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Reply to the Letter to the Editor: "Methodological Considerations Regarding the Combined Use of Erectile Dysfunction and Frontal QRS-T Angle for Predicting Coronary Artery Disease Severity"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the author[1] for the interest shown in our study entitled "The synergistic relationship between erectile dysfunction and frontal QRS-T angle in predicting coronary artery disease severity."[2] We appreciate the thoughtful methodological comments and the opportunity to further clarify several aspects of our analysis.

First, the author raised concerns regarding the derivation of the frontal QRS-T angle (fQRSTa) cut off value using receiver operating characteristic analysis within the same study cohort. We agree that external validation may strengthen the generalizability of threshold values. However, there is currently no universally accepted cut off value for the fQRSTa, and previous studies have highlighted the challenges of applying fixed thresholds across different populations.[3]Our aim was not to define a universal diagnostic threshold but to identify a population-specific value suitable for exploratory risk stratification within the study cohort. To address the concern that our findings might be an artifact of this specific cut off, we performed a sensitivity analysis incorporating fQRSTa as a continuous variable in our regression models. The interaction term between erectile dysfunction (ED) and fQRSTa remained statistically significant for both the Gensini score ($\beta = 0.192$, $P = .023$) and the SYNTAX score ($\beta = 0.069$, $P = .009$). This demonstrates that the predictive value of ED and fQRSTa is robust and independent of the variable operationalization method.

Second, the author commented on covariate selection, specifically the exclusion of fasting glucose and serum calcium. In our dataset, fasting glucose and HbA1c were strongly correlated ($r = 0.780$, $P < .001$). Including both would significantly increase the risk of multicollinearity. HbA1c was selected as it reflects long-term glycemic burden and is a more stable predictor in cardiovascular risk modeling.[4] When fasting glucose was added in a sensitivity analysis, it was not an independent predictor (Gensini: $P = .454$; SYNTAX: $P = .184$), and the variance inflation factor (VIF) approached the collinearity threshold (VIF = 4.458). Similarly, adding serum calcium did not yield significance (Gensini: $P = .242$; SYNTAX: $P = .114$). Multicollinearity was rigorously assessed, and all VIF values in our final models remained below 5. Crucially, even when all these additional covariates were included, the interaction term maintained its significance (Gensini: $\beta = 18.319$, $P = .020$; SYNTAX: $\beta = 6.372$, $P = .008$), confirming the stability of our primary findings.

Third, the potential role of diabetic autonomic neuropathy (DAN) as an unmeasured confounder was suggested. While this is an insightful hypothesis, as autonomic dysfunction is indeed linked to both ED and ventricular repolarization abnormalities,[5]our data do not support it as the primary explanation for our findings. Diabetes mellitus was included as a covariate in our multivariable models, partially controlling for its effects. More importantly, we conducted a subgroup analysis stratified by diabetes status. The correlation between ED and

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fQRSTa remained significant in both non-diabetic ($r = 0.309$, $P < .001$, n = 156) and diabetic patients ($r = 0.326$, $P = 0.003$, n = 80), with remarkably similar coefficients. The relationships between ED and angiographic scores also remained consistent across both groups. Furthermore, the association between ED and coronary artery disease is well-established across diverse populations, independent of diabetes.[6] Given that the prevalence of autonomic neuropathy is exceedingly low in non-diabetic patients, these combined results strongly suggest that the observed associations are robust and independent of DAN.

Fourth, the author noted that dichotomizing continuous variables (IIEF-5 and fQRSTa) may result in information loss and questioned the statistical power given the wide CIs. While categorization was employed to enhance clinical interpretability and align with established thresholds (IIEF-5 ≤21),[7] we acknowledge this methodological concern. To address it, we re-tested the interaction term (IIEF-5 × fQRSTa) using their continuous forms. After adjusting for age, body mass index, diabetes, hypertension, hyperlipidemia, smoking, HbA1c, eGFR, and hemoglobin, the interaction remained significant for both the Gensini ($\beta = -0.015$, $P = .008$) and SYNTAX scores ($\beta = -0.005$, $P = .003$). It should be noted that the negative sign of the interaction coefficient in the continuous model reflects the mathematical direction of the product term, as higher IIEF-5 scores indicate less severe ED; this is fully consistent with the positive direction observed in the dichotomized model, where the presence of ED (lower IIEF-5) combined with a widened fQRSTa was associated with greater coronary disease severity. Furthermore, to address concerns regarding statistical power and precision, we performed a bootstrap analysis with 5000 resamples. The BCa 95% CIs did not cross zero for either the Gensini (−0.025 to −0.002) or SYNTAX models (−0.009 to −0.002), thereby confirming the statistical robustness of the interaction effect.

Finally, regarding the term "synergistic," we agree that a statistically significant interaction does not necessarily establish a definitive biological synergy. We used this term to describe the observed statistical and predictive interaction, where the coexistence of both factors is associated with greater disease severity than either alone. To address the author's argument that this interaction merely reflects a common upstream pathophysiological process (such as DAN), our subgroup stratified by diabetes status provides crucial counter-evidence. We found that the ED−fQRSTa association remained consistently significant in both non-diabetic ($r = 0.309$, $P < .001$) and diabetic patients ($r = 0.326$, $P = .003$). If the interaction were solely driven by a diabetes-related upstream process, we would not observe such robust and parallel relationships in the non-diabetic cohort. Therefore, we believe that our findings provide valuable additive predictive value, and we welcome future mechanistic studies to further elucidate these links.

We appreciate the constructive comments and believe that continued investigation in larger, multicenter cohorts will further clarify the clinical utility of combining ED and electrocardiographic markers in cardiovascular risk assessment.

Declaration of Interests: The authors have no conflicts of interest to declare.

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