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Lian-Sheng Ma, President and Company Editor-in-Chief
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

RE: Manuscript ID 37044 to World Journal of Hepatology

Dear Dr. Ma,

I am pleased to resubmit our manuscript ID 37044 "**Vitamin D levels do not predict the stage of hepatic fibrosis in patients with non-alcoholic fatty liver disease: A PRISMA compliant systematic review and meta-analysis of pooled data.**"

We genuinely appreciate the opportunity to re-submit our findings to your journal's special issue. We have included the changes to our manuscript based on recommendations from the reviewers. We think that our manuscript has improved significantly following these corrections.

We have included the changes in the manuscript. We have rearranged the order of the references after adding a few more references to support our work. We have not made any changes to the prior 5 figures that were included. We have added an additional 2 figures in the supplementary material to support our analysis. We confirm that vitamin D levels do not predict the stage of hepatic fibrosis in patients with non-alcoholic fatty liver disease. Please see our response to reviewer comments attached to this letter.

We hope that you and your editorial team permit us to share our findings with your fine journal.

On behalf of the authors.

Sincerely,

A handwritten signature in black ink that reads "Gerard E. Mullin, MD". The signature is written in a cursive, flowing style.

Gerard E. Mullin, MD

Reviewer comments:

Reviewer #1: Saberi et al. performed meta-analysis to show no relationship between serum 25-hydroxyvitamin D concentrations and NAFLD fibrosis. There are several points to be solved. 1. Abstract: The statement regarding methodology is involved in Results section. 2. Core tip is different from your conclusion in Abstracts and text. 3. The authors should state the validity of 25-hydroxyvitamin D measurement for assessment of vitamin D insufficiency. Is this type of vitamin D the most suitable indicator for vitamin D metabolism? 4. The authors should discuss the influence of diet, circadian rhythm, and season for serum 25-hydroxyvitamin D concentrations. Based on these shortcomings, it is difficult to evaluate the association between serum vitamin D and NAFLD.

Reviewer #2: The paper, meta-analysis study, presents the relationship between 25(OH)D levels and fibrosis stage in NAFLD. In the Introduction section the Authors present the epidemiology of NAFLD and the role and metabolism of 25(OH)D in human body and potential links of vitamin D serum level and fibrosis of NAFLD. This part is well prepared and contains the most important information. Further, the results of selected studies are analyzed. They are controversial. However, on their base the Authors tried to conclude that the relationship between 25(OH)D serum level and fibrosis in the course of NAFLD is not found. This paper considers the essential issue of vitamin D deficiency in patient with liver diseases not only with NAFLD. This association is ambiguous and difficult to clarify. Nevertheless, the paper is the successful attempt to answer the question about the role of vitamin D in pathogenesis of liver fibrosis in NAFLD.

Reviewer #3: The authors investigated the relationship between 25-hydroxyvitamin (OH)D levels and fibrosis stage in patients with non-alcoholic fatty liver disease (NAFLD). The manuscript is very well written, easily to be followed, the literature search is comprehensive, inclusion and exclusion criteria - well defined. Statistical analysis of the included studies is very well performed. Results are clearly presented, with attention to details. Figures and Tables are illustrative and show the most important data. The "Discussion" paragraph is beautifully written, including studies where vitamin D was given as a supplement. Limitations of this meta-analysis are also mentioned by the authors. References are up to date and relevant studies have been included and discussed. I have one major comment: There are 2 (two titles) mentioned in the manuscript and they are controversial – one says "NO", the other says "YES": 1. "Vitamin D levels do not predict hepatic fibrosis in NAFLD. A systematic review and meta-analysis." 2. "Vitamin D Levels in Patients with Non-Alcoholic Fatty Liver Disease Predicts the Stage of Hepatic Fibrosis: A PRISMA Compliant Systematic Review and Meta-analysis of Pooled Data" (should be "predict", but this is not the issue) Also, 1. In the core tip is written "Our systematic review of the literature and meta-regression confirms that the serum 25-hydroxyvitamin D levels in patients with NAFLD are associated with the severity of hepatic fibrosis" 2. However, the conclusion of the abstract and of the study supports the idea that "Low vitamin D status is not associated with higher stages of

liver fibrosis in patients with NAFLD” meaning that “progression of fibrosis in subjects with NAFLD is not linked to low vitamin D status”. This major controversy should be corrected.

