

Comment On: Association of Fasting C-Peptide to High Density Lipoprotein Cholesterol Ratio with Non-Alcoholic Fatty Liver Disease in Chinese Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study [Response to Letter]

Qian Liang ¹⁻³, Haofei Hu ⁴

¹Department of Endocrinology, Shenzhen People's Hospital, Shenzhen, Guangdong, People's Republic of China; ²Department of Endocrinology, The First Affiliated Hospital of Southern University of Science and Technology, Shenzhen, Guangdong, People's Republic of China; ³Department of Endocrinology, The Second Affiliated Hospital of Jinan University, Shenzhen, Guangdong, People's Republic of China; ⁴Department of Nephrology, Shenzhen Second People's Hospital, Shenzhen, Guangdong, People's Republic of China

Correspondence: Haofei Hu, Email huhaofei0319@126.com

Dear editor

Thank you for the opportunity to respond to the thoughtful comments by Hu and Xu¹ regarding our manuscript titled "Association of Fasting C-Peptide to High Density Lipoprotein Cholesterol Ratio with Non-Alcoholic Fatty Liver Disease in Chinese Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study".² We appreciate their engagement with our work and address each point below with reference to our original study.

Study Design

Comment: Sample

The single-center design limits external validity, and no sample size calculation is reported, nor are the key parameters, particularly concerning for underpowered subgroup analyses, which may lead to insufficient statistical power and unstable effect estimates.

Response

Single-Center Design

We acknowledge that single-center studies may affect generalizability. However, our cohort was consecutively recruited from a large tertiary hospital in Southern China, reflecting real-world clinical practice. We explicitly stated this as a limitation (Page 13–14) and recommended multi-center validation in the conclusion.

Sample Size Calculation

While not explicitly detailed, the study included 718 participants after screening 982 individuals, a sample size consistent with similar cross-sectional studies in the field. Post-hoc power analysis for the primary analyses indicated >0.9, confirming sufficient statistical power to detect the observed significant associations ($P < 0.0001$).³ Therefore, despite the absence of a prospective calculation, the robust sample size and strong effect sizes provide confidence in the stability of the primary findings. Nevertheless, we acknowledge that subgroup analyses may be underpowered due to smaller stratum-specific sample sizes. Therefore, these findings should be interpreted as exploratory. Future studies with larger and more diverse populations are warranted to confirm and extend our results.

Comment: Outcome

NAFLD diagnosis relies on ultrasound without reported quality control (such as inter-observer agreement among radiologists), risking misclassification. FHR failing to capture long-term stability and introducing measurement error.

Response**Ultrasound Diagnosis and Quality Control**

NAFLD was diagnosed by certified radiologists blinded to laboratory data to minimize bias (Page 3). Standard sonographic criteria (≥ 2 out of 4 features) were applied as per established guidelines.⁴ Although ultrasound has limitations in mild steatosis, it remains the most widely used non-invasive method in epidemiological studies, as noted in our Discussion (Page 12,14)).

FHR Measurement Stability

We recognize that single-timepoint measurements may not capture biological variability. This point is also acknowledged as the third limitation in the Discussion section (Page 14). However, fasting C-peptide measurements under standardized conditions are commonly used in clinical and research settings for lipid and peptide biomarkers due to their practicality and established reference ranges. Future studies with repeated measures are encouraged to better understand the long-term stability and intra-individual variation of FHR.

Statistical Analysis**Comment: Methodological Inconsistency**

The Abstract incorrectly cites “multiple linear regression” for the binary NAFLD outcome (actual logistic regression).

Response**Regression Method**

The term “multiple linear regression” in the Abstract was an oversight. We used logistic regression for binary NAFLD outcome throughout the analysis, as clearly described in the Methods (Page 4) and Results (Tables 3, 4). We apologize for the wording inconsistency.

Comment: Missing

The findings should be interpreted with caution due to potential selection bias from participant attrition and missing data exceeding 10%. Furthermore, extreme outliers are unaddressed.

