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## Polycystic liver disease: Classification, diagnosis, treatment process, and clinical management

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### Abstract

Polycystic liver disease (PLD) is a rare hereditary disease that independently exists in isolated PLD, or as an accompanying symptom of autosomal dominant polycystic kidney disease and autosomal recessive polycystic kidney disease with complicated mechanisms. PLD currently lacks a unified diagnostic standard. The diagnosis of PLD is usually made when the number of hepatic cysts is more than 20. Gigot classification and Schnelldorfer classification are now commonly used to define severity in PLD. Most PLD patients have no clinical symptoms, and minority with severe complications need treatments. Somatostatin analogues, mammalian target of rapamycin inhibitor, ursodeoxycholic acid and vasopressin-2 receptor antagonist are the potentially effective medical therapies, while cyst aspiration and sclerosis, transcatheter arterial embolization, fenestration, hepatic resection and liver transplantation are the options of invasion therapies. However, the effectiveness of these therapies except liver transplantation are still uncertain. Furthermore, there is no unified strategy to treat PLD between medical centers at present. In order to better understand recent study progresses on PLD for clinical practice and obtain potential directions for future researches, this review mainly focuses on the recent progress in PLD classification, clinical manifestation, diagnosis and treatment. For information, we also provided medical treatment processes of PLD in our medical center.

**Key words:** Polycystic liver disease; Autosomal dominant polycystic kidney disease; Autosomal recessive polycystic kidney disease; Isolated polycystic liver disease; Diagnosis; Treatment

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**Core tip:** Polycystic liver disease (PLD) is a rare hereditary disease. However, there is no unified strategy in the treatment of PLD so far. In order to better understand recent progresses on clinical practice of PLD and contribute to potential directions for future researches, we conducted this review mainly focusing on recent progresses of PLD classification, clinical manifestation, diagnosis and treatments. For information, we also

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provided medical treatment process of PLD that is being used in our medical center.

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## INTRODUCTION

Polycystic liver disease (PLD) is a rare hereditary disease and often defined as multiple diffuse cysts of the liver<sup>[1]</sup>. It can independently exist in isolated PLD (PCLD), or as an accompanying symptom of autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD), while the mechanisms of cysts in PLD and PKD are complicated. In the one hand, they are both related to the primary cilia of biliary epithelial cells and the key proteins associated with cilia function, thus classified as fibrocystic diseases or ciliary diseases<sup>[2]</sup>. In the other hand, some scholars have classified them as cholangiopathic disease due to the source of PLD cysts which is from congenital bile duct dysplasia through multiple mechanisms<sup>[3]</sup>. Meanwhile, there is an opinion that the two mentioned above are actually associated with each other for there is a causality between fibrocystic malformation and dysgenesis of the biliary structures. In the limited treatments of PLD, drug therapy has gradually become a hot spot along with the deepening understanding on the pathogenesis of PLD, while there are still controversies in surgical treatments. In order to better understand recent progresses on PLD for clinical practice and contribute to potential directions for future researches, we conducted this non-systematic review mainly focusing on the recent progresses on PLD classification, clinical manifestation, diagnosis and treatments.

## BRIEF SUMMARY OF EPIDEMIOLOGY AND MECHANISMS

Despite the genes associated with pathogenesis, the natural courses of various PLD in the liver are basically the same, showing as a continuous increase in the number and volume of cysts in liver<sup>[4]</sup>. However, it is essential to clarify the various forms of PLD (Table 1).

### PLD in ADPKD

ADPKD is the most common monogenic genetic disease in the kidneys, with a global incidence of about 0.25% to 1%<sup>[5]</sup>. PLD is the most common extrarenal symptom of ADPKD, which involved with 94% ADPKD patients<sup>[6]</sup>. Mutations in two genes (PKD1 and PKD2) cause the development of ADPKD. PKD1 is located at chromosome 16p13.3 with 80% of cases related to it, while PKD2 is located at chromosome 4q21-22, which is responsible for the remaining 5-10% of cases<sup>[5]</sup>. PKD3 was once thought to be associated with ADPKD but excluded according to the recent family reanalysis<sup>[7]</sup>. Additionally, GANAB, which is involved in protein folding, was also reported to be responsible for ADPKD<sup>[5,8]</sup>.

