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Observational Study

Risk factors for hepatocellular carcinoma in cirrhosis due to nonalcoholic fatty liver disease: A multicenter, case-control study

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COMMENTS TO AUTHORS: Reviewer 1

The topic of NAFLD -->cirrhosis --> HCC is important and still under-appreciated. The study is retrospective but well executed with decent numbers. The main result that older men were at greater risk/had higher rates of HCC development fits with observations with respect to other etiologies of HCC--this point might be emphasized.

A few clarifications would improve the manuscript:

1) what were the NAFLD/NASH durations (ages at onset) in cases and controls?

Unfortunately, this data is not available and we have added this limitation to our discussion.

2) Where there gender differences with respect to occurrence of cirrhosis, i.e. was it more common in females overall?

Our study looked only at those with cirrhosis and did not include non-cirrhotics controls but would be an excellent idea for future projects.

3) It would be of interest to consider metabolic syndrome as a variable rather than its components.

We agree but were limited by a lack of waist circumference to correctly identify those with MetS.

4) with regard to histopathology, were there differences in severity of fatty liver [grades] between cases and controls, men and women? This is not a question about fibrosis or cirrhosis--just the degree of steatosis and steatohepatitis

We appreciate this comment. No differences was seen but a limited number had normal (non-tumor) liver tissue to evaluate. We plan to do more evaluation in prospective cohorts.

5) Since males predominated for HCC, it would be of interest to analyze data along sex lines to try

identifying factors in men or women associated with HCC.

This is an excellent point. We attempted this but likely due to small numbers after dividing by gender, no significant differences were seen.

COMMENTS TO AUTHORS: Reviewer 2

Kathleen et al. found male gender, increased age, and non-Hispanic ethnicity are associated with HCC in NASH cirrhosis, and suggested that these parameters may be useful for diagnosis and treatment of NASH cirrhosis associated HCC. It is an important report and I think that it is suitable for publication in World Journal of Gastroenterology if author have revised the following points.

1. Author should clarify whether some biochemical parameters, which have reported the involvement in the progression of NASH, for example AST/ALT and iron level, is associated with HCC in NASH cirrhosis.

We appreciate this thoughtful comment. We did not see a difference by HCC status by ALT (shown in table 1) or AST (data not shown). Unfortunately, we did not have sufficient data in this retrospective study to assess the relationship between iron or ferritin and we will plan to do this moving forward in prospective studies.

2. It should be suggested why the risk of HCC is decreased in the Hispanic ethnicity

The risk of HCC in any chronic liver disease has been found to be increased in US born Hispanics (Setiawan Cancer 2016) and in all individuals with diabetes (Setiawan JNCI 2014). Given our cohort of NASH cirrhotics, one might expect diabetes and/or Hispanic ethnicity to be associated with the risk of HCC. The absence of diabetes as a risk may, in part, explain this result in our findings. The manuscript has been amended to address this issue. As aforementioned, we plan to investigate these covariates in a larger analysis of subjects who develop HCC across different etiologies of chronic liver disease to further explore this unexpected finding.