

Dear Editors and Reviewers,
World Journal of Hepatology

We appreciate your time and positive feedback on our manuscript entitled “Polycystic liver disease: classification, diagnosis, treatment process, and clinical management” with constructive and valuable comments and suggestions from the reviewers, which has helped us to greatly improve our manuscript.

We have revised our manuscript according to your valuable suggestion and is submitting our modified version here with a point to point response to the questions and suggestions. We believe that this revised version of the manuscript will satisfy the criteria for publication, and hope to hear from you soon. Thanking you and the reviewers for their remarks, and suggestions and for the opportunity given for us to publish our research work in your journal.

I will be happy to hear from you regarding any further queries in this required.

Best wishes,

Dr. Yun Huang

Reviewer 1

Well researched narrative review on polycystic liver disease. I found the review to be complete, however, it did not present almost nothing novel that has not been mentioned in the multiple review articles on the subject. The English in this paper is just not acceptable on its current format.

Some comments:

- If the review performed was not a systematic one, please state this fact.

Response: Thank you for your comment. We have stated in Introduction part of revised manuscript.

- “However, the effectiveness of these therapies except liver transplantation are still uncertain”. You detailed afterwards some proofs of the effectiveness of medical, percutaneous, and other surgical options.

Response: Thank you for your comment. As we stated afterwards, there were inconsistent researches of medical, percutaneous and surgical approaches showing both significant and insignificant results regarding to effectiveness of treating PLD. For example, mTOR: ‘However, in the clinical randomized controlled trials by Serra A L et al. and Walz G et al. 18 months 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).’

TAE: ‘Meanwhile, a study showed its failure rate is as high as 69.6%, including

uncontrolled symptoms, postoperative liver failure and death.’
Furthermore, we need large-scale RCTs to validate the effectiveness of these therapy.

- Please clarify: “while the mechanisms of cysts in PLD and polycystic kidney disease (PKD) are complicated”.

Response: Thank you for your comment. We have clarified subsequently in the manuscript.

‘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. 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.’

- The diagnosis of PLD is made with 4 or more cysts if familiar precedents exist. What you stated is incorrect.

Response: Thank you for your comment. We included the same diagnosis criteria in Diagnosis part, line 2 and 3.

- Please reorganize the different treatments by type (medical, percutaneous, surgical).

Response: Thank you for your comment. We have reorganized manuscript and put Cyst aspiration & sclerosis and Transcatheter arterial embolization in percutaneous method.

- You stated: “a study showed the benefits of lanreotide still persisted 4 months after cessation of the drug”, clarify that this study only showed improvement on volumetrics, not in symptoms relief.

Response: Thank you for your comment. We have clarified it in revised manuscript as ‘a study showed the benefit to reduce liver volume from lanreotide still persisted 4 months after cessation of the drug.’.

- You stated: “A meta-analysis showed that the recurrence rate through open surgery was lower than through laparoscopic approach (5% vs 6%), and most recurrent cysts do not require second surgery”. The reference you put is from an Italian series of laparoscopic cyst fenestrations. Disregarding this, a reduction of 1% on the recurrence based on this evidence is clinically insignificant.

Response: Thank you for your comment. We have clarified its statistical insignificance in revised manuscript as ‘A meta-analysis 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’.

- I would recommend this be rewritten with someone who has a mastery of the English (scientific) language to make it more legible.

Response: Thank you for your comment. We have had this manuscript revised by a

native speaker.

Reviewer 2

This review was well written, but there are some concerns.

1. (Page 5, Line 28~Page 6, Line 5) The authors described “global incidence of about 1% to 2%”. However, incidence described by the authors seems to be higher than that described recent literature, such as a 2018 Nature Disease Primer by Bergmann et al.. In addition, the frequency of mutations in PKD1 and PKD2 gene also seems to be inadequate. Therefore, the authors should need the correction.

Response: Thank you for your comment. We have cited the paper you mentioned and associated corrections have been made in revised manuscript.

2. (Page 6, Line 20) The authors described GANAB gene. However, mutations of GANAB gene often involve polycystic kidney, like ADPKD. The authors should consult a 2018 Nature Disease Primer by Bergmann et al.. Therefore, the authors should classify GANAB mutations to ADPKD. Table 1 also need the correction.

Response: Thank you for your comment. We have corrected the manuscript and Table 1 as your suggestion.

3. (Page 13, Line 20) Junichi may be the first name, so the authors should correct this to Hoshino.