### PLD in ARPKD

ARPKD is pretty rare with the incidence about 1:20000. It often occurs in children, of which 30% die from severe lung dysplasia and secondary respiratory failure, with renal collecting duct dilatation, bile duct dysplasia and portal fibrosis as the mainly clinical manifestations<sup>[9]</sup>. At present, a mutation of *PKHD1* gene on the short arm of chromosome 6 encoding a fibrocystic protein, of which function is still not well-known, is found to be responsible for ARPKD. As well as PKD1 and PKD2, PKHD1 is also involved in the processes of forming the original cilia of liver and kidney, eventually causing cyst formation<sup>[2]</sup>.

### PLD in PCLD

Unlike ADPKD and ARPKD, PCLD often does not involve the kidneys<sup>[10]</sup>. In the previous studies of variant genes in PCLD, *PRKCSH* gene mutation accounted for the highest proportion of 15%, followed by SEC63 and LRP5. Meanwhile, GANAB is the first gene found to be associated with PCLD with a small proportion (approximately

**Table 1** Brief summary of various polycystic liver disease

Disease	Genes mutation	Kidney involvement
ADPKD	<i>PKD1, PKD2, GANAB</i>	Yes
ARPKD	<i>PKHD1</i>	Yes
PCLD	<i>PRKCSH, SEC63, LRP5, GANAB, ALG8, SEC61B, PKHD1</i>	Usually not

ADPKD: Autosomal dominant polycystic kidney disease; ARPKD: Autosomal recessive polycystic kidney disease; PCLD: Isolated polycystic liver disease.

1%). However, there are still a big amount of cases where a pathogenic gene cannot be found. The products of *PRKCSH*, *SEC63* and *GANAB* genes are important proteins involved in the process of co-translational transport and maturation of glycoproteins in the endoplasmic reticulum<sup>[11]</sup>, while the unidirectional transmembrane molecules encoded by *LRP5* gene, with Frizzled receptors together, can bind to Wnt proteins, thereby initiating the Wnt signaling pathway and participating in the pathophysiological changes of PCLD<sup>[12]</sup>. Furthermore, in the recent PCLD pathogenic gene research, mutations in three genes, *ALG8*, *SEC61B* and *PKHD1*, are also found to be involved in the development of PCLD, which together with the above-mentioned *PRKCSH*, *SEC63*, and *GANAB* genes can explain nearly 50% PLD cases<sup>[13]</sup>. The  $\alpha$ -1,3-glycosyltransferase encoded by the *ALG8* gene is an endoplasmic reticulum integral membrane protein<sup>[14]</sup>, and the *SEC61B* gene-encoded product is an important component of the SEC63 protein complex on the endoplasmic reticulum. Both the two genes play important roles in protein quality regulation<sup>[15]</sup>. In addition, recent study<sup>[16]</sup> showed cholangiocyte autophagy contributed to hepatic cystogenesis in PLD and represented as a potential therapeutic target.

## CLINICAL MANIFESTATION

Although the volume of PLD liver increases by 1.8% per 6 to 12 mo<sup>[17,18]</sup>, most patients have no clinical symptoms regardless of the type of PLD. About 20% of patients develop obvious clinical symptoms including dyspnea, early satiety, abdominal distension, malnutrition, gastroesophageal reflux, back pain due to hepatomegaly pressing surrounding organs or cyst complications, which will seriously affect the quality of life<sup>[19-21]</sup>. Moreover, patients suffering from PLD may develop hepatic venous outflow obstruction because of cystic mass effect, resulting in portal hypertension, ascites, variceal haemorrhage or splenomegaly<sup>[22,23]</sup>. Gabow *et al*<sup>[24]</sup> found that the risk factors for hepatic cyst symptoms in ADPKD patients were older age, female gender and multiple pregnancy history. Studies<sup>[25,26]</sup> have also shown that in female, hepatic cysts grow rapidly under the influence of hormones, which may be related to the expression of estrogen receptors  $\alpha$  and  $\beta$ <sup>[27]</sup>. Moreover, lower age was reported to be independently associated with larger liver volume in ADPKD females patients, whereas the higher age in male patients<sup>[28]</sup>. The gender differences and related mechanisms should be investigated in future.

