Supplementary data

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Diabetes mellitus as a risk factor of hepatocellular carcinoma in patients with chronic hepatitis B on nucleot(s)ide analogues

To the Editor:

We read with interest the article by Hsu and colleagues, who suggested that diabetes mellitus was a risk determinant for the prediction of hepatocellular carcinoma (HCC) in Asian patients with chronic hepatitis B, receiving antiviral therapy.[1] However, we have several concerns about the design and analysis of the study.

The time relationship and association between diabetes, chronic liver disease and development of HCC have not been corroborated in areas with high prevalence of chronic viral hepatitis. It is controversial whether diabetes is a risk factor for HCC in Taiwan. Most studies indicated that it was not a risk factor for HCC.[2–6] A possible link was reported in some subgroups.[7–9] However, using the same database,[1] another population-based study reported that diabetes increased HCC risk.[10]

This study used the National Health Insurance database in Taiwan.[1] It was not designed as a randomized clinical trial for research purpose. It was a retrospective and an observational study, thus selection bias was possible. The definition of disease was exclusively based on claim data and coding with the International Classification of Diseases, Ninth Revision, without laboratory data to confirm the diagnosis. The diagnostic accuracy is unknown. Nevertheless, errors in coding or recording tend to occur at random as a result of the same codes being used in both groups of patients (diabetes and non-diabetes). There might be many biases in both the risk and the outcome of interest (diabetes and HCC), such that statistical association could not be well verified. Though most patients with a diagnosis of diabetes were likely to have actual diabetes, those without a diabetes diagnosis might have had diabetes but not been recognized. Additionally, cirrhosis itself could have driven the development of diabetes, which might have been clinically silent and therefore gone undetected. Meanwhile, cryptogenic cirrhosis derived from diabetes might be a misclassified bias which might modify the true effects of diabetes on the risk of HCC. Additionally, it was hard to confirm whether diabetes had a causative role in HCC or whether both diseases were the product of other factors, particularly chronic liver disease.

Several issues remain unresolved. Other possible confounding factors, such as alcohol drinking and smoking, diabetes-induced metabolic changes (dyslipidemia, steatohepatitis and fibrosis) and antidiabetic medications have not well been analyzed.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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Reply to: "Diabetes mellitus as a risk factor of hepatocellular carcinoma in patients with chronic hepatitis B on nucleot(s)ide analogues"

To the Editor:

We thank Drs. Tsai and Perng for their interest in and comments on our study.[1] They questioned whether diabetes mellitus (DM) was a risk factor of hepatocellular carcinoma (HCC) in Taiwan, where chronic viral hepatitis was prevalent. Indeed, not every study found a significant association between DM and HCC risks. However, the pooled analyses have collectively shown that DM was associated with an increased risk for HCC and the association was independent of alcohol use and viral hepatitis.[2,3] The biological mechanism underlying this association remains incompletely understood but most likely involves non-alcoholic fatty liver disease, which is highly prevalent in diabetic patients.[4]

Conceivably, it is challenging to elucidate whether DM adds to the excessive risk of HCC in patients with chronic hepatitis B (CHB), given that CHB is a dominant HCC risk factor. In principle, cohort studies with clear chronology are preferred over cross-sectional or case-control designs to untangle the association. Moreover, the number of patients with CHB, with and without DM, and the duration of follow-up are crucial to attain sufficient statistical power. To our knowledge, several large longitudinal studies from Taiwan have tackled this perplexing issue and identified DM or relevant metabolic derangement as a risk factor of HCC among patients with CHB.[5–7] In particular, Fu and colleagues restricted the exposed cohort to patients with CHB and newly diagnosed DM in order to clarify the chronological relationship,[6] which Drs. Tsai and Perng raised as a concern.

In our analysis using the National Health Insurance Research Database (NHIRD) to uncover risk determinants of HCC in patients with CHB on tenofovir or entecavir therapy, a higher incidence of HCC was observed in patients with DM than in those without. The final multivariable model confirmed that DM was a significant predictor independent of cirrhosis, age, male sex, and hepatitis C coinfection.[8] As a result, DM should be taken into account in the risk calculation although cirrhosis and age were far more influential in determining the risk. These predictors were thus weighted by their regression coefficients and rounded into integers in the CAMD (cirrhosis, age, male sex, DM) score to facilitate convenient application in daily practice. In accordance with our finding, a large international consortium recently also reported that DM was an independent risk factor of HCC in patients with CHB treated with oral antiviral therapy, after adjusting for other risk factors including cirrhosis, age, male gender, platelet count, and alpha-fetoprotein.[9]

We agree with their comment that there are apparent limitations in the NHIRD and analysis of this insurance claim database requires caution and expertise.[10] In fact, we did not simply rely on an International Classification of Diseases-Ninth Revision (ICD-9) code to define the study outcome and important covariates. For instance, the occurrence of HCC needed to be certified in the registry of catastrophic illness patient database.[8] Because a certified malignancy would waive copayment for the disease, the health insurance administration strictly reviewed pathological and/or radiographic data and would not approve the certification without robust evidence. The presence of DM was not simply defined by an ICD-9 code, either. It necessitated prescription of antidiabetic medication for at least 3 months as well. Furthermore, our analysis also accounted for relevant pharmacotherapies including antidiabetic agents, statin, antihypertensive regimens, and so on. Still, unmeasured confounding, such as lacking direct information on cigarette smoking or alco-