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Does Endothelial Activation and Stress Index Provide Information Beyond Established Risk Scores, or Does It Mainly Repackage Routinely Available Markers of Disease Severity?

LETTER TO THE EDITOR

To the Editor,

We read with great interest the article by Erzurum et al[1] published ahead of print in the *Anatolian Journal of Cardiology*, on the prognostic value of the endothelial activation and stress index (EASIX) in non-ST-segment elevation myocardial infarction (NSTEMI).[1] In this single-center retrospective study, EASIX independently predicted in-hospital mortality and achieved an area under the receiver operating characteristic curve (AUC) of 0.770, outperforming several conventional laboratory surrogates. The findings are promising; yet, they raise a central question: does EASIX add prognostic information beyond validated risk scores, or does it largely repackage routinely measured markers reflecting general disease severity?

First, EASIX is calculated from lactate dehydrogenase (LDH), serum creatinine, and platelet count, each of which can be substantially influenced by non-cardiac comorbidities. Creatinine primarily mirrors renal function. Elevated LDH may stem from hemolysis, non-cardiac tissue injury, infection, or malignancy. Thrombocytopenia can result from immune-mediated conditions, bone-marrow disorders, liver disease, or drug toxicity. Patients with preexisting chronic kidney disease, hematological disorders, or hepatic dysfunction were neither excluded from the present cohort nor assessed in dedicated sensitivity analyses. This consideration is clinically relevant, given that EASIX has been linked to mortality across heterogeneous clinical settings, including myocardial infarction in critical-care cohorts,[2] stable coronary artery disease,[3] and acute decompensated heart failure,[4] supporting its role as a non-specific marker of systemic stress. Accordingly, a high EASIX may signal global organ injury rather than NSTEMI-specific endothelial activation. Without subgroup analyses confined to patients free of primary renal, hematological, or hepatic disease, we cannot rule out that its prognostic performance is driven by these confounding comorbid conditions.

Second, although both Global Registry of Acute Coronary Events (GRACE) score and EASIX remained independently associated with in-hospital mortality in the multivariable model, the GRACE score already incorporates age, heart rate, blood pressure, serum creatinine, and cardiac biomarkers. The study did not report incremental prognostic metrics such as net reclassification improvement (NRI) or integrated discrimination improvement when EASIX was added to the full GRACE risk model. A recent cohort of 624 NSTEMI patients offers a useful comparative reference: after excluding individuals with hematological disease, severe liver dysfunction, and end-stage kidney disease, adding EASIX to GRACE only increased the AUC by 0.015, despite a continuous NRI of 0.385 for 1-year mortality.[5] The authors of that study also emphasized overlapping creatinine input between the 2 tools and the modest gain in discriminative power. It remains unknown whether comparable incremental benefit exists for in-hospital mortality, and whether such benefit persists without these stringent patient exclusions. Statistical significance of

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a marginally higher AUC does not equate to tangible clinical added value.

Third, the single-center retrospective design limits external generalizability. Inter-laboratory measurement variability for LDH, creatinine, and platelet counts may alter EASIX cut-point values, and the authors did not propose any validated threshold specifically for NSTEMI. Externally validated cut-offs across diverse real-world populations are required before EASIX can be incorporated into routine early risk-stratification workflows.

We commend the authors for evaluating a risk index derived solely from standard admission laboratory tests, requiring no extra costs or specialized assays. Nevertheless, we urge caution when interpreting EASIX as a specific biomarker of myocardial-related endothelial activation, because its prognostic performance may partially reflect non-cardiac organ stress. Future multicenter studies should quantify the true incremental prognostic yield of EASIX relative to the GRACE score, evaluate its performance in high-risk subgroups including patients with renal impairment and platelet disorders, and establish clinically actionable, validated decision thresholds.

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