Reviewer's report

Title: MicroRNA signatures associated with diagnosis and prognosis of patients with intrahepatic cholangiocarcinoma

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Reviewer: Kwang-Huei Lin

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Detailed comments to the author

The manuscript by Zhang et al. showed that a 30-miRNA signature and a 3-miRNA signature was established, which might be potential biomarkers for diagnosis and prognosis of ICC. Further, a 30-miRNA signature consisting of 10 up-regulated and 20 down-regulated miRNAs in ICC was established for distinguishing ICC from NIBD with 100% accuracy. Another 3-miRNA signature was identified for predicting prognosis in ICC and associated with high-risk overall survival and disease-free survival than those with low-risk. Further studies focusing on these miRNAs may shed light on the mechanisms associated with ICC pathogenesis and progression. Overall, this manuscript is not sufficiently to address 3-miRNA signature identified for predicting prognosis in ICC. Some suggestions for this paper are as follows:

Major Compulsory Revisions:

1. The diagnostic accuracy of a test is the first thing we concern. Sensitivity and specificity (ROC curve) are the most widely used to indicate the accuracy of the markers. The authors should perform the ROC analysis for individual miRNA as well as various combinations. The authors are suggested to perfume ROC analysis compared with known markers or published miRNAs. Also, why authors selected those three miRNAs but not miRNA-566, -423-5p or -143-3p, -451a? Although the authors studied on 30-miRNA signature the diagnosis role in ICC, there is no strong evidence to indicate that. The author should provide more experimental evidence to show the 30-miRNA signature affect diagnosis.

2. Since 3-miRNAs (miR-675-5p, miR-652-3p and miR-338-3p) signature has been reported as a prognostic factor of other cancer type (eg. breast, gastric, liver, neuroblastoma, cervical and colon cancer), the authors should combine the published miRNAs (miRNA-204, 31, 376c, 124, 200...) for a panel of ICC signature to increase the specificity of ICC.

3. It is interesting that 3-miRNAs (miR-675-5p, miR-652-3p and miR-338-3p) signature are so dramatically dyregulated in ICC as well as other cancers. Do the authors investigate which factors that may account for the down or over-expression of the 3-miRNAs signature?
Minor Essential Revisions

4. Among 3-miRNAs (miR-675-5p, miR-652-3p and miR-338-3p) signature, however, miR-652-3p didn’t appear in 30-miRNA signature (Table 2). Could you also discuss this?

5. In the Figure 2, the author use patients were divided into a high-risk group and a low-risk group by the median signature risk score as the cut-off point. But the patient numbers vs OS (Figure 2A) and patient numbers vs DFS (Figure 2B) Plot are not corrected matching with number shown below each panel. The authors should explain and correct them.

6. There are several similar studies published. The authors should discuss more detail about the similarity or difference.

7. The authors report 30-miRNAs dysregulated in ICC without further study. Whether those 30-miRNAs associated any diagnosis or prognosis value are still questionable.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

'I declare that I have no competing interests'