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LETTER

Comment on the Association Between the GGT/HDL-C Ratio and Diabetic Kidney Disease Risk [Letter]

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Dear editor

We read with interest the study by Teng et al exploring the association between the gamma-glutamyl transferase to high-density lipoprotein cholesterol ratio (GHR) and the risk of diabetic kidney disease (DKD) in individuals with type 2 diabetes.[1] The use of routinely available laboratory parameters to inform risk identification is clinically appealing and addresses an important practical need.

Before GHR is considered for broader clinical application, however, several issues deserve closer examination in the context of real-world diabetic kidney disease management.

First, information on medication use was not reported in detail. In particular, exposure to renoprotective therapies such as renin–angiotensin system inhibitors and sodium–glucose cotransporter-2 inhibitors was not specified, nor were other commonly prescribed agents that may influence liver enzymes or lipid profiles. In routine practice, these treatments are closely intertwined with both metabolic markers and renal outcomes. Incomplete adjustment for such therapies therefore has the potential to obscure, rather than clarify, the observed associations.

Second, the biological interpretation of GHR and its implications for clinical decision-making remain closely linked and should be considered together. GHR reflects a combination of hepatic enzyme activity and lipid metabolism.[2] Its association with DKD may reasonably be interpreted as capturing the overall burden of metabolic disturbance, particularly insulin resistance, rather than indicating a kidney-specific pathogenic pathway. This interpretation is supported by the mediation analysis, in which the TyG index accounted for approximately 26.6% of the observed association. Under this view, GHR functions primarily as an integrated metabolic signal rather than a direct causal driver of renal injury.

This perspective also bears directly on the clinical meaning of the nonlinear association identified by restricted cubic spline analysis. While the identification of an inflection point (84.5) is statistically sound, its biological and clinical significance is less clear. It remains uncertain whether this value represents a meaningful threshold or simply reflects the distribution of GHR within the study population. More importantly, even if a high-risk range can be defined, the appropriate clinical response is not self-evident. Should clinicians aim to modify GGT or HDL-C specifically, or should GHR be interpreted as a prompt to intensify comprehensive metabolic management? Decision curve analysis could help clarify whether adding GHR to established indicators such as albuminuria, estimated glomerular filtration rate, and blood pressure meaningfully improves clinical decision-making. Ultimately, intervention studies would be required to determine whether targeting GHR itself leads to better renal outcomes.

Finally, the marked heterogeneity of diabetic kidney disease should be kept in mind when interpreting GHR-based risk stratification.[3] Renal function decline in diabetes does not arise from a single mechanism.[4] Alongside metabolically driven disease, progression may be dominated by long-standing hypertension, hemodynamic stress, age-related changes, or inflammatory processes. As a strongly metabolism-related marker, GHR is likely to perform best in patients with

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predominantly metabolic disease, while offering more limited insight in other phenotypes. If applied indiscriminately, this limitation could result in underestimation of risk in non-metabolic forms of DKD.

In summary, the authors present a simple and accessible metabolic index that is associated with DKD risk. Clarifying its causal relevance, its added value beyond established clinical markers, and its role across different disease phenotypes will be essential before its clinical utility can be fully defined. Further longitudinal and mechanistic studies are therefore warranted.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

MY: Conceptualization, Writing – original draft, Writing – review and editing.

HJ: Writing – review and editing.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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