THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Cross-Sectional Mediation and Biomarker Interpretation in the Report by Yan and Gao

LETTER TO THE EDITOR

To the Editor,

Yan and Gao evaluated 3170 NHANES 2017-2020 participants and reported a graded association between cardiometabolic index (CMI) and liver fibrosis (LF), with an adjusted odds ratio of 2.27 and nonlinear dose-response. They also estimated modest mediation proportions for albumin, uric acid, and gamma-glutamyl transferase (GGT).[1] The analysis is clinically appealing because CMI combines triglyceride-to-high-density lipoprotein cholesterol ratio and waist-to-height ratio, 2 accessible markers that connect cardiometabolic risk with hepatic injury. Several analytic issues merit attention before the mediation findings are translated into risk stratification.

First, the study was cross-sectional. Mediation implies temporal ordering from CMI to oxidative stress biomarkers and then to LF, but NHANES measured exposure, mediators, and liver stiffness in the same survey cycle. Cross-sectional mediation can yield biased indirect effects even when the underlying longitudinal pathway is real.[2] Causal language should therefore be avoided, and the reported indirect effects should be interpreted as decomposition of contemporaneous associations.

Second, the mediator set mixes mechanistic and diagnostic information. Albumin, uric acid, and GGT may reflect oxidative stress, but they also index nutrition, renal handling, cholestasis, alcohol exposure, and hepatic synthetic or enzymatic activity.[3] GGT is especially close to metabolic liver injury and may lie on several overlapping paths rather than a single oxidative stress pathway. A sensitivity analysis that excluded GGT or modeled a composite oxidative stress score would test whether the mediation signal depends on a liver-enzyme marker.

Third, LF was defined by a liver stiffness cutoff. Noninvasive stiffness measurement is useful for population studies, but cutoffs depend on disease etiology, inflammation, congestion, steatosis, probe selection, and fasting status.[3,4] A single threshold can therefore create misclassification, particularly around intermediate stiffness values. Analyses using alternative liver stiffness cutoffs, FIB-4 categories, or a continuous stiffness outcome would help determine whether the CMI signal is robust.

Finally, the sample restriction to participants with complete transient elastography and biochemical data may have selected a metabolically healthier analytic cohort. Survey-weighted missingness tables and inverse-probability weighting would clarify whether selection affected the estimates. The main CMI–LF association is plausible and useful as a screening hypothesis, but the mediation component requires longitudinal validation with temporally separated exposure, mediator, and fibrosis assessments.[2,5] The authors of the relevant article were given the opportunity to reply, but they chose not to send a response.

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Available Online Date: August 11, 2026

Cite this article as: İşleyen HB, Bulut S. Cross-sectional mediation and biomarker interpretation in the report by Yan and Gao. *Anatol J Cardiol.* 2026;30(11):831-832.

DOI: 10.14744/AnatolJCardiol.2026.6665

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Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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