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Reviewer A

Major issue:
Zhu and colleagues (reference Zhu L, Jiang J, Zhai X, et al. Hepatitis B virus infection and risk of non-alcoholic fatty liver disease: A population-based cohort study. Liver international: official journal of the International Association for the Study of the Liver. 2019;39(1):70-80) performed a much larger analysis of greater than 2300 patients and had similar methodology to the current paper. A re-write is required to highlight what extra information this current work provides compared to Zhu et al; as it stands it appears to provide no extra insights to this important issue and uses less than a tenth of the cohort size compared with Zhu.

Reply: In Zhu et.al's article, they looked at the rate of incidental NAFLD in patients with CHB. Out of the 2393 patients, 283 progressed into NAFLD. On the contrary, our study focused on the interaction of CHB and established NAFLD with more severe hepatic steatosis. Zhu et.al's study also recruited an entirely Chinese population due to geography, with diagnosis by ultrasound. Our study subjects are more diverse and pertaining to our patient population, and our diagnosis of hepatic steatosis and its stage is made by more sensitive and valid method of TE. We rewrote the text per your suggestion, and highlighted these differences.

Changes in text: Please see page 11, line 326-330 (tracking version) for change, "In Zhu et al's large population-based cohort study, 283 out of the 2393 Chinese adult CHB patients developed NAFLD. The incidence of NAFLD, detected by sonogram, was not associated with viral factors except a negative relationship between detectable HBV VL with incidental NAFLD in patients with concurrent type 2 diabetes mellitus (HR, 0.37; 95%CI, 0.14-0.98)."

Other feedback:
Consider changing NAFLD to MAFLD to be consistent with modern definitions

Reply: Our initial screening of study subjects were based on the ICD-9/10 codes for NAFLD. It may not be appropriate to replace "NAFLD" by "MAFLD" in this particular population.
Changes in text: None

Line 119 need units for BMI

Reply: Added.
Changes in text: Page 7, Line 179 and 190 (tracking version), “kg/m2” added

Please define CAP scores that correlate with HS>2

Reply: We added the cutoff values we used for S2 and S3.
Changes in text: Page 7, Line 185-187 (tracking version), added cutoff values. “The cut-off for steatosis stage 2 (S2) and 3 (S3), were defined as CAP > 268 dB/m and > 280 dB/m, respectively, by multi-etiology model.”

Line 148 needs a “0” prior to the decimal point in the p value

Reply: Added
Change in text: We corrected all p values as appropriate

A few parameters were described as mean values (eg age, HDL-c, liver biochemistry) were the data for these all normally distributed? If not should be median.

Reply: We changed to median in the text and table.
Changes in text: We replaced “mean” and “standard deviation” with “median” and “interquartile range” in all applicable places.

Line 168: Again this is all information that has been presented previously in much larger studies. You need to explain how some of your findings are novel.

Reply: We modified the discussion.
Changes in text: Major modifications for discussion, especially page 11, line 330-334 (tracking version), “Our study not only reveals the lack of basic correlations between HBV viremia and severity of HS, but also provides evidence for lack of interactions between HBV VL and MetRFs in the progression of HS. This may further strengthen the assumption that HBV viremia and MetRFs act as independent modulators in the progression of NAFLD.”

Line 194 missing “individuals” after non-cirrhotic
Reply: We meant to describe the subjects as non-cirrhotic and anti-HBe positive. We added “and” to make more obvious.

Change in text: In all applicable places, e.g. page 10, line 282 (tracking version),

Line 197 should be ROR not Ratio of OR
Reply: Noted and changed.
Changes in text: changed to ROR, page 10, line 285 (tracking version)

Reviewer B

I read with interest the article on effect modification of viral load on hepatic steatosis. The authors demonstrated that viral load had no impact on the pressence of steatosis nor modified the assocation between metabolic riskfactors and steatosis. Their cohort comprised predmoninantly treated individuals. This information is relevant, even though it is a negative finding. However I think the authors can improve their manuscript and shorten it significantly. Perhaps it may be published as a ”short communication” if that type of article exists in TGH. The message is important and relevant and helps to understand the complex interplay between viral load, metabolic risk and steatosis.

Comments
Line 43-45: “When controlled for age, sex, and hepatitis B treatment, the odds of hepatic steatosis > stage 2 increased significantly by 79% for each additional metabolic risk factor in undetectable group (odds ratio 1.79, 95% confidence interval 1.21–2.74, P = 0.0049).” This fragment is not clear to me, because based on the Table 2 I conclude that metabolic risk factors are associatied with 1.79 higher risk of steatosis (regardless undetectable or detectable HBV DNA). The interaction term in this table illustrates that there is no effect modification, hence this reported odds ratio is applicable to the population regardless of the HBV DNA level in my opinion. Similarly in line 47 I think “in the absence of metabolic riskfactors” can be removed. This occurs again in the results section e.g. line 169-170, 194-195 and on several other occaisons.

Reply: We agree that the absence of significant interaction permits a broader interpretation of these coefficients, not limited to subgroups.

Changes in text:

- **Removed** “in undetectable group” on line 47 (tracking version)
- **Removed** “in the absence of metabolic risk factors” on line 49 (tracking version)

- The sentence was changed to "Interpreted in the setting of an insignificant interaction variable, the odds of HS > 2 increased significantly by 79% for each additional MetRF when controlled for age, sex and HBV treatment." Line 253-254 (tracking version)
- "Due to the interaction terms, there was no scientifically meaningful interpretation of the exponentiated coefficient for the log HBV DNA plus one." was changed to read "In the setting of insignificant interaction variables, the odds of HS > 2 does not change for each unit increase in Log(HBV+1) (OR = 1; 95% CI 0.2-4.1)." See line 275-277 (tracking version)
- Removed "in subjects without detectable HBV VL" on line 255 (tracking version)

You may consider replacing the "ROR" by interaction term, which may be a more common term and have better understanding with the readership.