Reviewer #4: This was an interesting systematic review with meta-regression aiming at evaluating the relationship between 25-hydroxyvitamin (OH)D levels and fibrosis stage in patients with non-alcoholic fatty liver disease (NAFLD). A large number of patients have been analyzed (937 subjects from six cross-sectional studies). By using adequate methodology, the authors have concluded that low vitamin D status is not associated with higher stages of liver fibrosis in patients with NAFLD. This is a relevant topic, given the high prevalence of NAFLD worldwide and the long lasting controversy on the association between advanced liver fibrosis and vitamin D in patients with different chronic liver diseases. The manuscript is well written and has scientific value. Authors are kindly asked to correct the text in the “Core Tip” section: “...Our systematic review of the literature and meta-regression confirms that the serum 25-hydroxyvitamin D levels in patients with NAFLD are NOT associated with the severity of hepatic fibrosis.”

Response:

Response to reviewer #1: We thank reviewer # 1 for excellent and useful comments of our manuscript.

1. Thank you for bringing this to our attention. We have now restructured the methods and results section of the abstract based on your comments.
2. Thank you for bringing this up this point. We have now modified the core tip to reflect our title and our findings. Our systematic review of the literature, meta-analysis, and meta-regression confirm that the serum 25-hydroxyvitamin D levels are not associated with the severity of hepatic fibrosis in patients with NAFLD.
3. We agree with your comments. We have now included a statement in the result section in "definition of vitamin D levels". Clarifying this point: "Precisely defining vitamin D deficiency or insufficiency by 25(OH)D values is still a matter of much debate. The most stable and plentiful metabolite of vitamin D in human serum, 25(OH)D has a half-life of about three weeks, making it the most suitable indicator of vitamin D status." In this section, we have also discussed the definitions of vitamin D deficiency and insufficiency. We have also included the method by which vitamin is measured D in different studies, included in table 3. We have added appropriate references for these statements.
4. We completely agree that other factors are critical when evaluating serum 25-hydroxyvitamin D concentrations such as the influence of diet, circadian rhythm and season. One of the challenges in

performing meta-analysis is heterogeneity of the included studies. Most of the included studies did not have data regarding this information. We have now added these shortcomings in the discussion of our manuscript in the limitation section.

Response to reviewer #2: We wanted to thank reviewer # 2 for the positive evaluation of our systematic review and meta-analysis. As you mentioned the studies are heterogeneous with conflicting results that made it challenging for us to analyze but we performed the meta-analysis to answer the question about the link between low vitamin D levels and severity of liver fibrosis. This manuscript focused on NAFLD and did not address the other etiologies of liver disease. The association of low vitamin D status with different etiologies of liver disease should be evaluated in additional but separate meta-analyses. For instance, we recently showed the association of lower vitamin D levels in patients with higher stages of fibrosis in the context of hepatitis C, in a different analysis that was published in the World Journal of Hepatology earlier this year.

Response to reviewer #3: We wanted to take this opportunity and thank reviewer # 3 for the positive assessment of our manuscript. We agree with your criticism regarding the title and core tip of the study, and we appreciate for bringing this to our attention. We have now changed the core tip to reflect our title and our findings. Our systematic review of the literature and meta-regression confirms that the serum 25-hydroxyvitamin D levels in patients with NAFLD are not associated with the severity of hepatic fibrosis. We also have changed the title based on your recommendations. However, we could not locate the two conflicting manuscript titles in our submission. I believe in the call for papers we submitted a different proposed title (leading to the confusion) but following a rigorous analysis, we discovered that there was no statistical association between serum 25-hydroxyvitamin and the severity of liver fibrosis in NAFLD. We apologize for the confusion. To further test whether there was or was not an association of 25-hydroxyvitamin D with hepatic fibrosis in NAFLD among the six included studies we conducted a meta-regression across each stage of fibrosis (rather than by high vs. low fibrosis) which reaffirmed the lack of an association (Supplemental Figures 1 and 2). We have also changed the title to the correct form in the letter associated with the resubmission.

Response to reviewer #4: We wanted to thank reviewer # 4 for the positive review of our manuscript. We agree with your criticism regarding the core tip of our manuscript. We have now changed the core tip to reflect our title and our findings. Our systematic review of the literature and meta-regression confirms that the serum 25-hydroxyvitamin D levels in patients with NAFLD are not associated with the severity of hepatic fibrosis.