Reviewer’s report

Title: A proteomic strategy to identify novel serum biomarkers for liver cirrhosis and hepatocellular cancer in individuals with fatty liver disease.

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Reviewer: Jie Liu

Reviewer’s report:

Serum biomarkers for diagnosis of cirrhosis and HCC, such as AFP, have been proposed. Considering their limitation, authors of this article performed a pilot proteomic study to seek new, safe and cost-effective markers. A pattern of serum apolipoproteins which, in combination with CD5L, can discriminate between precirrhotic NAFLD, cirrhotic NAFLD, and cirrhotic NAFLD with HCC. Methods used are appropriate and well described, and the data are credible. As mentioned in the discussion, these methodologies contribute significantly to this field and provide the hope that improved serum biomarkers may yet become available as surveillance, diagnostic and prognostic tools in patients with chronic liver disease, even in small pilot studies requiring additional validation.

- Major Compulsory Revisions
  1. about specificity:

Table1 showed that AFP level was much higher in the patients with cirrhosis plus HCC than with only cirrhosis, how did this Phenomenon reflect in your 2-D results? CD5L has been reported up-regulated in several diseases such as atopic dermatitis, HCV infected HCC, etc. what is the advantage of CD5L compared with AFP as a serum biomarker?

According to the answer given by authors, CD5L may be a assistant marker combined with AFP for Individuals with a normal AFP who may have an HCC, or may be at a high risk of developing one. It still has its significance in HCC diagnosis.

- Minor Essential Revisions
  1. Can CD5L been detected in normal people? How about its sensitivity as a diagnostic biomarker? The results would be more convincing if there are some tests (at least westernblotting or PCR) between normal and abnormal cases.

mRNA study in combination with the ELISA assays proved that the individuals with a very low risk of developing liver cancer have relatively low levels of serum CD5L protein, although there is only one case of cirrhosis and HCC in this tissue set.

- Discretionary Revisions
  1. The alternative expressions of 5 spots in 2-D gel electrophoresis would be more clear if data of MS analysis been added (figure 1).
This has been provided in the manuscript.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests