Dear Editorial Board Members and Reviewers,

Thanks for the overall positive assessments of our manuscript and your instructive comments. We have carefully dealt with your valuable comments, and our responses are shown below in blue fonts and are preceded by ">>>".

Point-by-point responses to each of the issues raised in the peer-review report:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The research article reports the differential expression of sEV in both ALI and CLI. The authors performed extensive bioinformatic analysis and identified a panel of miRNAs that would be potentially utilized as diagnostic biomarker for liver injury diseases. Subsequent mechanistic studies provided the evidence that ALI sEVs may induce macrophage polarization to M2 type. The manuscript is well structured. The story line is clear and coherent.

>>> Thanks, we appreciate the positive comments.

However, there are some minor concerns as below:

1. CLI model. From Figure 1D, we can clearly appreciate that ALT level change was very subtle at 8W and 12W. Also, the histological changes were attenuated at 12W. All the results indicate the chronic liver injury was not well established (i.e. not 'chronic' per se). Pls justify and explain in the discussion session.

>>> Sorry for the confusion. In the present study, we established a mouse model to simulate acute liver injury (ALI), chronic liver injury (CLI), and recovery. For chronic liver injury (CLI), mice were treated with CCL_4 (0.5 mL/kg) twice a week for eight weeks. The mice were sacrificed 48 h after the last injection at 8 weeks or 12 weeks (Figure 1A). The 8W group represented chronic liver injury, while the 12W group represented the recovery stage. The level of serum ALT returned to the baseline of the control group (CC) by 4 weeks after cessation of CCL_4 treatment at 12 weeks (Figure 1D). And also, Sirius Red staining showed obvious collagen deposition and pseudolobule formation in 8W CLI mice, but these morphological changes were alleviated in 12W mice (Figure 1E). Therefore, ALT level change was very subtle at

12W, and also, the histological changes were attenuated at 12W, which indicated that the chronic liver injury and recovery model was established.

To be more explicit, we explained the establishment of the liver injury and recovery model in the results and discussion sessions according to the reviewer's suggestion. We added two paragraphs and related references to the context of the revised manuscript:

(1) Page 12, RESULTS, Establishment and validation of CCL_4-induced ALI and CLI in mice, paragraph 2, " Although the ALT level change in CLI at 8W was not as prominent as those in ALI at 2D, the change was comparable to the ALT level changes reported by other study groups using the same mice CLI model [17, 18]".

Page 28, [Ref 17] **Kwon HJ**, Won YS, Park O, Chang B, Duryee MJ, Thiele GE, Matsumoto A, Singh S, Abdelmegeed MA, et al. Aldehyde dehydrogenase 2 deficiency ameliorates alcoholic fatty liver but worsens liver inflammation and fibrosis in mice. *Hepatology* 2014; **60**(1): 146-157 [PMID: 24492981 PMCID: 4077916 DOI: 10.1002/hep.27036]

Page 28, [Ref 18] **Ma X**, Luo Q, Zhu H, Liu X, Dong Z, Zhang K, Zou Y, Wu J, Ge J, et al. Aldehyde dehydrogenase 2 activation ameliorates CCL_4-induced chronic liver fibrosis in mice by up-regulating Nrf2/HO-1 antioxidant pathway. *Journal of cellular and molecular medicine* 2018; **22**: 3965-3978 [PMID: 29799157 PMCID: 6050510 DOI: 10.1111/jcmm.13677]

(2) Page 20, DISCUSSION, paragraph 1, "The 2D group and 8W group represented acute and chronic liver injury, respectively, while the 7D group and 12W group represented the recovery stage of acute and chronic liver injury. The ALT and AST levels elevated in the 2D group and 8W group, and returned to the baseline of the control groups (Figure 1B, D). Moreover, the histological changes also reversed in the 7D and 12W recovery groups (Figure 1C, E), which indicated that the acute and chronic liver injury and recovery models were well established".

2. For Figure 5C and Table 2, suggest to change to Venn diagram format, which better visualizes the result and readable.

>>> We appreciate the suggestion and have changed Figure 5C and Table 2 to Venn diagrams. Table 2 has been removed, and the Venn diagram format for Table 2 was provided as Figure 5 in the revised manuscript. The previous Figure 5 and Figure 6 were renamed as Figure 6 and Figure 7 in turn.

3. Table 1 is confusing and misleading. The miRNA list of GSE78792 liver database

is duplicated several times. The ALI/CLI rank are duplicated as well, but just represent in different order. Suggest to combine as ONE simple summary table. First column is the miRNA list of GSE database. Second column ALI rank. Third column CLI rank. The specific miRNA annotation columns are optional.

>>> Thanks for the suggestion, we have improved Table 1 accordingly.

4. The representation of Figure 6C can be improved by changing the Y-axis scale from log2 to linear. Log2 data make difficult to evaluate the changes of relative expression of cytokines.

>>> Thanks, we have changed the Y-axis scale from log2 to linear in Figure 6C.

Responses to the Editorial Office's comments and suggestions:

(1) Science editor: 4 papers were sent to me. I have reviewed 2 of them. Due to lack of further dedicated time, it will not be possible for me to review this manuscript

>>> Thanks for the efforts.

(2) Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

>>> Thanks for your recognition and important suggestion. We have carefully checked all the figure legends and the table notes and have unified the presentations throughout the manuscript and the supporting information.

We have invited a native English speaker professional to proof-read the revised paper. We sincerely hope that the revised manuscript is now to the reviewer's and editors' satisfaction. If you have any further questions, don't hesitate to get in touch with me via e-mail at: jijuling@ntu.edu.cn

Best regards,

Ji Juling M.D Ph.D

Department of Pathology

Medical School of Nantong University

Qixiu road 19# 1-2338, Nantong, China 226001

Email: jijuling66@126.com jijuling@ntu.edu.cn