Response**Missing Data**

Missing values were handled via imputation (mean/median for continuous, separate category for categorical) as described (Page 4). The proportion of missing data was low for most variables ($\leq 5\%$) except VPT (n=28) and ABI (n=35), which were not primary covariates. Sensitivity analyses supported robustness.

Outliers

Extreme values were reviewed; non-parametric tests and robust regression approaches were applied where appropriate. The wide confidence intervals in some estimates (eg, eGFR) reflect data variability.

Comment: Nonlinear and Subgroup Analyses

The FHR threshold lacks stability validation and biological rationale. Subgroup analyses omit multiple comparison correction, inflating Type I error.

Response

Threshold Validation

The inflection point (FHR=1.23) was identified using generalized additive models (GAM) and piecewise linear regression with maximum likelihood estimation (Page 8–9, Table 4). The log-likelihood ratio test showed significant nonlinearity ($P=0.013$). Biological plausibility is discussed in the context of C-peptide and HDL-C pathophysiology (Page 12–13).

Subgroup Analysis and Multiple Testing

We presented interaction tests with P-values but did not adjust for multiple comparisons due to the exploratory nature of subgroup analyses. This is a common approach in observational studies;⁵ findings are interpreted as hypothesis-generating.

Comment: ROC Curve

The performance of FHR has not been validated against established insulin resistance indices (eg, TyG-BMI) identified in previous studies using statistical tests. This prevents conclusions about whether FHR offers incremental value over existing biomarkers.

Response

Comparison with Established Indices

We agree this is a valuable point, which we explicitly acknowledged in the manuscript. As stated in the Discussion (Page 14): “Fifthly, while we demonstrate a significant association between the FCP/HDL-C ratio and NAFLD, we did not compare its performance to other established indices. This important validation represents a key objective for future research”. Our current study was designed to introduce and internally validate FHR as a novel composite marker. The ROC analysis confirmed that FHR provided better predictive performance than its individual components. However, we fully recognize that a formal statistical comparison with established indices (eg, TyG-BMI) was not conducted, which limits our ability to assess its incremental value over existing biomarkers. This acknowledged limitation underscores the need for future studies to directly benchmark FHR against such scores to determine its potential clinical utility.

Comment: Collinearity

The manuscript does not report collinearity diagnostics for covariates in the multivariable model.

Response

Collinearity: While collinearity diagnostics were not originally reported in the manuscript, we have now performed a post-hoc analysis focusing specifically on the variables included in the fully adjusted model (Model II). The variance inflation factor (VIF) was calculated for all covariates in the final multivariable logistic regression model (gender, age, BMI, DBP, ALT, ALB, FBG, SUA, UACR, TG, and alcohol drinking history). The results indicated that the VIF for each variable was less than 2, which is well below the conventional thresholds of 5 or 10.⁶ This suggests no evidence of significant multicollinearity among the predictors in the final model. Furthermore, our covariate selection strategy – based on clinical relevance and a change-in-estimate criterion ($\geq 10\%$) – inherently reduces the risk of including redundant or highly correlated variables. Therefore, we are confident that the effect estimates (ORs) for the association between FHR and NAFLD are stable and not distorted by collinearity.

Overinterpretation

Comment: Causal Inference

Cross-sectional design cannot support claims like “mitigating NAFLD through FHR reduction,” which inappropriately implies causality.

Response

Causal Inference

We explicitly stated that “cross-sectional design cannot clarify causal relationship” (Page 13) and used cautious language (eg, “association,” “correlation”). The phrase “mitigating NAFLD through FHR reduction” was posed as a hypothetical rationale for future research, not a causal conclusion.

Comment: Conclusion-Data Mismatch

The conclusion misrepresents the threshold effect - $FHR \leq 1.23$ shows a stronger association ($OR=3.07$) than $FHR > 1.23$ ($OR=1.20$). Additionally, the Discussion mentions “Longitudinal increases in FHR during follow-up”, creating confusion about the study design.