In most patients with PLD, liver function tests are usually normal because liver parenchyma is not completely destroyed<sup>[29]</sup>, however elevated  $\gamma$ -glutamyltransferase, alkaline phosphatase, aspartate aminotransferase and total bilirubin are reported in some serious cases<sup>[30,31]</sup>. Elevation of  $\gamma$ -glutamyltransferase and alkaline phosphatase may be the result of biliary cell activation<sup>[24,32]</sup>, while the increase in total bilirubin can be seen in some cases of cystic compressing the bile duct. Furthermore, a study by Waanders *et al*<sup>[33]</sup> found that 45% PLD patients showed an increase in CA19-9 with a degree of elevation positively correlated with polycystic liver volume. Besides, the possibility of cysts infection is needed to consider when detecting a significant increase of CA19-9, and decrease of CA19-9 can be seen following effective anti-infective treatments.

## DIAGNOSIS

The diagnosis of PLD is usually made when the number of hepatic cysts is more than 20<sup>[31]</sup>. However, patient with a family history of PCLD can be diagnosed when number of cysts more than 4<sup>[10]</sup>. However, the type of PLD can be hard to distinguish. Because PCLD patients may have renal cysts while ADPKD or ARPKD patients may have hepatic cysts as the main clinical manifestations, the identification between them



without family history may be difficult and requires genetic analysis.

Currently there are mainly two clinical classifications on PLD: Gigot classification<sup>[34]</sup> (Table 2) and Schnelldorfer classification<sup>[35]</sup> (Table 3). Both of them include the number and size of cysts and the remaining liver parenchyma volume as the criteria for typing, while the latter also considers the inflow and outflow of pre-retained liver segments, which is more conducive to the choice of treatment. There was a Qian classification<sup>[19]</sup> relying on the number of cysts and the presence of symptomatic hepatomegaly (Table 4), however it is seldom used now because of oversimplification and, more importantly, having no contribution to selection of treatments.

## TREATMENTS

Most patients with asymptomatic PLD do not need any treatment, while minority need only when incapacitating symptoms and a lower quality of life caused by hepatomegaly or complications such as cyst rupture, infection, bleeding, or hepatic venous outflow obstruction<sup>[21,36]</sup>. At present, the treatments of PLD are divided into three main categories: drug therapy, percutaneous therapy and surgical therapy.

### Drug therapy

**Somatostatin analogues:** Although there is currently no approved effective treatment for PLD, recent progresses in somatostatin analogues have been achieved with positive results<sup>[37]</sup>. Somatostatin is a neurohormone with a wide range of effects through combining with somatostatin receptor (SSTR). There are five subtypes of SSTR (SSTR-1 to SSTR-5), which are expressed in varied tissues of human body. Somatostatin analogues such as octreotide, lanreotide and *etc.* are able to interact with the SSTR on the surface of the cyst wall to reduce the cAMP level of the bile duct epitheliums, inhibit the secretion of cyst fluid and hyperplasia of the bile duct cells, therefore inhibiting the growth of hepatic cysts<sup>[38,39]</sup>.

