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ORIGINAL RESEARCH

Modified Endothelial Activation and Stress Index (mEASIX) Predicts Long-Term Mortality in Patients with Acute Coronary Syndromes

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ABSTRACT

Endothelial dysfunction, inflammation, and microvascular injury are key mechanisms involved in the development and progression of acute coronary syndrome (ACS). The Endothelial Activation and Stress Index (EASIX) and its derivatives have emerged as readily available biomarkers of endothelial stress; however, the prognostic value of modified EASIX (m-EASIX), which incorporates C-reactive protein, remains uncertain. This study evaluated the prognostic performance of EASIX-derived indices and investigated whether high admission m-EASIX was independently associated with long-term post-discharge all-cause mortality in patients with ACS. Adult patients admitted with ACS between January 2019 and February 2020 who survived the index hospitalization and were discharged alive were retrospectively identified from a tertiary referral center. EASIX, simplified EASIX (s-EASIX), and m-EASIX were calculated from admission laboratory measurements, and their prognostic performance was evaluated using receiver operating characteristic analysis, Kaplan–Meier survival curves, and multivariable Cox proportional hazards models. Among 102 patients who survived the index ACS hospitalization, 29 (28.4%) died during a mean post-discharge follow-up of 68.2 ± 28.0 months. m-EASIX showed the numerically highest AUC for post-discharge all-cause mortality (AUC 0.730, 95% CI 0.617–0.843; p<0.001), followed by EASIX (AUC 0.715) and s-EASIX (AUC 0.629). However, paired DeLong comparisons showed no significant difference between m-EASIX and EASIX (p=0.809) or between m-EASIX and s-EASIX (p=0.158). Patients with m-EASIX ≥1.21 had significantly higher mortality than those with lower values (53.7% vs. 11.5%; p<0.001). After adjustment for age, hemoglobin concentration, and left ventricular ejection fraction, high m-EASIX remained independently associated with post-discharge all-cause mortality (HR 2.759, 95% CI 1.109–6.865; p=0.029). Among the evaluated indices, m-EASIX showed the numerically highest AUC, although its discriminatory performance was not statistically superior to that of EASIX or s-EASIX. Further prospective validation is required before clinical implementation.

Keywords: Acute coronary syndrome. Endothelial dysfunction. EASIX. m-EASIX. Inflammation. Mortality. Risk stratification.

Akut Koroner Sendrom ile Başvuran Hastalarda Modifiye Endotelyal Aktivasyon ve Stres İndeksinin (mEASIX) Uzun Dönem Mortaliteyi Öngörmedeki Değeri

ÖZET

Endotelyal disfonksiyon, inflamasyon ve mikrovasküler hasar, akut koroner sendromun (AKS) gelişim ve ilerlemesinde rol oynayan temel mekanizmalardır. Endotelyal Aktivasyon ve Stres İndeksi (EASIX) ve türevleri endotelyal stresi yansıtan kolay erişilebilir biyobelirteçlerdir. Ancak, C-reaktif proteini içeren modifiye EASIX'in (m-EASIX) prognostik değeri net değildir. Bu çalışmada, EASIX türevi indekslerin prognostik performansı değerlendirildi ve başvuru anındaki mEASIX düzeyinin AKS ile başvuran hastalarda uzun dönem tüm nedenlere bağlı mortalite ile bağımsız ilişkisi araştırıldı. Ocak 2019 ile Şubat 2020 tarihleri arasında üçüncü basamak bir merkezde AKS tanısıyla başvuran erişkin hastalar retrospektif olarak değerlendirildi. Başvuru laboratuvar verileri kullanılarak EASIX, basitleştirilmiş EASIX (s-EASIX) ve modifiye EASIX (m-EASIX) hesaplandı. İndekslerin prognostik performansı ROC analizi, Kaplan–Meier sağkalım eğrileri ve çok değişkenli Cox orantısal risk regresyon analizi ile değerlendirildi. m-EASIX, taburculuk sonrası tüm nedenlere bağlı mortaliteyi öngörmede sayısal olarak en yüksek AUC değerini gösterdi (AUC: 0,730; %95 GA: 0,617–0,843; p<0,001); bunu EASIX (AUC: 0,715) ve s-EASIX (AUC: 0,629) izledi. Bununla birlikte, eşleştirilmiş DeLong karşılaştırmalarında m-EASIX ile EASIX (p=0,809) veya s-EASIX (p=0,158) arasında anlamlı fark saptanmadı. m-EASIX ≥1,21 olan grupta mortalite oranı, m-EASIX <1,21 olan gruba kıyasla anlamlı olarak daha yüksekti (%53,7'ye karşı %11,5; p<0,001). Yaş, hemoglobin düzeyi ve sol ventrikül ejeksiyon fraksiyonu için düzeltme sonrasında yüksek m-EASIX, taburculuk sonrası tüm nedenlere bağlı mortalite ile bağımsız olarak ilişkiliydi (HR: 2,759; %95 GA: 1,109–6,865; p=0,029). Değerlendirilen indeksler arasında m-EASIX sayısal olarak en yüksek AUC değerini göstermekle birlikte, ayırt edici performansı EASIX veya s-EASIX'ten istatistiksel olarak üstün değildi. Klinik kullanıma geçilmeden önce prospektif çalışmalarda doğrulanması gerekmektedir.

