January 9, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7794-Revised with Track Changes.docx).

Title: Risk factors of chronic hepatitis C mortality: a deceased case-living control study

Author: Qing-Lei Zeng, Guo-Hua Feng, Ji-Yuan Zhang, Yan Chen, Bin Yang, Hui-Huang Huang, Xue-Xiu Zhang, Zheng Zhang and Fu-Sheng Wang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript No: 7794

On behalf of all authors, I appreciate you and the reviewers very much for your instructive suggestions and the expert comments on our manuscript entitled as "Risk factors of chronic hepatitis C mortality: a deceased case-living control study". We express our sincere thanks to you for your allowing us to revise our manuscript. We also appreciate the comments from the reviewers which have helped us to improve our manuscript. As suggested, we send our manuscript to an American paper editing company (**American Journal Experts http://www.journalexperts.com/**) to improve the quality of the manuscript for the **second time**, and win the editing certificate granted by **American Journal Experts** (Previous Certificate Verification Key is 06B6-FADC-986B-E7E5-A041 and current Certificate Verification Key is EB95-BFF0-ACAF-C9AB-7C9F). In addition, the revised parts have been highlighted with red color according to your suggestions and the comments raised by reviewers.

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

1 Format has been updated.

Thanks for the suggestions of the editor. We have already modified the title of manuscript from 15 words to 12 words according to the Journal's WRITING REQUIREMENTS OF BRIEF ARTICLES. Additionally, a decomposable figure 1 has been provided in the format of PPT. Furthermore, as suggested, we added the COMMENTS at the end of the revised manuscript.

2 Revision has been made according to the suggestions of the reviewers.

Reviewer No. 02456596:

Comment 1: The authors should elucidate the case number of CHC, compensated liver cirrhosis, decompensated liver cirrhosis and hepatocellular carcinoma (HCC) in 8250 inpatients chronically infected with HCV.

Answer: Thanks a lot for paying attention to our manuscript. We have already involved your suggestion in the revised manuscript.

Comment 2: The authors should illustrate the inclusion and exclusion criteria of conditional logistic regression analysis in the Statistical analysis of SUBJECTS AND METHODS, and give the regression coefficient in Table 3.

Answer: Thanks for your suggestions. As suggested, we have already emphasized the inclusion and exclusion criterion in the Statistical analysis of SUBJECTS AND METHODS as following: "*A conditional logistic regression model was used to estimate the relative magnitude in relation to the potential factors mentioned above*" in the manuscript, which in order to avoid repeating the similar statement in "Potential factors". In addition, we divided the Table 3 into two tables (Table 3 and 4) so as to give the regression coefficient according to your suggestion, because the previous Table 3 is too large to fill the regression coefficient data.

Comment 3: The HBcAb in manuscript should be anti-HBc.

Answer: We appreciate your suggestions very much, and have already corrected this point throughout the manuscript.

Reviewer No. 02527647:

Comment: The authors investigated a large number of HCC patients using the hospital clinical database. The results indicated that interferon-α treatment, the stage at the initial diagnosis and comorbidities are all independent risk factors for liver-related HCV mortality. The most outstanding is the big size sample. The authors already revised the paper according to the first reviewer. But, at the interferon therapy part, the authors should illustrate the influence of SVR or not SVR, cause it is well known, SVR is a key point for CHC prognosis.

Answer: We all appreciate your kindly positive comments regarding to our manuscript. SVR, which defined as HCV RNA negativity by 24 weeks after the cessation of standard of care, were all detected consecutively in these inpatients with exception of some special conditions discussed in manuscript. Minority of cases and controls achieved SVR, however, majority of inpatients were not, which were shown in Table 1 of the manuscript.

Reviewer No. 02861277:

Comment: Zeng QL and colleagues reported an interesting deceased case-living control study concerning hepatitis C virus-related mortality. The authors found that initial diagnostic stage of disease, alcohol consumption, diabetes and other comorbidities are independent risk factors for liver-related mortality while antiviral therapy is able to decrease mortality rate in CHC

patients. I believe that several points should be clarified and discussed. The authors compared two groups of patients with a different liver disease severity (Table 3), the case group, as compared to the control, had an advanced liver disease (higher percentage of liver fibrosis and hepatocellular carcinoma) thus as expected shown an earlier and higher mortality rate. The authors did not mention and analyze factors affecting antiviral treatment efficacy for instance HCV genotype 1, 2…, IL28B polymorphisms, insulin resistance also without diabetes. HCV RNA was undetermined in about 17% of the patients and the authors did not describe the presence of anti-HCV antibodies. Alcohol consumption should be quantified to distinguish between heavy drinkers, moderate and so on.

Answer: Thanks for your kindly suggestions. This study is a retrospective case-control study with a large number of patients from 2002 to 2012, and some of the subsidiary data were not very complete, so it is difficult for us to uniform all the parameters. Such as the predicting role of IL-28B SNP, which was first reported by two Nature papers in 2009 (Genetic variation in IL28B and spontaneous clearance of hepatitis C virus, PMID: 19759533; Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance, PMID: 19684573), and the patients in our study were involved from 2002 to 2012, so before 2009 this no IL-28B data, and it is difficult for us to supplement the lacking data currently. For the different liver disease severity raised in your comments, we have already included the difficult stages (different liver disease severity) as the risk factors for evaluation in our study. Furthermore, we discussed some of the issues more detailed, and have already added your advice within our manuscript.

Reviewer No. 02860577:

Comments: (Invaluable comments provided by Reviewer No. 02860577 were directly pointed within manuscript)

Answer: We all appreciate your invaluable suggestions and comments in manuscript. As suggested, we have already corrected, re-phrased and discussed these points raised by you in manuscript, with exception of those where you have already kindly done.

3 References were also corrected.

We believe that our improved manuscript is of merit and the paper is worthy of publication in a high quality peer reviewed journal such as yours.

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

Sincerely yours,

Fu-Sheng Wang, MD, PhD

The Institute of Translational Hepatology

Beijing 302 Hospital, Peking University

Beijing 100039, China

Fax: +86-10-6693-3332

E-mail: fswang302@163.com