Reviewer's report

Title: Prevalence of and the factors associated with diabetes mellitus in patients with chronic liver disease

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Reviewer: Gregory Kirk

Reviewer’s report:

General

Alavian and colleagues have performed blood glucose testing to diagnose diabetes (DM) among sequential patients at a referral hepatitis center in Tehran. They provide prevalence and risk estimates for DM which suggest DM’s association with advancing liver disease (chronic "inactive" HBV carriers, HBV/HCV "active" infection, and cirrhosis). The data provided are interesting and the results discussed appropriately. A major limitation is sample size, as many of the subgroups have small numbers. There also needs to be strengthening of many of the case definitions and clearer explanation of some methods. There are additional analyses that may provide interesting information.

Unfortunately, the cross-sectional nature of the study is unable to provide information regarding the primary research question of whether DM in CLD is simply a function of progressive liver disease or if hepatitis infections (particularly HCV) convey an increased risk for DM even after controlling for severity of liver disease. The novel aspect of this manuscript therefore lies in the evaluation of the association within an Iranian population, which can be further emphasized.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Study design issues:
1) Population - Methods describe recruitment of consecutive patients and gives multiple exclusion criteria. However, all patients stated as enrolled (n=185) are included in later analysis. The subjects with NASH are said to be excluded but weren’t included in initial enrollment number. How many subjects were excluded, for what reasons, and were there any etiologic or demographic factors associated with exclusion vs inclusion?

Also, provide more background on the referral patterns of care. Who gets to the Tehran Hepatitis Center? Please address referral bias and generalization to the Iranian population. Related to this, I would advocate looking strongly at any racial, ethnic, religious factors which may be determinants of DM in this population. Most of the negative studies of HCV and DM are in racially homogenous southern European populations and there may be racial difference in susceptibility. Explore this in your study as well.

2) Case definitions - Authors need to provide more information regarding how the 60% of cirrhotic patients were diagnosed without histology. How many were clinical vs. ultrasound vs. varices? What were ultrasound criteria for cirrhosis?

3) DM diagnosis - It is repeatedly stated that ADA diagnostic criteria were used, but they require FPG at 2 different measurements. Was a single elevated level used or were all diagnoses in the
Clinic based on the OGTT? Give the proportions diagnosed by each method. If only 10 patients were newly diagnosed, how many of the others were based on self-report of taking meds? Perhaps, the well-controlled DM's should be looked at separately in the analysis to see if there is less of an association with CLD? What about those with different durations of DM?

4) Chronic hepatitis patients - describing patients with "viral hepatitis serologic and molecular assays" is inadequate. This area could be greatly strengthened by providing the methods of lab testing and incorporating the actual data into your analysis. Is DM in CLD associated with level of HBV DNA, with HCV genotype, etc?? Also I would advocate stratified analysis by HBV vs HCV infection. Your control group for much of the analysis is HBV carriers but that is not an adequate comparison for HCV CLD or cirrhosis. Is the DM risk different between the HBV and HCV groups?

Analysis issues-
1) OR estimates with 95% CI's are much more informative than listing the p values. Since this analysis has already been done, I would incorporate this for presenting the data in both the results and in the abstract.
2) Many additional analysis have been described above, including incorporation of ethnic,dietary information, of stratified by HBV/HCV status or by DM treatment status. Also, although the IGT and IFG groups are identified through testing, they are not used in any analysis. Compare your findings by including them with the DMs in a larger outcome of impaired glucose tolerance vs DM alone as the outcomes. You could also look at other case definitions of DM (WHO criteria) and compare the agreement between classification.

Discussion
Finally, be cautious about making cause-effect statements and in referring to "development" of DM.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1) abstract - bacKground not bacHground. Give ages by study group, not overall mean.
2) background - list "other factors" related to DM often overlooked in other studies that you will investigate.
3) discussion - The TG/Chol data in the discussion is not clearly written.
4) tables - #1 - HCV% with DM should be 33.5 not 23.5
   #2 Age - should be <45 yrs as referent group
   no need for * to denote significance, can be seen by CI's

Discretionary Revisions (which the author can choose to ignore)

Title - Add Iran to title, i.e, "Prevalence and determinants of DM among Iranian CLD patients"

In results - please update to use the correct and consistent number of significant digits.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No
Declaration of competing interests:

None