

## Answering reviewers

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**Title:** 3-Dimensional Liver Volume Assessment in Patients with Hepatitis B Virus-Related Liver Cirrhosis during Long-term Oral Nucleos(t)ide Analogues Therapy

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Dear Executive Managing Editor of World Journal of Gastroenterology

We appreciate your kind review of our manuscript entitled “3-Dimensional Liver Volume Assessment in Patients with Hepatitis B Virus-Related Liver Cirrhosis during Long-term Oral Nucleos(t)ide Analogues Therapy”. Suggested changes have been raised during the review of the manuscript. We have addressed these suggested changes and modified the manuscript in response to the reviewer’s comments. A point-by-point response to the reviewer’s comments is enclosed.

Once again, thank you very much for your time and consideration. We hope that the revised manuscript is satisfactory for publication in the World Journal of Gastroenterology.

Sincerely Yours,

In Hee Kim, M.D., PhD

\*\* We would like to inform you that we changed the authors list (Baik Hwan Cho withdrawn, Jae Do Yang added) with consideration of contribution to the manuscript. We confirmed that authors list was modified accordingly in the revised manuscript and other documents including the copyright form. Please check the final authors list.

#### **Reviewer #1**

In this manuscript, Kim et al have examined effects of nucleos(t)ide analogues (NUCs)-based therapy on liver volume and on liver functions in patients with HBV-related liver cirrhosis. The authors have initially performed a careful selection and chose 55 patients from total number 192. This careful selection allowed to make a correct interpretation of the results. The analyzed patients were treated with NUCs for 2 years. The authors found that NUCs therapy in these patients with HBV-related cirrhosis significantly increases liver volume and improves liver functions as measurements of ALT/AST show. This is the first study which evaluates liver volume in cirrhotic patients. This work is highly significant for the field of liver cirrhosis and treatments of patients. The study uses a special technique/program which is called a 3 dimensional virtual liver extraction measurement program. The results of the study are convincing. In summary, the manuscript provides a significant contribution to the understanding of liver cirrhosis and treatments by NUCs. This manuscript would be of great interest for the readers of the World Journal of Gastroenterology.

There is one minor weakness which should be addressed before publication. Figure 2 shows 3D reconstruction images of livers for two patients. 6 images are shown for each patient. Although these results look very impressive, it is not clear what each image shows. It is necessary to label each image and provide clear description in the legend to the figure.

Answer: Thank you for your thoughtful comment. As you mentioned, we noticed that images in Figure 2 need to provide additional information what each image shows. Among 6 images for each patient, upper images are baseline images and lower images are follow-up images in different views (anterior, anteroinferomedial, and

posteroinferomedial). We modified the figure image and described additional information in the legend to the figure as below for readers' better understanding. (Revised manuscript page 17)

- Figure 2 image was modified.
- Among 6 images for each patient, upper images are baseline (pre-NUCs therapy) images and lower images are follow-up (post-NUCs therapy) images in different views (anterior, anteroinferomedial, and posteroinferomedial).

## Reviewer #2

In this study, oral NUCs therapy was initiated on one of the NUCs, including LAM (100 mg), LdT (600 mg), and ETV (0.5 mg). ADV (10 mg) and ETV (1.0 mg) were used as a rescue drug for patients with treatment failure. I suggest that authors should compare the efficacy of different NUCs in increasing liver volumes. Moreover, the efficacy of NUCs in increasing liver volumes ought to be compared between compensated and decompensated cirrhosis.

Answer: I appreciate your new perspective suggestion. We reviewed the data and the number of initial NUCs is 26 patients for LAM, 6 patients for LdT, and 23 patients for ETV. We compared the efficacy of different NUCs on liver volume by dividing two groups: LAM and LdT versus ETV. The results are as follows:

Initial NUCs	LAM or LdT (N=32)	ETV (N=23)	Total (N=55)	p
Pre.CT.Vol	1022.2 ± 230.6	954.4 ± 258.8	993.8 ± 242.8	0.312
Post.CT.Vol	1125.1 ± 235.7	1084.5 ± 301.4	1108.1 ± 263.3	0.578
Vol. change	102.9 ± 155.2	130.0 ± 186.4	114.3 ± 167.8	0.559
Vol. change (%)	11.4 ± 14.5	15.0 ± 21.9	12.9 ± 17.9	0.499

We also compared the liver volume changes between compensated and decompensated cirrhosis regarding initial CTP grading. (CTP A versus CTP B and C)

The results showed that, although baseline and follow-up liver volume was diminished in decompensated LC rather than compensated LC, there was marked increase in liver volume even in decompensated LC. The results are as follows:

Presence of decompensation	Compensated LC (N=21)	Decompensated LC (N=34)	Total (N=55)	p
Pre.CT.Vol	1063.8 ± 238.9	950.6 ± 238.4	993.8 ± 242.8	0.093
Post.CT.Vol	1127.9 ± 250.8	1095.9 ± 273.6	1108.1 ± 263.3	0.666
Vol. change	64.1 ± 137.7	145.2 ± 178.9	114.3 ± 167.8	0.081
Vol. change (%)	6.6 ± 12.5	16.7 ± 19.7	12.9 ± 17.9	<b>0.023</b>

We added columns in Table 2 of revised manuscript. (Revised manuscript page 19)

Variables	No	Pre-Volume	Post-Volume	Volume change	Volume change (%)	P value
<i>Initial NUCs: LMV or LdT</i>	32	1022.2±230.6	1125.1±235.7	102.9±155.2	11.4±14.5	0.559
<i>Initial NUCs: ETV</i>	23	954.4±258.8	1084.5±301.4	130.0±186.4	12.9±17.9	
<i>Compensated LC</i>	21	1063.8±238.9	1127.9±250.8	64.1±137.7	6.6±12.5	0.081
<i>Decompensated LC</i>	34	950.6±238.4	1095.9±273.6	145.2±178.9	16.7±19.7	

We also added a sentence as follows in results of revised manuscript. (Revised manuscript page 11)

- *The liver volume changes regarding baseline sex, type of initial NUCs, and presence of decompensation were not significantly different.*