Author's response to reviews

Title: Hepatitis B vs. Hepatitis C Infection on Viral Hepatitis-Associated Hepatocellular Carcinoma

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Author's response to reviews: see over
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Dr. Nigel Bird  
Associate Editor  
*BMC Gastroenterology*  

Dear Dr. Bird,

Thank you very much for your letter of April 11, 2012 regarding our manuscript entitled “Hepatitis B vs. Hepatitis C Infection on Viral Hepatitis-Associated Hepatocellular Carcinoma” (Ms. No. 4875267526842128). We greatly appreciate the concerns raised by the reviewers and have revised manuscript accordingly.

Enclosed please find a point-by-point response to the reviewers’ comments and the revised manuscript with changes highlighted in blue. Thank you very much for considering the revised manuscript. We look forward to hearing from you.

Sincerely yours;

Spiros P Hiotis, MD, PhD  
Associate Professor of Surgery
Reply to Reviewer 1  
Ms. No. 4875267526842128

We would like to thank Dr. Weber for the interest in our paper and the thoughtful reviews. Listed below is our point-by-point response to address the concerns.

1. “The authors should outline how many pts did not have tissue dx of HCC. In these pts, how was dx obtained? Was this based solely on imaging findings?”

Fifty one of 127 patients (40%) did not have tissue diagnosis of HCC. For cases in which no tissue was available, patients were diagnosed with HCC if dynamic imaging findings (CT with intravenous contrast or MRI only) of a hypervascular solid liver mass with features characteristic for HCC were present in a setting of underlying risk factors, along with a clearly elevated serum alpha-fetoprotein (>100 ng/ml). We have included this information in the revised manuscript (p.6, Methods).

2. “Re. differences in AFP production, were these results replicated if the cut off of nl vs abnl was used vs cutoff of 100?”

A cutoff for serum AFP of 100 ng/ml, in defining AFP-producing HCCs, was used to increase the sensitivity of this assessment in patients with HCV. Unlike patients with HBV, those with HCV commonly have modest elevations in their serum AFP (usually under 100) as a consequence of cirrhosis, and not necessarily as a result of production by tumor.

We have performed a more detailed analysis of AFP that included the comparison of median values and proportions of AFP at multiple breakdown levels (Table 1, p.9 and p.10, Results). The data indicate that HCV-associated HCC had much lower median AFP levels (37 ng/ml vs. 1000 ng/ml for HBV-HCC). While the proportion with normal AFP (<20ng/ml) was not different between HBV-associated HCC’s and HCV-associated HCC’s, HCV-associated HCC’s had much lower proportions that produced serum AFP greater than 100 ng/ml, 1,000ng/ml or 10,000ng/ml. These data are included in the revised manuscript (p.9 and p.10, Results, Table 1).

3. “It would be interesting if the authors correlated longterm outcomes (eg RFS, OS) with hepatitis type.”

Given the clinical environment in which this study was conducted, we were unable to perform a longitudinal assessment of long term outcomes according to underlying viral etiology.

We agree with Dr. Weber that determining whether viral etiology is an independent prognostic factor for HCC is important, and requires further dedicated investigation. Unfortunately we were unable to obtain these data mainly due to demographic-specific obstacles in maintaining long-term follow-up after diagnosis. The majority of patients (80%) were not eligible for treatment with curative intent (resection or transplantation), which often led to return of our transient
immigrant patients to their native countries of origin. Therefore, this study is not adequately
designed to determine whether underlying HBV or HCV is an independent prognostic factor in
patients with HCC following surgical resection or liver transplantation. We are currently
conducting studies to evaluate the impact of viral status on clinical outcomes following surgical
resection or transplantation in additional patient cohorts, and hope to address this question in the
near future.
Reply to Reviewer 2  
Ms. No. 4875267526842128

We would like to thank Dr. Bloomston for the interest in our paper and the thoughtful reviews. Listed below is our point-by-point response to address the concerns.

1. “The authors suggest that screening for HCC in HBV carriers should start earlier than age 40 as recommended by AASLD. It would be helpful if they include data on HBV DNA concentrations to determine the correlation with cancer risk. The AASLD considers high HBV titers as high risk for HCC regardless of age.”

We agree with Dr. Bloomston that the viral load is an important factor to consider. However, the proportion of the patients with available viral data at the time of diagnosis in this cohort was limited (21 out of 89 patients). Of these, only 3 patients were under the age of 40. Therefore, we were not able to determine the impact of HBV viral load in this data set. We are currently conducting a study in a larger patient cohort to evaluate the impact of HBV viral load on patient outcome, and hope to address this exact question in the very near future.

2. “The authors suggest that AFP may not be a useful screening tool for HCV-associated HCC based upon an arbitrary threshold of 100, acknowledging that this is well above their lab's upper limit of normal. This should be tempered in the discussion as trends in AFP may more important in a screening program than a threshold value.”

We agree that a level of 100 for AFP is somewhat arbitrary, and did not intend to suggest this as a threshold for HCC screening. We have therefore performed a more detailed analysis of AFP which includes a comparison of median values and proportions of AFP at multiple threshold levels (Table 1, p.9 and p.10, Results). The data indicate that HCV-associated HCC had much lower median AFP levels (37 ng/ml vs. 1000 ng/ml for HBV-HCC), with lower proportions of patients expressing serum AFP at thresholds of 100 ng/ml, 1,000ng/ml or 10,000ng/ml. These data indicate a clear difference in AFP levels, and suggest that the sensitivity of serum AFP as a screening tool may be different between HBV-associated HCC and HCV-associated HCC. We have revised the manuscript to include these changes (p.9, p.10, and p.14).

3. “As a reader, I would be interested to know what proportion of patients actually underwent definitive therapy with curative (i.e. resection, transplant, ablation) or palliative (i.e. TACE, chemo) intent. Suggesting that curative therapy was not available to patients outside of Milan criteria is not a fair estimation of who could (or did) undergo curative therapy since a large single lesion or limited multifocal disease >3cm without major invasion may still be curable with resection.”

We agree with Dr Bloomston that patients outside of Milan criteria are often eligible for surgical resection with curative intent. However, our intent in applying Milan criteria to this patient
cohort was to determine eligibility for treatment with curative intent and expectation of a favorable outcome. This is articulated in the last paragraph of the discussion, with references to literature describing more favorable outcomes in resection patients when survival analyses are performed using application of Milan criteria. It is not our intent to suggest that Milan criteria should be applied in determining eligibility for resection. Nor is it our intent to suggest that patients are incurable if diagnosed outside Milan criteria. We have simply attempted to apply an objective, widely accepted system in determining which patients could be treated with the best expectation of cure.

4. “Table 3 is not helpful as this single data point is already in the text.”

We agree, and have removed Table 3 from the revised manuscript.

5. “...highly statistically significant...” is a misnomer and should not be in the results section.”

We agree, and have removed them from the revised manuscript (p.8-11, Results).

6. “Although I doubt it will change the p value much, fisher's exact test is more appropriate than chi-square when the # of events is <10 (table 1).”

We reanalyzed the data using the Fisher’s exact test, and have included the new analysis in the revised manuscript (p.7, p.8, and Table 1).

7. “Data is introduced in the discussion regarding ethnicity which is not included in the results.”

We have included these data in the revised Table 1 and Results section (p.8, Results, and Table 1).

8. “Throughout the paper are multiple misuses of commas and hyphens.”

We have corrected these mistakes.