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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

To the Editor,

I read with great interest the article by Liu et al[1] entitled "Association Between Triglyceride-Glucose Index and Prognosis of Patients with Hypertrophic Cardiomyopathy and Heart Failure with Preserved Ejection Fraction," recently published in the *Anatolian Journal of Cardiology* [2025;29(11):619-629]. The authors deserve credit for addressing an underexplored intersection between metabolic dysregulation and myocardial structural disease.

Their observation that a higher triglyceride-glucose (TyG) index was associated with lower all-cause and cardiovascular mortality in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF) challenges the conventional view that elevated TyG reflects adverse cardiometabolic risk. This intriguing "metabolic paradox" warrants deeper consideration.

In my opinion, the unexpected inverse relationship may reflect adaptive metabolic remodeling rather than a true protective effect of insulin resistance. In hypertrophied myocardium, a shift from fatty acid oxidation toward glucose utilization is an established compensatory mechanism to maintain energy efficiency. Enhanced glycolytic flux in this setting could theoretically translate into higher TyG values, yet indicate more active glucose metabolism rather than systemic insulin resistance. This interpretation aligns with positron emission tomography studies showing increased glucose uptake in hypertrophic segments of HCM hearts.

Furthermore, the study excluded patients with reduced left ventricular ejection fraction and low N-terminal pro–B-type natriuretic peptide levels, potentially enriching the cohort with metabolically stable individuals. Consequently, the higher TyG index might simply mark better metabolic reserve rather than protection against adverse outcomes. It would be informative to analyze whether this relationship persists after adjusting for body composition, nutritional parameters, and inflammatory status, which are known to influence both TyG and survival in chronic heart failure.

Another aspect worth exploring is the sex-specific metabolic adaptation observed in the subgroup analysis. The inverse association between TyG and mortality was significant only in males. This finding may reflect sex-related differences in myocardial substrate preference, mitochondrial function, and hormonal modulation of insulin signaling. Investigating these mechanisms in future studies could illuminate the biological basis of this disparity.

Finally, this work opens an important discussion about whether metabolic indices such as TyG should be interpreted uniformly across different cardiac phenotypes. While TyG is a reliable surrogate of insulin resistance in metabolic syndrome and atherosclerosis, its prognostic meaning may diverge in structural heart diseases characterized by altered myocardial energetics. Clarifying this distinction could substantially refine the use of TyG as a clinical biomarker in cardiomyopathies.

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We sincerely congratulate Liu et al for stimulating a new line of thought in cardio-metabolic research and hope that future prospective and mechanistic studies will further elucidate whether the "protective" TyG signal in HCM-HFpEF reflects a compensatory phenomenon or a true prognostic advantage.[2-5]

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