

Dear Editors and Reviewers,

Thank you for reviewing our paper and providing such valuable comments. The manuscript has been revised in accordance with your recommendations. Below, we list the point-by-point responses to these comments.

We will be honored if the revised paper is accepted for publication in your esteemed journal.

Sincerely yours,

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Reviewer #1 (Reviewer's code: 03646639):

Major issues

1. It would be helpful if the authors compared the cumulative incidence of patients between HBeAg-negative non-cirrhotic patients with a baseline HBsAg level of <2.4 log IU/mL and those with a baseline HBsAg level of ≥ 2.4 log IU/mL HBeAg.

Ans:

(1) The cumulative incidence of virological response in HBeAg-negative non-cirrhotic patients, categorized by baseline HBsAg < 2.4 and ≥ 2.4 log IU/mL, had been presented in Figure 1(D). The result had also been mentioned in the Result section (Manuscript: Page 16, Paragraph 2, Line 5 to Line 7).

(2) The cumulative incidence of biochemical response in HBeAg-negative non-cirrhotic patients, categorized by baseline HBsAg < 2.4 and ≥ 2.4 log IU/mL, is shown as bellow.

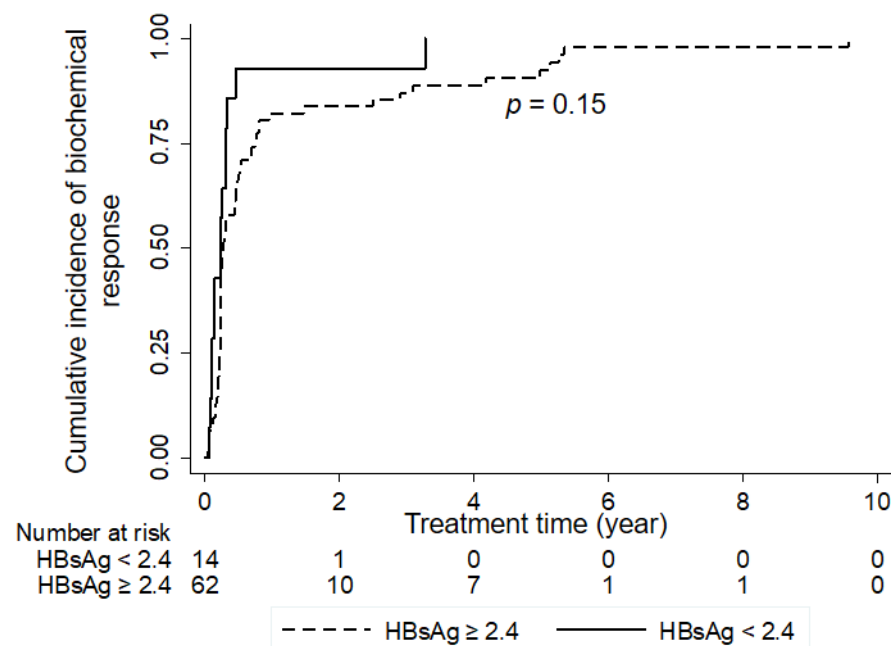


Figure 1. The cumulative incidence of biochemical response in HBeAg-negative non-cirrhotic patients, categorized by baseline HBsAg < 2.4 and ≥ 2.4 log IU/mL

The baseline HBsAg level failed to predict biochemical response in HBeAg-negative patients, irrespective of cirrhosis status. The result had been mentioned in the Result section (Manuscript: Page 18, Paragraph 1, Line 10 to

Line 13).

2. It would also be helpful if the authors compared the cumulative incidence of HBeAg-positive patients between HBeAg-negative non-cirrhotic patients with a baseline HBsAg level of <4.0 log IU/mL and those with a baseline HBsAg level of ≥ 4.0 log IU/mL HBeAg.

Ans:

(1) The cumulative incidence of virological response in HBeAg-positive patients, categorized by baseline HBsAg < 4 and ≥ 4 log IU/mL, had been presented in Figure 1(A). The result had also been mentioned in the Result section (Manuscript: Page 15, Paragraph 2, Line 4 to Line 7).

(2) The cumulative incidence of serological response in HBeAg-positive patients, categorized by baseline HBsAg < 4 and ≥ 4 log IU/mL, had been presented in Figure 2. The result had also been mentioned in the Result section (Manuscript: Page 17, Paragraph 1, Line 4 to Line 6).

(3) The cumulative incidence of biochemical response in HBeAg-positive patients, categorized by baseline HBsAg < 4 and ≥ 4 log IU/mL, had been presented in Supplemental Figure 1. The result had also been mentioned in the Result section (Manuscript: Page 18, Paragraph 1, Line 3 to Line 6).

(4) Because HBeAg-negative patients had lower baseline HBsAg levels than HBeAg-positive patients, the cut-off values of HBsAg for predicting treatment response in HBeAg-negative patients (2.4 log IU/mL) were lower than that in HBeAg-positive patients (4 log IU/mL). This issue had been mentioned in the Discussion section (Manuscript: Page 22, Paragraph 2, Line 3 to Line 6).

Therefore, baseline HBsAg of 2.4 log IU/mL was a better cut-off value for HBeAg-negative non-cirrhotic patients. The cumulative incidence of virological response in HBeAg-negative non-cirrhotic patients, categorized by baseline HBsAg < 2.4 and ≥ 2.4 log IU/mL, had been presented in Figure 1(D). The result had also been mentioned in the Result section (Manuscript: Page 16, Paragraph 2, Line 5 to Line 7).

3. The authors can make a stronger case by conducting a one-way ANOVA instead of student's t test for Figure 3B

Ans:

The results presented in Figure 3(B) were not calculated by student's t test. The results presented in Figure 3, including Figure 3(B) were calculated by a

linear mixed model with a random intercept, which is a better method for variables with repeated measurements (Twisk JWR. Applied longitudinal data analysis for epidemiology: a Practical Guide, second edition. Cambridge, New York, USA 2013). This method had been mentioned in the Patients and methods section (Manuscript: Page 14, Paragraph 1, Line 8 to Line 11).

Minor issues

1. The authors should cite the following paper for the idea of interpreting HBsAg changes during entecavir therapy Pronounced decline of serum HBsAg in chronic hepatitis B patients with long-term effective nucleos(t)ide analogs therap.: Wang ML, Chen EQ, Tao CM, Zhou TY, Liao J, Zhang DM, Wang J, Tang H. Scand J Gastroenterol. 52(12):1420-

Ans:

The recommended paper was cited in the revised manuscript (Manuscript: Discussion section, Page 23, Paragraph 2, Line 13 to Line 14; References section, Page 31, Paragraph 4, Line 1 to Line 5).

Reviewer #2 (Reviewer's code: 02936069):

1. This article can be accepted. In this research manuscript, the authors observed a global view and clinical utility of hepatitis B surface antigen kinetics in treatment-naïve chronic hepatitis B patients during long-term entecavir therapy. No seriously grammar mistakes were found and no statistical methods were observed. I think this article can be accepted.

Ans:

Thank you for your valuable comments.