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**Name of Journal:** *World Journal of Hepatology*

**ESPS Manuscript NO:** 26210

**Manuscript Type:** Review

The manuscript has been improved and edited according to the suggestions of reviews and editors. Format, references and typesetting were corrected.

(#here means comments of reviewers; # here means my response):

# Reviewed by 00005986:

This is a review from China on Primary Biliary Cholangitis. The paper discusses points not usually discussed in reviews on PBC, but the global accuracy is poor. In addition, a critical discussion of the literature cited is completely missing. In addition, the review is not written in an easy to understand way. Finally, the review is mainly based on reviews and not on original data. INTRODUCTION (this section focuses on pathogenesis, should be renamed)? Ref 1: this paper has been published in more journals, all publications must be cited. In addition, this paper only addresses the nomenclature change, and is not adequate for citation about disease's characteristics. ? Regarding PBC diagnosis, it would be more accurate to say that ALP elevation must lack another, in particular extrahepatic, explanation. ? Add references when stating that the number of PBC patients is increasing. ? References about GWAS in PBC only cite 1 GWAS out of 4, Ref 5 is not appropriate in this context? Add references about autophagy and apoptosis, Ref 7 is a review on senescence. It is better to cite papers generating original data than reviews. ? Ref 8 is again a review, focusing on new treatments. ? Ref 9 is a review, and Ref 10 is a paper with

original data: it is not accurate to cite them together. Again, cite papers with original data instead of reviews. ? Ref 11 is a review, the following one, ref 12, is a research paper in humans, ref 13 is a research paper in animal models, ref 14 is again a review: one cannot cite different kind of papers when discussing PBC pathogenesis. ? Again: ref 1 deals only with nomenclature change, cannot be cited when describing the disease. ? You cannot say that the clinical presentation and the natural history of PBC patients have improved due to UDCA: please clarify. ? Early diagnosis should also be cited as an important factor contributing to improved clinical outcome

### RENAME OF PRIMARY BILIARY CIRRHOSIS

This section needs a careful correction of the English grammar, which is very poor.

### EPIDEMIOLOGY?

Ref 19 is not a population-based study, is a review on PBC epidemiology, should not be cited in this context. ? Ref 18 is also not a population-based epidemiological study on PBC, is a study comparing the incidence of extrahepatic malignancies in PBC patients and in the general population. ? Some important, classical studies on PBC incidence and prevalence should also be cited (e.g.: (1, 2)? It is not accurate to state that PBC is encountered in all over the world: e.g., regarding Africa, only a small case series has been reported from Tunisia. ? When discussing geographical differences in PBC epidemiology, is not correct to cite ref#16, which is an epidemiological study in Crete. ? It is not correct that PBC is less frequent in Asia: the study by Liu found a very high prevalence (almost 50:100'000): this is probably due to the methodology used in this study, but this point must be pointed out more accurately.

### RISK FACTORS?

Again, the authors cite ref#22, which is a review, instead of citing original data. ? Please cite all GWAS on PBC? Ref# 31 is not appropriate in the context of concordance in monozygotic twins and female preponderance? In the second-last sentence of the section, the authors cite "another study": the same study has been cited previously in the same section already. ? While discussing risk factors, the authors cite reviews and papers with original

data: again, it is better to cite original data, and avoid mixing the 2 different kinds of publications in the same list. CLINICAL CHARACTERISTICS? Ref# 22 and 37 are inadequate in this context? Fat-soluble vitamin deficiency: again, reviews and original data are cited together. At the beginning of the section, it is stated that vitamin D deficiency is uncommon, but later in the same section, the authors say that "low vitamin D levels are common". Please clarify this point. ?

