



Overview of polycystic liver disease

Chaitanya Rajendra Javnjal^{1*}, Akanksha Jagannath Gavade², Kajal Rajendra Adsul², Afroj A Shaikh³

¹ Department of Pharmacy, Yashoda Technical Campus, Faculty of Pharmacy, Satara, Maharashtra, India

² Department of Pharmacy, Yashoda Technical Campus, Yashoda Collage of Pharmacy, Satara, Maharashtra, India

³ Department of Pharmacy, HSBPVT'S, GOI, College of Pharmacy, Shrigonda, Maharashtra, India

Abstract

Polycystic liver disease is a hereditary liver disorder which may present independently or as a consequent symptom of autosomal dominant polycystic kidney disease or autosomal recessive polycystic kidney disease. The pathophysiology remains complicated and yet to be understood completely which makes it difficult to standardize diagnostic and management protocols. Gigot classification and Schnellendorfer classification are used to determine severity in PLD. Clinical presentation of PLD in most patients remains ill-defined and only a few patients present with complications and need the treatments. However various imaging studies such as magnetic resonance imaging and computed tomography makes it possible to identify and diagnose PLD at ease. The management strategies include somatostatin analogues, ursodeoxycholic acid and vasopressin 2 receptor antagonists are potentially effective while fenestration, cyst aspiration and sclerosis, hepatic resection and liver transplantation are other invasive therapeutic options. This review focuses on briefing the classification, diagnostic techniques, and various management strategies to obtain potential directions for future researches.

Keywords: polycystic liver disease, autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, isolated polycystic liver disease

Introduction

Polycystic liver disease (PLD) is a rare hereditary disease and is often defined as multiple diffuse cysts of the liver [1]. Initially, it was thought that PLD could develop only in the context of Autosomal Dominant Polycystic Kidney Disease (ADPKD). The notion that isolated PLD might be a separate condition was proposed in the 1950s. In 2003, a linkage analysis of eight Finnish families confirmed that PLD is genetically distinct from ADPKD [2]. Asymptomatic patients usually do not require any intervention [3]. In some patients, massive hepatomegaly can cause pain or compression of the adjacent gastrointestinal organs, vasculature and diaphragm. This can have a significant effect on patients' quality of life and performance status [3, 4]. For these patients, the main aim is to reduce their symptoms by decreasing liver volume [5, 6]. Current surgical options include open or laparoscopic cyst fenestration with or without hepatic resection and liver transplantation (LT). Significant advances in surgical techniques have improved the outcomes of PLD patients. However, the selection of the appropriate approach remains a clinical challenge, and there is no consensus on the optimal timing and what represents the best therapeutic modality.

Epidemiology

Polycystic liver disease affects around 100,000 people on worldwide [7]. Males and females are affect equal numbers, but most patients with symptoms and with severe disease are women [8]. The suggested cause of this difference is that, female sex hormones such as estrogen contribute to growth of liver cysts [9, 10]. Oral contraceptives and estrogen replacement therapy are also associated with more severe disease. Cysts can begin to grow at any age, but are rare in childhood and more common with age. The age at which symptoms begin to occur varies with individuals, but is usually around 50 years old.

Causes

Changes (mutations) in three genes i.e., PRKCSH, LRP5, and SEC63 are linked to polycystic liver disease [11]. These genes are not associated with AD-PKD. Individuals with mutations in SEC63 or PRKCSH tend to have more severe symptoms compared to individuals with the polycystic liver disease without mutations in one of these two genes [11]. However, less than 50% of individuals with polycystic liver disease have a mutation in one of these genes, so other genes may be involved in this condition [12]. GANAB, ALG8 and SEC61B are three genes potentially involve di-n-polycystic liver disease and are being investigated as possible causes of the disease [13].

Disease-causing (pathogenic) mutations in SEC63 and PRKCSH lead to defects in processing, folding and translocation of newly synthesized glycol-proteins. This is associated with embryological mal formations which cause the formation of fluid-filled cysts throughout the liver ^[10, 12].

