Format for ANSWERING REVIEWERS

December 4, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:14869-review.doc).

Title: Model for predicting HBeAg seroconversion to interferon-α in chronic hepatitis B patients

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The manuscript has been improved according to the suggestions of reviewers and editor:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1.

1.1: Major revision is required concerning language in term of grammar and structure?
Reply: We revised the English throughout the manuscript.

1.2: However, the authors have to carefully revise the following: o First paragraph: Refs 1-4 (2004-2007) are better to be updated. o The authors are advised to add other predictors like LHBS. Zhu et al, (2013) found that on-treatment quantification of serum LHBs is a useful parameter for predicting VR in patients on peginterferon alfa-2a. Combining LHBs, HBsAg and HBV DNA can predict VR and SR more effectively and earlier.
Reply: The requested references have been added and updated in the first paragraph. References and typesetting were corrected.

1.3: However, some important data are incomplete and have to be fulfilled: o HBV genotyping: Test used, Country of origin o Serum HBsAg, Anti-HBs, HBeAg, Anti-HBe, and Anti-HBc were tested using commercially available kits (Abbott Laboratories): Test used, Country of origin have to be added.
Reply: Complete information on the origins of all lab tests has been provided in the methods section of the revised manuscript.

1.4: By the end of treatment, 47 patients (32%) experienced HBeAg seroconversion and those patients had lower HBeAg than those without HBeAg seroconversion (2.55 ± 0.07 vs. 2.30 ± 0.13, P = 0.016)'. This is not comparable to figures in table (1) and has to be revised. It is (2.30 ± 0.13 vs. 2.67 ± 0.07) o Title of Table 1:Is not informative and need to be revised.Figure S1: Different numbering is given! Better to unify the way of numbering figures. o Tables S1-S2: Negative and

positive predictive values were missing. Anyhow, both tables are better to be deleted and only clarify their content within the related paragraphs.
Reply: We thank you for the corrections. The accurate HBeAg levels have now been given in the results section of the manuscript. All patient data have been checked and corrected where necessary. The title of Table 1 has been changed to be more descriptive. Figure S1 and Tables S1-S2 have been deleted according to suggestions of multiple reviewers.

1.5: An overall theoretical analysis of the study results is not well covered. Some data were discussed without being clarified within the result section.
Reply: We have modified the discussion to make it more robust.

Reviewer 2.

2.1: Minor (professional) language revision would be appreciated.
Reply: We revised the English throughout the manuscript and utilized a professional language editing service.

2.2: Full information on origin of all lab. tests used should be provided.
Reply: Full information on the origins of all lab tests has been provided in the methods section of the revised manuscript.

2.3: Discrepancy in baseline levels of HBeAg between responders end nonresponders between text and Table 1 should be corrected.
Reply: We thank you for the corrections. The accurate HBeAg levels have now been given in the results section of the manuscript. All patient data has been checked and corrected where necessary.

2.4: In Tables S1-2 provide data on PPV and NPV. Data/comments on NPV and PPV should be included in Results section.
Reply: Data on NPV and PPV have been included in the results section of the manuscript. Tables S1-2 have been deleted.

2.5: Table S3A-C and Figure S1 could be removed. Table and Figure are very "busy" with much data provided and not commented in text. Presentation is not very informative.
Reply: Table S3A-C and Figure S1 have been removed according to your suggestion.

Reviewer 3.

3.1: In this study, “HBeAg seroconversion was defined as the loss of HBeAg (≤1 S/CO; Abbott Laboratories, Abbott Park, IL, USA) and positive Anti-HBe (≤1 S/CO, Abbott Laboratories) at 52 weeks”. Why Anti-HBe should be ≤1 S/CO? Usually, the loss of HBeAg is companied by the appearance of Anti-HBe, but in some patients, the HBeAg-/anti-HBe- or HBeAg+/anti-HBe+ can exist for a long time, especially in those who are infected with pre-C stop codon mutants. The authors need to specify in the ms that among the 47 patients who were classified in the HBeAg seroconversion group, how many were HBeAg-/anti-HBe-.
Reply: Two cases were HBeAg-/anti-HBe-, which did not have a large effect on the overall results

of the study. We have added this information in the results section of the manuscript.

3.2: Patients with missing data at week 52 were classified as non-responders at the end of treatment. This is not a proper way for data analysis.
Reply: The reason for the majority of missing data at week 52 in this study was adverse drug reactions or poor efficacy of treatment. In these cases, patients changed treatment regimens or added other drugs, usually at 6 months. Therefore, evaluation of these patients at 1 year would have been misleading. This method of analyzing data was similar to references such as Janssen HL et al. (2005, Lancet) and W.-M. Xu et al. (2009, Journal of Viral Hepatitis). Patients with missing data at week 52 were classified as non-responders at the end of treatment. After consultation with a biostatistician, we maintain that we can use this method.

3.3: The title "Model to predict response to interferon-α in HBeAg-positive chronic hepatitis B patients" does not properly reflect the major content of the ms.
Reply: We revised the title to more accurately reflect the major content of the manuscript.

3.4: response to interferon-α should include loss of HBeAg and reduction of HBV-DNA level. But in this study, the authors only observed the HBeAg seroconversion.
Reply: According to the AASLD, EASL, and APASL, monitoring responses to IFN-α treatment requires evaluating sustained suppression of HBV replication, biochemical remission, histological improvement, and HBeAg/HBsAg loss or seroconversion in HBeAg-positive patients. According to some studies, HBeAg seroconversion usually predicts long-lasting suppression of HBV, reduced infectivity, and improved clinical prognosis. There are only two cases in this study that were HBeAg/anti-HBe-. Therefore, HBeAg seroconversion can be used as an evaluation of interferon efficacy.

3.5: The English language of this ms needs extensive editing.
Reply: We revised the English throughout the manuscript.

3. The references and typesetting were corrected.

Thank you for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

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