Dear editor and reviewers,

Thank you very much for your comments and professional advice. These opinions help to improve academic rigor of our article. Based on your suggestion and request, we have made corrected modifications on the revised manuscript. Meanwhile, the manuscript had be reviewed and edited by language services company. We hope that our work can be improved again. Furthermore, we would like to show some important details as follows, other details of the specific changes are in the manuscript.

Point-by-point response to the reviewers' comments.

Comments for the Authors:

Reviewer #1:

Comments: Authors investigated prevalence and clinical features of osteoporosis in Chinese patient with primary biliary cholangitis (PBC). They showed that osteoporosis in PBC is very common and it is associated with older age, lower BMI, previous steroid therapy and the severity of liver disease. The work was logically designed and nicely described.

Response: Thank you very much for your comments.

Reviewer #2:

Comment 1: This paper presents deals with the prevalence of osteoporosis in Chinese patients with Primary Biliary Cholangitis (PBC). The paper is well written with interesting results regarding the prevalence of osteoporosis among patients with PBC.

Response 1: We are very grateful for your comments.

Comment 2: The size of the sample is relatively small. It would be interesting to explore the same objective for larger sample size with a with a fairly balanced number of women and men.

Response 2: We appreciate your comments. Due to limited retrospective collection

and low prevalence of PBC in the population, the sample size of this study is relatively small. We are also aware that the sample size is not sufficient, so we have included it as a limitation of this study in the discussion section of the manuscript. However, this may not affect the reliability of our conclusions. Due to the fact that PBC mainly occurs in women, the number of men cases in this study is relatively small. Thus, we strongly agree with your point that exploring the same objective for larger sample size with a fairly balanced number of women and men would be interesting and necessary. We also incorporate your views in the seventh paragraph of the discussion section of the revised manuscript. Thank you again for your comments. We hope you will be satisfied with our response.

Comment 3: The reviewer wonders if the populations were matched for age.

Response 3: We appreciate your comments. This study population did not undergo age matching. As this study is a retrospective study, it is difficult to age match the study population. We hope you will be satisfied with our response.

Reviewer #3:

Comment 1: General impression In this study, the authors assessed the prevalence and clinical characteristics of osteoporosis in Chinese patients with primary biliary cholangitis (PBC). And they concluded that osteoporosis is very common in Chinese patients with PBC, allowing for prior screening of BMD in those PBC patients with older age, lower BMI, previous steroid therapy and advanced liver disease on the basis of current results. I evaluate this clinical report includes so valuable information for the physicians to manage liver diseases. For these reasons, I think this manuscript is appropriate for publication.

Response 1: We are very grateful for your comments.

Comment 2: However, I have one minor request to be revised as stated below. After they have been resolved, I will judge this manuscript can be accepted and published by World Journal of Gastroenterology. *I ask the authors that correction parts will be

shown in red color in the revised manuscript.

Response 2: Thanks for your suggestions. We have marked the revised content in the manuscript in red color.

Comment 3: Onset mechanism of osteoporosis in PBC I recommend the literature level hypothesis of onset mechanism of osteoporosis in PBC should be introduced in the introduction section or discussion section.

Response 3: Thanks for your kind suggestions. We have revised the related discussion part (Paragraph 6) of the manuscript. We have included some literature on the pathogenesis of PBC osteoporosis and provided a brief explanation, the revision is as follows: Up to now, the pathogenesis of PBC osteoporosis is still unclear. Most experts believed that it seems to be mainly caused by reduced bone formation, although increased bone resorption may play a role in certain situations, such as in post-menopausal women and patients with hypogonadism[10]. Osteoblast mediated bone formation and osteoclast dependent bone resorption are two opposite processes that affect bone mass: when absorption exceeds formation, bone mass will inevitably decrease, and this negative balance will lead to bone loss and osteoporosis[31]. Several studies assessing bone histomorphometry have shown that most of the osteoporosis patients with PBC had reduced tetracycline double labeling, bone formation rate, osteoblasts numbers, and reduced serum osteocalcin level, all of which indicate that osteoblast dysfunction and bone formation deficiency are the core of the pathogenesis of PBC-related osteoporosis[32-34]. In addition, other changes, increased levels of bilirubin and bile salts, and production of fibronectin may also reduce bone formation by inhibiting the proliferation and survival of osteoblasts in PBC or cholestasis[26,35]. Other conditions of PBC patients, including increased formation of osteoclast, low vitamin D levels, calcium malabsorption and sarcopenia, may be contributing factors to the panorama of PBC osteopathy[31,33,36,37].

The added references are as follows:

31 **Pugliese N**, Arcari I, Aghemo A, Lania AG, Lleo A, Mazziotti G. Osteosarcopenia in autoimmune cholestatic liver diseases: Causes, management, and challenges. *World J Gastroenterol* 2022;**28**:1430-1443 [PMID:35582674 DOI:10.3748/wjg.v28.i14.1430]

32 **Hodgson SF**, Dickson ER, Wahner HW, Johnson KA, Mann KG, Riggs BL. Bone loss and reduced osteoblast function in primary biliary cirrhosis. *Ann Intern Med* 1985;**103**:855-860 [PMID:4062087 DOI:10.7326/0003-4819-103-6-855]

33 **Guañabens N**, Parés A, Mariñoso L, Brancós MA, Piera C, Serrano S, Rivera F, Rodés J. Factors influencing the development of metabolic bone disease in primary biliary cirrhosis. *Am J Gastroenterol* 1990;**85**:1356-1362 [PMID:2220729]

34 **Guichelaar MM,** Malinchoc M, Sibonga J, Clarke BL, Hay JE. Bone metabolism in advanced cholestatic liver disease: analysis by bone histomorphometry. *Hepatology* 2002;36:895-903 [PMID:12297836 DOI:10.1053/jhep.2002.36357]

35 **Kawelke N**, Bentmann A, Hackl N, Hager HD, Feick P, Geursen A, Singer MV, Nakchbandi IA. Isoform of fibronectin mediates bone loss in patients with primary biliary cirrhosis by suppressing bone formation. *J Bone Miner Res* 2008;**23**:1278-1286 [PMID: 18348696 DOI:10.1359/jbmr.080313]

36 **Olivier BJ**, Schoenmaker T, Mebius RE, Everts V, Mulder CJ, van Nieuwkerk KM, de Vries TJ, van der Merwe SW. Increased osteoclast formation and activity by peripheral blood mononuclear cells in chronic liver disease patients with osteopenia. *Hepatology* 2008;**47**:259-267 [PMID:18022900 DOI:10.1002/hep.21971]

37 **Saeki C**, Oikawa T, Kanai T, Nakano M, Torisu Y, Sasaki N, Abo M, Saruta M, Tsubota A. Relationship between osteoporosis, sarcopenia, vertebral fracture, and osteosarcopenia in patients with primary biliary cholangitis. *Eur J Gastroenterol Hepatol* 2021;**33**:731-737 [PMID:32558699 DOI:10.1097/meg.0000000000001791]

Comment 4: Discussion line 21 Is “Notely” a correct word? I hope the authors will confirm its rightness.

Response 4: Thanks for your kind suggestions. “Notely” is not a correct word. We

have modified it to “Notably” in the revised manuscript.