**#Reply to reviewer 00005986:**

Thank you very much for your kind comment and suggestion. According to your suggestion, the global accuracy of the revised entire manuscript, which is written in an as easy as possible to understand way, has been improved significantly, due to the fact that the review is not only mainly based on original data instead of citing reviews, but also some recent original literature have been added to the revised manuscript. In addition, the section of "PBC complicated with nephritis" (the related contents cited from Ref # 41 as well as Ref #55-#64) not only have been added to the chapter of CLINICAL CHARACTERISTICS, but also both the section of "Serum markers of infections in PBC" (the related content cited from Ref #117) and the section of "Serum biomarkers in PBC" (the related contents cited from Ref #118- Ref #120) have been added to the chapter of SEROLOGICAL FEATURES in the revised manuscript, respectively . Moreover, the section of "PREDICTIVE SCORES IN PBC" (the related contents cited from Ref #128-129) has been added to the revised manuscript. In addition, my some responses to specific comments are as follows:

- 1) The content of pathogenesis of PBC in the section of INTRODUCTION {Genome-wide association studies have revealed several human leukocyte antigen (HLA) and non-HLA risk loci in PBC, HLA and non-HLA genes has been proved to have strongest association with PBC susceptibility [5,6], senescence, autophagy, apoptosis in biliary epithelial cells (BECs) [7] and complex environmental-host immunogenetic interactions are believed to

underlie the etiopathogenesis of the disease[8]. Immunologic tolerance, imbalance between Th17 cells and regulatory T lymphocytes (Tregs) may also play an important role in the pathogenesis of PBC [8-10]. In addition, microRNAs [11], FCyR3A and PRF1 expression in peripheral blood mononuclear cells [12], TGF- $\beta$ 1 signaling [13], anti-interleukin-12/interleukin-23, nuclear factor-kb, tumor necrosis factor, phosphatidylinositol signaling and hedgehog signaling pathways [14] may participate in the pathogenesis and progression of PBC. } as well as the corresponding references (Ref 5-14) in the manuscript have been deleted, respectively.

2) According to your suggestion, this paper (Ref1) has been published in more journals, so, all publications journals such as Gastroenterology [1], Am J Gastroenterol [2], Gut [3], Hepatology [4], J Hepatol [5], Dig Liver Dis [6], Clin Res Hepatol Gastroenterol [7], Clin Gastroenterol Hepatol [8] have been cited, respectively in the revised manuscript.

3) The section headings of RENAME OF PRIMARY BILIARY CIRRHOSIS in the manuscript has been changed into CHANGING NOMENCLATURE FOR PBC FROM "PRIMARY BILIARY CIRRHOSIS" TO "PRIMARY BILIARY CHOLANGITIS" in the revised manuscript.

4) Both some information cited from Ref 18、Ref 19 and Ref 18、Ref 19 in the manuscript have been deleted respectively, at the same time, several relevant original epidemiological data have been added to the section of EPIDEMIOLOGY (the related contents cited from Ref #13, Ref #15-22) in the revised manuscript.

5) Some information cited from Ref# 22 as well as Ref# 22 in the manuscript have been deleted respectively, due to inadequate in this context.

6) Some information cited from Ref# 22, Ref# 31 in the section of RISK FACTORS ,as well as Ref # 22 and Ref # 31 in the manuscript have been deleted, respectively.

7) “Low vitamin D levels are common” in the section of CLINICAL CHARACTERISTICS in the manuscript has been deleted due to mistake.

# Reviewed by 00006258:

The review is a useful and comprehensive account of the current knowledge of PBC. The terms 'cholangitis' and 'choleangitis' are both used within the title and early sections. The authors should standardise terminology/spelling and probably go for 'cholangitis' throughout. The section on serological features/autoantibodies describes the multiple antibody specificities detected but the abstract gives the impression only AMA are detected. This should be changed to reflect the variations in specificity/target. The entire manuscript should be carefully proofread and language edited as there are multiple grammatical errors. Some of the section headings in particular are not sufficiently descriptive or informative. Figure legends also need careful reading and correcting. Figures 1 and 2 would be better combined as panels A and B of a single figure and care should be taken to ensure that figures are cited at the appropriate point in the text (e.g. Fig 3 should be cited in the section on histopathological figures). The tables are poorly considered - it would make sense to combine them as a single table of comorbidities/disease associations with a descriptive legend. It would also be useful for readers if an additional column supplied information on relative frequency of each comorbidity. Whilst the review is certainly comprehensive it doesn't add any new information and similar reviews exist elsewhere. It would be nice if the conclusion section ended with informed opinion about the likely direction of future treatment strategies and future challenges for patients in an environment where there are greater demands on available transplantable organs. Similarly informed opinion on disease recurrence post-transplant and discussion of this problem might be warranted.

