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Reply to the Letter to the Editor: "Comment on 'Association Between Triglyceride-Glucose Index and Prognosis of Patients with Hypertrophic Cardiomyopathy and Heart Failure with Preserved Ejection Fraction'"

LETTER TO THE EDITOR REPLY

To the Editor,

We sincerely thank the reader[1] for their thoughtful and constructive comments regarding our study[2] on the triglyceride-glucose (TyG) index in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF). We appreciate the opportunity to further discuss the potential mechanisms and implications of our findings.

The reader aptly characterizes the observed inverse relationship between the TyG index and mortality as a "metabolic paradox." We agree that this finding challenges the conventional view of the TyG index as a marker of adverse cardiometabolic risk. As the reader suggests, this paradox may indeed reflect adaptive metabolic remodeling in the context of HCM. In the hypertrophied myocardium, energy substrate preference shifts from fatty acid oxidation toward glucose utilization to maintain ATP production under pressure overload. This compensatory increase in glycolytic flux may contribute to higher TyG values, which in this specific setting could indicate a more favorable metabolic phenotype rather than systemic insulin resistance.

Regarding the potential influence of cohort selection, we acknowledge that our exclusion of patients with reduced left ventricular ejection fraction and low N-terminal pro-B-type natriuretic peptide may have enriched the study with a more metabolically stable population. However, our multivariable models extensively adjusted for key clinical, biochemical, and echocardiographic confounders, including N-terminal pro-B-type natriuretic peptide, left ventricular ejection fraction, renal function, and inflammatory markers.[2] While we did not have data on body composition or detailed nutritional parameters, the consistency of the association across multiple models and subgroup analyses supports the robustness of the findings. We agree that future studies incorporating these additional parameters would be valuable.

The sex-specific association, where the protective relationship was significant only in males, is indeed intriguing and warrants further investigation. As noted, this may reflect underlying differences in myocardial substrate metabolism, mitochondrial efficiency, or hormonal regulation. Our subgroup analysis was exploratory, and we emphasize the need for dedicated studies to dissect the sex-specific metabolic adaptations in patients with HCM and HFpEF.

Finally, we fully concur with the reader's concluding insight: the interpretation of the TyG index must be contextualized within the specific cardiac phenotype. While it reliably indicates insulin resistance in general populations, its prognostic significance appears to be reversed in patients with HCM and HFpEF, a population

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with distinct myocardial energetics. This underscores the importance of disease-specific biomarker validation.

We thank the reader for their insightful critique and for highlighting the need to explore whether the TyG index reflects compensatory metabolism or a true prognostic advantage. Further prospective studies will be essential to clarify these mechanisms.

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