Anahtar Kelimeler: Akut koroner sendrom. Endotelyal disfonksiyon. EASIX. m-EASIX. İnflamasyon. Mortalite. Risk sınıflandırması.

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Acute coronary syndrome (ACS), including unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), continues to impose a substantial global health burden despite major advances in pharmacological therapy and coronary revascularization[1,2]. Because patients with ACS exhibit considerable heterogeneity in both their clinical presentation and subsequent outcomes, accurate risk assessment remains a fundamental component of contemporary management. Although several established risk scores are routinely used in clinical practice, there is ongoing interest in simple, inexpensive, and readily available biomarkers that more closely reflect the biological processes underlying disease progression.

In addition to epicardial coronary artery obstruction, endothelial dysfunction and systemic inflammation are now recognized as key mechanisms contributing to the pathophysiology of ACS. These processes promote plaque instability, impair coronary microvascular function, enhance oxidative stress, activate inflammatory and platelet pathways, and contribute to myocardial injury and adverse ventricular remodeling[3–5]. Consequently, biomarkers capable of integrating endothelial injury with systemic inflammatory activity have attracted growing interest as potential tools for improving prognostic assessment in cardiovascular disease.

The Endothelial Activation and Stress Index (EASIX), calculated using serum lactate dehydrogenase (LDH), creatinine, and platelet count, has recently gained attention as a laboratory-based marker reflecting endothelial stress in cardiovascular disease[6]. Higher EASIX values have been associated with an increased risk of long-term mortality in patients with coronary artery disease, beyond that explained by conventional cardiovascular risk factors[6]. More recent investigations have expanded the clinical relevance of EASIX by linking higher values to a range of adverse outcomes, including early mortality, the no-reflow phenomenon, contrast-induced nephropathy, and in-hospital complications among patients treated with primary percutaneous coronary intervention for acute myocardial infarction[7–11]. Collectively, these findings suggest that EASIX reflects several interconnected biological pathways involved in ACS, including endothelial dysfunction, inflammation, platelet activation, renal impairment, and cellular injury.

Despite these encouraging findings, important knowledge gaps remain. Most available studies have focused on patients with STEMI, evaluated predominantly short-term outcomes, or examined only a single EASIX-derived index. Whether m-EASIX, which incorporates C-reactive protein (CRP) as an indicator of systemic inflammation, provides prognostic information across the entire spectrum of ACS and how its performance compares with other EASIX-derived indices remain unclear. In this study, we evaluated the prognostic performance of EASIX-derived indices and assessed whether admission m-EASIX was associated with long-term post-discharge all-cause mortality in a consecutive cohort of patients with ACS.

Materials and Methods

Study Design and Patient Population

We retrospectively evaluated consecutive adult patients admitted to the coronary intensive care unit of Bursa Uludag University Faculty of Medicine, a tertiary referral center, between January 1, 2019 and February 1, 2020 with a suspected diagnosis of acute coronary syndrome (ACS). Eligible patients included those diagnosed with unstable angina pectoris (USAP), non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI). The final diagnosis of ACS was established in accordance with contemporary European Society of Cardiology recommendations by integrating clinical presentation, electrocardiographic findings, cardiac biomarker results, and coronary angiographic data when indicated.

Ethical approval was obtained from the Institutional Ethics Committee of Bursa Uludag University Faculty of Medicine (approval no. 2026/312-11-16). The study was performed in accordance with the Declaration of Helsinki, and the requirement for written informed consent was waived owing to its retrospective design.

Data Collection and Definitions

A total of 366 consecutive patients admitted with suspected ACS were initially screened. Patients younger than 18 years and those subsequently determined not to have a final diagnosis of ACS were excluded. Additional exclusion criteria included Takotsubo syndrome, myocarditis, type 2 myocardial injury, severe sepsis or active systemic infection, cardiogenic shock at index admission, in-hospital

death, and other established non-ACS diagnoses. Because patients who died during the index hospitalization were excluded, the final analytic cohort comprised patients who survived the index ACS hospitalization and were discharged alive. After application of these predefined criteria, 158 patients constituted the eligible ACS cohort. Patients with missing admission laboratory data required for calculation of EASIX-derived indices, including serum lactate dehydrogenase (LDH), serum creatinine, C-reactive protein (CRP), and platelet count, were excluded, yielding a final study population of 102 patients. No imputation procedures were performed. A detailed study flowchart is presented in Figure 1.

