivariate models, the backward selection was used. All statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc.). A *p*-value of <.05 was considered statistically significant.

3 | RESULTS

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

3.1 | Baseline characteristics

Baseline characteristics for the entire cohort are shown in Table 1. Mean age for our cohort was 55.4 years and most patients were female (81.0%). Overall, livers were enlarged in our entire cohort since 28.5% of cases were rated Gigot type 1, 37.0% type 2 and 34.5% type 3. TLV was available in only 170 (35.1%) patients and in these

TABLE 1 Baseline characteristics

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

Note: Age, BMI and rectus abdominis thickness are expressed as mean (standard deviation); hTLV and hTKV expressed as median (interquartile range) were available in 170 (35.1%) and 51 (10.5%) respectively. TKV was only determined in ADPKD patients. Nominal variables are expressed as *n* (%).

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; hTKV, height-adjusted total kidney volume; hTLV, height-adjusted total liver volume.

^aType of surgery available in 479 (99.0%) cases.

^bPregnancy information was only available in 196 women (50.0%).

patients hepatomegaly was evident with a median height-adjusted TLV (hTLV) of 2645 (IQR 2296) ml/m, compared to a normal hTLV of approximately 816 ml/m for Dutch men and 880 ml/m for Dutch women.^{17,18} Baseline characteristics for MRI and CT images separately can be found in the supplementary files (Table S1).

3.2 | Prevalence of abdominal wall hernias

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

TABLE 2 Abdominal wall hernias and subtypes

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

Abbreviation: IQR, interquartile range.

^a*N* represents the number of hernias in which the diameter could be measured in two different directions (laterolateral and craniocaudal).

^bComplex hernia according to Slater criteria; 13 cases were unknown because hernia repair was performed before the imaging.

Baseline characteristics for patients with and without AWH are shown in Table 3. Patients with an AWH were more frequently male, had larger TLV, higher Gigot types and had undergone abdominal surgery more often. No differences were found with respect to age, diagnosis, BMI, hTKV, rectus abdominis thickness, history of smoking, connective tissue disease, aneurysm aorta or pregnancy rate. Comparable results were found in a subgroup of patients with known hTLV (Table S2).

Compared to patients with a single hernia, patients with multiple hernias were older (62.1 vs. 55.1, $p = .001$) and were more often male (50.0% vs. 22.0%, $p = .001$; Table S3).

3.3 | Risk factors

Univariate logistic regression showed that the variables age, sex, diagnosis, BMI, hTLV, Gigot and abdominal surgery were potential risk factors for the presence of AWH ($p < .02$; Table 4). Because hTLV and Gigot could not be included in the same model because

