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Letter to the Editor

Interpreting the Association Between Hypertension and Extrahepatic Cancers in MASLD: Insights from NHANES

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Dear Editors,

We read with great interest the multicenter cross-sectional study by Zhao *et al.*, which examined associations of hypertension and fibrosis-4 index (FIB-4)-defined fibrosis risk with extrahepatic cancer in 103,652 Chinese patients with metabolic dysfunction-associated steatotic liver disease (MASLD).[1] Its large multicenter sample provides valuable evidence from tertiary care settings. To assess the generalizability of these findings, we explored the hypertension–extrahepatic cancer association in a population-based US sample.

Using nine consecutive cycles of the National Health and Nutrition Examination Survey (NHANES; 2001–2018), we conducted an exploratory cross-sectional analysis of adults aged ≥ 20 years with presumed MASLD. For 2001–2016, when liver imaging was unavailable, presumed MASLD was operationally defined as alanine aminotransferase > 40 U/L plus at least one cardiometabolic risk factor after exclusion of prespecified competing causes of liver injury[2]; this was considered a surrogate rather than imaging-confirmed steatosis. For 2017–2018, MASLD required steatosis detected by vibration-controlled transient elastography and at least one cardiometabolic risk factor. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current antihypertensive treatment. Extrahepatic cancer was based on a self-reported physician diagnosis, excluding liver cancer. Survey-weighted logistic regression incorporated sampling weights, strata, and primary sampling units; the multivariable model included the covariates shown in Figure 1.

Among 7,266 participants, 529 reported extrahepatic cancer. The distribution of individual extrahepatic cancer subtypes among these cases is presented in Supplementary Table 1. Compared with participants without cancer, those with cancer were older (60.9 vs. 43.7 years, $P < 0.001$), were more frequently women, ever smokers, and non-Hispanic White, and had higher prevalences of hypertension, hyperglycemia, and type 2 diabetes mellitus (all $P \leq 0.001$). They also had higher FIB-4 values (1.30 [0.91–1.91] vs. 0.83 [0.54–1.24]; $P < 0.001$). In univariable analysis, hypertension was associated with approximately twofold higher odds of prevalent extrahepatic cancer (OR = 2.18, 95% CI 1.74–2.74; $P < 0.001$; Fig. 1), consistent with the association reported by Zhao *et al.* After multivariable adjustment, however, the estimate was markedly attenuated and no longer significant (adjusted OR = 0.94, 95% CI 0.70–1.25; $P = 0.660$), whereas older age, ever smoking, and non-Hispanic White race/ethnicity remained associated with extrahepatic cancer. Similar nonsignificant associations for hypertension were observed across several sequentially adjusted models with different sets of covariates. Consistently, the sensitivity analysis restricted to the 2017–2018 subsample with hepatic steatosis confirmed by the controlled attenuation parameter on vibration-controlled transient elastography reproduced the same pattern: hypertension showed a significant positive association in the unadjusted model (OR = 1.94, 95% CI 1.38–2.71; $P < 0.001$), which became nonsignificant after multivariable adjustment (adjusted OR = 0.85, 95% CI 0.51–1.41; $P = 0.460$).

Exploratory unadjusted subgroup analyses provided additional, although qualified, directional support. Among adults aged ≥ 40 years, hypertension was associated with 54% higher odds of prevalent extrahepatic cancer (OR = 1.54, 95% CI 1.18–2.01), whereas the estimate among younger adults was imprecise (OR = 0.76, 95% CI 0.33–1.75; Fig. 2). The forest plot in Fig. 2 presents these exploratory subgroup estimates only; no formal interaction tests were performed for the forest plot. Interaction testing was instead conducted separately across all prespecified subgroups to assess potential effect modification, with no statistically significant interaction observed (all P for interaction > 0.05; Supplementary Table 2). Given the marked age imbalance between groups (Supplementary Table 3 and Supplementary File 1), age is a