Response: Thank you for your comment. We have corrected the manuscript as you suggested

Reviewer 3

Polycystic liver disease: classification, diagnosis, treatment process, and clinical management

Zeyu Zhang, Zhiming Wang, Yun Huang

Dr Zhang and colleagues have produced a seminal paper on polycystic liver disease. This is a narrative review centered on the classification, diagnosis, treatment process, and clinical management. This paper aims to provide a better understanding of progress in the field as well as obtain potential directions for future research. As such they have achieved their goals, and the authors have to be commended with this feat.

The core tips, abstract ad paper contains the line that “However, unfortunately, there is no significant breakthrough in the treatment of PLD so far”. I am not sure what the authors would consider as a “significant breakthrough” and what would be needed for that. I think that this would be more interesting for the readership than a general, rather sobering, message.

Response: Thank you for your comment. We have removed this sentence to avoid misunderstanding.

The authors contrast the mechanisms of cysts in PLD and polycystic kidney disease (PKD): the primary cilia of biliary epithelial cells vs congenital bile duct dysplasia through multiple mechanisms. I am not sure whether these statements are actually

contrasting with each other. The disorders described in this review are broadly termed fibrocystic diseases. Fibrocystic liver disease is a collective definition of a group of congenital and rare diseases affecting the biliary tree deriving from a perturbed development of the embryonic ductal plate. Together with fibrocystic renal disease, they are often part of the multisystemic hepatorenal fibrocystic diseases in which dysgenesis of the biliary structures is associated with the fibrocystic malformation of the kidneys.

Response: Thank you for your comment. This is an intriguing opinion and we have put it in our revised manuscript as ‘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.’.

The paper opens up the discussion on PKD3 , the third ADPKD gene and cites a paper that revisited this issue. (Kidney Dis (Basel)). I think that it would be worthwhile to mention that 8 genes have been associated with ADPKD (PKD1 and PKD2), ADPLD (PRKCSH, SEC63, LRP5, ALG8, and SEC61B), or both (GANAB). Thus GANAB (although rare) is considered to be the bonafide 3rd PKD gene. J Am Soc Nephrol. 2018 Jan;29(1):13-23

Response: Thank you for your comment. We have add it in revised manuscript and also the Table 1 as well with associated papers cited.

The authors are right in stating that there is “no widely accepted international guideline for treatment of PLD”. Kidney Health Australia – Caring for Australasians with Renal Impairment Guidelines have attempted to formulate guidance in the field, and I think that it would be useful to look that up. <http://www.cari.org.au/CKD/CKD%20adpkd/12.%20PLD.pdf>

Response: Thank you for your comment. We have read the paper you mentioned and we found it hardly involved in recommending treatments of PLD in different situation. But it did attempt to formulate guidance like you said. So we revised our manuscript and cited the paper as ‘Although some institutions have attempted to make guidance in treating PLD,⁹⁴ there is currently no widely accepted international guideline for treatment of PLD.’

It would be interesting to know how computerized three-dimensional imaging contributes to the design of the treatment plan as this is not a routine product from radiological imaging. If it would be helpful it would be necessary to convince imaging specialists, and to do so you need arguments why this would be beneficial.

Response: Thank you for your comment. We are sorry for making our words unclear. As surgeons majoring in liver, computerized three-dimensional imaging is regularly used to calculate liver volume and estimate resident liver volume after resection in our every patient. In PLD cases, we also need to apply it to make sure the sufficient resident liver volume after the resection and we consider that its significance requires no illustration. We are sorry for our miss and further explanation has been made in revised manuscript as ‘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.’.

The discussion on the two clinical classifications on PLD is helpful, but a picture / cartoon depicting the affected / non affected liver would be probably useful here.

Response: Thank you for your comment. We failed to find a more appropriate picture of PLD than the cited papers of these two classifications. Thus, we encouraged readers to find original pictures in cited papers for avoiding misunderstanding.

I do not agree that “organ malfunction” is needed to trigger treatment in PLD. In fact in the majority of patients who are in need of treatment suffer from incapacitating symptoms and a lower quality of life, not “organ malfunction”. United European Gastroenterol J. 2018 Feb;6(1):81-88

Response: Thank you for your comment. We have revised our manuscript as ‘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.’

The authors mention that “Frederik et al. increased the therapeutic dose of lanreotide non-responder from 90mg to 120mg, which led to stopping liver volume growing”. I think that what this study shows is that both lanreotide 90 as well as 120 mg are effective in terms of reducing liver volume, and that the dose can be reduced from 120 to 90 mg in case side effects occur.