Reply: At this time, we would like to continue using ROR with current study, and will look into interaction term for future studies.
Changes in text: None

Line 54-56, the conclusion may be worded more specifically. I do not see any evidence that hepatitis B viremia has any impact of hepatic steatosis. Therefore I would suggest to rephrase that into something like: "The odds of hepatic steatosis in CHB patients is affected by metabolic risk factors and not by hepatitis B viremia."

Reply: The text has been changed.
Changes in text: Page 4, Line 65-67 (tracking version)

Line 105, which cut-off was used for CAP to determine S2 steatosis?
Reply: We added the cutoff values we used for S2 and S3.
Changes in text: Page 7, Line 185-187 (tracking version), "The cut-off for steatosis stage 2 (S2) and 3 (S3), were defined as CAP > 268 dB/m and > 280 dB/m, respectively, by multi-etiology model."

Line 133-142, in order to make it more concise, you can start the second prespecified model by " In the second pre-specified model we replaced the number of metabolic riskfactors with the individual metabolic riskfactors" In addition, you may want to reconsider if the information in 139-142 is necessary to report in the methods section

as this is standard for logistic regression.

Reply: The text has been re-worded.

Changes in text: page 8, line 214-216 (tracking version), “In the second pre-specified model we replaced the number of metabolic risk factors with the individual metabolic risk factors and included interaction variables between HBV VL and each of these risk.”

Although it is correct, please remove “plus one” after the log HBV DNA. This improves readability and it has already been mentioned in the methods section.

Reply: “Plus one” has been removed.

Change in text: Page 10, line 277 (tracking version), removed “plus one”.

Line 181-183 may be sumarized as “The individual metabolic riskfactors were not associated with steatosis, nor was effect modification by viral load observed” because this information is depicted in the table and otherways difficult to read with so many numbers in it.

Reply: The text has been changed.

Change in text: Page 10, line277-279 (tracking version), “Controlled for age, sex, and past HBV treatment, the individual metabolic risk factors were not associated with steatosis, nor was effect modification by viral load observed.”

Could the authors explain why they only select Hbe antibody positive patients?

Reply: We made a decision to focus our analysis on a particular phase because CHB is vastly heterogenous in patient demographic and disease progression. We would like to minimize the confounding factors. We chose to look at the patients in immune-active phase for this study, and may expand the analysis onto other phases in the future.

Change in text: Page 11-12, line 339-378, “In addition, we focused our analysis on subjects with positive HBe antibody with the intent to investigate patients in the immune-active phase. CHB is a vastly heterogenous disease with a wide range of patient demographic and stages of disease. By focusing on one particular phase of the disease progression, we intended to minimize the confounding factors.”

Consider using a more lenient cut-off of HDL-c < 50 mg/dl in female in line with for example the novel MAFLD criteria.

Reply: We will modify the cut-off values accordingly in the future studies, and to take into account of the sex-appropriate cut-off.

Change in text: none

Please be consistent in the numbers after the decimal provided for P-value throughout

the paper (2 for age, 3 for sex/race)
Reply: We have changed all p-values to 3 digits.
Change in text: All P-values

Reviewer C

The article by Shi et al is a retrospective, cross sectional study of 184 chronic hepatitis B patients with concurrent NAFLD. The study aims to explore whether HBV VL alters the relationship between metabolic risk factors and hepatic steatosis via the use of interaction terms in multivariable logistic regression.

While the statistical analysis appears sound, I question the utility of this study's aims.

Major comments
1. What is the clinical significance of identifying an effect modification on metabolic factors and HS? Why not investigate the debated question of whether HBV VL affects HS itself and related sequalae (ie cardiovascular or metabolic complications)
Reply: Our study has shown that HBV VL does not correlate with the severity of HS in our patient population, and we further analyze the effect modification. We will consider expanding our study to clinical sequalae for future projects.
Change in text: No major change apply to this comment.

2. I don't think the study is large enough to detect a difference, especially in pre-specified model 2 where all the variables are non-significant. The study conclusions are worded too strong
Reply: We have re-worded our conclusion accordingly.
Change in text: Page 12, Line 380-387. “In conclusion, we do not find evidence of effect modification of HBV VL on the association between MetRFs and HS in our non-cirrhotic and HBe antibody positive CHB patients. Our study suggests that the odds of hepatic steatosis in CHB patients is affected by metabolic risk factors and not by hepatitis B viremia. The impact of HBV VL on the progression of NAFLD is unlikely to be modulated through the advancement of HS. Larger studies including different phases of CHB are warranted to determine the interaction amongst HBV VL, HS and MetRFs, as well as to clarify the role of other hepatitis B viral factors in the progression of NAFLD in patients with or without MetRFs.”

3. Why not test a basic model without interaction terms first?
Reply: Our study shows that HBV viremia does not have basic correlation with severity of HS. The basic model is also commonly seen in existing literature with conflicting

conclusions. Our interest is also to detect if there is any interactions between the HBV viremia and MetRFs in the progression of HS with the assumption that if HBV viremia doesn't increase severity of HS (which is shown in current literature), and the interaction between viremia and prevalent MetRF also doesn't increase severity of HS, then we will be more confident to conclude that the presence or absence of viremia should not change the correlation between MetRFs and HS.

Change in text: We made major modification in discussion. Page 10-11