PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of chronic hepatitis B infection on major adverse cardiovascular events and all-cause mortality in diabetic patients: a nationwide population-based study from Taiwan
AUTHORS	Kuo, Chin-Sung; Chen, Yung-Tai; Hsu, Chien-Yi; Chang, Chun-Chin; Chou, Ruey-Hsing; Li, Szu-Yuan; Kuo, Shu-Chen; Huang, Po-Hsun; Chen, Jaw-Wen; Lin, Shing-Jong

VERSION 1 - REVIEW

REVIEWER	Thomas Deleuran Department of Hepatology and Gastroeterology, Aarhus University Hospital
REVIEW RETURNED	06-Mar-2017

GENERAL COMMENTS	Chin-Sung and colleagues have conducted and interesting and thought provoking study on the association between hepatitis B-infection, and cardiovascular disease and all-cause mortality in diabetes patients using data from nationwide health insurance data. Overall, I find the methods adequate, the discussion interesting and I recommend publication. However, I have few reservations/suggestion to improvements of the manuscript that needs to be addressed. First, as the authors points out death as competing risk is important in this study. Importantly, competing risks do not affect the hazard ratio for non-fatal events for HBV vs. no-HBV patients, because the hazard ratio can interpreted as the incidence rate ratio and compares the instantaneous risk of having the event of interest. Therefore, I suggest leaving out the Fine-Gray regression. On the other hand, the risk interpreted as the percentage of patients that experience an event within a specified time interval (i.e. 1-year risk) is affected by competing risk. The Kaplan Meier method relies on an assumption of non-informative censoring, and therefore this methods overestimate risk in the presence of competing risk. The cumulative incidence function accounts for competing risks. I suggest replacing the Kaplan-Meier curves in Figure A and B with curves based on the cumulative incidence function, and to emphasis the risk estimates in the text and in the Tables. This approach will also benefit the paper by placing more weight on the clinical significance of the result. Even though it is interesting to discuss the pathophysiology behind the protective effect of HBV on cardiovascular disease, it is mostly speculative and despite rigorous adjusted for covariates confounding remains a possibility, whereas the clinical relevance of risk estimates can be interpreted without speculating on causation [1].

	In addition, I suggest the manuscript undergoes professional language editing. All in all I recommend publication, the authors should use the cumulative incidence function to compute the risk of non-fatal events and place more emphasis on these estimates rather than speculation on the pathophysiology. I've added a reference that on competing risk in liver disease. Congratulations with a nice paper. References 1. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015;62:292-302. Epub 2014/11/08. doi: 10.1002/hep.27598 PMID: 25376655.

REVIEWER	Knut Boe Kielland Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders
REVIEW RETURNED	16-May-2017

GENERAL COMMENTS	The study has addressed an important subject in a nice way. The title is informative, informal and acceptable. The abstract, introduction, and methods are satisfactory. The use of propensity score matching is impressing and brings increased quality to the study. I am not an expert in statistics, but as far as I can evaluate it, both the methods employed, and the presentation seem acceptable. Several groups of medicationsare taken into account, but I miss notice on antiviral medication which probably is used by a number of the patients in the HBV cohort. The use of antiviral medication is a factor which obviously makes a difference between the two cohorts, and this may theoretically be of significance for the end points, even if that is not probable. The use of such medication may also be a proxy for the degree of liver disease in the HBV cohort. The figures are illustrating. I am surprised by the high rate of all-course mortality especially in the control group during the first year of observation (Figure 2A). A similar trend is not seen for MACE in Figure 2B. The reason for this should be explained or discussed in the Discussion section. There is some need for proofreading, and also better language, particularly in the Discussion section which wrongly has been named "Conclusions". I have given som examples in the text. The discussion section may also be rearranged and supplemented in accordance with what BMJ Open proposes, beginning with "a statement of the principal findings" The discussion addresses comparisons with other studies, but there is a need for revision in that section.

