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Reply to the Letter to the Editor: "Concerns Regarding the Interpretation of Triglyceride-Glucose Index as a Protective Factor in Hypertrophic Cardiomyopathy"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the authors of the letter for their thoughtful commentary[1] on our recent article[2] about the association between triglyceride-glucose (TyG) index and prognosis of patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF). We appreciate the opportunity to address the points raised.

We acknowledge that the association we observed between the TyG index and the prognosis of patients with HCM and HFpEF appears counterintuitive when viewed through the lens of general cardiometabolic pathophysiology. The readers note that in broader HFpEF populations, an elevated TyG index typically signifies insulin resistance and is associated with worse outcomes. However, we believe the unique metabolic milieu of HCM warrants a distinct interpretation.

Firstly, we agree that increased glucose utilization in HCM has been linked to mitochondrial stress. However, the biological response to metabolic stress is not monolithic. In the context of HCM with increased left ventricular pressure load, a substrate switch toward glucose oxidation may represent a compensatory adaptation to maintain myocardial energy production when fatty acid oxidation becomes inefficient. This concept of metabolic remodeling as a transient compensatory mechanism, rather than solely a marker of dysfunction, is supported by prior work in cardiac energetics.[3,4] While the studies by Vaniya et al[5] and Wijnker et al[6] highlight associated pathology, they do not preclude the possibility that this metabolic shift could be linked to a phenotype with slower progression or different mortality drivers in a specific clinical context. Our mediation analysis, showing N-terminal pro B-type natriuretic peptide as a significant mediator, suggests that the TyG index may indirectly reflect a hemodynamic or neurohormonal profile with a more favorable prognosis in this particular cohort.

Secondly, we fully concur that the lack of genetic data is a significant limitation. Genetic heterogeneity undoubtedly influences metabolic phenotype in HCM. However, the observed association remained significant after adjusting for numerous clinical covariates, including family history. While genetic confounding cannot be ruled out, our findings generate a hypothesis that merits testing in genetically characterized cohorts. We did not claim definitive causality but reported a novel association that could guide future, more detailed investigation.

Thirdly, the apparent contradiction with the general HFpEF literature underscores the specificity of the HCM-HFpEF population. HCM is a primary myocardial disease with distinct pathophysiology, whereas most HFpEF studies enroll patients with secondary hypertrophy due to hypertension or metabolic syndrome. Applying findings from 1 population directly to the other may be inappropriate. Our study precisely aimed to explore whether established biomarkers behave differently in this distinct entity.

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Finally, concerning methodological points, we acknowledged the limited power for the sudden cardiac death analysis due to the low event rate and called for further studies. Regarding the N-terminal pro B-type natriuretic peptide cutoff, we used a widely accepted guideline-recommended threshold for HFpEF diagnosis, while also transparently noting its potential limitation in HCM as a study limitation. The consistency of our results across multiple adjusted models and the competing risk analysis adds robustness to the primary findings for all-cause and cardiovascular mortality.

In conclusion, we agree that labeling the TyG index as universally "protective" is premature. We welcome the reader's call for integrated studies incorporating genetics, longitudinal TyG trajectories, and advanced metabolic phenotyping. It is through such rigorous, multifaceted research that we can determine whether this association reflects adaptive metabolic flexibility, uncovers a novel HCM subtype, or is confounded by unmeasured factors.

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