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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-

hol misuse, remained possible. These methodological considerations and limitations were explicated in our papers.[1,8]

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.11.031.

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Influenza virus infection as precipitating event of acute-on-chronic liver failure

To the Editor:

With great interest we have read the outstanding Grand Rounds article by Gustot *et al.* describing the current management of acute-on-chronic liver failure (ACLF),[1] which is a frequent and devastating complication of liver cirrhosis with mortality rates of up to 80% within 28 days. Specific hepatic and extrahepatic organ failures are the defining feature of ACLF and discriminate ACLF from classical decompensation of liver cirrhosis.[1]

While bacterial infection, reactivation of HBV and alcohol consumption are described as important precipitating events, in 44% no precipitating event could be identified. Systemic inflammation is a cardinal feature and – likely – driver of ACLF, which is, however, paralleled by a state of pronounced immunosuppression.[2] Still, apart from HBV reactivation,[3] little is known about the role of other viruses, such as respiratory viruses, as potential triggers of ACLF.

During winter 2017/2018, there was a serious outbreak of influenza virus infections in Germany. In order to locally control this outbreak and to manage patient flows, the wards of the Department of Gastroenterology and Hepatology of the University Hospital Essen were dedicated for cohorting patients with proven or suspected influenza infection, irrespective of the underlying medical condition of patients. In that given scenario, we aimed to characterize the association of the presence of liver cirrhosis with the risk of organ failures and the incidence of ACLF during influenza infection. From the end of January to