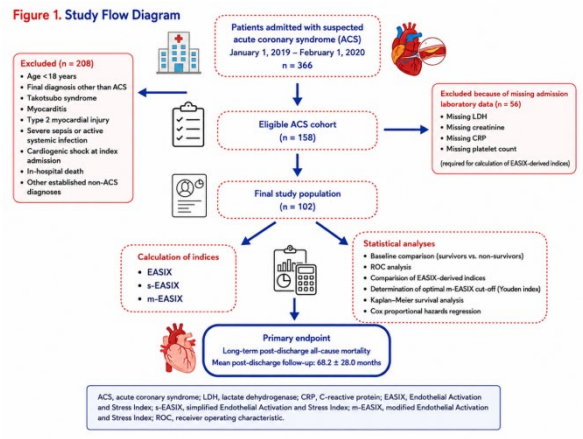


Figure 1:
Study Flow Diagram

Demographic characteristics, cardiovascular risk factors, laboratory findings, echocardiographic parameters, and medical treatments were retrospectively retrieved from institutional electronic medical records. Laboratory measurements were obtained from blood samples collected at admission. Transthoracic echocardiography was performed during hospitalization according to current recommendations, and left ventricular ejection fraction (LVEF) was assessed using the biplane Simpson method whenever feasible. ACS subtypes were classified according to contemporary ESC criteria.

EASIX-Derived Scores

Endothelial Activation and Stress Index (EASIX), simplified EASIX (s-EASIX), and modified EASIX (m-EASIX) were calculated from laboratory measurements obtained at hospital admission using previously published formulas. EASIX was calculated as lactate dehydrogenase (LDH, U/L) × serum creatinine (mg/dL) / platelet count (10^9/L), whereas s-EASIX was calculated as LDH (U/L) / platelet count (10^9/L). m-EASIX was calculated as LDH (U/L) × C-reactive protein (CRP, mg/dL) / platelet count (10^9/L). Because CRP concentrations were routinely reported by the institutional laboratory in mg/L, these values were divided by 10 to convert them to mg/dL before calculating m-EASIX.

Each index was initially evaluated as a continuous variable. Their ability to discriminate long-term post-discharge all-cause mortality was assessed using receiver operating characteristic (ROC) curve analysis. The optimal m-EASIX threshold was identified using the Youden index, after which patients were categorized into low- and high-m-EASIX groups for subsequent survival analyses.

Study Endpoint

The primary endpoint was long-term post-discharge all-cause mortality. Survival status and dates of death were obtained from the national death notification system and institutional electronic medical records. Follow-up commenced on the date of discharge following the index ACS hospitalization. For patients who died, follow-up was calculated from the date of discharge to the date of death; for survivors, it was calculated from the date of discharge to the last documented clinical contact.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed variables are presented as mean ± standard deviation, whereas non-normally distributed variables are expressed as median and interquartile range. Categorical variables are presented as frequencies and percentages.

Comparisons between groups were performed using the independent-samples t test or Mann–Whitney U test for continuous variables, as appropriate, and the χ^2 test or Fisher exact test for categorical variables. ROC curve analyses were performed to assess the discriminative performance of EASIX-derived scores for post-discharge all-cause mortality, and optimal cutoff values were identified using the Youden index. Because all EASIX-derived indices were evaluated in the same patients, pairwise comparisons of the AUCs were performed using two-sided paired DeLong tests.

Overall survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression analyses were performed to identify variables associated with post-discharge all-cause mortality. Variables with $p<0.10$ in univariable analyses together with clinically relevant covariates were considered for multivariable Cox regression analysis. To avoid model

overfitting, the final multivariable model included age, hemoglobin concentration, left ventricular ejection fraction, and high m-EASIX. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

Results

Baseline characteristics according to survival status

A total of 102 patients who survived the index ACS hospitalization and were discharged alive were included in the study. During a mean post-discharge follow-up of 68.2 ± 28.0 months, 29 patients (28.4%) died. Non-survivors were older than survivors (69 [64–80] vs. 66 [58–71] years, p=0.041) and more frequently had hypertension (72.4% vs. 50.7%, p=0.046). Hemoglobin levels were significantly lower in non-survivors (11.3±2.2 vs. 13.6±2.0 g/dL, p<0.001), whereas creatinine levels were higher (1.27 [0.83–1.75] vs. 0.85 [0.79–1.12] mg/dL, p=0.006), resulting in lower eGFR values (50 [33.3–80.0] vs. 88 [66–99.5] mL/min/1.73 m², p<0.001). Non-survivors also had lower lymphocyte counts (1.35 [0.87–2.10] vs. 1.87 [1.37–2.78] ×10⁹/L, p=0.021), higher LDH levels (259 [205–345.5] vs. 219 [181–274] U/L, p=0.011), higher CRP concentrations (29.7 [6.1–76.4] vs. 3.8 [1.0–12.9] mg/L, p<0.001), and lower albumin levels (37 [34–40] vs. 39 [37–42] g/L, p=0.003). LVEF was significantly lower among non-survivors (48 [36–53] vs. 57 [50–60]%, p<0.001). Median EASIX, m-EASIX, and s-EASIX values were significantly higher in non-survivors than in survivors (1.66 [0.90–2.77] vs. 0.82 [0.60–1.24], p<0.001; 3.25 [0.81–11.16] vs. 0.40 [0.11–1.33], p<0.001; and 1.22 [0.88–1.78] vs. 0.97 [0.70–1.44], p=0.042, respectively) (Table I).

