ANSWERING REVIEWERS

July 24, 2013

Dear Editor,

On behalf of my co- authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript. Please find enclosed the edited manuscript in Word format (file name: 3538-revised.doc).

Title: The influence of chronic HBV infection on superimposed acute hepatitis E.

Author: Si-Hong Cheng, Li Mai, Feng-Qin Zhu, Xing-Fei Pan, Hai-Xia Sun, Hong Cao, Xin Shu, Wei-Min Ke, Gang Li, Qi-Huan Xu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 3538

The manuscript has been improved according to the suggestions of reviewers. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1 （Reviewer NO: 00053556）:

1. Response to comments on the ABSTRACT part:

1) More specification of both groups is required.

2) The details concerning statistical analysis have to be cancelled.

3) MELD scores has to be fully written

Response: According to the reviewer's suggestion, we have revised the ABSTRACT part:

1) The two groups have been specified: HBV+HEV group (a group with chronic HBV infection that was superinfected with acute hepatitis E); HEV group (a group with acute hepatitis E).
2) The details concerning statistical analysis have been cancelled.
3) MELD scores has been fully written as Model for End-Stage Liver Disease (MELD) scores.

2. Response to comments on the INTRODUCTION part:

1) The usefulness of MELD scores is needed to be elaborated.
2) The issue of acute super/co-infection -on-chronic liver failure needs more clarification.

Response: Considering the reviewer's suggestion, we have covered the following points in the INTRODUCTION part:

1) We have elaborated the usefulness of MELD scores in Paragraph 4.
2) We have made more clarification on the issue of acute superinfection -on-chronic liver failure in Paragraph 2 & 3.

3. Response to comments on the MATERIALS AND METHODS part:

1) Criteria for chronic HBV infection need more specification as for how long HBsAg is positive.
2) As real-time polymerase chain reaction was performed, level of HBV DNA is

better to be evaluated in order to study the relationship between the level of HBV DNA in serum, the hepatic function impairments and prognosis of chronic hepatitis B superinfected with acute hepatitis E.

3) Calculations of MELD scores need more clarification denoting its value and significance.

Response:

1) As people with HBV infection are not well managed and regularly followed-up in China, it's difficult for us to find out how long HBsAg is positive in our patients. Moreover, the mother-infant transmission is the major cause of chronic HBV infection in China, and all our patients in this study were adults, so we diagnosed the chronic HBV infection by "the presence of HBsAg and the absence of anti-HBc IgM" (Paragraph 1).
2) According to studies on Chronic HBV infection, the correlation between the level of HBV DNA, the hepatic function impairments and prognosis is uncertain. Additionally, as we regularly monitored our patients' level of HBV DNA during admission, we found that the level of HBV DNA changed during the HBV-HEV superinfection course. So, in this study, we didn't evaluate the relationship between the level of HBV DNA, the hepatic function impairments and prognosis of chronic hepatitis B superinfected with acute hepatitis E. But, this comment is quite valuable, which gives useful hints for our further research on this subject.
3) We have elaborated the usefulness of MELD scores in Paragraph 4 of the INTRODUCTION part.

4. Response to comments on the RESULTS part:

1) Inappropriate subheadings 1 & 4.
2) Subheadings 4: ① line 5: The incidence of complications is better to be the occurrence of complications. ② Complications need to be specified. ③ The serological status frequency of HBeAg (+) and anti-HBe (-), HBeAg (-) and anti-HBe (-), and HBeAg (-) and anti-HBe (+) are better to be covered.
3) Subheadings 5: clarify the start of the course of treatment in relation to the development of HEV superinfection.
4) Tables: ① * is better to denote those with significant p value; ② Titles of table one & two are poor and need to be informative; ③ Table 2: Values of MELD score are needed to be written in one row for more clarification. ④ status of anti-HBe is missing, although it was mentioned in materials & methods and discussion sections.

Response:

1) We have revised subheading 1 as “Demographic characteristics” and subheading 4 as “Influence of chronic status of HBV infection on acute hepatitis E”.
2) Subheadings 4: ① “the occurrence of complications” has been used for the whole paper. ② We have elaborated the complications that were observed in Paragraph 1 in the MATERIALS AND METHODS part. ③ In our study, the number of HBeAg (+) group was 20, so the sample size would be too small if the HBeAg (+) group was divided into anti-HBe (-) and anti-HBe (+) subgroups. So, we didn’t cover these subgroups.
3) Subheadings 5: for the patients who received anti-HBV treatment in this study,

the start of the treatment was various: first, some patients were given the anti-HBV treatment before they were referred to our hospital, which we couldn't accurately judge the start. Second, some patients received regular anti-HBV treatment for a long time for their chronic HBV infection, thus the start was not well defined. Third, some patients were given the anti-HBV treatment at admission because they were in serious disease when they came to our hospital. Fourth, some patients developed liver failure after admission, and were given the anti-HBV treatment. According to our retrospective data, we can't well clarify the start of the course of treatment in relation to the development of HEV superinfection. But it's an important and interesting question which we wish to solve in our subsequent further research.