Multiple controlled trials<sup>[17,18,40,41]</sup> showed that the liver volume of the group using somatostatin analogues was significantly reduced comparing to the control group. For octreotide, Caroli *et al.*<sup>[40]</sup> administered 40 mg of octreotide per month and found that the experimental group had a significant reduced liver volume  $71 \pm 57$  mL within 6 mo. Meanwhile, Hogan *et al.*<sup>[17]</sup> gave the same dosage of octreotide to patients with severe ADPKD and PLD and the liver volume decreased by  $4.95\% \pm 6.77\%$  within a year ( $P = 0.048$ ). In some patients with symptomatic PLD, octreotide were reported for significantly slowing disease progression, reducing symptoms and improving quality of life for 4 years<sup>[42]</sup>. For lanreotide, the liver volume of PLD patients using lanreotide decreased by 2.9% on average in 6 mo, and 4.0% in a year ( $P = 0.01$ )<sup>[18]</sup>. And more recently, lanreotide also showed positive effects on decreasing liver volume in patients with ADPKD and PLD, compared with control arm<sup>[43]</sup>. For the pattern of effectiveness, the 120 mg lanreotide group benefited more than the 90 mg lanreotide group and the control group<sup>[41]</sup>. In another study, Temmerman *et al.*<sup>[44]</sup> increased the therapeutic dose of lanreotide non-responder from 90 mg to 120 mg, which led to stopping liver volume growing. These studies have shown that the efficacy of lanreotide may be dose-dependent.

Pasireotide is a more stable somatostatin analogue than octreotide, with a half-life of 12 h and it is currently used to treat Cushing's syndrome. Unlike octreotide and lanreotide, pasireotide can combine with all the SSTR subtypes to function, except SSTR-4<sup>[45]</sup>. Studies<sup>[46]</sup> have shown that pasireotide is more effective in relieving hepatorenal cyst formation than octreotide in the PKD mouse model. Further clinical data are required to confirm its efficacy.

On the contrary, a research<sup>[47]</sup> systematically reviewed seven PLD drug treatment studies from January 1966 to August 2014 and found that though the use of somatostatin analogues significantly reduced liver volume in 6 mo, however the improvement of patient quality of life and relief of clinical symptoms were very limited. In addition, there are some controversies about duration of efficacy and effect of cessation of treatment (also called drug holiday). Some studies<sup>[48]</sup> have also shown that the efficacy of somatostatin analogue therapy can only last for 2 years, and cessation of treatment would lead to disappearance of effect or even a rebound effect<sup>[42,49,50]</sup>. However, a study<sup>[43]</sup> showed the benefit to reduce liver volume from lanreotide still persisted 4 mo after cessation of the drug. Meanwhile, second cycle of somatostatin analogues after a drug holiday would still be as effective as the first in reducing liver volume<sup>[50]</sup>. This issue should be investigated in future clinical practicing.

**Mammalian target of rapamycin (mTOR):** mTOR is a serine/threonine protein kinase belonging to the phosphatidylinositol 3-kinase-associated kinase (PI3K) family

Table 2 Gigot classification

	Number of cysts	Cyst size	Remaining areas of noncystic liver parenchyma
Gigot type I	< 10	Large (> 10 cm)	Large
Gigot type II	Multiple	Small, medium	Large
Gigot type III	Multiple	Small, medium	Few

and plays an important role in regulating signaling in many pathways. It mainly presents in two different complexes: Rapamycin target protein complex 1 (mTORC1) and rapamycin target protein complex 2 (mTORC2). mTORC1 is a growth regulator that can sense and aggregate trophic and environmental factors, while mTORC2 can promote cell survival, regulate cytoskeletal remodeling, ion transport and growth<sup>[51]</sup>. mTOR inhibitor is a targeted drug currently used in the treatment of cancer, including sirolimus, everolimus, and *etc.* In the PKD animal model, they showed significant inhibition of cyst growth and delaying the progression of the disease<sup>[52-55]</sup>. Qian *et al*<sup>[56]</sup> showed that sirolimus significantly reduced liver volume (11.9%) in ADPKD patients after renal transplantation ( $P = 0.009$ ). However, in the clinical randomized controlled trials by Serra *et al*<sup>[57]</sup> and Walz *et al*<sup>[58]</sup> 18 mo of sirolimus and 2 years of everolimus were used, respectively, and had no significant effect on progression of renal cysts ( $P = 0.26$ ,  $P = 0.06$ ). Chrispijn *et al*<sup>[59]</sup> used different drug regimens for PCLD and ADPKD patients. The efficacy of everolimus-octreotide combination therapy was not significantly different in reducing liver volume compared with octreotide monotherapy ( $P = 0.73$ ). On the other hand, as an immunosuppressive agent, mTOR inhibitors could increase the incidence of infection and malignant tumors as well as other side effects including dyslipidemia, thrombosis and lung diseases. Although most of them are moderate and may regress with lower doses, these side effects are unpredictable and idiosyncratic, which medics need to pay highly cautions to in clinical practice<sup>[60]</sup>.

