Author's response to reviews

Title: Prevalence and determinants of diabetes mellitus among Iranian patients with chronic liver disease

Authors:

Seyed M Alavian (manager@iranhepgroup.info)
Behzad Hajarizadeh (behzad_hj@hotmail.com)
Fariborz Nematizadeh (fariborz_nz@yahoo.com)
Bagher Larijini (emrc@sina.tumc.ac.ir)

Version: 2 Date: 9 September 2004

Author's response to reviews:

Dear editor,

We would offer our special thanks to reviewers to review our paper and recommend the helpful corrective points. We revised the manuscript considering the points mentioned by reviewers. As you asked for, detailed response to the concerns of the reviewers comes in follow. We have answered the comments one by one. Furthermore, we make the revised manuscript with manuscript formatting checklist.

- The comments by reviewer Gregory Kirk

Major Compulsory Revisions:

Study design issues:

1. Considering the inclusion and exclusion criteria (described in detail in first paragraph of Methods section) 193 patients firstly were eligible to enter the study. Consequently, we exclude 8 subjects with NASH from analysis because of low case number. At last analysis was performed for 185 patients. We clarified patients selection process in new version of manuscript (first and second paragraph of Methods). The age was the only demographic factor that was considered as exclusion criterion and homochromatosis and autoimmune disease were the etiologic factors for CLD that were considered as exclusion criteria.

More background about Tehran Hepatitis Center was provided at the beginning of Methods. All of the patients were Moslem and belonging to the white race. Actually there is no wide variation about religion and race in Iran. It is why we did not mention this point in the manuscript but we mentioned this point in new version.

2. The occurrence of signs or biochemical evidences of liver decompensation, ultrasound features of portal hypertension and/or esophageal varices in gastroscopy was used for the clinical diagnosis in cases without liver biopsy (Methods: paragraph 2, line 3-5). The separated data were not provided.

3. FPG and 2-hr PG measurement was repeated on two samples in two sessions. FPG 126 mg/dl or 2-hr PG 200 mg/dl on more than one occasion was used as diagnostic for DM. It was mentioned in Methods section of the manuscript, paragraph 3, 4. Thirty patients with DM were aware of their problem and were either on medication or diet.

It is very difficult to reveal the duration of DM as almost all of the patients were never screened periodically and the time of DM diagnosis is not as same as the time of DM occurrence.

4. The facilities for HCV genotype definition was not widely provided in the country at the time of the study. The data about HBV viral load was insufficient in most of the patients with CLD and we had to perform only qualitative PCR for this group due to budget limitation.

The cirrhotic patients and patients with CLD were analyzed separately. In Table 3 we showed that in both patients with cirrhosis and CLD there was no significant difference with respect to DM rate in HBV and HCV groups.

Analysis issues:
We incorporate OR in both Abstract and Results.

Discussion:

In revised manuscript we cautiously omit any expression that makes cause-effect statements.

Minor Essential Revisions:

1. The dictation of background was corrected. The age mean was mentioned in each group separately both in Abstract and in the text.
2. The overlooked factors such as BMI were added to the text (Background: end of first paragraph).
3. Because of summarizing the text we referred the readers for the details of TG and Chol data to table 3.
4. All of mentioned errors were corrected.

Discretionary Revisions:

The title was revised as what the reviewer recommended.

- The comments by reviewer Teh-la I Huo

Major Compulsory Revisions:

1. As the reviewer mentioned the low number of cases in each subgroup was one of the shortcomings in this study. Therefore our first aim in this study was the definition of overall prevalence of DM in CLD patients. In addition, as there is no data in this issue from Iran, this study should be considered as the first step to provide primary data for next works.

2. We clarified patients selection process and the inclusion and exclusion criteria in new version of manuscript. As the title of article is declaring we generally investigate the DM in the patients with chronic liver disease. Therefore, we expected to have a non-homogenous population. In addition, we have to exclude 8 subjects with NASH from analysis because of low case number. Some other patients with CLD were excluded according to exclusion criteria as well.

3. In new version of manuscript, P-values were given for significant variables in Table 2 and 4. In stepwise logistic regression (backward) firstly all variables are entered to model. Then in each step the variable with the highest P-value exits the model. At last the variables that remain to the model by the last step will be significant independent variables and the P-value in last step can be recorded. However for non-significant variables, we cannot mention a unique P-value as it may be different in each step.

4. The low case number in cirrhosis group may be responsible. Therefore, we decided to investigate the chronic hepatitis group and cirrhosis group separately. The analysis in both groups revealed that the more severe the liver disease, the higher rate of DM (Table 3, 4).

5. Since both DM and CLD usually are asymptomatic disease, it is very difficult to define the onset of CLD and DM in patients. Actually 10 out of 40 patients with DM in this study are unaware of their problem by the time of our screening. Therefore, in this study we revealed only an association between DM and CLD and we were very cautious not to make cause-effect statements in this study. This issue was discussed in the end of second paragraph of Discussion.

6. In new version of article the scoring method of histological grading and staging was given both in Methods and in subtitle of Table 3.

7. It is why we used multivariate analysis after univariate analysis. In univariate analysis you only consider single factor to find the association while this association could be due to the hidden effect of other factors.
that you did not consider. To omit these hidden effects, using multivariate analysis you enter all significant factors to a regression model. Therefore, you can find the independent association between two target variables. It is obvious that the results in multivariate analysis may not be as same as what you find in univariate analysis. As another example you observe that family history of DM was significantly associated with DM rate in univariate analysis (Table 3). However, it lost its significance after applying multivariate analysis (Table 4).

8. We revised the manuscript and corrected the typographical and grammatical errors.

Yours Faithfully

Seyed Moayed Alavian M.D.
Behzad Hajarizadeh M.D.