

Thank you very much for your letter and valuable advice regarding our manuscript (Manuscript NO.: 60707, Observational Study), entitled “Elevated soluble 4-1BB is associated with serum markers of hepatitis B virus in patients with chronic hepatitis B”. Authors would like to express our most sincere gratitude to the reviewers for your effort and patience in reviewing our manuscript. We deeply appreciate your-constructive comments that greatly help improve the quality and the presentation of this manuscript. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer’s comments are as following:

**Reviewer #1:**

**The overall quality of manuscript is very good and the data provided are clearly significant for clinic and understanding of CHB pathogenesis.**

**1、 One question what I have - the genotype of the HBV. Is this the same for all patients? (HBV C type or other?).**

It’s our negligence and we are sorry that we were not aware of the issue because there was no study indicating that 4-1BB was related to the HBV genotypes up to now. Besides it’s unnecessary to know the HBV genotype of the patients to start antiviral treatment, we didn’t get the information about HBV genotypes in our patients with CHB. Genotypes B and C are prevalent in Asia<sup>[1]</sup>. The most of persons infected with HBV were genotype C in China, the genotype B was the secondary. So we guess the most of our patients were

genotype C and B. However, we think that it will be an interesting research to study the relationship between 4-1BB and HBV genotypes and it. Maybe we will investigate it in the future.

**2、 I have also some minor remarks regarding the manuscript text.**

We are so sorry for our negligence. We have made correction according to the Reviewer s comments as following:

**① In Materials and Methods would be good to mention also manufacturer of Ficoll, used for PBMC separation**

Line 112, the manufacturer of Ficoll has been added.

**② and which antibodies were used in flow cytometry for CD4+ and CD8+ cell analysis.**

Line 131 and 132, the CD4+ and CD8+ antibodies used in flow cytometry were added.

**③ Also have to be checked the superscript numbers for cell counts (10 to 7 instead of 107).**

Line 128, the statement of “1 × 107/ml” were corrected as “1 × 10<sup>7</sup>/ml”.

**④ In the end of discussion is absent the reference (33?) for this " There was a study indicating that the expression of the costimulatory molecular?**

**OX40/OX40L, also belonging to the TNF(R)SF, was age-dependent during HBV infection, which can explain why in adult-acquired infection, HBV antigens are usually cleared, whereas in infancy-acquired infection, they persist. Is the word "molecular" have to be used here instead of molecules? Please check this place.**

Line 305, “the reference 33” was added;

Line 302, the word of “molecular” were corrected as “molecules”.

**⑤ Figure 1. Check the designation of graphs. (ABCDEF), the was AC instead of EF**

In the PowerPoint file, we have designed the alphabetical order of ABCDEF in Figure 1.

We think these suggestions improve the quality of this manuscript a lot. Thank you so much!

***Science editor:***

We are so sorry for our negligence. We have made correction according to the editor’s comments as following.

**Issues raised:**

**(1) I found the title was more than 18 words. The title should be no more than 18 words;**

We have modified the title of the article to meet the word requirements but

try not to change the original meaning of the title.

- (2) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);**

We have rewritten the part of the grant which was highlighted and provided the approved grant application form in the file.

- (3) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;**

We have rearranged the figures in the manuscript and in the PowerPoint as a file in which all graphs or arrows or text portions can be reprocessed. We hope to meet with approval.

- (4) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;**

We are sorry for that and we have added the PMID and DOI and list all authors of the references to each reference according to the guideline for the

part of references.

**(5) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text;**

We have written the “article highlight” section at the end of the main text.

**(6) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.**

We are sorry for that and we have modified the part of reference according to the guideline for the part of references: number the references in Arabic numerals and the reference numbers was superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.

Besides, the *Science editor* raised:

**The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. The authors need to download the STROBE checklist and fill out the STROBE checklist with page numbers.**

We have provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement as files and provided the STROBE checklist with page

numbers as file. We hope it can meet with the requirements of the journal.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.

I look forward to hearing from you soon.

Yours sincerely,

Junqi Niu

Reference:

1. Liaw YF, Chu CM. Hepatitis B virus infection. *Lancet* 2009;373:582-592.