

Dear Editors and Reviewers,

Thank you for your letter and for the reviewers' comments concerning our manuscript No.10812. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. Following are our response about reviewers' comments to our manuscript:

The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Reviewer #1:

1 The reviewer's comment: This reviewer is non-Chinese speaker and it is impossible to understand the ethics committee report.

The Authors' respond: Due to a few years ago when writing a report to be thoughtless, the report is written in Chinese, sorry about this. We will pay attention to this problem in the future.

2 The reviewer's comment: Figure 2 is lacking appropriate statistical analysis such as standard of error on top of each blue column.

The Authors' respond: Figure 2 had showed the mortality rate in three groups, respectively. If you feel inappropriate, we will continue to revise.

3 The reviewer's comment: References are lacking appropriate citation to follow WJG format.

The Authors' respond: Some references lacks of PubMed citation numbers and DOI citation or only with DOI citation when the paper was published in the past, we have provided the first page of the paper without PMID and DOI in the annex .

4 The reviewer's comment: Some tables lack of translation.

The Authors' respond: We offered some notes at the bottom of each table. If the problem persists, please let me know in order to modify.

5 The reviewer's comment: suggesting to include histology/pathology images to show liver repair.

The Authors' respond: Pathological image is indeed the most convincing "gold standard" to show liver repair. We have considered in the past to get liver tissue samples of patients with CHBLF, but it is difficult to get liver tissue samples through the liver tissue biopsy, because of the patient's critical condition, bleeding tendency and high risk. Moreover, the ethics committee failed to pass implementing liver tissue biopsy techniques, because it would harm the interests of patients. However, animal studies of regulation of liver regeneration by "TTKESC" we did in the past had shown the evidence of liver reconstruction (Li HM, Gao X, Yang ML, Mei JJ, Zhang LT, Qiu XF. Effects of Zuogui Wan on neurocyte apoptosis and down-regulation TGF- β 1 expression in nuclei of arcuate hypothalamus of monosodium glutamate-liver regeneration rats. *World J Gastroenterology* 2004; 10: 2823-2826; Song HL, Li HM, Lin LS, Gao X, Zhao BB, Zhang J, Wu Y, Yan XS, Xiao L. Effects of Diwuyanggan capsule on liver regeneration of rat with deficiency of kidney essence and liver blood. *Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases* 2013; 23: 90-92).

Reviewer #2:

1 The reviewer's comment: The cause of death should be specified.

The Authors' respond: In brief, the cause of death was multiple organ failure caused by CHBLF.

2 The reviewer's comment: The characteristic of patients should be described, especillay the presence of cirrhotic change, etc.

The Authors' respond: The enrolled patients in the clinical study were cases of mild chronic hepatitis B liver failure, with no severe ascites and hepatic encephalopathy. However, we had observed other relevant datas, such as TBIL, PTA, ALT. The paper had objective data.

3 The reviewer's comment: To compare therapeutic effect of antivral therapy, formalization of antiviral therapy should be considered.

The Authors' respond: Antiviral therapy played a role in reducing mortality of patients with CHBLF, but there was no difference among the three groups of using nucleoside drugs in the study. Moreover, we had observed the mortality rate was lower in groups with TCM("TQD" group and "TTKESC" group) than in modern medicine control group(MMC group) without TCM, and the lower mortality should be related to the effect of Chinese medicine.

4 The reviewer's comment: To rescue the patients, did you consider liver transplantation or artificial liver?

Liver transplantation was limited by the donated livers and economic conditions, and artificial liver was limited by the supply of enough plasma. As a result, the limited use in clinical studies.

Reviewer #3:

1 The reviewer's comment: Information on herbs is lacking.

The Authors' respond: There is the difference between liver failure caused by "drugs and alcohol" and CHBLF caused by chronic hepatitis B in the pathogenesis.

Integrative treatment(the treatment of integrated traditional and western medicine) of chronic hepatitis B liver failure can really improve the clinical efficacy and reduce mortality. Ministry of Science of People's Republic of China had set up "the National Key Technology R&D Program-Chronic Severe Hepatitis Syndromes and Research on Integrative Medicine treatment Programme" (No.2008ZX10005-007) had dropped mortality to below 40%.The study was just the optimization of Integrative Medicine program, and made the mortality of chronic hepatitis B liver failure declined further.

All Chinese medicine in the study had been used for a long time in clinical, and with no significant toxicity as well as adverse reactions. Because there was the imbalance between liver damage and liver regeneration for patients with CHBLF, and "TTKESC" had played the role in regulating the imbalance between liver injury and liver regeneration. If choosing the appropriate cases, in foreign countries, the application of Integrative medicine with "TTKESC" may get some benefits for patients.

What's more, the title is no more than 10~12 words/60 bytes, and if you have a better suggestion, please tell us, we will revise it. Thank you!

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Sincerely yours,

Li Han-Min

Professor of Hubei University of Chinese Medicine