Dear Dr Ze-Mao Gong,

Please find enclosed the revised version of the manuscript Manuscript NO.: 34042: **"Serum angiotensin-converting enzyme level for evaluating significant fibrosis in chronic hepatitis B"** by Ryuichi Noguchi, Kosuke Kaji, Tadashi Namisaki, Kei Moriya, Mitsuteru Kitade, Kosuke Takeda, Hideto Kawaratani, Yasushi Okura, Yosuke Aihara, Masanori Furukawa, Akira Mitoro, and Hitoshi Yoshiji for publication as an article in ***World Journal of Gastroenterology***.

We carefully evaluated the concerns raised by the Reviewers, performed the requested analyses, modified the text and added new data (please refer to Fig. 1-6) as suggested. Detailed responses to each of the Reviewers' comments are provided in the attached pages.

We would like to extend our thanks to the Reviewers for providing helpful and constructive comments on our work and to you for a chance to resubmit our manuscript.

I hope that we satisfactory addressed yours and Reviewers concerns and the revised manuscript is now acceptable for publication in ***World Journal of Gastroenterology***.

Sincerely,

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Reply to the points raised by the Reviewers.

We thank all Reviewers for his/her positive evaluation of our work.

Reviewer:03537407

The authors describe the use of Serum ACE Levels as a biomarker for HBV related liver fibrosis in a series of 70 human patients. Overall, the study is well planned and results are presented clearly. The Topic is of interest as non-invasive biomarkers esp for early stage fibrosis are still lacking. 1. In the Abstract, 90 patients are mentioned to be enrolled into the study, although actually on 70 were included. The authors should make this Statement clearer in the Abstract and correct the Patient numbers accordingly (it only becomes clear in the results' section). 2. What is the difference between data shown in Fig 2A and 2B?

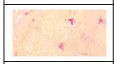
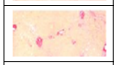
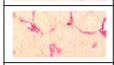
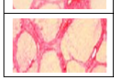
1. We apologize for the confusing statement about the enrollment of patients in the Abstract. As Reviewer mentioned, we correctly describe the number of patients in the Abstract of revised manuscript (page3, line6-7).
2. As Reviewer correctly stated, Fig 2B is similar to Fig 2A. We deleted the original Fig 2B and modified the original Fig 2A as the revised Figure 3A.

Reviewer:03536939

In this article, the authors present an impressive analysis for fibrosis stage determination using a measurement of serum angiotensin converting enzyme being indicative of portal hypertension in chronic hepatitis B infection without hepatic steatosis. The sensitivity of the test discriminating F0-F1 from F2-F3-F4 proved to be higher than that of APRI test. The authors present a thorough, informative and well-structured article. I have only a very few minor comments: 1. It might be important to know how levels of hyaluronic acid, type 4 collagen 7S and P-III-P were determined in serum samples of the patients. Nevertheless, it does not have to be mentioned if these levels are measured in a similar routine procedure all over the world. I am just not aware of this. 2. I found a mistyping in the legend of Fig. 3: the number for both p values is 0.01. Although this might be true only for 'a' and I think 0.05 could be the value for the 'b'. 3. Could the authors find a rational to present not

only the average in Table 1 for the most important values related to fibrosis but show the values also separately for F0, F1, F2, F3 and F4 patients groups? 4. I wonder how the data could look like when using Ishak scores instead of Metavir? Have the authors try this one as well?

1. Level of hyaluronic acid is measured by Latex Agglutination Turbidimetry, and both levels of type 4 collagen 7S and P-III-P are measured by Radio Immunoassay. We recognize that these assays are routine procedures all over the world.
2. We appreciate Reviewer's kind suggestion. We made corresponding corrections.
3. We modified Table 1 according to the Reviewer's suggestion.
4. As Reviewer mentioned, ISHAK Score is also convenient scoring system to histologically evaluate liver fibrosis as well as METAVIR, and ISHAK score shows subdivision of F2 and F3 in METAVIR into four classes (see as the right table). In current study, we ultimately aim to explore the non-invasive marker to diagnose significant fibrosis (F2≦ and score 2≦ indicated by METAVIR and ISHAK, respectively). Therefore, there should be no difference in the diagnostic performance of serum ACE for F2 fibrosis assessed by between Ishak and METAVIR scores.

