World Journal of Gastroenterology Manuscript Draft

ESPS Manuscript Number: 6735

Title: Hepatitis B Viral Load affects Prognosis of Hepatocellular carcinoma

World Journal of Gastroenterology Editorial Office

January17, 2014

Dear Editor,

Thank you for your kind advice for our manuscript entitled "**Hepatitis B Viral Load affects Prognosis of Hepatocellular carcinoma**" (**6735**). We also appreciate the constructive comments from the reviewers.These comments are most valuable for us in preparing a more concise manuscript. We have revised the manuscript according to the reviewer's suggestions. The revised portions in the manuscript have been highlighted (underlined and in blue).

Specific responses to reviewer's comments are described below:

Reviewer #01435182's Comments:

This is a well-written paper reviewing the impact of Hepatitis B viral load and antiviral therapy on post-treatment HCC recurrence, overall survival and underlying liver function. The authors give a relative short and comprehensive overview on the corresponding current knowledge on this topic. Given the evolving antiviral therapy during the recent years, the paper may benefit from some more precise information on the kind of applied antiviral therapy in the contemporary studies. Furthermore, the addition of a paragraph discussing the role of antiviral therapy on post-transplantation recurrence for HBV-related HCC would

strengthen the readability/citation of this review.

Author's Response:

We appreciate the reviewer's comment.According to reviewer's comment, we discussed the role of recent potent antiviral therapy on the prognosis of HCC in the "**Efficacy of antiviral therapy on post-treatment recurrence for HBV-related HCC"** section of revised manuscript on page 7, line 21–24, as following: "Multivariate analysis from a recent cohort study showed that recurrence free survival was significantly improved in patients receiving antiviral therapy including entecavir [odds ratio (OR)=0.625, 95% confidence interval (CI) 0.448–0.873, P=0.006]." and in the **"HBV viral load and the impact of antiviral therapy on the underlying liver"** section of revised manuscript on page 9, line 11–18, as following: "Even in patients with decompensated liver cirrhosis, antiviral therapies were proven to be effective in restoring liver function and improving survival especially if therapy is initiated early enough. Indeed, in a Phase 2, double-blind, multicenter, randomized trial conducted at 39 sites, tenofovir and entecavir were well tolerated in these decompensated CHB patients and associated with comparable improvement in Child and MELD scores at week 48; 37.5% of patients achieved a ≥ 2 point decrease in Child score and median change from baseline in MELD score was –2."

In addition, we discussed the role of high HBV viral load & antiviral therapy on post-transplantation recurrence for HBV-related HCC in the "**HBV viral load and post-treatment recurrence for HBV-related HCC**" section of revised manuscript on page 6, line 4–7, as following: "In cases of liver transplantation, high HBV viral load (> 10^5 copies/mL) before transplantation were reported to be associated with frequent HCC recurrence after transplantation" and in the "**Efficacy of antiviral therapy on post-treatment recurrence for HBV-related HCC"** section of revised manuscript on page 8, line 1–4, as following: "In cases of liver transplantation, lamivudine and hepatitis B immunoglobulin (HBIG) combination prophylaxis were independent predictors of HCC recurrence free survivals and showed a significantly lower mortality than those without prophylaxis."

Reviewer #00069297's Comments:

The manuscript does a good job of summarizing the rapidly evolving literature regarding the potential association between high HBV viral load and poor survival outcome of HCC patients due to cancer progression. It is anticipated that long-term antiviral therapy results in the long-lasting suppression of HBV replication, reduction in HCC progression, and eventually in improved overall survival. In Page 5, Page 7~8, the Authors displayed HBV replication can indirectly induce MDM2 and p53 polymorphisms, and chromosomal instability, and chronic hepatic inflammation, and HBV DNA load could lead to hepatic fibrosis and hepatocarcinogenesis by triggering immune responses. The Reviewer suggests the recent papers, Zhu et al. The rs391957 variant cis-regulating oncogene GRP78 expression contributes to the risk of hepatocellular carcinoma. Carcinogenesis vol.34 no.6 pp.1273–1280, 2013, and Zhu X, et al. An Intronic Variant in the GRP78, a Stress-Associated Gene, Improves Prediction for Liver Cirrhosis in Persistent HBV Carriers. PLoS ONE 6(7): e21997, should be cited in their pertinent location. Through the analogical reports so far are abundant, the paper gives a comprehensive overview of what has been done. It is very well-written and should be of great interest to the readers of World Journal of Gastroenterology. Thus, I do not hesitate that this would be acceptable if the Author(s) give a Minor Revision.