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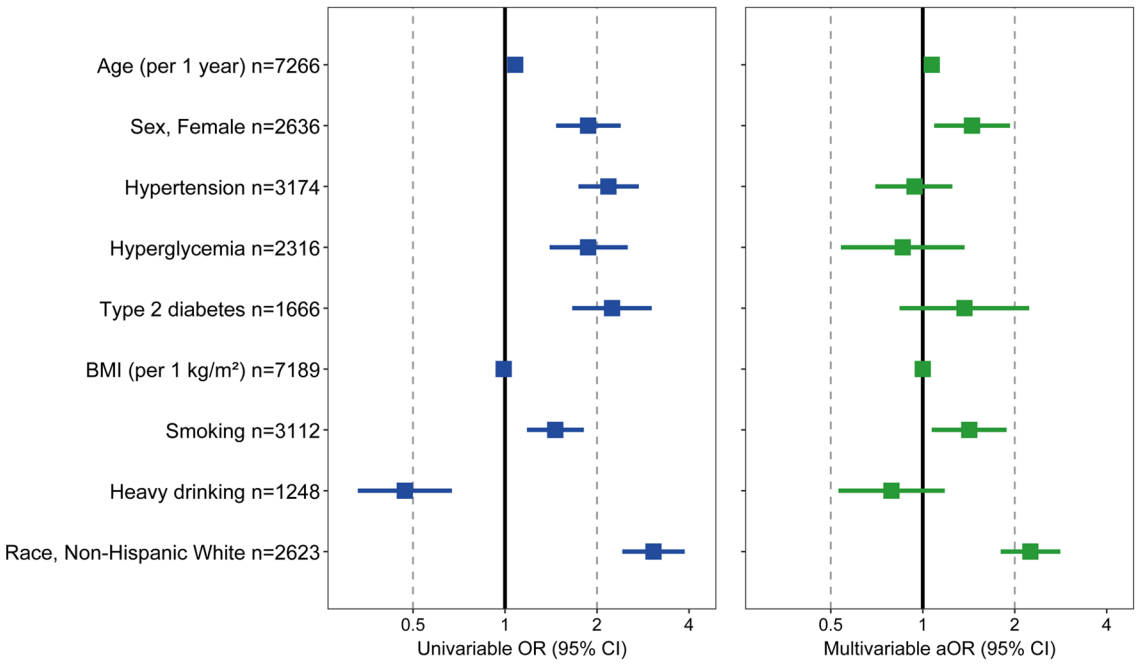


Fig. 1. Survey-weighted associations with prevalent extrahepatic cancer among NHANES participants with operationally defined MASLD. The left panel shows unadjusted ORs and the right panel shows mutually adjusted ORs with 95% CIs. All displayed variables were included in the multivariable model. The vertical line indicates OR = 1. CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