In summary, though with acceptable safety profile, there is not enough evidence to prove that mTOR inhibitors can benefit PLD patients. Thus, the use of mTOR inhibitors for the treatment of PLD is not recommended until more systematic and comprehensive results are obtained.

**Ursodeoxycholic acid:** Ursodeoxycholic acid (UDCA), which is a  $\text{Ca}^{2+}$  agonist in hepatocytes and biliary epithelial cells, has been shown to delay the growth of hepatic cysts in PLD animal model experiments. The mechanism is to inhibit cystic hyperplasia of biliary epithelial cells by inhibiting the proliferation of cystic bile duct epithelium and decreasing cytotoxic bile acid levels in the liver without affecting apoptosis by the PI3K/AKT/MEK/ERK1/2 pathway<sup>[61]</sup>. However, a multicenter randomized controlled trial<sup>[62]</sup> showed that liver volume insignificantly increased by  $4.6\% \pm 7.7\%$  in advanced PLD patients after 24 wk of UDCA treatment, with a liver volume increase of  $3.1\% \pm 3.8\%$  in the control group ( $P = 0.493$ ), but subgroup analysis showed significant delay on the growth of hepatic cysts in ADPKD patients ( $P = 0.049$ ).

**Vasopressin-2 receptor antagonist:** Vasopressin-2 receptor (V2R) is localized in the renal tubular epithelium, which promotes vesicle secretion and cell proliferation by up-regulating cAMP level<sup>[63]</sup>. Studies<sup>[64]</sup> have shown that antagonizing V2R in the kidney can delay the growth of renal cysts and improve renal function in the PCK mouse model. In a randomized controlled trial<sup>[65]</sup>, the growth rate of renal cysts in the treatment group treated with tolvaptan was slower than the control group ( $P < 0.001$ ). Meanwhile, even in advanced ADPKD patients, tolvaptan also showed protective effect on kidney function<sup>[66]</sup>. Although V2R is theoretically not expressed in biliary epithelial cells, meaning V2R antagonists are not effective against hepatic cysts, successful V2R treatment in reducing liver volume in PLD patients have recently been reported<sup>[67]</sup>.

### Percutaneous therapy

**Cyst aspiration and sclerosis:** This treatment is often used for patients with a single giant cyst, as the Gigot type I<sup>[68]</sup>. Besides completely suction of fluid, the sclerosing agent will be injected into the cyst to destroy the epitheliums of the cyst wall. The most commonly used agent is ethanol, followed by ethanolamine oleate, minocycline, tetracycline, *etc.*<sup>[68,69]</sup>. A retrospective study by Benzmira *et al*<sup>[70]</sup> collected 58 cases of hepatic cysts treated with puncture and ethanol sclerotherapy, and the cyst volume was reduced by an average of 94% and the symptom relief rate was 95%. In meta-