Response: Thank you for your comment. In the paper by Frederik et al., the authors did mention that ‘In nonresponders (n = 32), liver volume increased by a mean volume of 120 ± 42 mL at 6 months. However, no further increase was observed after dose escalation in the 24 patients who continued to the 18-month end point’ in their results. Of course, we are aware of the main conclusion of the research as exact as you stated, however we have stated similar contents in original manuscript and the detail information in that research is what we want to show.

*Clin Gastroenterol H. 2015;13(13):2353-2359.

Perhaps it would be useful to mention the effect of stopping somatostatin analogues (so called drug holiday) here. Therap Adv Gastroenterol. 2018 Oct 3;11:1756284818804784.

Response: Thank you for your comment. We have mentioned it in revised manuscript. **‘In addition, there are some controversies about duration of efficacy and effect of cessation of treatment (also called drug holiday).** Some studies have also shown that the efficacy of somatostatin analogue therapy can only last for 2 years,⁵⁰ and cessation of treatment would lead to disappearance of effect or even a rebound effect.^{44, 51, 52} However, a study showed the benefit to reduce liver volume from lanreotide still persisted 4 months after cessation of the drug.⁴⁵ **Meanwhile, second cycle of somatostatin analogues after a drug holiday would still be as effective as the first in reducing liver volume.⁹⁶’**

I think that the statement that wraps up the paragraph on the efficacy of somatostatin analogue therapy could be sharper formulated. Somastatin analogues have a rapid onset of effect (within first months of therepay), the effect persists while patients are on therapy (there is evidence that the effect is there up to 3 or even 4 years), that cessation of treatment results in a significant increase of liver volume (rebound effect with re-emergence of symptoms) and that re-introduction of the drugs replicates

the success of initial treatment (or the effect is probably similar in treatment experienced vs previously non-exposed patients).

Response: Thank you for your comment. We consider that our statements were sharp enough and we do not want to be too radical because of our own clinical experience. But we do recognize the effectiveness of somatostatin analogue in PLD. In addition, the contents associated with drug holiday and re-introduction of the drug have been added according to your previous valuable suggestion.

I think that the safety profile of mTOR inhibitors is well known (contrasting the authors statement “is not totally understand at present”). There have been a number of excellent reviews detailing on the safety profile of these drugs Expert Opin Drug Saf. 2013 Mar;12(2):177-86

Response: Thank you for your comment. We have revised the associated contents according to the paper you suggested.

‘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.’⁹⁷

In summary, though with acceptable safety profile, there is not enough evidence to prove that mTOR inhibitors can benefit PLD patients’

The authors cite the paper on “Alcohol sclerotherapy of hepatic cysts: its effect in relation to ethanol concentration Hepatol Res. 2000;17(3):179-184. to support a statement on a meta analysis on aspiration sclerotherapy. The data cited do not come from this paper published in Hepatol Res. I looked for a meta analysis in this field but could only identify a systematic review (AJR Am J Roentgenol. 2017 Jan;208(1):201-207.). I stand to be corrected.

Response: Thank you for your comment. We are sorry for mistake. Relevant corrections have been made in revised manuscript.

‘In meta-analysis review 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.’⁷²

The authors devote a paragraph on transcatheter arterial embolization. It would be great if they could cite their own personal experience as this would be useful for the readership.

Response: Thank you for your comment. To be honest, our exploration of TAE in PLD is on an early stage and we are still lacking in experience of TAE in PLD. However, we consider the contents we included in our manuscript have explicitly showed accurate and adequate information about TAE in PLD.

I am not sure whether the statement “incidence of complications after liver transplantation is 41%, and the mortality rate is 17%.” Is currently correct. I think that a mortality rate of 17% would be a contra indication to perform this procedure in this population. The cited paper mentions “ Estimates of 3- and 5-year survival probability for LT recipients with PCLD were 88.8% and 85.1% compared to 79.3% and 70.8% with HCC, and 80.5% and 74.2% with CLF, respectively (Table 3)”.I suggest that the authors cite their own data or refer back to more recent data.

Response: Thank you for your comment. We searched and found that the most recent data was the one we cited, and corrections have been made in revised manuscript. In the meantime, we found another earlier but more authoritative data from European Liver Transplant Registry, which have also been cited in revised manuscript.

‘It has been reported that the 5-year survival rate was 92.3%,⁹⁸ while a more recent research found it as 85.1%.⁸⁹’