Response letter

Dear reviewers:

I really appreciated your constructive comments and professional advice, which has significantly improved the quality of our manuscript. Based on your suggestion and request, we have fully revised our manuscript, and the manuscript has been polished by the language services. Words in yellow are the changes I have made in the manuscript. Now I response the reviewers' comments with a point by point and highlight the changes in revised manuscript. Full details are shown as follows:

Reply to Reviewer 1#

Dear Reviewers,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits.

To facilitate this discussion, we first retype your comments in *italic font* and then present our responses to the comments. Words in yellow are what we think are important.

SPECIFIC COMMENTS TO AUTHORS: *I congratulate authors for a well-written and informative article. There are few language errors that need to be addressed. For instance, see line 8 of subsections 3.2 and 3.3 and line 7 of conclusion. The conclusion can be made more succinct.*

Response: Base on your kind advice, we have double-checked the manuscript, and this manuscript has been thoroughly revised and edited. The changed parts are highlight in yellow in the revised manuscript. For example, "Further investigation revealed higher miR-122 levels in the serum and liver tissue of ALF survivors compared with those in the non-recovered patients[77]." (*line 8 of subsections 3.2);* "Further investigation revealed that downregulation of miR-

370 reduced the levels of proinflammatory cytokines, but had no effect on the apoptosis and proliferation of hepatocytes during HIRI[79]. Moreover, the NF-κB gene was suggested as a potential target of miR-370[80].” *(line 8 of subsections 3.3)*. Meanwhile, I have refined our conclusions. I hope these modifications will meet your requirements. Thank you.

We would like to take this opportunity to thank you for all your time involved and this great opportunity for us to improve the manuscript. We hope you will find this revised version satisfactory.

Sincerely,

The Authors

Reply to Reviewer 2#

Dear Reviewers,

Thank you very much for your time involved in reviewing the manuscript and your very constructive suggestions. We appreciate your clear and detailed feedback and hope that the explanation has fully addressed all of your concerns. In the remainder of this letter, we discuss each of your comments individually along with our corresponding responses. To facilitate this discussion, we first retype your comments in *italic font* and then present our responses to the comments. Words in yellow are what we think are important.

1) The contents of Table 1 include miRNAs, Change, Targets, Effects on HIRI, Models, and References. On the contrary, the contents of Table 3 include Manuscript, Years, Type of model, lncRNAs and Description. It appears to be better to show the contents

in Table 3 as with Table for better understanding.

Response: We gratefully appreciate for your valuable suggestion. We have modified **Table 3** to the format of **Table 1**, and we hope this modulation will meet your requirements. Thank you again.

2) The authors mentioned the molecular mechanisms of HIRI including oxidative stress, inflammatory response and immune response, and cell death. How about other mechanism of HIRI? Some ncRNA may be related to the other mechanism?

Response: Thank you for your rigorous consideration and insightful suggestion. Based on your suggestion, I have added a new paragraph 2.4 **Other mechanisms** "Many other regulatory mechanisms, in addition to those mentioned in previous sections, are involved in the progress of HIRI. For instance, mitochondrial dysfunction (such as mitophagy and impairment of mitochondrial permeability) plays a vital role in HIRI[16]. Acidic microenvironment has been reported to be a key factor affecting HIRI through the regulation of PPAR-γ[27]. Besides, lipid metabolites[59, 60], calcium overload[58], adenosine triphosphate depletion[57], gap junctions[6], dysfunctional microcirculation[5, 55], and endoplasmic reticulum stress [26, 30] can affect the development of HIRI." to address the other mechanisms involved in HIRI. As to whether some ncRNA may be related to the other mechanisms, the relevant information has been displayed in **Table 2** and **Table 4.** We hope this modulation will meet your requirements. Thank you again.

3) Minor points: The manuscript includes a mix of HIRI, hepatic I/R injury and I/R injury. Kupffer cells (KCs)include : no space before include Zhang et al found : no period after al modulatory effects no HIRI (in 3.5 The downregulated miRNAs) : on HIRI

Response: We are very sorry for our careless mistake and it was rectified thoroughly. This manuscript has been thoroughly revised and edited. Thank you for your careful check.

We would like to take this opportunity to thank you for all your time involved and this great opportunity for us to improve the manuscript. We hope you will find this revised version satisfactory.

Sincerely,

The Authors