Table 3 Schnelldorfer classification

	Symptoms	Cyst characteristics	Areas of relative normal liver parenchyma	Isosectoral portal vein or hepatic vein occlusion of preserved sector
Type A	Absent or mild	Any	Any	Any
Type B	Moderate or severe	Limited Number with large cysts	> 2 sectors	Absent
Type C	Severe (or moderate)	Any	> 1 sector	Absent
Type D	Severe (or moderate)	Any	< 1 sector	Present

analysis review<sup>[71]</sup> of cystic puncture and sclerotherapy including a total of 526 patients in 16 studies, 76%-100% of cases had partial cyst volume remission, while 72%-100% of cases had partial symptom remission, and 56%-100% of cases reported disappearance of symptoms. However, some researchers reported that the recurrence rate of cysts was as high as 80% undergone cyst aspiration and sclerosis, and the recurrence rate of symptoms was as high as 50%<sup>[72]</sup>. Nevertheless, PLD patients are often diagnosed with multiple cysts, thus this procedure actually is seldom used in PLD patients.

**Transcatheter arterial embolization:** Transcatheter arterial embolization (TAE) is using embolic agents to selectively embolize the branches of the arteries that supply blood to the cysts, thereby destroying the cells of the cystic wall, cutting off the source of the cystic fluid, and controlling the disease progression<sup>[73]</sup>. The application of this treatment is mainly due to the recent study showed that the cysts in PLD were mainly supplied by the hepatic artery<sup>[74]</sup>. A retrospective study with a small sample by Zhang *et al*<sup>[75]</sup> found that liver volume of PLD patients after TAE decreased by 32%, 31%, and 33% at 1 year, 2 years, and 3 years, respectively, while liver cyst volume reduced by 36%, 37%, 38%. Hoshino *et al*<sup>[76]</sup> collected 244 PLD cases undergone liver TAE, and the liver volume decreased by 94.7% (95% CI: 93.5%-95.8%) at 6 mo and 90.8% (95% CI: 88.7%-92.9%) at 1 year after TAE, respectively. A recent preliminary study<sup>[77]</sup> also showed positive effects on improvement of symptoms and shrinkage of cyst volume in PLD patients. Meanwhile, a study<sup>[78]</sup> showed its failure rate is as high as 69.6%, including uncontrolled symptoms, postoperative liver failure and death. Nevertheless, there is still a need for more well-designed large-scale studies to investigate their safety and efficacy before widespread adoption. And efforts should be made to investigate its potential as an adjuvant therapy.

### Surgical therapy

**Fenestration:** Being different with cyst puncture and sclerotherapy, fenestration is often used for the treatment of multiple cysts, as Gigot type I-II or Schnelldorfer type B patients. In addition, the procedure can also be applied to cases when cyst puncture and sclerotherapy failed<sup>[79]</sup>. With the development of laparoscopic techniques, fenestration is now usually performed using laparoscope, but sometimes it has to be completed under the ordinary surgery due to uncontrollable bleeding, blind spots or technique, *etc*<sup>[1]</sup>. Symptoms are greatly relieved in 92% of cases undergone fenestration<sup>[80]</sup>, however 33.7% of patients suffer symptomatic recurrence and 26.4% need reintervention<sup>[81]</sup>. Patients with multiple cysts larger than 5 cm in diameter have a higher recurrence rate than patients with smaller volume cysts<sup>[82]</sup>. Common complications of this procedure include ascites, pleural effusion, hemorrhage, and bile leakage. A meta-analysis<sup>[83]</sup> showed that the recurrence rate through open surgery was slightly lower, however without statistical significance, than through laparoscopic approach (5% *vs* 6%), and most recurrent cysts do not require second surgery. However, we believe the incidence of complication of laparoscopic fenestration will reduce, which is related to the continuous updating of surgical instruments and the increasing experience of surgeons. Besides, considering the convenience and small trauma, we still recommend laparoscope as first priority.