Author's Response: We appreciate the reviewer's comment.According to reviewer's comment, we cited recent papers in the "**HBV viral load and post-treatment recurrence for HBV-related HCC**"section of revised manuscript on page 6, line 19–25 & page 7, line 1–6, as following: "Like other viruses, HBV induce endoplasmic reticulum (ER) stress. To alleviate the ER stress, unfolded protein response (UPR) including glucose-regulated protein 78 (GRP78) is up-regulated upon high HBV viral load. GRP78 pathway is one of the most important responders to disease-associated stress and might play an important role in the stepwise progression of HBV-related hepatocarcinogenesis. Recently, Zhu X, et al. has reported that rs430397 polymorphism of GRP78 gene may be a contributing factor to cirrhosis. In addition, the 'G' allele of SNP rs391957 in the promoter of GRP78 was strongly associated with increased HCC risk by permitting cells to acquire growth advantages under hepatocarcinogenesis and cis-regulated GRP78 expression by providing an Ets-2 binding site.

Ets-2 expression has been associated with hepatic cell regeneration and also with the development of HCC."

Reviewer #00182114's Comments:

Dear Authors

HCC is the third most common cause of cancer related death worldwide and HBV is associated with 70% of all HCC cases. Accumulating data have shown that a high HBV viral load is another risk factor for de novo HCC development and a predictor of postoperative recurrence of HCC. Authors concluded that long-term antiviral therapy results in the long-lasting suppression of HBV replication, reduction in HCC progression, and eventually in improved overall survival.

You write "Antiviral therapy promoted postoperative viral clearance, increased residual liver volume, and enhanced hepatocyte regeneration in HCC patients associated with active hepatitis B"." Antiviral therapy group had a significantly greater increase in the residual liver volume per unit surface area after liver resection."

This is very interesting paper. But I ask you question.

Please explain the reason why antiviral therapy increased residual liver volume and enhanced hepatocyte regeneration.

Author's Response: We appreciate the reviewer's comment.The explanation of the reason why antiviral therapy increased residual liver volume and enhanced hepatocyte regenerationis in the "**HBV viral load and the antiviral therapy on the overall survival of HBV-related HCC**"section of revised manuscript on page 11, line 11–15, as following: "HBV evades the innate immune response to persist by simply not inducing it. However, antiviral treatment can overcome CD8+ T cell hyporesponsiveness in chronic HBV infection and may restore liver regeneration through reducing the epigenetic dysregulation of liver regeneration signals by HBx."

Reviewer #00158698's Comments:

Overall: As I have reviewed this manuscript thoroughly, I found out that this article helps a comprehensive understanding of the relation between hepatitis B viral load and the prognosis of hepatocellular carcinoma. Minor issues: 1. abstract: the 1st paragraph is duplicated with the 1st paragraph of introduction. 2. Similarity index is 33% by iThenticate. Please rephrase the sentences of the article as your English, so that the similarity index could be down to < 10%. All come to the conclusion that this paper is suitable for publication provided the authors revise the minor issues listed above.

Author's Response: We appreciate the reviewer's comment. We revise the 1st paragraph of abstract as following: "Hepatocellular carcinoma (HCC) is a complex disease that is dually challenging to treat due to underlying chronic liver disease in addition to the cancer itself. The prognosis of patients with HCC is determined by intrahepatic tumor status and reserved hepatic function. Hepatitis B virus (HBV) is an established major risk factor of HCC development, and HBV viral load is being increasingly recognized as a prognostic factor in the presence of established HCC."and rephrase the sentences of the article as our own English to decrease the similarity index less than 10%.

Editor's Comments:

1. Please provide the author contributions.

Author's Response: According to editor's comment, we provided the author contributions on page 1, line 9–10, as following: "Author contributions: Yoon Jun Kim designed research; Su Jong Yu performed literature search and wrote the paper."

2. Please list 5–10 key words.

Author's Response: According to editor's comment, we provided key words on page 3, line 1, as following: "KEYWORDS: HBV; DNA; hepatocellular carcinoma; progression; prognosis."

3. Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Author's Response: According to editor's comment, we provided core tip on page 3, line 3–8, as following: "CORE TIP / High HBV viral load reduces overall survival of patients with HCC by the rapid progression of HCC after treatment and deterioration of hepatic function associated with HCC progression. The use of long-term antiviral therapy is recommended to result in the long-lasting suppression of HBV replication, reduction in HCC progression, and eventually in improved overall survival."

4. Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

Author's Response: We added PubMed citation numbers and DOI citation to the reference list and list all authors.