Most cases of polycystic liver disease are inherited in an autosomal dominant pattern. Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary to cause a particular disease. The abnormal gene can be inherited from either parent or can be the result of a mutated (changed) gene in the affected individual. The risk of passing the abnormal gene from an affected parent to an offspring is 50% for each pregnancy. The risk is the same for males and females.

Pathophysiology

Mal formation of the hepatic ductal plate and cilia of cholangiocytes is the main characteristic linked to the pathophysiology of PLD ^[9].

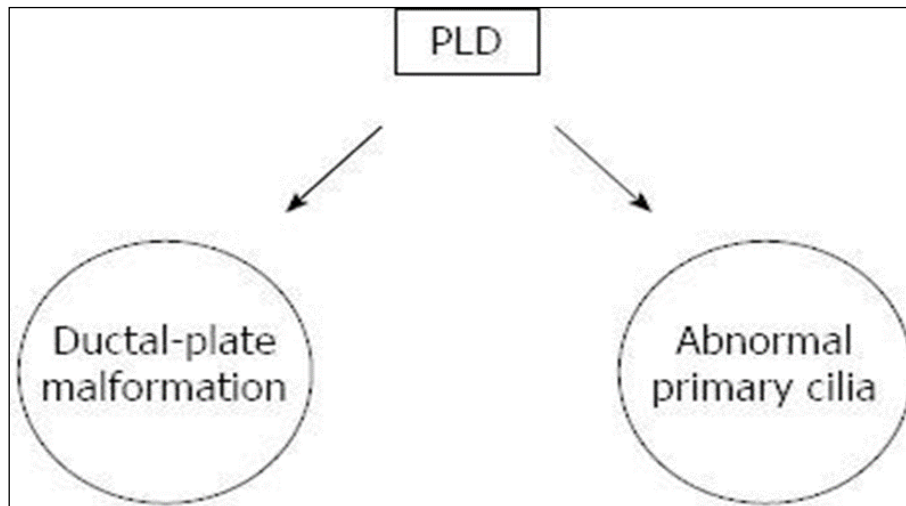


Fig1: Conversion of PLD to Ductal- Plate Malformation & Abnormal Primary Cilia

Ductal- Plate Malformation

Ductal plate malformations (DPMs), also known as fibro polycystic liver diseases, represent a unique spectrum of pathological abnormalities that are caused by an insult to the embryonic ductal plate development at various stages. This results in the formation of congenital cystic lesions of the biliary tract that involve the intra as well as extra hepatic bile ducts. The importance of detecting these DPMs at an early stage is their predisposition for pancreatitis, cholangitis, lithiasis, and malignancy. The purpose of this pictorial essay is to acquaint the readers with imaging features in DPMs ^[14].

Abnormal Primary Cilia

In the past decade, a class of disorders known as cilio-pathies has become recognized, comprising a unique spectrum of genetic syndromes. These disorders are caused by dysfunction of primary cilia i.e., small non-motile, hair-like organelles that are found to protrude from the surface of nearly all vertebrate cell types, at a frequency of one per cell, and are highly conserved throughout evolution. The cilium comprises a micro tubule-based core, the axoneme, which extends from a specialized centriole at the base of the cilium, termed the basal body, and a region between the axoneme and the basal body known as the transition zone ^[15]. The specialized structure of the primary cilia offers a unique opportunity for the partitioning of sensory and signal transduction away from the main body of the cell in a different cytoplasmic environment to enable fine-tuning of biological responses to various stimuli, such as mechanical stimuli and light. For instance, flow-induced passive bending of cilia present on kidney tubular epithelial cells mediates the mechanosensation of extracellular urine flow, while in retinal photoreceptors; a specialized primary cilium connects the inner segment, which contains the cellular nucleus, with the outer segment, which contains the photopigment. Furthermore, many receptors expressed on the primary cilium surface are necessary to bind specific hormones (for example, somatostatin), growth factors (for example, platelet derived growth factor), or morphogens (for example, sonic hedgehog [SHH] and Wnt), which have essential roles especially during embryonic development. Indeed, primary cilia sense and transduce many extracellular signals to influence a wide variety of processes, such as cell proliferation and polarity, developmental processes, and neuronal growth ^[16].