#Reply to reviewer 00006258:

Thank you very much for your kind comment and suggestion. According to your suggestion, my some responses to specific comments are as follows:

- 1) The abstract in the revised manuscript has increased the information on the serological features including biochemical markers , immunoglobulins, infections markers, biomarkers, predictive fibrosis marker, specific antibody such as AMAs (anti-M2, anti-M4, anti-M8, and anti-M9), antinuclear antibodies (ANAs) such as anti-multiple nuclear dot antibodies (anti-sp100, PML, NDP52, anti-sp140), antinuclear envelope antibodies, anti-rim-like/membranous antibodies (anti-gp210, anti-p62), and anti- centromere antibodies (ACAs), as well as some novel antibodies.
- 2) Some of the section headings in the manuscript, for example, the section heading of IMAGING CHARACTERISTICS has been changed to RADIOLOGIC APPROACHES TO ASSESS FIBROSIS IN PBC in the revised manuscript.
- 3) Figures 1 and 2 not only have been better combined as panels A and B of a single figure, but also entire tables (Table 1-Table 6) have been deleted due to poor.
- 4) Figures 5 (cholangiographic classification of IgG4-SC and differential diagnosis) has been added to the chapter of IgG4-related sclerosing cholangitis (IgG4-SC) in the revised manuscript.
- 5) Furthermore, the conclusion section, which ended with informed opinion about the likely direction of future treatment strategies and future challenges for patients in an environment where there are greater demands on available transplantable organs, has been modified on the basis of your suggestion.

# Reviewed by 03473665:

It is a complete review of PBC but the entire manuscript should be improved for language and proofread for grammar. Pay attention: 1) In the chapter “Fat soluble vitamin deficiency” says that deficiency of vit D is not

common (“Malabsorption, steatorrhea, and fat-soluble vitamin D deficiency are uncommon”) and after they say the opposite in the same chapter (“Low vitamin D levels are common among patients with PBC and correlate with advanced disease [38-40, 42, 43]”) 2) I think it should be useful having a section dedicated to other diagnosis of ALP elevation. 3) You must complete the chapter of AIH-PBC OVERLAP SYNDROME citing PARIS criteria for diagnosis!!!

**#Reply to reviewer 03473665:**

Thank you very much for your kind comment and suggestion. According to your suggestion, my some responses to specific comments are as follows:

- 1) In the chapter “Fat soluble vitamin deficiency”, “Low vitamin D levels are common among patients with PBC and correlate with advanced disease” has been deleted due to mistake.
- 2) Although it should be useful having a section dedicated to other diagnosis of ALP elevation, other causes of serum ALP elevation including bone disease such as rickets, fracture healing, osteosarcoma and bone metastases, extrahepatic bile duct obstruction such as biliary calculi, biliary ascariasis, biliary tract inflammation, postoperative bile duct benign stricture, cholangiocarcinoma, pancreatic head carcinoma, pancreatic pseudocyst, and intrahepatic bile duct obstruction such as viral hepatitis, drug-induced liver damage, alcoholic liver disease, intrahepatic cholestasis of pregnancy, primary sclerosing cholangitis (PSC), IgG4-related sclerosing cholangitis (IgG4-SC), as well as overlap syndrome (AIH/PBC, AIH/PSC, PBC/PSC, PBC/IgG4-SC) have not been discussed one by one in the manuscript in addition to the part mentioned, due to the limitation of the space.
- 3) According to your suggestion, not only the Paris diagnostic criteria, but also the revised diagnostic criteria and the simplified diagnostic criteria, as well as the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue of AIH/PBC overlap have

**been added to the chapter of AIH/PBC overlap syndromes, respectively.**

Thank you very much for publishing my manuscript in the World Journal of Hepatology.

Sincerely yours,

Ying-Qiu Huang, Professor of Medicine, Chief physician.

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