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CV outcomes of oral antidiabetics in MASLD

Network meta-analysis of liver transplant criteria
ERBB3 blockade sensitizes HCC to regorafenib
ACSS2 as a metabolic target in HBV-related HCC

KASL

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Correspondence

Correspondence to letter to the editor 2 on "Glucagon-like peptide 1 receptor agonist and reduced liver and non-liver complications in adults with type 2 diabetes and metabolic dysfunction-associated steatotic liver disease: a target trial emulation study"

Xianhua Mao[1,2] and Mindie H. Nguyen[1,3]

[1]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA, USA; [2]Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong; [3]Department of Epidemiology and Population Health, Stanford University Medical Center, Palo Alto, CA, USA

Keywords: MASLD; HCC; Cirrhosis; Type 2 diabetes

Dear Editor,

We appreciate the comments from Dr Yao regarding the methodological concerns for the association of glucagon-like peptide-1 receptor agonists (GLP-1RAs) with liver and non-liver complications among patients with type 2 diabetes and metabolic dysfunction-associated steatotic liver disease (MASLD).[1,2] Although we had conducted several analyses to test the robustness of our results, several methodological limitations cannot be ruled out.

Indeed, several previous studies have shown distinct effects of individual agents within the GLP-1RA class on these clinical outcomes (e.g., liver and renal disease).[3,4] In the current study, we described the distributions of the GLP-1RA subclasses, as well as dipeptidyl peptidase-4 (DPP-4) inhibitors, in all five cohorts (Supplementary Table 7), and the primary individual agents of GLP-1RAs were semaglutide, dulaglutide, and liraglutide (total proportion >95%). Furthermore, findings were largely consistent across all secondary analyses regarding the association between individual agents and the studied outcomes (Supplementary Table 9), indicating that all individual agents might exert the protective effects.

We agree with Dr Yao that time-varying confounding (e.g., GLP-1RAs and SGLT-2 inhibitors) might be a concern in this study. To address this confounding, we repeated the analysis using a per-protocol design, which set the diabetic medications discontinuation as an endpoint of the follow-up (Supplementary Table 10). Moreover, we have now conducted a time-varying analysis that identified all the included medications in each three-month interval during follow-up (hazard ratios: 0.56–0.92). Both analyses suggest that these confounders are less likely to be associated with the clinical outcomes.

Corresponding author : **Mindie H. Nguyen**
Division of Gastroenterology and Hepatology, Stanford University Medical Center, 780 Welch Road, Palo Alto, CA 94304, USA
Tel: +1-650-498-6081, E-mail: mindiehn@stanford.edu
https://orcid.org/0000-0002-6275-4989

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We acknowledge that relatively short follow-up might lead to an inability to assess the long-term effects of GLP-1RA on the risk of liver-related outcomes, although we included large sample sizes to ensure the power of the statistical analyses. Nonetheless, these data represent the reality of medication use in routine clinical practice in the MarketScan database, and future large-scale clinical studies, with adequate duration of follow-up, are required for the accurate estimation of the effect of GLP-1RAs on adverse liver-related outcomes.

We thank Dr Yao for allowing us further discussion of potential methodological concerns in improving the robustness of our findings. We hope the suggested study will be performed in the future as we all work together to reduce the clinical burden of MASLD.

Authors' contribution

Xianhua Mao and Mindie H. Nguyen: Conceptualization; Data acquisition and analysis; Writing—original draft; Writing—review and editing.

Conflicts of Interest

Mindie H. Nguyen received research grants via Stanford University from Pfizer, Enanta, Astra Zeneca, GSK, Delfi, Innogen, Exact Science, CurveBio, Gilead, Vir Biotech, Helio Health, National Cancer Institute, Glycotest and personal fees from consulting/advisory board from Intercept, Exact Science, Gilead, GSK. Xianhua Mao has nothing to disclose.

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Abbreviations:

DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor; MASLD, metabolic dysfunction-associated steatotic liver disease

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