Defects in the primary cilia can lead to a wide array of clinical phenotypes and in fact, ciliopathies can affect nearly every major body system, including the brain, eyes, liver, kidneys, skeleton, and limbs. Advances in our understanding of the biology of primary cilia have provided important insights into the unifying features of these distinct disorders. In turn, elucidation of the genetic basis of many ciliopathies has informed our understanding of ciliary biology and helped identify many of the key molecular components that underlie cilium formation and function ^[16].

Signs and Symptoms

Polycystic liver disease is characterized by the growth of more than 10 cysts in the liver, ranging in size from a few millimeters to over 15 cm in diameter. Symptoms usually begin to show in people around 50 years old, as cysts grow in size and number with age [7]. Some people begin to have symptoms in early adulthood and many affected individuals do not have symptoms. The growth and accumulation of cysts can cause enlargement of the liver (hepatomegaly) and compression of adjacent anatomical structures, leading to abdominal pain, Discomfort, Shortness of breath (dyspnea), Indigestion (dyspepsia).

Gastro-esophageal reflux and limited mobility [9]. More rarely, liver cysts can also compress the bile duct and lead to yellow (jaundice). Compression of the blood vessels of the liver by cysts can lead to accumulation of fluid in the abdomen (ascites), bleeding, and high blood pressure in the blood flow from intestines to the liver (portal hypertension) [17]. In rare cases, patients can suffer from cyst bleeding (hepatic cyst hemorrhage), or a cyst can be infected by bacteria (hepatic cyst infection), causing pain and fever. Infrequently, large liver cysts may rupture, causing severe abdominal pain. Even with the presence of many cysts, the liver of individuals with polycystic liver disease functions normally [10].

Diagnosis

Most patients with polycystic liver disease (PLD) are asymptomatic with simple cysts found following routine investigations. After confirming the presence of cysts in the liver, Magnetic resonance

Imaging (MRI), computed tomography (CT) scan, and ultrasound (US) are used to take picture soft liver to see if cysts are present. The images are used for diagnosis and monitoring of cysts growth laboratory tests may be ordered to check for liver function including bilirubin, alkaline phosphatase, alanine amino-transferase, and prothrombin.

It is also possible to test for blood levels of two markers of liver and bile duct disease: gamma- glutamyl transferase (GGT) and alkaline phosphatase (ALP). These two markers might be elevated in patients with severe polycystic liver disease.

The diagnosis of PLD is usually made when the number of hepatic cysts is more than 20. However, a patient with a family history of PCLD can be diagnosed when the number of cysts more than 4. 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 and Schnelldorfer classification. 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 classification relying on the number of cysts and the presence of symptomatic hepatomegaly however it is seldom used now because of oversimplification and, more importantly, having no contribution to the selection of treatments.

ADPKD: Autosomal dominant polycystic kidney disease; ARPKD: Autosomal recessive polycystic kidney disease; PCLD: Isolated polycystic liver disease [1].

