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Commentary on the Prognostic Interpretation of the Triglyceride-Glucose Index in Patients with HCM and HFpEF

LETTER TO THE EDITOR

To the Editor,

I read with great interest the article by Liu et al,[1] titled "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*. The authors should be congratulated for addressing the prognostic relevance of the triglyceride–glucose (TyG) index in a challenging and understudied clinical population. Several methodological and pathophysiological considerations, however, merit further discussion.

The proposed physiological explanation for the "protective effect" of higher TyG levels appears insufficient. Elevated TyG is widely recognized as a marker of insulin resistance, metabolic impairment, and proarrhythmogenic electrical abnormalities.[2-4] In high-risk populations such as hypertrophic cardiomyopathy (HCM) with heart failure with preserved ejection fraction (HFpEF)—where electrical instability and myocardial remodeling are prominent—an increase in TyG would typically be expected to worsen, rather than improve, mortality. The hypothesis of "adaptive glucose oxidation" in hypertrophied myocardium remains speculative and lacks mechanistic evidence. More plausible explanations, including residual confounding, selection bias, metabolic reverse epidemiology, and unmeasured clinical variables, should be considered. Clarifying this paradox requires prospectively designed and phenotypically more homogeneous studies.

The markedly unequal distribution of diabetes across TyG quartiles introduces additional confounding. Diabetes prevalence increases from 7.3% to 21.3% across quartiles, and patients in the upper quartile are more likely to receive cardioprotective agents—particularly sodium-glucose co-transporter 2 (SGLT2) inhibitors—that independently reduce mortality and hospitalization.[5] Such therapeutic effects may obscure or distort the true association between TyG and outcomes. Adjustment or stratification by antidiabetic therapy would help disentangle these overlapping effects.

Further limitations include substantial heterogeneity within the HCM/HFpEF population—comprising obstructive, non-obstructive, apical, and restrictive phenotypes—which may mask phenotype-specific associations. The retrospective design also precludes causal inference, and residual confounding related to nutritional status, body composition, metabolic comorbidities, and hemodynamic parameters cannot be excluded. Moreover, the lack of external validation limits generalizability, particularly given inter-population differences in TyG distribution. Finally, only 56 cases of sudden cardiac death (SCD) were recorded, rendering the study underpowered to draw firm conclusions regarding the absence of a TyG–SCD relationship.

In conclusion, while this study provides valuable preliminary insight, the paradoxical direction of the associations, the potential for metabolic and therapeutic confounding, the phenotypic heterogeneity of the cohort, and the limited power for SCD outcomes warrant cautious interpretation. Future prospective studies with standardized metabolic profiling, adequate adjustment for medical therapies,

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and external validation are essential to determine whether TyG truly carries prognostic significance in patients with HCM-HFpEF.

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