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Methodological Considerations Regarding the Combined Use of Erectile Dysfunction and Frontal QRS-T Angle for Predicting Coronary Artery Disease Severity

LETTER TO THE EDITOR

To the Editor,

I read with great interest the article by Özmen Yıldız and Özbilen,[1] which proposes combining erectile dysfunction (ED) and frontal QRS-T angle (fQRSTa) as a composite predictor of coronary artery disease severity. The hypothesis is thought-provoking; however, several methodological concerns may affect the interpretation of the findings.

First, the fQRSTa cutoff of 52.5° was derived via receiver operating characteristic analysis from the same cohort subsequently used for group stratification and regression modeling. This circular approach can inflate the threshold's apparent discriminative performance and bias group comparisons. Without validation in an independent cohort or through internal resampling methods such as bootstrapping, the generalizability of this cutoff remains uncertain.

Second, the regression models have notable gaps in covariate adjustment. Fasting glucose differed significantly between groups ($P < .001$, Table 3) yet was excluded from the models; only hemoglobin A1c (HbA1c) was entered. Since HbA1c may underestimate glycemic burden when hemoglobin is low—as observed in group 4 (median 13.6 g/dL)[2]—this omission is clinically relevant. Moreover, the authors cite "unmeasured factors such as… electrolyte disturbances" among study limitations, yet serum calcium was measured, showed significant between-group differences ($P = .009$), and was nonetheless excluded from the models. This internal contradiction undermines the claim of "full adjustment." Additionally, variance inflation factors were not reported, leaving multicollinearity—particularly between diabetes status and HbA1c (diabetes $\beta = 0.869$, $P = .881$)—unquantified.

Third, diabetic autonomic neuropathy (DAN) represents a critical unmeasured confounder. Both ED and ventricular repolarization heterogeneity reflected by fQRSTa are recognized manifestations of autonomic dysfunction.[3] With approximately 34% of the cohort having diabetes mellitus and group 4 showing the highest prevalence (40.7%), DAN could account for the observed ED–fQRSTa association without requiring a synergistic mechanism. Without autonomic function testing or subgroup analysis stratifying by diabetes status, this alternative explanation cannot be excluded.

Fourth, dichotomizing IIEF-5 scores and fQRSTa—2 continuous variables—into binary categories results in information loss and may obscure dose–response relationships.[4] The wide confidence interval of the interaction term for the Gensini score ($\beta = 17.233$, 95% CI: 1.906-32.560) illustrates the imprecision of this estimate and raises concerns about whether sufficient statistical power existed to detect interaction effects in 236 patients.

Finally, the term "synergistic" warrants caution. A significant interaction term indicates departure from additivity on a given scale but does not establish

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biological synergy.[5] Given that ED and fQRSTa share pathophysiological underpinnings—particularly through the autonomic pathway discussed above—the observed interaction may reflect confounding by a common upstream process rather than a true multiplicative biological effect. Future multicenter studies incorporating external threshold validation, comprehensive autonomic assessments, and continuous variable modeling would substantially strengthen the evidence for this promising dual-marker approach.

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