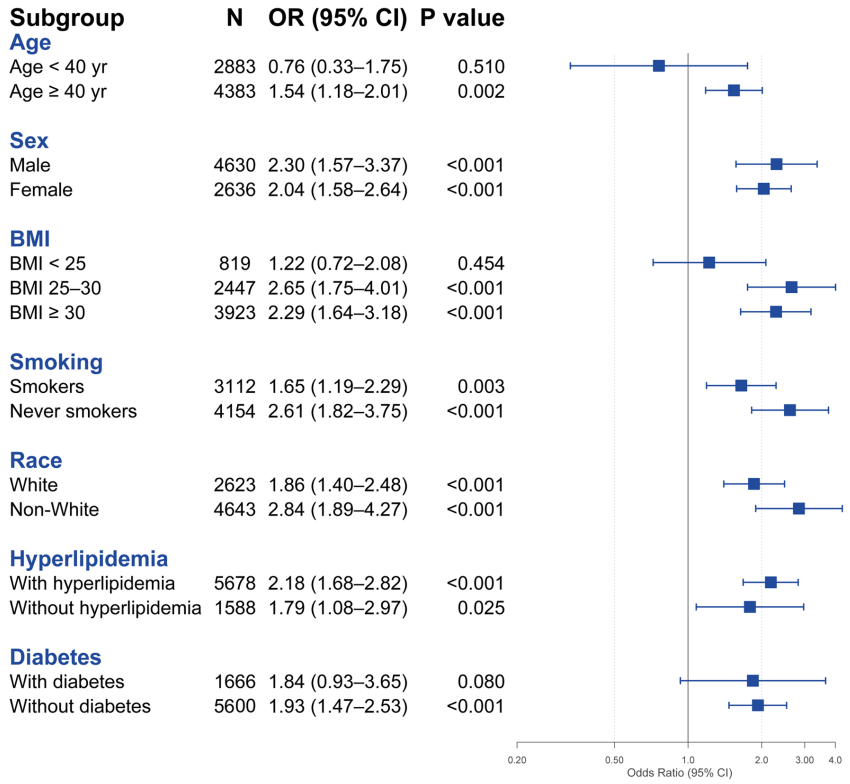


Fig. 2. Exploratory subgroup associations between hypertension and prevalent extrahepatic cancer among NHANES participants with operationally defined MASLD. Survey-weighted univariable ORs and 95% CIs are shown. No interaction tests were performed. CIs exceeding the plotting range are truncated, and the vertical line indicates OR = 1. CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

plausible source of confounding, although its specific contribution cannot be isolated from the fully adjusted model. The age-stratified estimates raise the possibility of age-related heterogeneity, but differences in subgroup significance do not establish effect modification without a statistically supported hypertension-by-age interaction. Participants with cancer also had higher FIB-4 values, consistent with Zhao *et al.* and longitudinal evidence linking elevated FIB-4 to incident malignancy.[3] However, because age is incorporated into FIB-4, the observed difference does not independently demonstrate a fibrosis-related pathway.[4]

Several mechanisms nevertheless support biological plausibility. Renin-angiotensin system signaling may promote angiogenesis, cellular proliferation, extracellular matrix remodeling, and tumor-associated inflammation.[5] Oxidative DNA damage is increased in individuals with hypertension compared with normotensive controls.[6] Beyond these pathways, MASLD-related immunological dysregulation may further contribute to extrahepatic oncogenesis. Lipotoxicity, oxidative stress, and free fatty acid accumulation within the steatotic liver drive metabolic reprogramming of $CD4^+CD25^+Foxp3^+$ regulatory T cells (Tregs). Upregulation of lipid scavengers such as CD36 and fatty acid-binding proteins in tissue-resident Tregs enhances local and peripheral immunosuppressive capacity, generating a tumor-permissive microenvironment in both the liver and the systemic circulation.[7] These processes overlap with the metabolic and inflammatory milieu of MASLD, which is increasingly recognized as a multisystem disorder associated with extrahepatic malignancy.[8] Accordingly, hypertension may partly represent cumulative cardiometabolic burden rather than an isolated carcinogenic exposure, which is compatible with the attenuation after adjustment. Epidemiological associations also vary across cancer sites and are most consistent for renal cancer, cautioning against assuming a uniform relationship for all extrahepatic cancers.[9]

The difference between our adjusted estimate and the positive association reported by Zhao *et al.* may reflect variation in demographic structure, referral setting, MASLD ascertainment, cancer type distribution, and covariate distributions between a nationally representative US sample and a Chinese tertiary care cohort. Both studies are cross-sectional and cannot establish temporality or causality. Our use of self-reported prevalent cancers, pooled cancer types, and cycle-dependent MASLD definitions may introduce recall, survivorship, and classification biases. Overall, our findings complement Zhao *et al.* by reproducing the crude hypertension–extrahepatic cancer association, including a positive unadjusted estimate among adults aged ≥ 40 years, while showing that the association was not robust to multivariable adjustment. Prospective studies using consistently imaging-defined MASLD, incident site-specific cancers, objective fibrosis assessment, and formal interaction testing are warranted to determine whether hypertension is independently associated with extrahepatic cancer.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JCTH.2026.00704.

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Conflict of interest

CS has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2020. The other authors have no conflict of interests related to this publication.

Author contributions

Writing-original draft preparation (JT, LR, YD); writing-review and editing (YD, CS). All authors approved the final version and publication of the manuscript.

Ethical statement

This study was conducted with publicly available NHANES data, which were collected by the CDC with ethical approval from the National Center for Health Statistics (NCHS) Research Ethics Review Board. All participants in the NHANES provided informed consent, and the procedures adhered to the ethical standards of the Declaration of Helsinki (as revised in 2024). Since this study involves secondary analysis of deidentified data, no further ethical approval was needed.

Data sharing statement

All data relevant to the study are publicly available from the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

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