Baseline characteristics according to m-EASIX category

ROC analysis identified an optimal m-EASIX cut-off value of 1.21. Patients were subsequently categorized into low (<1.21, n=61) and high (≥1.21, n=41) m-EASIX groups. Patients with high m-EASIX values were older (70 [65–78] vs. 64 [57–70] years, p=0.002) and more frequently had hypertension (70.7% vs. 47.5%, p=0.020). They had lower hemoglobin concentrations (12.0 [10.0–13.5] vs. 14.0 [12.5–14.9] g/dL, p<0.001), lower lymphocyte counts (1.26 [0.78–2.03] vs. 2.07 [1.59–2.86] ×10⁹/L, p<0.001), lower platelet counts (195.8 [161.2–254.6] vs. 238.2 [189.6–293.4] ×10⁹/L, p=0.020), lower albumin concentrations (37 [34–39] vs. 39 [38–42] g/L, p<0.001), and lower LVEF values (50 [44–56] vs. 58 [50–60]%, p<0.001). In contrast, LDH (259 [197–302] vs. 217 [181–274] U/L, p=0.030), creatinine (1.14 [0.86–1.75] vs. 0.84 [0.77–1.02] mg/dL, p<0.001), and CRP concentrations (45.6 [21.1–89.8] vs. 1.0 [1.0–4.5] mg/L, p<0.001) were significantly higher in the high m-EASIX group. As LDH, CRP, and platelet count are direct components of the m-EASIX formula, the observed between-group differences in these variables were expected and should not be interpreted as independent associations. Post-discharge all-cause mortality occurred more frequently in patients with high m-EASIX values than in those with low m-EASIX values (53.7% vs. 11.5%, p<0.001) (Table II).

Table I. Baseline characteristics according to survival status

Variable	Survivors (n=73)	Non-survivors (n=29)	p value
Age, years	66 (58–71)	69 (64–80)	**0.041**
Male sex, n (%)	51 (69.9)	17 (58.6)	0.277
ACS subtype			0.129
STEMI, n (%)	21 (28.8)	6 (20.7)	
NSTEMI, n (%)	32 (43.8)	19 (65.5)	
USAP, n (%)	20 (27.4)	4 (13.8)	
Hypertension, n (%)	37 (50.7)	21 (72.4)	**0.046**
Diabetes mellitus, n (%)	26 (35.6)	9 (31.0)	0.660
Coronary artery disease, n (%)	22 (30.1)	13 (44.8)	0.159
Current smoking, n (%)	22 (30.1)	6 (20.7)	0.335
Hemoglobin, g/dL	13.6 ± 2.0	11.3 ± 2.2	**<0.001**
Creatinine, mg/dL	0.85 (0.79–1.12)	1.27 (0.83–1.75)	**0.006**
eGFR, mL/min/1.73 m²	88.0 (66.0–99.5)	50.0 (33.3–80.0)	**<0.001**
Lymphocyte count, ×10⁹/L	1.87 (1.37–2.78)	1.35 (0.87–2.10)	**0.021**
Platelet count, ×10⁹/L	232.0 (176.9–284.0)	231.6 (175.2–284.9)	0.815
LDH, U/L	219 (181–274)	259 (205–345.5)	**0.011**
CRP, mg/L	3.8 (1.0–12.9)	29.7 (6.1–76.4)	**<0.001**
Albumin, g/L	39 (37–42)	37 (34–40)	**0.003**
Total cholesterol, mg/dL	179.5 ± 47.1	182.3 ± 39.1	0.655
HDL, mg/dL	37.5 (30.3–42.0)	40.0 (33.0–44.5)	0.167
LDL cholesterol, mg/dL	112.2 ± 35.2	114.8 ± 36.3	0.764
Triglycerides, mg/dL	138 (99.5–200.0)	131 (92.5–144.5)	0.237
Left ventricular ejection fraction, %	57 (50–60)	48 (36–53)	**<0.001**
EASIX	0.82 (0.60–1.24)	1.66 (0.90–2.77)	**<0.001**
m-EASIX	0.40 (0.11–1.33)	3.25 (0.81–11.16)	**<0.001**
s-EASIX	0.97 (0.70–1.44)	1.22 (0.88–1.78)	**0.042**

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage), as appropriate. ACS: acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; USAP: unstable angina pectoris; eGFR: estimated glomerular filtration rate; LDH: lactate dehydrogenase; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; EASIX: Endothelial Activation and Stress Index; m-EASIX: modified Endothelial Activation and Stress Index; s-EASIX: simplified Endothelial Activation and Stress Index.