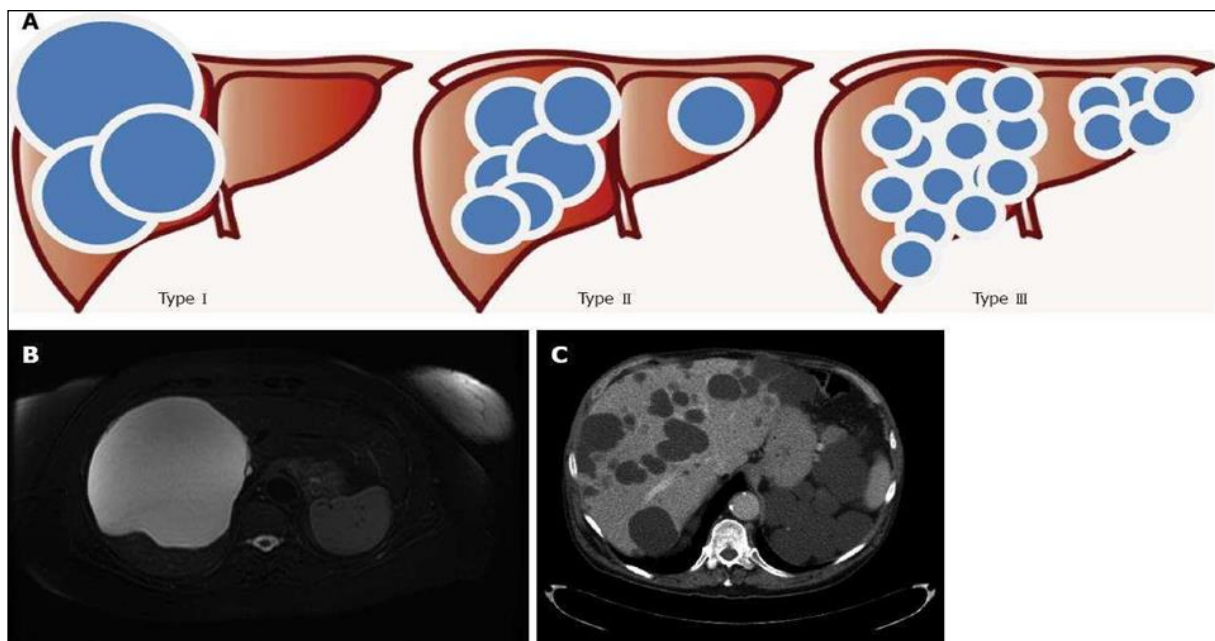


Fig 2: Gigot's classification for polycystic liver diseases

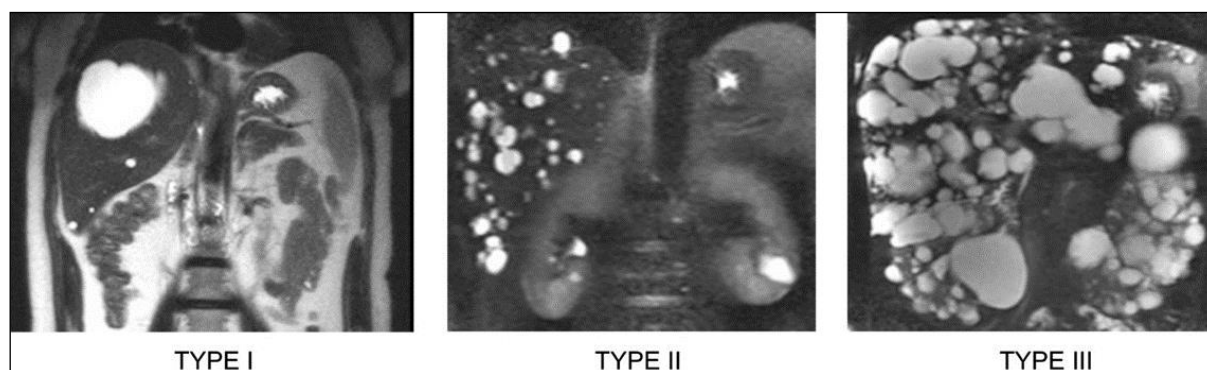
A: Graphical representation; B: Abnormal Magnetic resonance imaging of a patient affected by Gigot I cystic liver disease; C: Abnormal computerized tomography of a patient affected by Gigot II cystic liver disease.

Table 1: Gigot classification

Gigot Classification	
Type I	Patients with a limited Number (<10) of Large cysts (>10cm)
Type II	Patients with Diffuse involvement of liver parenchyma by multiple medium-sized cysts, with remaining large areas of non-cystic liver parenchyma on preoperative CT
Type III	Massive, diffuse involvement of liver parenchyma by small and medium size liver cysts. only a few areas of normal liver parenchyma between cysts

Schnelldorfer's Classification

Schnelldorfer's classification aims at differentiating patients who could benefit from resection or transplantation as summarized in Table

**Fig 3:** Schnelldorfer classification**Table 2:** Schnelldorfer classification

Symptoms	Type A	Type B	Type C	Type D
Cyst Charact	Any	Limited No. Large Cysts	Any	Any
Normal Liver	Any	>2 sector	>1 sector	>1 sector
Treatment	Observation or medical treatment	Cyst Fenestration	Hepatectomy + Cyst Fenestration	Liver transplanting

Treatment

Treatment may not be necessary in many cases of polycystic liver disease and is only indicated in severely affected or symptomatic patients. Medication to slow down cyst growth and fluid secretion in the liver (somatostatin analogs, namely octreotide, and lanreotide) is also useful in reducing liver volume [10, 18].