Appearance	Ishak stage: Categorical description	ISHAK	METAVIR
	No fibrosis (Normal)	0	F0
	Fibrosis expansion of some portal areas ± short fibrous septa	1	F1
	Fibrosis expansion of most portal areas ± short fibrous septa	2	F2
	Fibrosis expansion of most portal areas with occasional portal to portal(P-P) bridging	3	
	Fibrosis expansion of portal areas with marked portal to portal(P-P) bridging as well as portal to central(P-C)	4	F3
	Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)	5	
	Cirrhosis, probable or definite	6	F4

Reviewer:03476635

To: Editorial board World Journal of Gastroenterology Title: "Serum angiotensin-converting enzyme level for evaluating significant fibrosis in chronic hepatitis B". Dear Editor, I read through this manuscript and I think that: - 1.Were the

patients on ACE inhibitors treatment? I mean, did the authors excluded all the hypertensive patients or at least only those were on ACE inhibitors treatment? – 2. How many patients did the authors exclude? - Please include a flow chart of the study. – 3.What about alcohol fibrosis? Please discuss such confounding factors which was not so fairly assessed. – 4.Please discuss the role of ST2/IL33 in such a context. Please consider the paper from Ciccone MM et al. Molecules. 2013 Dec 11;18(12):15314-28.

1. We apologize for insufficient statement about exclusion of hypertensive patients and appreciate for Review's kind indication. In current study, all the hypertensive patients were excluded regardless of the type of antihypertensive agent. 10 patients with hypertension (3 patients were treated with ARB) have been already excluded in enrolling 90 patients. Therefore, we described this process in the selection of study population in the new Patients and Methods of the revised manuscript (page7, line16-18).
2. As Reviewer correctly mentioned, a flow chart of the study is very important, so we include it as the new Figure 1. Additionally, we modified the original Figure 5 as the new Figure 6.
3. We appreciate that Reviewer provides kind suggestion to account for the patients with alcoholic fibrosis more clearly. All the 8 patients with habitual alcoholic consumption were included in 20 patients who histologically diagnosed as hepatic steatosis. We add this description in the new Results of revised manuscript. (page9, line8-9)
4. We also consider that serum ST2/IL33 is efficient marker as well as serum ACE to for differentiate significant fibrosis from mild fibrosis in CHB patients. According to the Reviewer's comment, we add the description about the role of ST2/IL33 in the new Discussion of revised manuscript. (page13, line16-22)

Reviewer:03322697

Although this study is interested, several revisions are needed. 1) A major concern is that prospective evaluation was not performed in this study. Therefore, it is difficult to conclude that serum angiotensin-converting enzyme level is a reliable marker of disease progression especially associated with liver fibrosis. 2) In abstract, the authors

should clarify the number of patients who were evaluated for the study. 3) In discussion section , paragraph 1.: ''…antiviral therapies with nucleos(t)ide analogs (NAs), including lamivudine, adefovir, entecavir, and tenofovir [27-34]. …'' these sentences seems not to be necessary, so this section can be removed from the paper. 4) What is the difference between data shown in Fig 2A and 2B? 5) References is too long. Please shorten it. 6) English language should be corrected. Some sentences and statements are confusing. The syntax and grammar should be corrected by an English editor.

1. We agree with Reviewer's comment. To validate the reliability of serum ACE as the predictive marker for liver fibrosis, it is required for prospective study in addition to this observational study. Therefore, we have already started the new project to evaluate the chronological change in serum ACE levels during the attenuation of liver fibrosis by the antiviral therapies with nucleos(t)ide analogs. We hope to provide a novel report in the near future.
2. We apologize for the confusing statement about the enrollment of patients in the Abstract. As Reviewer mentioned, we correctly describe the number of patients in the revised manuscript. (page3, line6-7)
3. We agree with the Reviewer's comment. We removed a series of sentences from Discussion in the new manuscript.
4. As Reviewer correctly stated, Fig 2B is similar to Fig 2A. We deleted the original Fig 2B and modified the original Fig 2A as the revised Figure 3A.
5. According to the Reviewer's comment, we decreased the number of references.
6. We appreciate Reviewer's kind suggestion. The syntax and grammar in the revised manuscript is corrected by an English editor.