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Jing Yu, Editor, World Journal of Gastroenterology

Dear Jing Yu

Thank you for the helpful and insightful peer-review report from reviewer code 00068250 for ESPS manuscript number 23511 (Urinary NMR Spectroscopy of a Bangladeshi Cohort with Hepatitis-B Hepatocellular Carcinoma: a Biomarker Corroboration Study, I. Jane Cox, Abil E. Aliev, Mary M.E. Crossey, Mahvish Dawood, Mamun Al-Mahtab, S.M.F. Akbar, S. Rahman, Antonio Riva, Roger Williams and Simon D. Taylor-Robinson).

In reply to the points made:

1. **Query:** Some data in this study seem questionable. For example, HBV background of the 42 patients with HCC should be described in detail. Patients with a past history of HBV infection are quite different from those with HBsAg positive result currently in respect to the risk of HCC development.
   Reply: Thank you for suggesting more information about the HBV background of the HCC patients is given to show whether the HCC patients had past or current HBV infection. The following additional information has been included in the Methods to summarise all had current HBV infection: All patients with HBV-related HCC provided a 5-10 year history of their liver disease and all were sero positive for hepatitis B surface antigen (HBsAg) and were expressing antibodies to hepatitis B core antigen (anti-HBc) at the time of sampling. Forty two of these patients had hepatitis B e-antigen (HBeAg) status determined and levels of HBV DNA were quantified in 35 subjects.
2. **Query:** The diagnosis of the 42 patients with HCC is also problematic. A diagnosis of HCC only by image technique or serum AFP level is unreliable.
   Reply: The final HCC diagnosis was confirmed by fine needle aspiration cytology following clinical and biochemical diagnosis. The following additional information has been added to the Methods: The diagnosis of HCC was made from past history of HBV-related chronic liver disease, clinical presentation, ultrasound assessment of HCC nodules, elevated AFP levels. The diagnosis was confirmed by fine needle aspiration cytology (FNAC). and the Results: All HCC patients had underlying cirrhosis and the diagnosis of HCC was confirmed by FNAC in all cases. The levels of HBV DNA showed considerable variation (Table 2).

3. **Query:** Patients with advanced HCC are quite different in biochemical condition from those with early HCC and should be described separately.
   Reply: As now summarised in the Results, all patients were considered to have advanced HCC, which is a typical finding in Bangladesh. As part of the Discussion, it is suggested that further studies are undertaken to document urinary NMR parameters in patients with very early HCC.
4. **Query:** The typical biomarkers should be summarized but not only NMR spectroscopy which is just a means of examination.
   Reply: Clinical and biochemical results have already been summarised in Tables 1 and 2. We do agree that further prospective studies are warranted to compare the NMR findings with the diagnostic biomarkers in more detail and so have added/modified the following sentences for further studies in the Discussion. Increased study numbers would allow inclusion of training and validation data sets and also a more detailed comparison of NMR findings with currently available diagnostic serum and clinical biomarkers. Further prospective studies looking at the urinary NMR differences in patients with very early HCC, for example stage 0 using the Barcelona Clinic Liver Cancer score[23], and also following treatment, would underline the potential of implementing a urinary screening test for HCC.
5. **Query:** There are numerous typo and grammatical errors in the manuscript.
   Reply: Some of the sentences have been rewritten for clarity. The typographical errors have been corrected.

I enclose all the documents required for resubmission and we hope that the paper is now acceptable for publication in the World Journal of Gastroenterology.

Yours sincerely

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