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To: Lian-Sheng Ma
Science Editor, Company Editor-in-Chief, Editorial Office
Baishideng Publishing Group
Re: Ms. Ref. N^{o}: 61728; ***World Journal of Gastroenterology***

Fortaleza, January 19th 2021

Dear Lian-Sheng Ma,
Thank you for your Email of 10th January informing us that the above manuscript may be acceptable for publication after appropriate revision.
We were pleased to learn this and below we have replied one-by-one to each of the comments made by the 3 Reviewers. Additionally, the changes to our text that we describe below have been highlighted in yellow within the revised manuscript, to facilitate the re-review step you mention.
We believe our changes are a worthy response to the thoughtful comments of your Reviewers and we trust that our revised manuscript is now acceptable for publication in *World Journal of Gastroenterology*.

Responses to Reviewer Comments

Reviewer # 1:

Dear Authors, thank you for submitting your work to the World Journal of Gastroenterology, it is certainly an important study which was performed on solid scientific ground.
Authors' reply: We appreciate this very positive comment from the Reviewer that our study was scientifically solid.

However, I have few comments about your paper; It is very confusing and little disorganized the way you presented the information about the study design and data analysis. There are multiple paragraphs about the same topic (data analysis and statistical analysis) which can be grouped in one comprehensive section under Data and statistical analysis. I think the paper needs little organization to make the information flow smoothly and make the readers engaged.
Authors' reply: We accept the reviewer's comments and, as requested, now group several paragraphs in one section named "***Data and statistical analysis***". In addition, we reorganize the now entitled "MATERIALS AND METHODS" into just 4 different subsections, rather than the 10 sections originally submitted. We believe this facilitates the information flow and is reader-friendly without losing the original description and text detail. We hope that the Reviewer agrees.

Reviewer # 2 comments:

The liver is the main place for protein synthesis. Transplanted liver changes the alleles of the original cirrhotic liver, and the protein synthesis function will change. So, liver transplantation can cure

Wilson's disease and other metabolic liver diseases. The ApoE level and APOE may be changed after liver transplantation. In this article, DNA extraction is from oral cells, therefore, the evidence of "Apolipoprotein E Polymorphism Influences Outcomes in Patients after Liver Transplantation" is insufficient, and the genotype of the transplanted liver and postoperative blood ApoE level detection are lacking.

Authors' reply: The Reviewer raises an important question, which we recognized in our Discussion: the unknown transplanted liver APOE genotype was cited as a study limitation in our penultimate paragraph. Unfortunately, as stated we were unable to APOE genotype the donor liver and nor did we carry out ApoE blood level assays before or after transplanting patients. We accept this as a limitation, though not one vital to acceptance of our article given our additional landmark observations and positive conclusions. Moreover, we plan to continue our studies including mechanistic investigations, and will address this question in a subsequent report.

However, to respond positively to the Reviewer we have amended the final 1 paragraph of our Discussion – see below and page 14, lines 365-374 of the revised manuscript.

"This study has some limitations: data from liver transplant patients were obtained retrospectively from medical records; no data from liver graft donors, including APOE genotype, were collected; and the sample size, though large, may have been insufficient to draw strong, definitive conclusions. Isoform studies have previously shown that transplanted donor livers supply >90% of plasma ApoE [10]. The remainder is synthesized by circulating macrophages and immune cells, or by tissues such as kidney, adipose and muscle, and hence this ApoE retains the recipient's phenotype. However, to date, there are no reports of how each source, hepatic ApoE or circulating non-liver ApoE, particularly that of macrophages, might affect the inflammation and fibrosis status of the transplanted liver.

Such research will be important, and will require knowledge of the donor liver APOE genotype plus the pre- and post-operative plasma levels of each ApoE isoform. These data were not available for the present study, but our documented findings herein highlight their importance for future clinical and biochemical investigations. Indeed, in-depth and long-term monitoring of the role of APOE alleles in liver transplantation outcomes is now an important focus of our future collaborative efforts."

Reviewer # 3 comments:

HCV infection is responsible for a chronic liver inflammation, causing end-stage liver disease and HCC. ApoE is a key player in cholesterol metabolism. The authors investigated whether APOE polymorphisms may influence HCV-induced liver damage. The authors found that the E4 allele has protective effect against progression of liver fibrosis and degree of inflammation in HCV-infected patients. The study is well performed and well explained, I would suggest it publish in WJG.

Authors' reply: We are most grateful for these very encouraging and positive comments from the Reviewer.

We very much appreciate the thoughtful comments from you and the Reviewers comments, which have helped us improve further our manuscript.

We look forward to hearing your response, and specifically that our revised manuscript is now acceptable for publication.

Sincerely,

Reinaldo Barreto Oriá

Corresponding author