**Hepatic resection:** Hepatectomy is often used in severe Gigot II PLD patients with at least one liver segment that is not affected by the cysts<sup>[35]</sup>. The extent of resection depends on the size and distribution of the cysts. However, due to the compression of the cyst, the distorted Glisson system and hepatic venous outflow obstruction increase the difficulty of resection. Thus, for cysts that cannot be removed, fenestration is often performed with hepatic resection<sup>[3]</sup>. Meanwhile, hepatic venous outflow obstruction is frequent in PLD and has major consequences on intraoperative bleeding and

Table 4 Qian classification

	Number of cysts	Symptomatic hepatomegaly
Grade 0	0	No
Grade 1	1-10	No
Grade 2	11-20	No
Grade 3	> 20	No
Grade 4	> 20	Yes

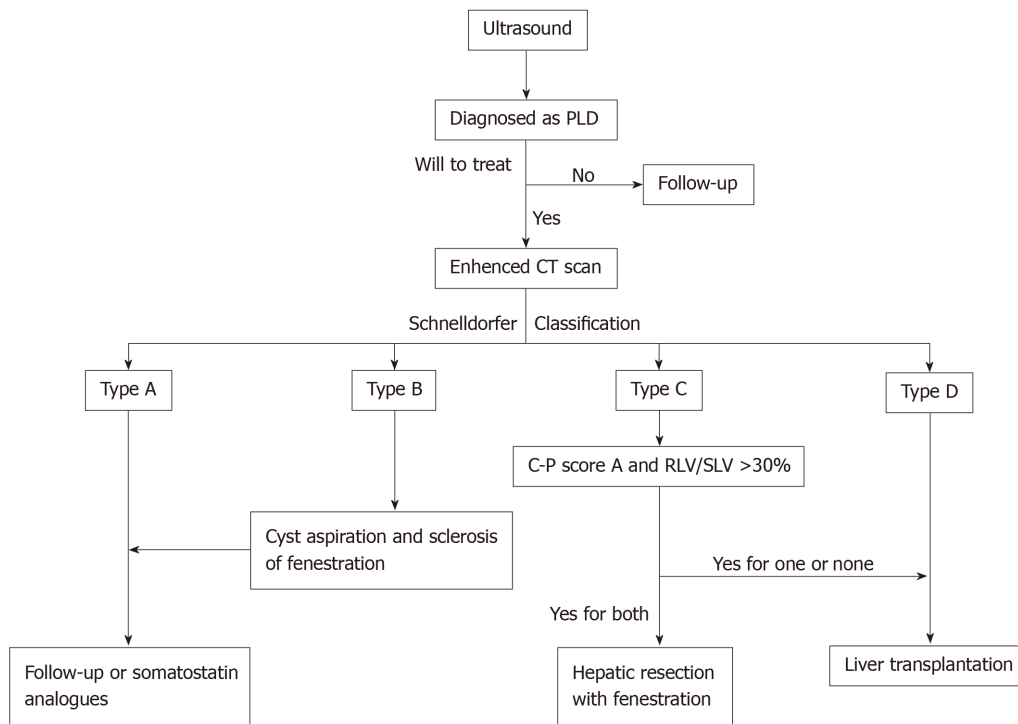
postoperative ascites and liver failure<sup>[84]</sup>. In a retrospective study by Chebib *et al*<sup>[85]</sup> including 186 PLD patients undergone hepatectomy, postoperative liver volume is reduced by an average of 61% comparing to preoperative, with a high complication rate of 21% and a mortality rate of 2.7%. On the other hand, some studies<sup>[83,86]</sup> claimed that hepatectomy could greatly alleviate symptoms and prolong the needs of liver transplantation with an acceptable safety profile. In addition, application of somatostatin analogues after hepatectomy can inhibit the growth of residual cysts and prevent the occurrence of new cysts<sup>[86]</sup>. Despite the compromising relief of symptom and reduction of liver volume, it is presently not recommended as a first-line treatment plan, because of the high complication and mortality rate and the potential difficulties for the future liver transplantation due to abdominal adhesion<sup>[1,87]</sup>. Nevertheless, we consider the most important issues may be when and how to perform this procedure, or in other words, which group of patients benefit from hepatectomy, which would maximize the value of the surgery.

