

Tuesday, January 10, 2017

Dear Editor,

This is a manuscript by Shu Dong, Zong-ying Zhan, Hongyan Cao, Chao Wu, Yanqin Bian, Jianyuan Li, Genhong Cheng, Ping Liu\* and Ming-yu Sun\*, entitled “Urinary Metabolomics Analysis Identifies Key Biomarkers of Different Stages of Nonalcoholic Fatty Liver Disease”. It’s to be considered as a “Basic Study” in your journal. Neither the entire paper nor any part of its content has been published or has been accepted elsewhere. All authors have seen the manuscript and approved to submit to your journal (World Journal of Gastroenterology). ESPS Manuscript NO: 31752. Should any question arise, please do not hesitate to contact us. Thank you very much for your consideration.

The following is according to the suggestions and replied one by one.

**Answers to editor’s questions:**

1. When you send back, please provide the format of doc.

**Answer: We provided the format of doc.**

2. Please provide language a certificate letter from a professional English language editing company (Classification of the manuscript language quality evaluation is B).

**Answer: We have had our paper polished by professional English language editing company and we provided the language certification.**

3. A short running title of less than 6 words should be provided.

**Answer: The short title is “Biomarkers of Stages in NAFLD”.**

4. Provide relevant files.

**Answer: Institutional review board statement, Institutional animal care and use committee statement, Conflict-of-interest statement and Data sharing statement had been provided.**

5. Please write a summary of no more than 100 words to present the core content of your manuscript, highlighting the most innovative and important findings and/or arguments. The purpose of the Core Tip is to attract readers’ interest for reading the full version of your article and increasing the impact of your article in your field of

study.

**Answer: The highlight of our manuscript has been added in revised manuscript.**

6. Please read the core tip then provide the audio core tip: Acceptable file formats: .mp3, .wav, or .aiff Maximum file size: 10 MB

**Answer: We have provided the audio core tip in the format of wav.**

7. Please put the reference numbers in square brackets in superscript at the end of citation content or after the cited author's name.

**Answer: I have put the reference numbers in square brackets in superscript at the end of citation content.**

#### **Answers to reviewers' comments:**

Reviewer 1 (Reviewer's code: 00003472):

1. The authors found that 31 metabolites were different between NAFLD and NASH in urine samples. The authors should demonstrate that these potential markers are correlated with the histological severity of NASH.

**Answer: Thanks for your suggestions. Considering the clinical situation, usually patients don't take histological tests. So we may not demonstrate the relationship of these potential markers and histological severity of NASH.**

2. In addition, the author should demonstrate levels of some nucleic acids and amino acids in blood samples. The readers of WJG want to know these potential markers are correlated with hepatic inflammation (ALT levels) and/or fibrogenetic markers (M2BPGi, type 4 collagen S etc).

**Answer: Thanks for your suggestions. Considering the limited time, we would add the relevant experiments in our further study.**

3. Same data are presented in Table 2 and Figure 2. In addition, no units are shown in Table 2.

**Answer: Thanks for your suggestions. We have added units in Table 2.**

4. Some uncommon methods are used in the present study. For instance, ESI in Figure

3, PLS and OPLS in Figure 4. The authors should explain these methods (not technical explanations but the purpose of these methods)

**Answer: Thanks for your suggestions. The purpose of PLS and OPLS was to show the difference between different groups.**

5. The authors mentioned that S-plot showed obvious metabolic difference in figure 3. However, it is difficult to understand the authors' description.

**Answer: Thanks for your suggestions. S-plot showed obvious metabolic difference between patients and healthy controls.**

Reviewer2 (Reviewer's code: 00007116):

1. I have found that their definition of NASH can be rather controversial. The authors defined NASH as hepatic steatosis by image or histology, and significant increase in ALT activity while the current guidelines specifically require a liver biopsy for its diagnosis.

**Answer: Thanks for your suggestions. In clinical, patients with NAFLD or NASH usually do not take a liver biopsy. Liver biopsy is gold diagnosis, while is not the only method to diagnosis.**

2. No validation group was presented to support their findings. Minors thing to comment are that the excessive use of table and figures distract readers a bit and the table 2 doesn't have any unit information for its figures.

**Answer: Thanks for your suggestions. We have added units in Table 2.**

I'm looking forward to hearing from you soon.

Best regards

Sincerely yours,

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