

Letter to the Editors

## Limitations of NLR×GDF-15 as a Predictor of Major Adverse Events after CABG: Methodological Concerns

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**Abstract:** Recent studies have examined the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and growth differentiation factor-15 (GDF-15), used alone or in combination, for predicting major adverse cardiovascular events (MACE) after coronary artery bypass grafting (CABG). The authors concluded that NLR×GDF-15 has moderate prognostic ability. Although the idea of combining biomarkers is attractive, we highlight its significant limitations: small sample size, lack of validation and calibration, arbitrary transformation of biomarkers, short follow-up period, heterogeneous endpoint definitions, lack of comparison with established risk scores, and the confounding effect of renal function. Current methodological standards (TRIPOD+AI, PROBAST+AI) emphasize the importance of rigorous validation and transparency. Until larger multicenter studies confirm these findings, NLR×GDF-15 should not be considered a reliable prognostic marker in CABG patients.

**Keywords:** neutrophil-to-lymphocyte ratio, growth differentiation factor-15, coronary artery bypass grafting, major adverse cardiovascular events, prognostic models.

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Dear Editors,

We carefully reviewed the article by Garganeeva et al., which reported the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and growth differentiation factor-15 (GDF-15), both individually and in combination, for predicting major adverse cardiovascular events (MACE) after coronary artery bypass grafting (CABG) [1]. The authors concluded that the product of NLR×GDF-15 predicted MACE at 12 months with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.687. While we appreciate the attempt to identify simple biomarkers for risk stratification, we would like to draw attention to several important methodological limitations that reduce the reliability of the obtained results.

First, the study included only 80 patients with 22 MACE events over the course of a year. This small number of outcomes is below the recommended threshold for events per variable, exposing the model to overfitting and instability. Recent methodological guidelines [2] emphasize that insufficient sample size leads to overly optimistic discrimination and unreliable calibration.

Second, the lack of internal or external validation further undermines the credibility of the reported results. The model was tested on a single cohort without bootstrapping, cross-validation, or replication in an independent dataset. TRIPOD+AI [3] and PROBAST+AI [4] explicitly emphasize that validation is essential to assess optimism and data transportability.

Third, the combination of NLR and GDF-15 via simple multiplication was not predetermined and appears to be data-

driven. Although exploratory analyses can generate hypotheses, presenting such composites as clinically meaningful predictors is premature without biological plausibility or replication. A 2024 review [5] highlighted the dangers of transforming biomarkers based on data without appropriate adjustment for multiplicity.

Fourth, the model's discrimination was moderate with an AUC of 0.687, and decision curve analysis was not provided. Discrimination alone is insufficient to justify its clinical implementation. BMJ methodological articles [6] recommend supplementing AUC with decision curve analysis to determine whether markers improve net clinical benefit.

Fifth, calibration was not provided. Without calibration curves, slope, or y-intercept, it is impossible to assess whether predicted risks correspond to observed outcomes. A model with moderate discrimination may still misestimate absolute risks, thereby limiting its usefulness. International guidelines consider calibration essential in predictive modeling.

Sixth, the study did not compare the biomarker approach with established risk scores such as EuroSCORE II or STS. These tools are validated worldwide and serve as a benchmark for predicting outcomes after CABG. In 2024, Zhang et al. [7] demonstrated that biomarkers can improve the value of EuroSCORE II, but only when tested against it in multicenter cohorts.

Seventh, GDF-15 levels are strongly dependent on age and kidney function. Because estimated glomerular filtration rate (eGFR) was not included in the model, residual confounding is likely. Li et al. [8] confirmed that GDF-15 levels increase with decreasing

kidney function, making data interpretation challenging in cardiovascular populations.

Eighth, the follow-up period of only 12 months was too short. Adverse outcomes after CABG persist for many years, and the value of this biomarker needs to be confirmed in the longer term. Longitudinal data [9] showed that GDF-15 predicts outcomes beyond two years, highlighting the need for long-term follow-up.

Ninth, the composite MACE endpoint combines hard outcomes such as death, myocardial infarction, and stroke with softer outcomes such as diuretic escalation. This heterogeneity increases the number of events but reduces interpretability. Methodological standards recommend more homogeneous endpoints for biomarker validation.

Tenth, excluding perioperative deaths introduces survivorship bias. Early mortality is a significant adverse outcome, likely dependent on preoperative inflammatory status. Excluding these cases reduces the external validity of the model.

Eleventh, only a single preoperative measurement was used. Biomarkers fluctuate dynamically during surgery, and serial measurements can provide meaningful prognostic information. Garcia et al. [10] demonstrated that perioperative biomarker trajectories improved prognostic accuracy compared with baseline-only measurements.

Finally, the study was a single-center, conducted at a single Russian center with a predominantly male participant population. Given geographic, genetic, and medical differences, the results may not generalize to broader populations. Current prognostic research highlights the need for diverse, multicenter validation to ensure the applicability of the model.

Taken together, these limitations suggest that, although NLR and GDF-15 are biologically valid markers, their prognostic role in CABG patients remains unproven. While the hypothesis of an interaction between NLR and GDF-15 is intriguing, current best practice requires multicenter studies with adequate power, rigorous methodology, validation, comparison with established indicators, along with calibration and decision curve analysis. Until such data are accumulated, NLR×GDF-15 should be considered exploratory rather than clinically ready.

#### Conflict of interest

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