

1 RE: *World Journal of Gastroenterology* Manuscript review Manuscript NO: 40775

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3 03 September 2018

4 Dear the Editor-in-Chief of the *World Journal of Gastroenterology*

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6 Thank you very much for the opportunity to revise our manuscript.

7 We would like to submit a revised manuscript: **“Long term outcome of antiviral**
8 **therapy in patients with hepatitis B associated decompensated cirrhosis”** to the
9 *World Journal of Gastroenterology*.

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11 The manuscript has not been submitted simultaneously to another journal, has not
12 been accepted for publication elsewhere, and has not already been published.

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14 The manuscript was revised based on valuable comments of the reviewer 1, 2, 3, and
15 4. Any changes or amendment were highlighted in RED-colored text.

16 Please find our detailed responses to comments raised by the reviewers as:

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18 **Our responses to comments raised by the Editors and Reviewers:**

19 **Reviewer #1 (code: 02861252)**

20 1. Good work ... Last two paragraph in introduction part could be extracted from the
21 paper. Already written later in a same fashion...

22 📩 We appreciate your compliments. As you recommended, we omitted the last two
23 paragraph in introduction part.

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26 **Reviewer #2 (code: 02438768)**

27 1. Comments for ESPS Manuscript NO 40775 This paper is interesting and well written.
28 There are no major and few minor concerns. Regarding the latter, except when it is
29 first mentioned, HCC, the abbreviation form of hepatocellular carcinoma, should be
30 used instead of hepatocellular carcinoma throughout the paper.

31 📩 We appreciate your interest in our study. We changed the hepatocellular carcinoma

to HCC after second mention, the abbreviation form of hepatocellular carcinoma, throughout the manuscript.

2. In addition, the grammar of the manuscript should be carefully corrected. For example, one spelling mistake in the Abstract section was noticed: “in patients with” was misspelled “in patient with”

☞Thank you very much for your comment. We changed the misspelled “in patient with” to “in patients with” and carefully checked spelling mistakes and corrected them throughout the manuscript.

☞We also added ‘HIRA’, the abbreviation form of the Korean Health Insurance Review and Assessment, as the first mentioned such as following (page 4, line No. 89).
Methods: We used the Korean Health Insurance Review and Assessment (HIRA).

Reviewer #3 (code: 03538158)

1. Only problem of this study is that this study lacks untreated control, especially those with HBV and decompensated cirrhosis. Authors should use proper references as follows. Chu CM, Liaw YF. Hepatitis B virus-related cirrhosis: natural history and treatment. Semin Liver Dis. 2006 May;26(2):142-52. Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy .J Hepatol. 2012 Aug;57(2):442-50. And authors should discuss more.

☞Thanks for your recommendations. We added two wonderful reports in our discussion parts regarding natural course of decompensated cirrhosis under supportive treatment such as following (Page 13, Line No 350).

.....Previous reports showed 5-year survival rate of decompensated cirrhosis at 14-35% under supportive treatment. (Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy .J Hepatol. 2012 Aug;57(2):442-50) There are two Asian studies. (J Clin Gastroenterol 2002;34:569-572., Liver Int 2010;30:1033-1042). 5-year survival rate was 19% in 102 untreated decompensated cirrhosis patients. In our study, 5-year cumulative survival rate was 67.4% in 1st decompensated CHB treatment-naïve subjects.

☞We also added several reports in our discussion parts regarding clinical course of decompensated cirrhosis after antiviral treatment such as following (Page 13, Line No

360).

..... Antiviral treatment was effective in improving survival rate in decompensated cirrhosis. (Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy .J Hepatol. 2012 Aug;57(2):442-50) 2-year survival rate of 70 decompensated patients was 83% in entecavir treatment group. (J Hepatol 2010;52:176–182) In our study, 2-year cumulative survival rate was 76.0% in 1st decompensated CHB treatment-naïve subjects.

Reviewer #4 (code: 00034151)

The study entitled "Long term outcome of antiviral therapy in patients with hepatitis B associated decompensated cirrhosis" have important clinical implications. However, there are several concerns and rooms to refine the manuscript (not limited to below comments).

Comments:

1. Lay Summary, What is new here: Do not duplicate results.

☞Thanks for your comments. As you recommended, we changed ‘what is new here’ to such as following (page 3, Line No. 77).

