

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*

5

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*.

10

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.

13

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:

17

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.

24

25

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

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

34

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

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

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

44

45

46 **Reviewer #3 (code: 03538158)**

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

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

56Previous reports showed 5-year survival rate of decompensated cirrhosis at 14-35% under
57 supportive treatment. (Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver
58 cirrhosis: benefits of antiviral therapy .J Hepatol. 2012 Aug;57(2):442-50) There are two Asian studies.
59 (J Clin Gastroenterol 2002;34:569-572., Liver Int 2010;30:1033-1042). 5-year survival rate was 19% in 102
60 untreated decompensated cirrhosis patients. In our study, 5-year cumulative survival rate was 67.4%
61 in 1st decompensated CHB treatment-naïve subjects.

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

64 360).

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

70

71

72 **Reviewer #4 (code: 00034151)**

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

77 Comments:

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

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

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

84

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

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

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

91

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

93 ☞Thanks for your comments. We analyzed HIRA database from 2007 to 2014. Because
94 at least five year follow up period was needed to investigate the mortality and
95 incidence of hepatocellular carcinoma, we included treatment naïve patients until
96 2009. Unfortunately TDF and TAF were available at 2011 in Korea, so TDF and TAF

97 patients were not included our cohort.

98

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

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

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

119

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

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

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

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

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

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

132

133 The following files have been uploaded into the F6Publishing system.

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

136 (1) 40775- Revised Manuscript

137 (2) 40775- Answering Reviewers_Point by Point

138 (3) 40775-Audio Core Tip

139 (4) 40775- Biostatistics Review Certificate

140 (5) 40775- Conflict-of-Interest Disclosure Form

141 (6) 40775- Copyright License Agreement

142 (7) 40775- Institutional Review Board Approval Document

143 (8) 40775-Non-Native Speakers of English Editing Certificate

144 (9) 40775-STROBE Statement

145 (10) 40775-Audio Core Tip

146

147 Your consideration is very much appreciated.

148 Your sincerely,

149 Dae Won Jun, MD, PhD, Professor

150 Corresponding author of the manuscript

151 Department of Internal Medicine, Hanyang University School of Medicine,

152 222 Wangsimni-ro, Seongdong-gu, Seoul, 04763, Republic of Korea.

153 noshin@hanyang.ac.kr

154 Telephon: +82-2-2290-8338

155 Fax: +82-2-972-0068