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Editorial

The latest evidence on the impact of fatty liver on liver-related outcomes and mortality in chronic hepatitis B

Xianhua Mao[1], Lung Yi Mak[1,2], and Wai-Kay Seto[1,2,3]

[1]Department of Medicine, School of Clinical Medicine, [2]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong; [3]Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

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Chronic hepatitis B (CHB) and non-alcoholic fatty liver disease (NAFLD) are both common liver diseases, with a global prevalence of 3.9% and 25.2% respectively.[1,2] Over 30% of individuals with CHB have co-existing fatty liver (FL).[3] While disease progression for each individual disease has been well-described, evidence regarding the impact of concomitant FL on liver-related outcomes, including cirrhosis, hepatocellular carcinoma (HCC), mortality, and hepatitis B surface antigen (HBsAg) seroclearance in individuals with CHB remains conflicting. For example, Kim et al.[4] reported an increased risk of HCC and mortality in CHB with FL (CHB-FL) than CHB without FL (CHB-no-FL) but another study paradoxically observed a lower risk of HCC.[5]

In the current issue of *Clinical and Molecular Hepatology*, Wong et al.[6] evaluated the impact of FL on long-term outcomes in patients with CHB via conventional meta-analysis and individual patient data meta-analysis (IPDMA). By searching PubMed, EMBASE, Web of Science, and the Cochrane Library databases, this meta-analysis initially screened 2,157 records and finally included 19 eligible full-text studies in conventional meta-analysis. In the random-effects model using aggregated data, no significant difference was found in the pooled incidence of HCC, liver cirrhosis, mortality, and HBsAg seroclearance among patients with CHB-FL as compared to patients with CHB-no-FL, with considerable heterogeneity in all analyses. The results were different from another recently-published meta-analysis reporting that co-existing FL was significantly associated with an increased risk of HCC and liver cirrhosis among patients with CHB but with a higher chance of HBsAg seroclearance.[7] This discrepancy in study findings is likely a result of different approaches in defining inclusion criteria: the present study analyzed comparative incidence in exposed and unexposed groups; while the second study[7] retrieved data about relative effect size from case-control and cohort studies. Moreover, it is important to note that in the present study, a significant association between FL and HCC was observed in a subgroup limiting indi-

Corresponding author : Wai-Kay Seto
Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China
Tel: 852 22556979, Fax: 852 28725828, E-mail: wkseto@hku.hk
https://orcid.org/0000-0002-9012-313X

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viduals with FL diagnosed by liver biopsy, which is consistent with the result of a similar subgroup in the second study.[7]

An IPDMA was performed by retrieving individual data from five authors in conventional meta-analysis in this study. Inverse probability of treatment weighting approach was applied to balance age, sex, baseline diabetes mellitus (DM), baseline cirrhosis, alanine transaminase, hepatitis B e Antigen (HBeAg) status, hepatitis B virus DNA levels, and antiviral treatment status between CHB-FL and CHB-no-FL groups. Significantly lower incidences of HCC, cirrhosis, and mortality were observed in the CHB-FL group than that in the CHB-no-FL group, which is different from the results of the second study.[7] Interestingly, both studies suggested that CHB-FL, when compared with CHB-no-FL, increased the chance of HBsAg seroclearance. While potential selection bias may exist in the present study since only 5 of 19 studies were included for IPDMA, the vast majority of individual patient-level data were retrieved from specific studies consisting of a large number of patients,[8-10] improving the data's representativeness. In addition, FL in the present study's IPDMA was diagnosed by non-invasive tests which may be less accurate than liver biopsy, and the additional analysis of CHB-FL and CHB-no-FL groups with liver biopsy results can potentially improve the data's robustness. Nonetheless, this study provides updated evidence regarding the impact of FL on liver-related outcomes and mortality in CHB which may facilitate therapeutic development. The differential results from various studies highlight the importance of developing mechanistic models to investigate biological interactions between hepatitis B virus and liver steatosis. Unfortunately, this is highly challenging since the vast majority of current hepatitis B virus-related animal models fail to replicate the complete life cycle of the virus and virus-host interactions.[11]

Multiple subgroup analyses, stratified by age, sex, DM status, baseline cirrhosis, HBeAg status, and antiviral treatment status, were performed for the outcomes with cirrhosis, HCC, mortality, and HBsAg seroclearance. In brief, significantly lower 10-year cumulative incidences of cirrhosis, HCC, and mortality were observed in CHB-FL than that in CHB-no-FL in patients >45 years, male patients, patients with DM or HBeAg-negativity, and patients without antiviral treatment; a higher cumulative 10-year incidence of HBsAg seroclearance was found in CHB-FL (vs. CHB-no-FL) in patients of age groups ≤45 years and >45 years, male and female patients, and patients without DM, baseline cirrhosis, HBeAg or antiviral treatment. The significant differences in cumulative incidence of all 4 outcomes between CHB-FL and CHB-no-FL are consistent across the majority of subgroups, suggesting that the impact of FL may be applicable to the broad at-risk population with CHB.

This current meta-analysis strengthens the robustness of evidence regarding the impact of concomitant FL on long-term outcomes in CHB. Metabolic risk factors, including body mass index (≥25 kg/m^2), DM, and metabolic syndrome, were associated with a lack of fibrosis regression during long-term nucleoside analogue therapy for CHB.[12] Oh et al.[13] observed that the cumulative HCC incidence was significantly lower in those with hepatic steatosis (i.e., controlled attenuation parameter [CAP] ≥222 dB/m) than in non-steatosis, while cumulative HCC incidence decreased in a dose-dependent manner based on values of CAP (24.0%, 13.9%, 12.8% and 6.0% at 5 years for <222 dB/m, 222–246 dB/m, 247–273 dB/m and ≥274 dB/m, respectively). Hui et al.[14] elucidated a stepwise decrease in median hepatitis B virus DNA levels with increased steatosis severity in 1,202 treatment-naïve CHB patients. It is believed that certain metabolic abnormalities, such as FL, may present a protective effect on liver-related outcomes in individuals with CHB, although FL and CHB have been recognized as common risk factors for advanced liver disease.

To conclude, by applying conventional meta-analysis and IPDMA, Wong et al.[6] report that CHB-FL was significantly associated with lower risks of liver cirrhosis, HCC, and mortality but with a higher chance of HBsAg seroclearance than CHB-no-FL. Elucidating the underlying mechanisms for these associations would be indispensible in the future. With CHB remaining a major public health worldwide threat[15] and the disease burden of NAFLD projected to rise in the coming decade,[16] understanding the interplay of CHB and FL may provide novel insight into therapeutic strategies and epidemiologic prevention of liver-related complications.

Abbreviations:

CAP, controlled attenuation parameter; CHB, chronic hepatitis B; DM, diabetes mellitus; FL, fatty liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; IPDMA, individual patient data meta-analysis; NAFLD, non-alcoholic fatty liver disease

Authors' contribution

XM and WKS drafted the manuscript. LYM and WKS reviewed and finalized the manuscript.

Conflicts of Interest

LYM is an advisory board member of Gilead. WKS received speaker's fees from AstraZeneca, is an advisory board member and received speaker's fees of Abbott, received research funding from Alexion Pharmaceuticals, Boehringer Ingelheim, Pfizer and Ribo Life Science, and is an advisory board member, received speaker's fees and researching funding from Gilead. XM has no conflicts of interest to disclose.

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