**Liver transplantation:** Liver transplantation is currently the only cure for PLD, which is mainly applied in Gigot type III patients with severe symptoms that seriously affect the quality of life of patients, as well as untreated complications such as portal hypertension and malnutrition<sup>[1]</sup>. In the PLD classification designed by Schnelldorfer *et al*<sup>[35]</sup>, liver transplantation is suitable for patients with type D. Compared with hepatocellular carcinoma and chronic liver failure, the survival rate of PLD is significantly higher than that of the former two, respectively<sup>[88,89]</sup>. It has been reported that the 5-year survival rate was 92.3%<sup>[90]</sup>, while a more recent research found it as 85.1%<sup>[88]</sup>. Meanwhile, most of patients have a significant improvement on health-related quality of life assessment after transplantation<sup>[91]</sup>. Even liver transplantation performs comparatively well in PLD, however, due to the lack of liver donors, relatively low urgency and low mortality rate, it is difficult to extensive perform and necessary to carefully evaluate the indications of liver transplantation.

## MEDICAL TREATMENT PROCESS

Although some institutions have attempted to make guidance in treating PLD<sup>[92]</sup>, there is currently no widely accepted international guideline for treatment of PLD. Various therapies were used to treat different types of PLD in different medical centers. Schnelldorfer *et al*<sup>[35]</sup> gave the corresponding preferred treatment based on Schnelldorfer classification. Base on this, we modified the process according to the clinical experience of our medical center in treating PLD, which is being used in our medical center, and here we summarize it as **Figure 1**.

Ultrasound should be the first choice for first visit of suspicious PLD patients. Enhanced computer tomography is used for patients diagnosed with PLD to determine Schnelldorfer classification. The treatment plan is determined based on the classification, liver function and computerized three-dimensional imaging which is used to calculate liver volume and estimate resident liver volume after resection for ensuring safety of hepatectomy. For patients with asymptomatic or mild symptoms, Schnelldorfer type A, simple observation or long-acting somatostatin analogue can be applied without any surgical interventions. Schnelldorfer B patients with large cysts but limited number should be treated with cyst aspiration and sclerosis or fenestration depending on situation of cysts, to reduce cyst volume and relieve symptoms. For Schnelldorfer type C patients with excessive cysts, normal liver function and sufficient liver parenchyma volume, only fenestration cannot achieve long-term relief of symptoms. Under the premise of ensuring the pre-retained inflow of the hepatic lobe and the safety of the outflow tract, it is more appropriate to choose hepatectomy with fenestration to remove the liver segment occupied by the cyst, which would minimize the liver volume for controlling symptoms for a longer time.



**Figure 1** Polycystic liver disease diagnosis and treatment process in our medical center based on Schnelldorfer classification. PLD: Polycystic liver disease; LV/SLV: Remaining liver volume / standard liver volume; CT: Computer tomography.

However, if Schnelldorfer is classified as type C with impaired liver function (child-pugh score B or C) or insufficient residual liver volume (remaining liver volume / standard liver volume < 30%), liver transplantation is recommended. In addition, somatostatin analogue can be considered after fenestration or hepatectomy. Hepatectomy is no longer suit for Schnelldorfer type D patients, and liver transplantation is most appropriate regardless of the condition of liver function.

## CONCLUSION

PLD is a hereditary genetic disease. Although PLD progresses with age, only a small number of patients have symptoms that require treatment. At present, the treatment of PLD is mainly drugs intervention, cyst puncture and sclerotherapy, fenestration, transcatheter arterial embolization, liver resection, liver transplantation. Clinical drug therapy for PLD is currently focused on somatostatin analogues, while many other drug targets are being developed as more and more clinical trials validating their effectiveness. Liver transplantation is now the only cure for PLD, but it cannot be carried out in large quantities due to complicated reasons. Except liver transplantation, the other four surgical and interventional treatments can be widely used for PLD patients with different conditions. But considering the high recurrence rate, serious complications and mortality, it is necessary to carefully consider the indications. Besides, various combination therapies should be investigated in future researches for better effectiveness. In addition, for reference, we provide the diagnosis and treatment process being applied in our medical center, which is based on Schnelldorfer classification and the experience of the medical center.

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