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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 36901

Title: The high burden of hepatocellular carcinoma and viral hepatitis in Southern and Central Vietnam: experience of a large tertiary referral center, 2010 to 2016

Reviewer's code: 02860622

COMMENTS TO AUTHORS

I have some remarks concerning the proposed article which is interesting especially for the number of CHC: 9% of patients without a viral cause? that mean ? other causes (dysimmune, NASH ...) or healthy liver - What are the modes of contaminations of viral infection ? - Given the common etiology is viral B? What is the proportion of patients who have received antiviral treatment and what is their genotype, viral load ? - Among the CHC diagnosed, what is the rate of patients from the screening program?

Author response:

We appreciate the comments made by the reviewer. We suspect that individuals for whom patients without a viral etiology identified, were likely from another cause of chronic liver disease as the reviewer points out- non-alcoholic steatohepatitis, autoimmune hepatitis, other metabolic hepatitis, toxic (alcohol, aflatoxin, etc.) or vascular etiologies all can result in advanced fibrosis and cirrhosis, all resulting in risk for development of hepatocellular carcinoma.

The patients receiving care at Cho Ray hospital represent individuals referred from other community providers either when HCC is suspected, or when it has been diagnosed. In this setting, not all patient data is available for analysis. Unfortunately, as a result we do not have information available on all patient disease characteristics, including antecedent patient treatment regimens (if any), viral genotype, or viral load. In response to all reviewer comments requesting additional covariate information, we have added a statement within the manuscript, acknowledging this as a limitation of our study.

Currently, there is not a large-scale, universal screening program in place to evaluate for chronic HBV/HCV, formal national care access pathway for those found to have chronic viral hepatitis, for HCC surveillance programs. We believe that our results emphasize the importance of establishing such programs in Vietnam.



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Reviewer's code: 03646639

COMMENTS TO AUTHORS

The paper written by Nguyen et al, entitled 'the high burden of hepatocellular carcinoma and viral hepatitis in Southern and Central Vietnam: experience of a large tertiary referral center, 2010 to 2016 is an interesting study. The authors analyzed data from 24,091 Vietnamese patients with primary hepatocellular carcinoma (HCC). They revealed the number of patients has increased from 2010 to 2016, with most those having chronic HBV or HCV infections and advance stage disease at diagnosis. They also stated that tumor marker; AFP was elevated in only approximately half of the patients and use of additional biomarkers as a surveillance tool is required to determine risk of HCC development. The data is presented clearly. I have the following concerns. 1) It would be useful if authors showed more clinical baseline characteristics of the patients including tumor size, tumor number and child-pugh classification. 2) It would be helpful if authors analyzed risk factors for HCC other than HBV and HCV infection, for example alcohol consumption, cigarette smoking, Aflatoxin B1 exposure, and coffee consumption.

Author response:

We appreciate the comments made by the reviewer. Unfortunately, patient tumor details are currently extracted in a state that does not allow for analysis, and we do not have information on assessments (if any) for alternative causes of chronic liver disease or HCC. We have added a comment acknowledging this as a limitation of our study. Additionally, data on patient evaluation for alternative causes of chronic hepatitis are not available in the records of Cho Ray Hospital as most patients were referred from community providers after diagnosis of HCC, thus it is unknown whether these patients had received past evaluation for other causes of liver disease. However, we maintain that despite the limitations in evaluation for alternative etiologies, this study is significant in that most patients were determined to have HBV or HCV, and that many patients were not treatable by the time of presentation to Cho Ray Hospital.



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Reviewer's code: 00187828

COMMENTS TO AUTHORS

The manuscript entitled The high burden of hepatocellular carcinoma and viral hepatitis in Southern and Central Vietnam: experience of a large tertiary referral center, 2010 to 2016 by Song-Huy Nguyen-Dinh et al. has been evaluated as follows: it is well-written and presented well. It is an observational study and gives extensive data on epidemiology of HCC regarding HBV and HCV infections.

Author response:

We appreciate the comments of the reviewer, and echo that we believe that our primary study strength lies in both the wide geographical catchment area of Cho Ray Hospital, the large numbers of patients from whom data were obtained, and multi-year time period included in this study.



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Reviewer's code: 00068348

COMMENTS TO AUTHORS

The article deals with the correlation of HCC and viral hepatitis in Vietnam. It is well written providing adequate information about the presence of HCC due to hepatitis. My only remark is that 9% of non-viral cause is somehow a large proportion and my second one is what about treatment and survival.

Author response:

We thank the reviewer for his or her comments. We believe that 9% non-viral cause may be an underestimate of the true epidemiological estimate, as this would presumably encompass all other causes of chronic liver disease (non-alcoholic fatty liver disease, autoimmune hepatitis, toxic or vascular liver injury such as aflatoxin exposure). For example, in the United States non-alcoholic liver disease is becoming the most common cause of chronic liver disease. Conversely, a 91% viral etiology as we had observed further emphasizes the high disease burden that viral hepatitis places on the Vietnamese population, through both HCC but also through cirrhosis and other manifestations of chronic viral infection.



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Reviewer's code: 03475479

COMMENTS TO AUTHORS

Authors described about the prevalence of HCC diagnosed at a large tertiary referral center in Southern and Central Vietnam. In this study, many patients were diagnosed with advanced disease. HCC treatment is determined according to HCC progression and liver reserve function. Several issues should be addressed. 1. Liver functions (e.g. Child-Pugh score, MELD, Alb, T-Bil,,,) should be clarified. 2. The staging of HCC should be shown. At least, the presence of extrahepatic metastasis and macroscopic vascular invasion should be clarified. 3. Authors should mention how patients were followed. Or authors should describe the main reason of referral to the hospital. 4. Authors should show the history of HBV vaccination. 5. HBV-viral load might be mentioned. 6. Authors should discuss more detail how patients with chronic liver diseases should be followed.

Author response:

We much appreciate the reviewer's comments and the recommendation for additional data. We agree that further information (laboratory testing, history of vaccination, evaluation for alternative causes of chronic liver disease) would allow for more granular assessment of disease etiology, severity, and risk. We have edited our manuscript to further acknowledge the need for detailed assessments including laboratory and clinical characteristics, and a standardized disease staging system (including consideration of the Child-Pugh or Barcelona Clinic Liver Cancer classification systems).

As recommended by the review, we have edited our manuscript to include a comment on context for patient presentation to Cho Ray Hospital, which is to receive further care for HCC, or after a new diagnosis of HCC. We additionally have added further details about implications of our findings for care of patients with chronic liver disease.



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Reviewer's code: 02441161

COMMENTS TO AUTHORS

This observational study elucidated the burden of primary HCC and viral hepatitis in the largest tertiary referral center in southern and central Vietnam, placed on the resource-limited medical system, as well as geographic and demographic epidemiological trends from 2010 to 2016. The authors find an increasing number of patients receiving care at the Hospital, with most patients having an advanced disease stage not amendable to treatment, and additionally these cases are reasonably attributed to chronic HBV or HCV infection. This is a well conducted and well written study. The results are shown nicely and the figure is impressive.

Author response:

We thank the reviewer for reviewing our paper.