VERSION 1 – AUTHOR RESPONSE

Responses to reviewer 1's comments

Q1. … Therefore, I suggest leaving out the Fine-Gray regression.

Response: Complied

We have left out the Fine-Gray regression.

Q2. On the other hand, the risk interpreted as the percentage of patients that experience an event within a specified time interval (i.e. 1-year risk) is affected by competing risk. The Kaplan Meier method relies on an assumption of non-informative censoring, and therefore this methods overestimate risk in the presence of competing risk. The cumulative incidence function accounts for competing risks. I suggest replacing the Kaplan-Meier curves in Figure A and B with curves based on the cumulative incidence function, and to emphasis the risk estimates in the text and in the Tables.

…it is mostly speculative and despite rigorous adjusted for covariates confounding remains a possibility, whereas the clinical relevance of risk estimates can be interpreted without speculating on causation [Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015;62:292-302.].

Response: Thank you very much for your suggestion and mention of the reference. This study involved no competing risk bias for all-cause mortality (two-state model). Use of the Kaplan−Meier method may lead to overestimation of the event (MACE) risk in the presence of a competing risk (death). However, we found lower risks of MACE and all-cause mortality in the HBV cohort. Use of the cumulative incidence function would result in a much lower risk of MACE than did the Kaplan−Meier method in this study. As the results would be the same, we did not change our method. However, we mention this consideration in the Discussion section. We also added citation of the reference you mentioned to clarify how we minimised the bias of competing risk. In addition, we decreased the emphasis on speculation about pathophysiology in the Discussion section.

Q3. …In addition, I suggest the manuscript undergoes professional language editing.

Response: This manuscript has been edited by a native English-speaking professional.

Part C. Responses to reviewer 2's comments

Q1. Several groups of medications are taken into account, but I miss notice on antiviral medication which probably is used by a number of the patients in the HBV cohort. The use of antiviral medication is a factor which obviously makes a difference between the two cohorts, and this may theoretically be of significance for the end points, even if that is not probable. The use of such medication may also be a proxy for the degree of liver disease in the HBV cohort.

Response: Thank you for your comments. The HBV cohort included 5710 subjects who were receiving antiviral therapy. We performed a subgroup analysis and found no significant difference in the hazard ratio for MACE between control subjects and subjects with HBV receiving and not receiving antiviral therapy. However, these results are not rigorous because we could not match the

HBV and control cohorts according to antiviral therapy (although no subject without HBV should have received antiviral therapy). Therefore, we did not report these findings in the manuscript.

Q2. I am surprised by the high rate of all-course mortality especially in the control group during the first year of observation (Figure 2A). A similar trend is not seen for MACE in Figure 2B. The reason for this should be explained or discussed in the Discussion section.

Response: Thank you for your comments. We have explained this finding in the Discussion section. The all-cause mortality rate in the current study was similar to that in a previous study of Taiwanese subjects with diabetes (Tseng CH. Factors associated with cancer- and non-cancer-related deaths among Taiwanese patients with diabetes after 17 years of follow-up. PLoS One. 2016 Dec 1;11(12):e0147916). The MACE rate in this study was also comparable to that in a previous report (Hsieh HM, Lin TH, Lee IC, Huang CJ, Shin SJ, Chiu HC. The association between participation in a pay-for-performance program and macrovascular complications in patients with type 2 diabetes in Taiwan: A nationwide population-based cohort study. Prev Med. 2016;85:53-9).

Q3. There is some need for proofreading, and also better language, particularly in the Discussion section which wrongly has been named "Conclusions". I have given some examples in the text. The discussion section may also be rearranged and supplemented in accordance with what BMJ Open proposes, beginning with "a statement of the principal findings"

Response: Complied

As you suggested, we have revised the Discussion section according to BMJ Open’s guidelines. We have also corrected some errors in the text. In addition, this manuscript has been edited by a native English-speaking professional.