Ursodeoxycholic acid (UDCA), which is a 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 [19]. Because they are very expensive, these medications are typically reserved for patients with moderate to severe disease with reduced quality of life. Large cysts (>5 cm) can be treated with aspiration sclerotherapy, which includes puncture of the cyst, removal of the fluid, and treatment of the cyst wall with a chemical allowing tissues to harden, (sclerosing agent) such as ethanol [20]. When multiple large cysts are causing symptoms, keyhole surgery can be a treatment option. The surgeon punctures and then removes the 'roof' of the cysts. This procedure is called laparoscopic fenestration [6]. It is also possible to remove parts of the liver (hepatic resection) to reduce symptoms related to hepatomegaly [10]. The only definitive treatment of PLD, used in only the most severe cases, is liver transplant [8, 21].

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 [6]. In the PLD classification designed by Schnelldorfer *et al* [21], liver transplantation is suitable for patients with type D. Meanwhile, most patients have a significant improvement in health-related quality of life assessment after transplantation [22]. 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 performance and necessary to carefully evaluate the indications of liver transplantation.

Referral to a specialized center is recommended. As estrogen promotes cysts' growth, it is recommended for women diagnosed with polycystic liver disease to stop hormonal contraceptives or estrogen replacement therapy [9, 10, 23]. Genetic counseling is recommended for patients and their families

Discussion

PLD is a rare hereditary disease, with age, only in a small number of patients mostly in Female patients. They have symptoms that require treatment. The Treatment of PLD is mainly somatostatin analogs, Ursodeoxycholic acid this is the oral medication treatment for the PLD. Surgical Procedures are sclerotherapy, cyst punctures and Liver transplantation (LP) is the only cure for PLD.

Conclusion

PLD is a hereditary genetic disease. Although the manifestation and progression of the disease intensifies with age only small populations require medical intervention. At present the diagnosis and management of PLD are still on the road to perfection. The current treatment strategies for PLD revolves around drugs intervention, cyst puncture and sclerotherapy, fenestration, trans catheter arterial embolization, Liver resection, liver transplantation. Pharmacological drug therapy for PLD is focused on vasopressin 2 receptor antagonists, ursodeoxycholic acid somatostatin analogues, while many other drug targets are being developed as more and more clinical trials are validating their effectiveness. At present, Liver transplantation is probably the only cure for PLD, but it cannot be done to the entire patient due to a wide variety of complications. 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.