Table II. Baseline characteristics according to m-EASIX category

Variable	Low m-EASIX (<1.21) (n=61)	High m-EASIX (≥1.21) (n=41)	p value
Age, years	64 (57–70)	70 (65–78)	**0.002**
Male sex, n (%)	43 (70.5)	25 (61.0)	0.318
Hypertension, n (%)	29 (47.5)	29 (70.7)	**0.020**
Diabetes mellitus, n (%)	22 (36.1)	13 (31.7)	0.649
Coronary artery disease, n (%)	19 (31.1)	16 (39.0)	0.411
Current smoking, n (%)	23 (37.7)	5 (12.2)	**0.005**
Hemoglobin, g/dL	14.0 (12.5–14.9)	12.0 (10.0–13.5)	**<0.001**
Creatinine, mg/dL	0.84 (0.77–1.02)	1.14 (0.86–1.75)	**<0.001**
eGFR, mL/min/1.73 m²	90.0 (68.5–103.2)	61.0 (33.3–80.5)	**<0.001**
Lymphocyte count, ×10⁹/L	2.07 (1.59–2.86)	1.26 (0.78–2.03)	**<0.001**
Platelet count, ×10⁹/L	238.2 (189.6–293.4)	195.8 (161.2–254.6)	**0.020**
LDH, U/L	217 (181–274)	259 (197–302)	**0.030**
CRP, mg/L	1.0 (1.0–4.5)	45.6 (21.1–89.8)	**<0.001**
Albumin, g/L	39 (38–42)	37 (34–39)	**<0.001**
Total cholesterol, mg/dL	190 (161–224)	166 (133–197)	**0.006**
HDL, mg/dL	39 (31.3–44.0)	37 (29.5–42.0)	0.293
LDL cholesterol, mg/dL	119 (104.3–142.8)	102 (74.0–128.0)	**0.007**
Triglycerides, mg/dL	132.5 (99.5–207.5)	133.0 (92.5–169.0)	0.349
Left ventricular ejection fraction, %	58 (50–60)	50 (44–56)	**<0.001**
Post-discharge all-cause mortality, n (%)	7 (11.5)	22 (53.7)	**<0.001**

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage), as appropriate. m-EASIX: modified Endothelial Activation and Stress Index; eGFR: estimated glomerular filtration rate; LDH: lactate dehydrogenase; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Receiver operating characteristic analysis

Receiver operating characteristic analysis showed that m-EASIX had the numerically highest AUC for post-discharge all-cause mortality (AUC=0.730, 95% CI 0.617–0.843; p<0.001), followed by EASIX (AUC=0.715, 95% CI 0.606–0.824; p<0.001) and s-EASIX (AUC=0.629, 95% CI 0.506–0.752; p=0.039) (Table III). In paired DeLong comparisons, the AUC of m-EASIX did not differ significantly from that of EASIX (difference in AUC=0.016; p=0.809) or s-EASIX (difference in AUC=0.101; p=0.158). Full pairwise comparisons are presented in Table IV. The optimal m-EASIX cut-off of 1.21 yielded a sensitivity of 75.9% and a specificity of 74.0%. The ROC curve for m-EASIX is shown in Figure 2.

Table III. Receiver operating characteristic analysis of EASIX-derived scores for prediction of post-discharge all-cause mortality

Score	AUC (95% CI)	p value
EASIX	0.715 (0.606–0.824)	<0.001
m-EASIX	0.730 (0.617–0.843)	<0.001
s-EASIX	0.629 (0.506–0.752)	0.039

AUC: area under the curve; CI: confidence interval; EASIX: Endothelial Activation and Stress Index; m-EASIX: modified Endothelial Activation and Stress Index; s-EASIX: simplified Endothelial Activation and Stress Index.

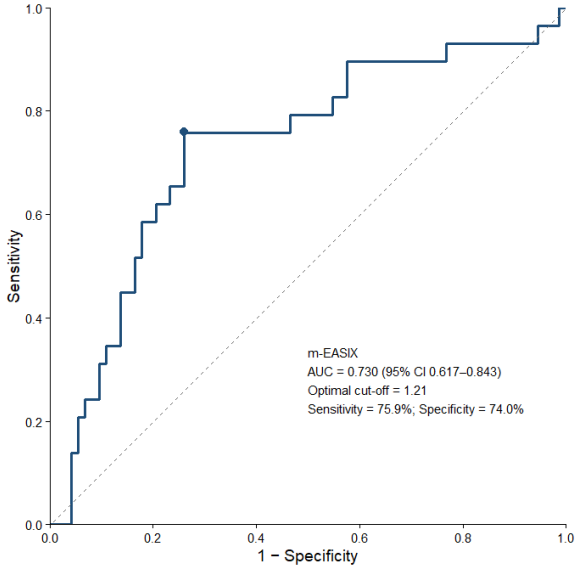


Figure 2:
Receiver operating characteristic curve of m-EASIX for prediction of post-discharge all-cause mortality. The optimal cut-off value of 1.21 yielded a sensitivity of 75.9% and a specificity of 74.0% (AUC=0.730, 95% CI 0.617–0.843).

