Answers to suggestions from the editor,

World Journal of Gastroenterology-25850-Review

X region mutations of hepatitis B virus related to clinical severity

Dear editor and reviewers,

We appreciate your kind comments and suggestions. All the comments were helpful and received careful consideration. We revised the manuscript according to reviewer's suggestions as follows:

[Reviewer(00052899)'s comment and answer]

In the review, the authors summarized several types of HBx mutations in patients with chronic HBV infection and analyzed the possible correlations between HBx mutations and clinical severity. They found that several types of HBx mutations might be contribute to HBV pathogenesis by regulating HBV replication or host genes related to cell homeostasis. Overall, the topic is interesting and the manuscript is well-written. 1) **However, the authors described that they mainly focused on the HBx mutations significantly related to clinical severity. But, the related discoveries were mainly from patients infected with genotype C**.

Answer) Recent papers regarding HBx mutations related to clinical severance including our papers have mainly focused on chronic patients of Asian countries such as South Korea, China or Japan which is prevalent in genotype C2 infections. So, mutations identified from genotype C2 infections were referred more frequently compared to those from other genotypes. But, 3 types of "hot spots", mutations in the EnhII/BCP region [one mutation in EnhII (H94Y: C→T of nt 1,653) and two mutations in BCP (I127L,T,N,S: T→V of nt 1,753, K130M and V131I: A→T of nt 1,762 and G→A of nt 1,764)] and deletion types are distributed irrespective of genotype or geographical factor. Details of genotype distribution were clearly summarized in Table 1. But, to resolve reviewer's concerns in the text, we added the following phrase the sentences regarding hot spot mutations and deletions **"from chronic hepatitis B patients, irrespective of genotype or geographical distributions (Table 1)" (Page 7, Line 163 and Page 12, Line 283)**. In addition, to clarify genotype distribution of A1383T mutation, the following phrase was also added in the revised version. **"In one clinical study using Chinese cohort mostly infected with genotype B and C," (Page 10, Line237)**. To clarify mutation origin of 1383, 1461, 1485, 1544, 1613, 1653, 1719, and 1753, we also added the following phrase. **"from a Chinese cohort mostly infected with genotype B and C." (Page 13, Line 300)**. Furthermore, we deleted the following phrases of genotype C in abstract, and Core tip. **", mainly from chronic patients infected**

with genotype C," (Page 3, Line 58) and ", particularly in chronic patients with genotype C2 infections." (Page 4, Line 75 and Page 14, Line 323).

2) Moreover, about 240 million of individuals chronic infected by HBV worldwide and annually 650,000 people died due to advanced liver diseases including cirrhosis and hepatocellular carcinoma. The epidemiology of HBV infection in the study was outdated.

Answer) We have corrected the epidemiology of HBV in our manuscript following as reviewer's comment. And the reference representing the chronic infection and death rate by HBV infection was added. (Page 3, Line 50 and Page 5, Line 100)

[Reviewer(02521203)'s comment and answer]

In this review where the authors provided a comprehensive review of HBX mutations and disease severity. The paper is well written and informative.

Answer) We appreciate your comment and decision. Thank you very much.

[Reviewer(0018339)'s comment and answer]

This paper reviews "X region mutations of hepatitis B virus related to clinical severity". The manuscript is well presented and of interest and can contribute to increase the knowledge of this topic.

Answer) We appreciate your comment and decision. Thank you very much.