Response

Threshold Effect Interpretation

There is an inaccurate statement in the Discussion section (Page 12). The sentence “having an FHR below 1.23 was associated with a lower NAFLD prevalence” contains a clerical error. It should correctly reflect the findings presented on Page 9, which state that below the inflection point of 1.23, the association with NAFLD is significantly stronger ($OR=3.07$). The intended meaning should be: “In T2DM patients, having an FHR below 1.23 was associated with a higher NAFLD prevalence, with a sharper positive correlation observed when FHR was under this threshold”. We apologize for this oversight and will seek correction.

Longitudinal Reference

We acknowledge that this phrase in the Discussion could cause confusion about our study design. Our study is explicitly cross-sectional, as stated in the title, methods, and limitations. The phrase was intended as a speculative discussion point regarding potential future changes and mechanisms, not a report of our own longitudinal data. We agree this was an unclear wording choice that could be misinterpreted.

General Comments

We fully agree with your assessment regarding the inherent limitations of the cross-sectional design, which precludes causal inference, and the need for validation using gold-standard methods. We have explicitly acknowledged these points in the “Limitations” section of our manuscript (Pages 13–14). Your proposed direction for future research – multicenter, prospective studies with standardized, comparative, and gold-standard measurements – is perfectly aligned with our own conclusions and recommendations for further investigation.

We thank Hu and Xu for your valuable feedback, which helps improve the clarity and accuracy of scientific communication.

Data Sharing Statement

Data sharing is not applicable to this communication as no new data were created or analyzed.

Author Contributions

Qian Liang: Conceptualization, Data Curation, Visualization, Writing-Original Draft. Haoifei Hu: Supervision, Formal Analysis, Writing-Review & Editing, Project Administration. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This work was supported by the Shenzhen Natural Science Foundation (JCYJ20250604142222029).

Disclosure

The authors report no conflict of interest in this communication.

References

1. Hu K, Xu H. Comment on: "association of fasting C-peptide to high density lipoprotein cholesterol ratio with non-alcoholic fatty liver disease in Chinese type 2 diabetes mellitus patients: a cross-sectional study" [Letter]. *Diabetes Metab Syndr Obes.* 2026;19:1–3. doi:10.2147/DMSO.S590804
2. Liang Q, Hu H, Chen X, et al. Association of fasting c-peptide to high density lipoprotein cholesterol ratio with non-alcoholic fatty liver disease in Chinese type 2 diabetes mellitus patients: a cross-sectional study. *Diabetes Metab Syndr Obes.* 2025;184507–184522. doi:10.2147/DMSO.S556539
3. Quach NE, Yang K, Chen R, et al. Post-hoc power analysis: a conceptually valid approach for power based on observed study data. *Gen Psychiatr.* 2022;35(4):e100764. doi:10.1136/gpsych-2022-100764
4. Fan JG, Jia JD, Li YM, et al. Guidelines for the diagnosis and management of nonalcoholic fatty liver disease: update 2010: (published in Chinese on chinese journal of hepatology 2010; 18:163-166). *J Dig Dis.* 2011;12(1):38–44. doi:10.1111/j.1751-2980.2010.00476.x
5. Bender R, Lange S. Adjusting for multiple testing--when and how? *J Clin Epidemiol.* 2001;54(4):343–349. doi:10.1016/s0895-4356(00)00314-0
6. Hsieh FY, Lavori PW, Cohen HJ, Feussner JR. An overview of variance inflation factors for sample-size calculation. *Eval Health Prof.* 2003;26(3):239–257. doi:10.1177/0163278703255230

Dove Medical Press encourages responsible, free and frank academic debate. The content of the Diabetes, Metabolic Syndrome and Obesity 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the Diabetes, Metabolic Syndrome and Obesity editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

Diabetes, Metabolic Syndrome and Obesity

Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-journal>

Dovepress
Taylor & Francis Group