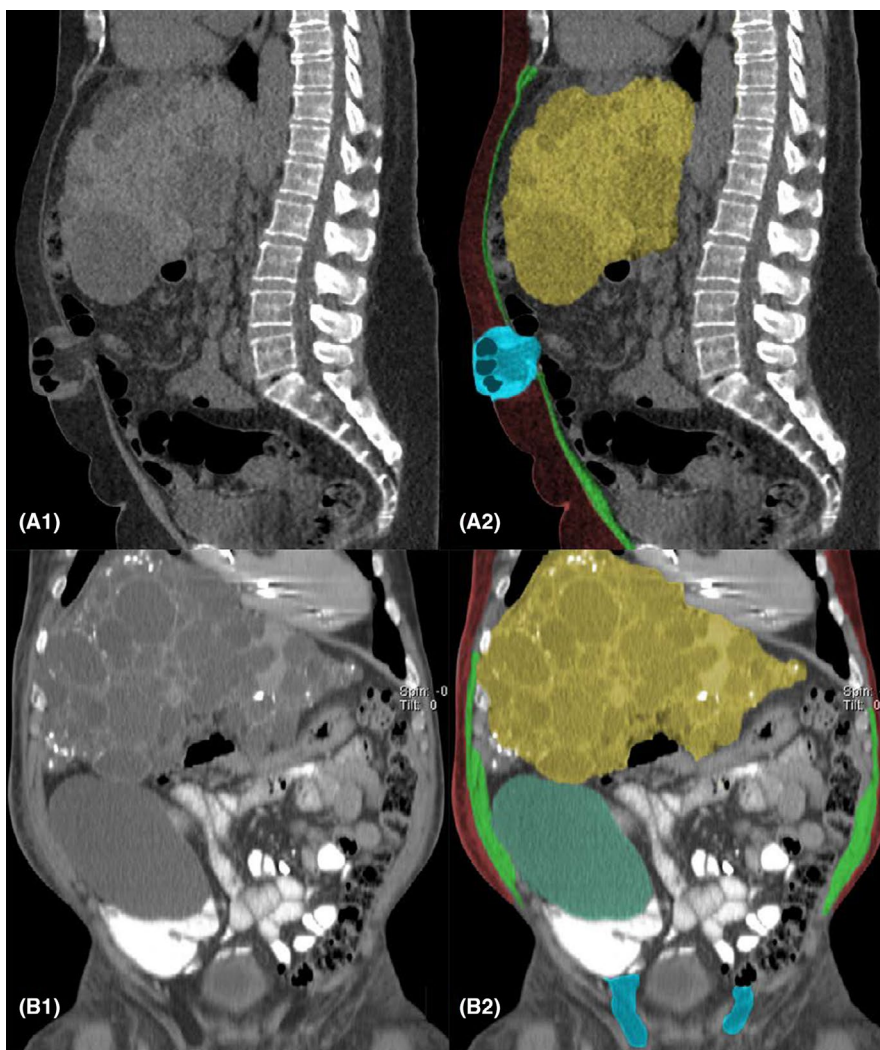


FIGURE 1 CT imaging of two patients with abdominal wall hernias. Patient A umbilical hernia and patient B double inguinal hernia. The subcutaneous tissue is coloured red, the abdominal muscle tissue light green, the AWH in cyan, the polycystic liver is coloured yellow and a single kidney cyst is coloured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

TABLE 3 Baseline characteristics for patients with and without hernias

	No (n = 290)	Yes (n = 194)	p-value
Age (years)	54.9 (10.5)	56.2 (10.4)	.160
Male sex	41 (14.1)	51 (26.3)	.001
Diagnosis ADPKD	146 (50.3)	112 (57.7)	.110
BMI	25.5 (4.2)	26.1 (4.1)	.144
hTLV (ml/m)	2413 (1935)	2969 (2881)	.002
Gigot classification			
Type 1	96 (33.1)	42 (21.6)	.002
Type 2	111 (38.3)	68 (35.1)	
Type 3	83 (28.6)	84 (43.3)	
hTKV (ml/m)	510 (565)	898 (939)	.135
Rectus abdominis thickness (mm)	8 (2)	8 (2)	.579
Abdominal surgery	121 (41.7)	123 (63.4)	.000
Smoking			
Present	54 (18.6)	33 (17.0)	.886
Former	59 (20.4)	37 (19.1)	
Never	177 (61.0)	124 (63.9)	
Connective tissue disease	7 (2.4)	4 (2.1)	.511
Aneurysm aorta present	2 (0.7)	0 (0.0)	.246
Pregnancy ^a	98 (79.7)	61 (83.6)	.501

Note: Age, BMI and rectus abdominis thickness expressed as mean (standard deviation); hTLV and hTKV expressed as median (interquartile range) were available in 170 (35.1%) and 51 (10.5%) respectively. TKV was only determined in ADPKD patients. Nominal variables expressed as n (%). p-values were determined using independent t-tests and Mann Whitney U test for continuous variables and Chi-squared for nominal variables.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; hTKV, height-adjusted total kidney volume; hTLV, height-adjusted total liver volume.