4) Tables: we have corrected the tables according to the reviewer's suggestions.

5. Response to comments on the DISCUSSION part:

1) Paragraph 2: the diagnosis of underlying cirrhosis needs more clarification.
2) Paragraph 4: It was mentioned that most patients in HBV+HEV group were HBeAb positive and had low level of HBV-DNA (data not shown in results section).
3) Paragraph 5: It was mentioned that it was not common to use anti-HBV treatment in patients without liver failure. The statement needs more clarification.
4) Precautions in order to avoid superinfection with HEV and measures adopted to decrease the mortality of patients with chronic hepatitis B are missing at the end of this section.

Response:

1) We have discussed the limitation of our diagnosis of underlying cirrhosis in Paragraph 8.
2) Paragraph 4: the statement of “most patients in HBV+HEV group were HBeAb positive and had low level of HBV-DNA” has been corrected as “most patients in the HBV+HEV group were HBeAg-negative, and nearly 50% were HBV-DNA-negative”.
3) Paragraph 5: the statement of “it was not common to use anti-HBV treatment in patients without liver failure” has been deleted.
4) We have covered the precautions and measures in order to avoid HEV infection in Paragraph 7.

6. Response to comments on the REFERENCES part:

1) The author has to follow the journal style in writing this section.
2) Ref. No: 1 has to be updated to Fact sheet N°204 July 2012.
3) Ref. No: 15: incorrect page numbers: 723-726 not 743-746.
4) PMID is well maintained for all included references except Ref. No: 16.
5) Ref. No: 17: incorrect PMID, it is for Ref. No: 16, the correct one is: 3489555.
6) Ref. No: 14, 15, 17 & 18 need to be updated.

Response: We are very sorry for our mistakes in the REFERENCES part. We have revised this part carefully according to the reviewer’s considerate comments.

1) We have updated Ref. No: 1 to Fact sheet N°204 July 2012.
2) We have corrected the mistakes in Ref. No: 15, Ref. No: 16, Ref. No: 17, which is

Ref. No: 19, Ref. No: 20, Ref. No: 23 respectively in the revised manuscript.

3) We have updated Ref. No: 14, 15, 17 & 18, which is Ref.No: 18, 19,23 & 25 respectively in the revised manuscript. We updated Ref. No: 18 with Ref. No: 3, Ref. No: 19 with Ref. No: 20, 21 & 22，Ref. No: 23 with Ref. No: 24，and Ref. No: 25 with Ref. No: 26.

4) We have tried our best to provide PMID and DOI for each reference.

Special thanks to you for your good comments.

Reviewer #2 （Reviewer NO: 00503536）:

1. Response to Point 1: HEV infection causes acute hepatitis, and most of the patients show high levels of serum ALT (over 1000 IU/L). The mean serum ALT levels in both groups in this study seem to be very low. At what timing, were those patients diagnosed as HEV infection?

Response: there are several reasons for the relatively low level of serum ALT & AST in our patients: ① Although liver function tests were performed at admission and regularly after admission, we compared the liver function indices at the timing when the most severe PT-INR/ prothrombin time occurred. ② In china, few patients go to hospital at the disease's early stage. ③ Some patients were referred to our hospital at the middle to end stage.

2. Response to Point 2: the authors should clarify "complications" in detail.

Response: we have elaborated the complications that were observed in Paragraph 1 in the MATERIALS AND METHODS part.

3. Response to Point 3: MELD score is usually used for predicting the prognosis of patients with end-stage liver cirrhosis, but not of patients with acute liver injury. Therefore, it seems not to be suitable for the use of the score in patients analyzed in this study.

Response: the use of a single liver function index is limited in assessing liver function, but the Model for End-Stage Liver Disease (MELD) score, which combines multiple indices, can play a useful role in this assessment. The MELD score system has been validated for use in CHB. Thus, the MELD score was applied for a comprehensive analysis of liver function. (Paragraph 4 of the INTRODUCTION part)

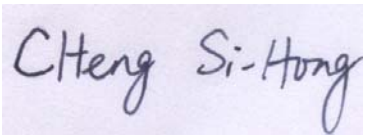
4. Response to Point 4: the authors divided the serum HBV DNA into just two categories, + or -. However, there should be a great variation in the levels of serum HBV DNA among patients with chronic HBV infection. Did the authors examine the relation between serum levels of HBV DNA and severity of liver injury or prognosis of the patients after superinfection with HEV?

Response: according to studies on Chronic HBV infection, the correlation between the level of HBV DNA, the hepatic function impairments and prognosis is uncertain. Additionally, as we regularly monitored our patients' level of HBV DNA during admission, we found that the level of HBV DNA changed during the HBV-HEV superinfection course. So, in this study, we didn't evaluate the relationship between the level of HBV DNA, the hepatic function impairments and prognosis of chronic hepatitis B superinfected with acute hepatitis E. But, this comment is quite valuable,

which gives useful hints for our further research on this subject.

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

Sincerely yours,



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