References

1. Zhang ZY, Wang ZM, Huang Y. Polycystic liver disease: Classification, diagnosis, treatment process, and clinical management. *World J Hepatol* [Internet],2020;12(3):72-83. Available from: <https://pubmed.ncbi.nlm.nih.gov/32231761>
2. McGarrity TJ, Koch KL, Rasbach DA. Refractory ascites associated with polycystic liver disease. *Dig Dis Sci* [Internet],1986;31(2):217-20. Available from: <https://doi.org/10.1007/BF01300712>
3. Torres VE. Treatment of polycystic liver disease: one size does not fit all. *American journal of kidney diseases: the official journal of the National Kidney Foundation. United States*,2007;49:725-8.
4. Arnold HL, Harrison SA. New advances in evaluation and management of patients with polycystic liver disease. *Am J Gastroenterol*,2005;100(11):2569-82.
5. Vauthey JN, Maddern GJ, Blumgart LH. Adult polycystic disease of the liver. *Br J Surg.*,1991;78(5):524-7.
6. Drenth JPH, Chrispijn M, Nagorney DM, Kamath PS, Torres VE. Medical and surgical treatment options for polycystic liver disease. *Hepatology*,2010;52(6):2223-30.
7. Gevers TJG, Drenth JPH. Diagnosis and management of polycystic liver disease. *Nat Rev Gastroenterol Hepatol*,2013;10(2):101-8.
8. Leão R, Salustio R, Ribeiro J. Polycystic liver disease. *BMJ Case Rep.*,2014.
9. Abu-Wasel B, Walsh C, Keough V, Molinari M. Pathophysiology, epidemiology, classification and treatment options for polycystic liver diseases. *World J Gastroenterol*,2013;19(35):5775-86.
10. Temmerman F, Missiaen L, Bammens B, Laleman W, Cassiman D, Verslype C, *et al.* Systematic review: the pathophysiology and management of polycystic liver disease. *Aliment Pharmacol Ther.*,2011;34(7):702-13.
11. Li A, Davila S, Furu L, Qian Q, Tian X, Kamath PS, *et al.* Mutations in PRKCSH cause isolated autosomal dominant polycystic liver disease. *Am J Hum Genet* [Internet]. 2003/01/15,2003;72(3):691-703. Available from: <https://pubmed.ncbi.nlm.nih.gov/12529853>
12. Everson GT. Polycystic liver disease. *Gastroenterol Hepatol (N Y)* [Internet],2008;4(3):179-81. Available from: <https://pubmed.ncbi.nlm.nih.gov/21904493>
13. Besse W, Dong K, Choi J, Punia S, Fedeles S V, Choi M, *et al.* Isolated polycystic liver disease genes define effectors of polycystin-1 function. *J Clin Invest*,2017;127(5):1772-85.
14. Sureka B, Rastogi A, Bihari C, Bharathy KGS, Sood V, Alam S. Imaging in ductal plate malformations. *Indian J Radiol Imaging* [Internet],2017;27(1):6-12. Available from: <https://pubmed.ncbi.nlm.nih.gov/28515578>
15. Valente EM, Rosti RO, Gibbs E, Gleeson JG. Primary cilia in neurodevelopmental disorders. *Nat Rev Neurol* [Internet]. 2013/12/03,2014;10(1):27-36. Available from: <https://pubmed.ncbi.nlm.nih.gov/24296655>
16. Goetz SC, Anderson KV. The primary cilium: a signalling centre during vertebrate development. *Nat Rev Genet* [Internet],2010;11(5):331-44. Available from: <https://pubmed.ncbi.nlm.nih.gov/20395968>
17. Barbier L, Ronot M, Aussilhou B, Cauchy F, Francoz C, Vilgrain V, *et al.* Polycystic liver disease: Hepatic venous outflow obstruction lesions of the noncystic parenchyma have major consequences. *Hepatology*,2018;68(2):652-62.
18. Chrispijn M, Nevens F, Gevers TJG, Vanslebrouck R, van Oijen MGH, Coudyzer W, *et al.* The long-term outcome of patients with polycystic liver disease treated with lanreotide. *Aliment Pharmacol Ther.*,2012;35(2):266-74.

19. Munoz-Garrido P, Marin JJG, Perugorria MJ, Urribarri AD, Erice O, Sáez E, *et al.* Ursodeoxycholic acid inhibits hepatic cystogenesis in experimental models of polycystic liver disease. *J Hepatol* [Internet]. 2015/06/01,2015;63(4):952-61. Available from: <https://pubmed.ncbi.nlm.nih.gov/26044126>
20. Wijnands TFM, Görtjes APM, Gevers TJG, Jenniskens SFM, Kool LJS, Potthoff A, *et al.* Efficacy and Safety of Aspiration Sclerotherapy of Simple Hepatic Cysts: A Systematic Review. *Am J Roentgenol* [Internet],2016;208(1):201-7. Available from: <https://doi.org/10.2214/AJR.16.16130>
21. Schnelldorfer T, Torres VE, Zakaria S, Rosen CB, Nagorney DM. Polycystic liver disease: a critical appraisal of hepatic resection, cyst fenestration, and liver transplantation. *Ann Surg.*,2009;250(1):112-8.
22. Kirchner GI, Rifai K, Cantz T, Nashan B, Terkamp C, Becker T, *et al.* Outcome and quality of life in patients with polycystic liver disease after liver or combined liver-kidney transplantation. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc.*,2006;12(8):1268-77.
23. Qian Q, Li A, King BF, Kamath PS, Lager DJ, Huston J 3rd, *et al.* Clinical profile of autosomal dominant polycystic liver disease. *Hepatology*,2003;37(1):164-71.