^aPregnancy information only available in 196 patients (n = 123 without AWH and n = 73 with AWH).

of collinearity, we performed multivariate analysis with backward selection in all patients using the Gigot variable and later in a subgroup of patients using the hTLV variable. A final multivariate logistic regression showed that males (odds ratio [OR] 2.727, $p < .001$), abdominal surgery (OR 2.575, $p < .001$) and Gigot classification (Type 3 OR 2.853, $p < .001$) were independent risk factors (Table 4). Similar results were found in the subgroup of patients with known hTLV (n = 170, Table S4), which showed that male sex (OR 12.184, $p = .021$), hTLV (OR 1.363 per L/m, $p = .001$) and abdominal surgery (OR 3.571, $p < .001$) were risk factors in this group. We performed a sensitivity analysis in the patients with umbilical hernias because of the close proximity of the liver to this hernia site. This sensitivity analysis showed that Gigot classification and abdominal surgery were relevant risk factors in this subgroup (Gigot classification type 3 OR 2.947, $p < .001$; and abdominal surgery OR 2.379,

$p < .001$; Table S5), while male sex was not a risk factor for umbilical hernias (male sex OR 1.740, $p = .065$; Table S5). Since inguinal hernias are known to occur predominantly in older males, we performed a subgroup analysis in this group.¹⁹ Multivariate logistic regression showed that male sex was the strongest risk factor in this group (OR 5.227, $p < .001$), but age (OR 1.044, $p = .001$), Gigot classification (type 3 OR 3.195, $p = .002$) and abdominal surgery (OR 1.858, $p = .039$) were also identified as risk factors (Table S6).

3.4 | Hernia repair

In our cohort, 40/194 (20.6%) of all patients with hernias had received hernia repair surgery. In these patients, 19 umbilical hernias were repaired, 12 inguinal, 11 cicatricial and 5 epigastric hernias. In 30 patients (75.0%), the cross-sectionally evaluated imaging that we evaluated, was performed after their repair. Repair was performed using mesh in 12/30 patients, primary closure was performed in 7/30 patients and in 11/30 patients it remained unknown what type of repair was used. The mean follow-up was 8.0 years (standard deviation 13.4). We found that 14 patients had no AWH after the repair, 7 patients had recurrence of the previously repaired hernia and 11 patients had a new hernia after their repair. A flowchart of patients with hernia repairs can be found in Figure S1.

4 | DISCUSSION

We found that AWHs are a frequent complication in PLD with a prevalence of 40.1%. Umbilical hernia is the most frequent (64.4%) hernia type in our population of PLD patients. We identified male sex and abdominal surgery, as well as severity of PLD (as assessed with Gigot classification [type 3] OR 2.853, $p < .001$ and hTLV OR 1.363 per litre, $p = .001$) as risk factors for AWH. In addition, using sensitivity analyses, hepatomegaly was confirmed as a risk factor for umbilical and inguinal hernias (Gigot type 3 OR of 2.947, $p < .001$ and 3.195, $p = .039$ respectively). Male sex was not identified as risk factor for umbilical hernias (OR 1.740, $p = .065$). Sarcopenia, measured through rectus abdominis thickness, was not identified as a risk factor (OR per mm 0.977, $p = .579$).

There is limited published data on AWHs in PLD patients and a smaller ADPKD study indicates prevalence rates of 13.4% for inguinal and 7.0% for umbilical hernias.²⁰ Unfortunately, no background information or methodology is provided in this paper, which precludes comparison with our data. Another study investigated hernia incidence in 85 ADPKD patients on renal replacement therapy.²¹ While the prevalence of 45% is comparable to our finding, the presence of hernias was evaluated using clinical notes. While the specific method used for hernia identification is unclear smaller and less symptomatic hernias may have been missed. Two other studies assessed the presence of AWHs in the general population by (i) using questionnaires and a physical examination and (ii) medical history and clinical examination in combination with ultrasound.^{22,23} These