..... ‘Long term outcome of treating hepatitis B-related decompensated cirrhosis using antiviral agents improved much compare to previous reports. Incidence of cumulative mortality rate and hepatocellular carcinoma was sharply decreased after one year antiviral treatment’.

2. Conclusions: Do not duplicate results. Describe implications of antiviral therapy in terms of mortality, HCC, and decompensation incidences.

☞Thanks for your comments. As your comments, we removed duplicated data and rewrote conclusion such as following (Page 5, Line No. 112).

..... Long term outcome of decompensated cirrhosis treated with antiviral agent improved much, and incidence of hepatocellular carcinoma and mortality sharply decreased after one year treatment.

3. Antivirals: More clearly describe on the high potency NUCs (TDF, TAF).

☞Thanks for your comments. We analyzed HIRA database from 2007 to 2014. Because at least five year follow up period was needed to investigate the mortality and incidence of hepatocellular carcinoma, we included treatment naïve patients until 2009. Unfortunately TDF and TAF were available at 2011 in Korea, so TDF and TAF

patients were not included our cohort.

4. Operational definitions & its validation: Operational definitions & its validation are critical in this study. More clear descriptions are required. For example, are 133 patients enough to validate for 7,166 decompensated patients' data?

☞Thanks for your comments. As you commented, validation of operational definition is very critical, so we tried to validate our operational definitions. As you know, the number of HBV associated decompensated cirrhosis patients is small, moreover we only included treatment naïve patients. That's the reason we used national HIRA database. Instead we tried to validate the operational definitions in various clinical settings, because patterns of prescribing antiviral agent might be quite different depending on the clinical settings. We investigated two different sized hospitals; one is tertiary hospital and the other is secondary hospital. Although we tried to validate the operational definitions using real world data from two different hospitals, we agreed that 133 patients were not enough to validate for 7,166 decompensated patients data. So we added the previously mentioned issue at discussion part such as following (page 15, Line No. 409).

..... We tried to validate the operational definitions in various clinical settings, because pattern of prescribing antiviral agent might be quite different depending on the clinical settings. We investigated two different sized hospitals; one is tertiary hospital and the other is secondary hospital. Although we tried to validate the operational definitions using real world data from two different hospitals, we thought 133 patients were not enough to validate for 7,166 decompensated patients data.

5. Stats: More clear descriptions are required. What are the meanings of range for incidence?

☞Thanks for your comments. We agreed that there are several ambiguous expressions for range for incidence. So we rewrote the vague expression such as following.....

(Page 4, Line No. 100).... But the annual mortality rates sharply decreased to 3.4% (2.4~4.9%, 2 yr-5 yr) after one year of antiviral treatment.

(Page 4, Line No.102).... Incidence of HCC at first year was 14.3%, the annual incidence of HCC decreased to 2.5% (1.8~3.7%, 2 yr~5 yr) after one year.

(Page 4, Line No. 105).... but the annual incidence of second decompensation events in decompensated CHB treatment-naïve patients was 3.4% (2.1-5.4%, 2yr-5yr) after one year antiviral treatment.

(Page 12, Line No. 322).... but the incidence remained steady even 1 year after the start of antiviral therapy, showing an annual incidence of 2.5% (1.8–3.7%, 2yr–5yr).

The following files have been uploaded into the F6Publishing system.

Kindly be noted that we have NO video file or supplementary material file to be uploaded.

(1) 40775- Revised Manuscript

(2) 40775- Answering Reviewers_Point by Point

(3) 40775-Audio Core Tip

(4) 40775- Biostatistics Review Certificate

(5) 40775- Conflict-of-Interest Disclosure Form

(6) 40775- Copyright License Agreement

(7) 40775- Institutional Review Board Approval Document

(8) 40775-Non-Native Speakers of English Editing Certificate

(9) 40775-STROBE Statement

(10) 40775-Audio Core Tip

Your consideration is very much appreciated.

Your sincerely,

Dae Won Jun, MD, PhD, Professor

Corresponding author of the manuscript

Department of Internal Medicine, Hanyang University School of Medicine,

222 Wangsimni-ro, Seongdong-gu, Seoul, 04763, Republic of Korea.

noshin@hanyang.ac.kr

Telephon: +82-2-2290-8338

Fax: +82-2-972-0068