Table IV. Pairwise comparison of ROC curves using the DeLong test

Comparison	AUC 1	AUC 2	Difference in AUC	Z	*p value*
m-EASIX vs EASIX	0.730	0.715	0.016	0.242	0.809
m-EASIX vs s-EASIX	0.730	0.629	0.101	1.411	0.158
EASIX vs s-EASIX	0.715	0.629	0.086	2.065	0.039

AUCs were compared using two-sided paired DeLong tests because all indices were evaluated in the same patients. Reported p values are unadjusted for multiple comparisons.

Survival analysis

Kaplan–Meier analysis demonstrated significantly worse long-term post-discharge survival among patients with high m-EASIX values (≥1.21) compared with those with low m-EASIX values (<1.21) (log-rank p<0.001; Figure 3). At 1 year, post-discharge survival rates were 98.4% and 82.9% in the low- and high-m-EASIX groups, respectively. The corresponding survival rates were 96.7% and 58.5% at 3 years and 90.2% and 51.2% at 5 years, respectively.

Cox regression analysis

In univariable Cox regression analysis, age, hypertension, eGFR, hemoglobin concentration, albumin, lymphocyte count, CRP-to-albumin ratio, LVEF, continuous m-EASIX, and high m-EASIX

were significantly associated with post-discharge all-cause mortality. In the multivariable model adjusted for age, hemoglobin concentration, and LVEF, high m-EASIX remained independently associated with post-discharge all-cause mortality (HR=2.759, 95% CI 1.109–6.865; p=0.029). Higher hemoglobin concentration (HR=0.620, 95% CI 0.499–0.771; p<0.001) and higher LVEF (HR=0.931, 95% CI 0.901–0.963; p<0.001) were independently associated with a lower risk of mortality, whereas age was not independently associated with the outcome (HR=1.009, 95% CI 0.976–1.043; p=0.592) (Table V).

Table V. Univariable and multivariable Cox proportional hazards regression analyses for post-discharge all-cause mortality

Factor	Univariable analysis				Multivariable analysis			
	HR	95% CI		p value	HR	95% CI		p value
		Lower	Upper			Lower	Upper	
Age, years	1.037	1.002	1.074	**0.039**	1.009	0.976	1.043	0.592
Hemoglobin, g/dL	0.667	0.565	0.789	**<0.001**	0.620	0.499	0.771	**<0.001**
LVEF (%)	0.941	0.915	0.967	**<0.001**	0.931	0.901	0.963	**<0.001**
High m-EASIX	6.564	2.796	15.410	**<0.001**	2.759	1.109	6.865	**0.029**
HT	2.304	1.020	5.205	**0.045**				
DM	0.845	0.385	1.856	0.675				
CAD	1.743	0.838	3.625	0.137				
Smoking	0.627	0.255	1.540	0.309				
eGFR, mL/min/1.73 m²	0.979	0.968	0.990	**<0.001**				
Albumin, g/L	0.866	0.806	0.931	**<0.001**				
Lymphocyte count	0.574	0.363	0.907	**0.017**				
Total cholesterol, mg/dL	1.001	0.993	1.009	0.847				
LDL, mg/dL	1.001	0.991	1.012	0.805				
HDL, mg/dL	1.020	0.989	1.052	0.212				
Triglycerides, mg/dL	0.996	0.991	1.002	0.189				
CRP/Albumin ratio	1.224	1.056	1.418	**0.007**				
EASIX	1.046	0.958	1.141	0.315				
m-EASIX	1.040	1.008	1.073	**0.015**				

HR: hazard ratio; CI: confidence interval; LVEF: left ventricular ejection fraction; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; EASIX: Endothelial Activation and Stress Index; m-EASIX: modified Endothelial Activation and Stress Index. Variables with p < 0.10 in univariable analysis together with clinically relevant covariates were considered for multivariable modeling.

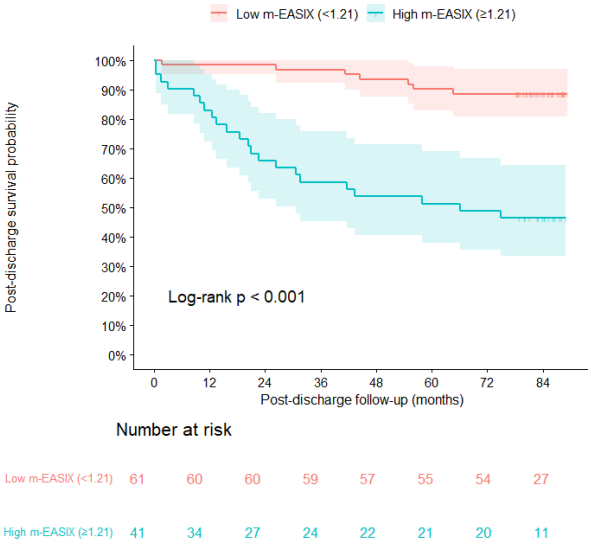


Figure 3:
Kaplan–Meier curves for long-term post-discharge survival according to m-EASIX category. Patients with high m-EASIX values (≥1.21) had significantly worse post-discharge survival than those with low m-EASIX values (<1.21) (log-rank p<0.001). Shaded areas represent 95% confidence intervals, vertical marks indicate censored observations, and the numbers at risk are presented below the curves.

