Format for ANSWERING REVIEWERS

October 29th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14176-revision.doc).

Title: HBV preS1 deletion is related to viral replication increase and disease progression

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14176

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. Revision has been made according to the suggestions of the reviewer

[Editor's suggestions]

(1) Please determine the Columns of this manuscript according to the attached file "ESPS-Columns scope note".
Answer: We determined the Columns of our manuscript "Evidence-Based Medicine".

(2) It's too short. Please add it to 80 words.
Answer: We extended it in the revised version as pointed.

(3) RESULTS (no less than 120 words): You should present P value where necessary and must provide relevant data to illustrate how it is obtained, e.g. 6.92 ±3.86 vs 3.61 ±1.67, P < 0.001.
Answer: We added the statistical data and P value in the revised version.

(4) CONCLUSION (no more than 26 words, in a definite, conclusive, and short statement, not indefinite, vague, or suggestive sentences)
Answer: We shortened the sentence in Conclusion in the revised version.

[Reviewer's suggestions]

(1) In table 5 and 6 ALT is not distributed normally, so how was it analyzed and compared by t test?
Answer: The difference in ALT mean values between cohort I and II may be due to disparity of sample collection and the patient disease status. Cohort I was randomly collected and consisted of chronic patients with 4 disease status, carrier, chronic hepatitis, liver cirrhosis and HCC. However, cohort II was recruited from consecutive chronic carriers without HCC and liver cirrhosis. For continuous variables, the Mann-Whitney U test was used when the data was not normally distributed. SPSS version 21.0 software was used for the performance of all statistical analyses and p value of < 0.05 (two-tailed) was considered statistically significant.

(2) The title is less expressive of the novelty of the research. Pre S1 deletion indicates duration of replication and progressive disease rather than number of replication.
Answer: We changed the Title as follows. "HBV preS1 deletion is related to viral replication increase and disease

progression" according to reviewer's comment.

(3) The conclusions are suggested to be weakened because the study population was limited to the Korean patients.
Answer: I agree with it. So, issue of whether the epidemiologic traits and clinical implication shown in this study about preS1 deletion is specific to Korean patients or not, should be checked by analyzing chronic patients of other areas in the future study.

(4) In addition, more information for the results is suggested to be added into the ABSTRACT for better understanding.
Answer: We added the statistical data and P value in the abstract of revised version.

(5) In table 1, for the Median of HBV-DNA (range), the unit should be consistent.
Answer: The serum DNA levels between cohort I and II were differently determined with each other. So, we added the flowing sentences in the revised version, "The serum HBV DNA level between cohort I and cohort II were differently determined. In cohort I, the serum HBV DNA levels were determined using the Digene Hybrid Capture II assay (Digene Diagnostic Inc., Gaithersburg, MD, USA), which has a lower limit of detection of 0.5 pg/mL. In cohort II, the serum HBV DNA levels were assessed using the COBAS Amplicor PCR assay, which has a lower limit of detection of 300 copies/mL (Roche Molecular Systems, Branchburg, NJ, USA)." (page 7, line 199 to 204)

(6) If there is no limitation of letter No. in Abstract Method, please add the reason of two different groups in this study.
Answer: We added the following sentence into revised version, "In an effort to further support the clinical implications of preS1 deletion, our developed RT-PCR method was applied to two patient cohorts." (page 7, line 187 to 188)

(7) According to their result, there was no significant difference of disease severity in WT and preS1 deletion HBV-infected patients. Therefore, their mentions (the HBV genotype C preC1 deletion might significantly contribute to disease progression ; 367-369 line No) in Discussion part should be changed.
Answer: We changed the pointed sentence into the following one, "the HBV genotype C preS1 deletion has the potential to lead to disease progression in chronic HBV subjects through the extended duration of HBeAg seropositive status and increases in HBV replications." (page 16 line 476 to 478)

(8) Typo error in 214 line No : 65+0.1C -> 65+0.1oC
Answer: We corrected it.

(9) Is genotypical C 100% in Korea?
Answer: Yes. To date, any other genotype strains have not been reported to infect Koreans.

(10) Does cohort II exclude cirrhosis and liver cancer?
Answer: Yes. It included just only carriers without liver cirrhosis and HCC.

(11) Do you seem to be related to liver cancer than the gene variation of other domains?
Answer: I am not sure. But, given that preS1 deletion is positively related to HBeAg positive serostatus, I think that preS1 deletion in chronic patient infected with genotype C has the potential to be associated with the disease progression at earlier stage, compared to other mutation.

3. References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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