January 13, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5704-edited.doc).

**Title: Hepatitis C-related liver cirrhosis—strategies for the prevention of hepatic decompensation, hepatocarcinogenesis, and mortality**

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 5704

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

1 Format has been updated.

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

(1) Comments made by Reviewer 00047453: I think it needs a couple of tables and figures to summarize the main issues.

Thank you very much for your suggestion. Following your suggestion, we have created two tables and added relevant sentences:

→ page 4, line 21 and page 5, line 1
Table 1 summarizes the outcomes of patients with LC due to HBV, HCV, alcohol, and NASH.

→ page 7, line 7
Table 2 lists antiviral therapies for HCV-related LC.

(2) Comments made by Reviewer 00047453: It would be interesting to see some comments on the rate of cirrhosis regression.

We appreciate this helpful advice. We added the following paragraph in *1.1.1. IFN therapy targeting a sustained virological response* (page 9, line 14 – 19).

→ Some data have suggested that SVR after IFN therapy can cause reversal of liver fibrosis. In studies that compared the histological findings of liver biopsy specimens between pre- and post-IFN therapy, 44–66% of HCV-related LC patients who achieved SVR had regression of LC[40-42]. In support of these results, SVR was reported to prevent or delay the de novo onset of esophageal varices in patients with compensated HCV-related LC[43].

(3) Comments made by Reviewer 00046378: My comments 1 - I advise to reduce its size of the text, due to some redundancy in details 2 - a hard polish for language and grammar in needed.

Thank you very much for the great advice. Following your advice, our manuscript has been improved by the use of an English language editing service, American Journal Experts. Furthermore, to avoid redundancy on the discussion about direct-acting antiviral angents, we deleted the following last sentences of paragraph 2, in *1.1.1. IFN therapy targeting a sustained virological response*.

→ Recent randomized controlled trials have demonstrated that triple therapy with pegylated IFN, ribavirin, and protease inhibitor resulted in a higher SVR rate than the combination of pegylated IFN and ribavirin in HCV patients with advanced fibrosis or LC (40–68% vs. 10–39%)[24, 40, 41]. Future follow-up studies may show whether the triple therapy provides more outcome benefits in these patients.

Alternatively, we added the following sentences in, *1.2. Direct-acting antiviral agents* (page 15, line 5 - 14).

→ Boceprevir and telaprevir are first-generation NS3/4A protease inhibitors and have been used combined with pegylated IFN and ribavirin in the antiviral therapy for HCV patients. Recent randomized controlled trials have demonstrated that triple therapy with pegylated IFN, ribavirin, and boceprevir or telaprevir resulted in a higher SVR rate than the combination of pegylated IFN and ribavirin in HCV genotype 1 patients with advanced fibrosis or LC (40–68% vs. 10–39%, respectively)[24, 79, 80]. A large population-based study verified the high efficacy of the triple therapy wherein an SVR rate of 42.7% was reported in HCV genotype 1 patients with LC[81]. Furthermore, several clinical trials with other DAAs for HCV-related LC patients suggested promising results.

(4) Comments made by Reviewer 00053724: I would suggest to add a chapter on hepatitis C and hepatic encephalopathy.

Thank you very much for your helpful advice. To respond your comment, we added a paragraph in *1.1.1. IFN therapy targeting a sustained virological response* (page 9, line 20 - 25 and page 10, line 1 - 9).

→ LC patients generally have reduced daily activity levels owing to impaired physical and neurocognitive functions[44-46]. As with LC due to other causes, neurocognitive impairment in patients with HCV-related LC has thus far been considered as a sign of hepatic encephalopathy due to liver disease progression. However, recent evidence has suggested that HCV infection per se also can impair neurocognitive function, regardless of the presence or absence of LC. In a recent study that supports the hypothesis that HCV may directly induce neurocognitive impairment, investigators not only detected HCV RNA in brain tissue of individuals infected with HCV but also noted that brain microvascular endothelia and brain endothelial cells expressed all of the major HCV entry receptors[47]. Furthermore, results from a recent study that investigated the effects of combination treatment with pegylated IFN and ribavirin on neurocognitive function in HCV patients revealed that patients who achieved SVR had improved cerebral metabolism and neurocognitive function[48]. Thus, SVR may contribute to the improvement of neurocognitive function in HCV patients, including LC patients, and may lead to increased daily activity levels.

(5) Comments made by Reviewer 00053724: It would make the paper more easy to read if some of the data (for example in the chapter "outcomes in patients with HCV....") is presented in table.

We appreciate this helpful advice. Following your advice, we have created two tables (Table 1 and 2).

(6) To update information, we added the following sentences:

→ page 11, line 3 - 9

A recent large retrospective analysis of LC patients with HCV genotype 1 who underwent IFN therapy determined that SVR was associated with reduced all-cause mortality (HR, 0.15) and clinical disease progression (HR, 0.16)[50]. This analysis also estimated that the number needed to treat to prevent clinical endpoints in those patients has markedly declined in relation to the improvement of antiviral therapy over five years, i.e., from 302 at 2% SVR (IFN monotherapy) to 13 at 35% SVR (pegylated IFN and ribavirin).

3 References and typesetting were corrected.

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

Sincerely yours,

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