Discussion and Conclusion

In this retrospective cohort of patients who survived the index ACS hospitalization and were discharged alive, admission m-EASIX was independently associated with long-term post-discharge all-cause mortality and showed the numerically highest AUC among the three evaluated EASIX-derived indices. However, paired DeLong comparisons demonstrated no statistically significant difference between the AUC of m-EASIX and those of EASIX or s-EASIX; therefore, the present findings do not establish the statistical superiority of m-EASIX over the other indices. Nevertheless, a high m-EASIX value identified a subgroup with markedly worse post-discharge survival, and this association remained significant after adjustment for age, hemoglobin concentration, and left ventricular ejection fraction. These findings support the prognostic relevance of m-EASIX as a potentially complementary marker of long-term risk among patients who survive hospitalization for ACS. An additional observation was the lower prevalence of current smoking in the high m-EASIX group compared with the low m-EASIX group (12.2% vs. 37.7%). This counterintuitive finding may reflect differences in age distribution, survivor selection, or residual confounding rather than a protective association,

particularly because current smoking was not associated with post-discharge mortality in the univariable Cox analysis (HR 0.627, 95% CI 0.255–1.540; p=0.309).

The prognostic association observed with m-EASIX is biologically plausible in view of the evolving understanding of ACS pathophysiology. Although ACS has traditionally been viewed primarily as a consequence of plaque rupture and coronary thrombosis, contemporary evidence indicates that adverse outcomes are also driven by a complex interplay between endothelial dysfunction, systemic inflammation, platelet activation, oxidative stress, and coronary microvascular injury[1–5,13,14]. These mechanisms contribute not only to the acute ischemic event itself but also to subsequent ventricular remodeling, recurrent ischemic episodes, and progressive cardiovascular deterioration. Accordingly, biomarkers integrating multiple interconnected biological pathways may provide a more comprehensive assessment of long-term cardiovascular risk than isolated inflammatory or injury markers[15].

Unlike the original EASIX, which incorporates creatinine as a marker of organ dysfunction, m-EASIX substitutes creatinine with C-reactive protein (CRP), thereby placing greater emphasis on the inflammatory component of disease activity. This modification appears particularly relevant in ACS, where inflammation plays a central role in plaque destabilization, endothelial injury, microvascular dysfunction, and adverse myocardial remodeling[3–5,16]. Persistent residual inflammatory risk despite contemporary secondary prevention strategies further supports the clinical relevance of inflammation-based biomarkers in patients with ACS[17]. Notably, although the CRP-to-albumin ratio was significantly associated with mortality in univariable analysis, this association was no longer significant in an exploratory multivariable model additionally including age, hemoglobin concentration, LVEF, and high m-EASIX (HR 0.998; p=0.985), whereas high m-EASIX retained statistical significance (p=0.046). These findings suggest that the prognostic association of m-EASIX may not be attributable to systemic inflammation alone, but may reflect a broader biological construct integrating inflammatory activation, endothelial stress, platelet-related microvascular dysfunction, and cellular injury. Such multidimensional assessment may contribute to the prognostic association observed with m-EASIX in the present cohort.

Our findings are consistent with an expanding body of evidence supporting the prognostic relevance of endothelial stress indices in cardiovascular disease. In the largest cardiovascular EASIX study to date, Finke et al. demonstrated that elevated EASIX independently predicted long-term mortality in patients with coronary artery disease, highlighting the relevance of systemic endothelial stress beyond angiographic disease severity[6]. Subsequent studies conducted in patients with acute myocardial infarction focused primarily on short-term or in-hospital outcomes, including 30-day mortality, in-hospital mortality, contrast-induced nephropathy, and coronary no-reflow[7–10]. In contrast, the present study specifically evaluated long-term post-discharge all-cause mortality among patients who survived the index ACS hospitalization, with a mean follow-up approaching six years. Thus, our findings extend the temporal scope of the available EASIX literature from acute and early outcomes to longer-term risk after hospital discharge.

Among the available comparative studies, Tekin et al. directly evaluated EASIX-derived indices in patients with ACS and reported m-EASIX as the strongest predictor of short-term mortality[11]. The present findings complement these observations by showing that the prognostic association of m-EASIX remains evident during prolonged follow-up in a post-discharge ACS survivor cohort. Although our paired DeLong analysis did not demonstrate statistical superiority of m-EASIX over the other indices, a high m-EASIX value identified patients with substantially worse long-term post-discharge survival and remained independently associated with mortality after multivariable adjustment. These findings suggest that m-EASIX may reflect sustained biological vulnerability rather than merely the severity of the index ischemic event.

A plausible explanation for this persistent prognostic value may relate to the inclusion of lactate dehydrogenase (LDH). Although traditionally regarded as a marker of tissue injury and cellular necrosis, accumulating evidence suggests that LDH is also associated with endothelial dysfunction, oxidative stress, metabolic imbalance, adverse ventricular remodeling, and the development of post-infarction heart failure[12,18,19]. Consequently, LDH may reflect the cumulative biological consequences of ischemic injury rather than myocardial necrosis alone. Combined with CRP and platelet count, LDH may enable m-EASIX to integrate multiple biological pathways involved in ACS progression, including inflammation, endothelial dysfunction, microvascular injury, cellular stress, and impaired tissue perfusion. This provides a biologically plausible explanation for the prognostic value of m-EASIX observed in our cohort.

