

Authors' Response to the Review Comments

We appreciate the time and efforts by the editor and reviewers in reviewing this manuscript. We have addressed all issues indicated in the review letter, and believe that the revised version can meet the *World Journal of Gastroenterology* journal requirements.

Reviewer One

The authors performed a systematic review of 380 articles and selected 19 articles to examine the association PNPLA 3 polymorphism and severity of chronic hepatitis C disease. The manuscript is well designed and clearly written, however, I have few comments: The introduction section is too short for a meta-analysis paper with a systematic review of a large number of articles. **(Introduction has been lengthened See paragraph 2)**

1- I would like the authors to add more information about PNPLA3 polymorphism across different ethnic groups (what is the frequency of GG genotype in different races?). The articles included in this meta-analysis studied only 4 ethnic groups (Asians, Caucasians, North Africans and mixed).
See introduction paragraph 2

2- In table 1, the ethnicity was not shown in some studies.
Added the missing information to the table with footnotes to explain all abbreviations

3- What are the components of the mixed group?
Added to the table footnotes

4- Is there any data on Sub-Saharan Africans, African Americans or Hispanics?
Addressed in Paragraph 2 in introduction

Reviewer Two

1. Please modify the sentence in the AIM of Abstract, "...with the whole liver disease spectrum." (target: CHC patients?)

Done

2. The first appeared medical term need its full name, such as "hepatocellular carcinoma (HCC)"

Done

3. No uppercase letters for keywords (please follow WJG's guideline)

Done

4. Please define "steatohepatitis" and "advanced fibrosis", and clarify if steatohepatitis had been studied in any selected articles.

In our Manuscript there are 3 possible articles that had "hepatitis" as a subgroup that can be grouped together but definition varied significantly that we thought it's inappropriate to pool the data from those into one analysis.

- **Ezzikouri et al.:** No biopsies done, so we can't tell if is steatohepatitis vs chronic HCV hepatitis.
- **Yasui et al.:** Biopsy was done to all patients and showed necroinflammatory changes (not steatohepatitis).
- **Petta et al.:** All patients have HCV infection and ALL of them have steatohepatitis.

We commented on this briefly in the discussion section, paragraph 3.

5. Please clarify the reason for citing reference 15 in Quality Assessment, i.e. the association between "antibiotics and development of inflammatory bowel disease (reference 15)"

and “discrepancies between three coauthors (the sentence in this manuscript)”

The reference the reviewer referred to is number 17 –two more references were added in introduction- now. It was supposed to cite the previous statement “Previous studies have reported that a score of seven or greater denotes a high-quality study.” rather than “Any discrepancies between the three coauthors were addressed by a joint reevaluation of the original article”. This is corrected now.

6. In the last paragraph of DISCUSSION, please clarify the sentence “..., beginning with fatty liver disease, cirrhosis, and HCC in patients with CHC.” (beginning with...and end up with HCV-related death event?)

Done

7. Should “steatohepatitis” take into account in the disease spectrum of PNPLA3 polymorphism like “advanced fibrosis” being mentioned in the Core tip behind the Abstract?

Addressed in discussion paragraph 3

Reviewer Three

PNPLA3 Polymorphism is changeable according to ethnicity.

There has been no evaluation in this respect.

We have addressed this in the second paragraph of Introduction and in Table 1. If editors ask for subgroup analysis based on ethnicity then we will run it