TABLE 4 Logistic regression AWH overall

	p-value	OR	95% CI lower bound	95% CI upper bound
Univariate				
Age	.161	1.013	0.995	1.030
Sex (reference = female)	.001	2.166	1.368	3.430
Diagnosis (reference = ADPKD)	.111	0.742	0.515	1.071
BMI	.146	1.035	0.988	1.084
hTLV (L/m)	.009	1.263	1.059	1.505
Gigot (reference = type 1)				
Type 2	.162	1.400	0.874	2.244
Type 3	.000	2.313	1.442	3.711
Rectus abdominis thickness (per mm)	.579	0.977	0.898	1.062
Abdominal surgery	.000	2.437	1.671	3.554
Smoking (reference = never)				
Present	.685	0.895	0.521	1.536
Former	.694	0.901	0.534	1.520
Connective tissue disease	.651	0.740	0.200	2.737
Aneurysm aorta	.999	0.000	0.000	
Pregnancy ^a	.502	0.771	0.361	1.647
Multivariate				
Sex (reference = female)	.000	2.727	1.659	4.481
Gigot (reference = type 1)				
Type 2	.178	1.409	0.855	2.322
Type 3	.000	2.853	1.718	4.740
Abdominal surgery	.000	2.575	1.741	3.809

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; hTLV, height-adjusted total liver volume; OR, odds ratio.

^aOnly investigated in women with known pregnancy status ($n = 196$).

studies found prevalence rates of 11.7% and 20.9%, respectively, which is considerably lower than the prevalence in PLD. Lastly, two other studies describe inguinal hernias to occur most frequently in the general population, followed by umbilical hernias.^{24,25} In contrast, we found a clear predominance of umbilical hernias in our cohort. This disparity may be the result of the increased intra-abdominal pressure exerted by the polycystic livers.

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

Our study comes with several limitations. First, as an approximation of intra-abdominal pressure we determined disease severity using two different methods: (i) Gigot classification¹⁵ and (ii) hTLV. Both approaches do not directly measure intra-abdominal pressure and it is possible that the effect is mediated through other ways than abdominal pressure. Gigot classification was determined in all patients, hTLV was only available in a subgroup of patients and is typically only measured in severe cases to assess the effect of treatment or before liver transplantation. Since direct intra-abdominal pressure measurements with manometry²⁶ or indirect measurements in the bladder,²⁷ are both too invasive and unethical for this study we believe Gigot classification and hTLV to be a reliable approximation. Second, our study did not include qualitative measures that determine the impact of hernias such as hernia-related symptoms and quality of life. Our current study is mainly aimed at quantifying the AWH prevalence instead of determining the impact of an AWH on affected individuals. Future studies should address this. Third, we did not directly compare the AWH prevalence from our cohort with a matched group of healthy controls. However, the

prevalence of AWH in our cohort was much higher than reported in general population studies, in accordance with previous ADPKD studies.²⁰⁻²³ Moreover, there were also profound differences in the prevalences of type of hernia. Lastly, all CT and MRI scans were made in a supine position. Small hernias might not be visible in this position because of the effect of gravity. However, these hernias are not probably to have much clinical relevance and our systematic and thorough methodology minimized the chance of missing small hernias.

While the focus of this study was to determine the prevalence of AWHs, from a clinical perspective the frequency and outcomes after surgical repair are paramount. To accurately determine the outcomes after surgical repair, a study aimed at this goal is needed addressing the specifics of these hernias and the type of repair. However, in our cohort hernia repair was common (20.6%), with frequent recurrence of hernias or development of new hernias after surgery (53.3%) and a high rate of surgically complex patients according to Slater criteria (25.8%). Recurrence rate of AWH in the general population is estimated between 15%–37% for primary repair²⁸ and around 5%–6% for laparoscopic mesh repair,^{29,30} suggesting that hernia repair is more challenging in PLD patients. In line with hernia guidelines, we recommend hernia repair should be reserved for symptomatic patients.^{31,32} Given the high rate of hernia recurrence, PLD patients should undergo AWH repair with mesh or an autologous reconstruction, and not primary closure. Referral to specialized clinics may be considered in PLD patients with Gigot type 3 phenotype or complex hernias according to the Slater.

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

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

ETHICS APPROVAL STATEMENT

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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