From a clinical perspective, m-EASIX has the practical advantage of being derived entirely from routinely available admission laboratory parameters and requires no additional testing or specialized infrastructure. However, because the present study did

not directly compare m-EASIX with established ACS risk scores such as GRACE or TIMI, its incremental prognostic value beyond current risk assessment strategies remains unknown. Accordingly, m-EASIX should not be regarded as a replacement for established clinical risk models. Rather, the present findings support its potential role as a complementary prognostic marker that warrants further evaluation. Prospective multicenter studies should determine whether adding m-EASIX to validated risk models improves discrimination, calibration, risk reclassification, or clinical decision-making. A summary of the study concept and principal findings is presented in Figure 4.

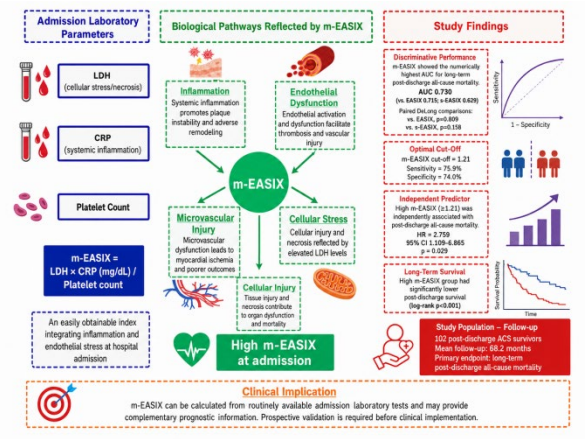


Figure 4:
Central Illustration.

High m-EASIX was independently associated with long-term post-discharge all-cause mortality and showed the numerically highest AUC among the evaluated endothelial stress indices. However, its discriminatory performance was not statistically superior to that of EASIX or s-EASIX. These findings suggest that m-EASIX may provide complementary prognostic information, although larger prospective multicenter studies are required to validate its clinical utility.

Study Limitations

Several limitations of the present study should be acknowledged. First, its retrospective, single-center design may have introduced selection bias and may limit the generalizability of the findings. Second, the relatively modest sample size and limited number of deaths may have reduced the precision of the risk estimates and restricted the number of covariates that could be included in the multivariable model, leaving the possibility of residual confounding. Third, because patients who died during the index hospitalization were excluded, the study population represents post-discharge survivors, and the findings cannot be extrapolated to in-hospital or very early mortality after ACS. Fourth, EASIX-derived indices were calculated using laboratory measurements obtained only at admission; therefore, the prognostic relevance of serial changes could not be evaluated. Fifth, direct comparisons with established ACS risk scores, such as GRACE or TIMI, were not performed, and the incremental prognostic value of m-EASIX beyond these models remains unknown. Finally, the primary endpoint was post-discharge all-cause mortality because cause-specific cardiovascular mortality was not consistently available. Nevertheless, the prolonged follow-up, inclusion of the major clinical presentations across the ACS spectrum, and concordant findings across ROC, Kaplan–Meier, and multivariable Cox analyses support the internal consistency of the results.

Researcher Contribution Statement:
Idea and design: C.A., B.Ö., F.Ç.H.
Data collection and processing: K.T., C.A.
Analysis and interpretation of data: C.A., Z.K., B.Ö., F.Ç.H.
Writing of significant parts of the article: C.A., Z.K., B.Ö., F.Ç.H.
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References

1. Byrne, R.A.; Rossello, X.; Coughlan, J.J.; Barbato, E.; Berry, C.; Chieffo, A.; Claeys, M.J.; Dan, G.-A.; Dweck, M.R.; Galbraith, M.; et al. 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the Task Force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *Eur. Heart J.* **2023**, *44*, 3720–3826. https://doi.org/10.1093/eurheartj/ehad191
2. Bauer, D.; Toušek, P. Risk stratification of patients with acute coronary syndrome. *J. Clin. Med.* **2021**, *10*, 4574. https://doi.org/10.3390/jcm10194574
3. Tsalamandris, S.; Koliastasis, L.; Miliou, A.; Oikonomou, E.; Papageorgiou, N.; Antonopoulos, A.; Hatzis, G.; Mourouzis, K.; Vogiatzi, G.; Siasos, G.; Xaplanteris, P.; Tousoulis, D. Endothelial function and pro-inflammatory cytokines as prognostic markers in acute coronary syndromes. *Diagnostics* **2025**, *15*, 1033. https://doi.org/10.3390/diagnostics15081033
4. Xiong, X.; Wang, J.; Ren, L.; Li, Z.; Liu, Y.; Xia, P.; Duan, L. The emerging pathological mechanism of coronary microvascular dysfunction: A narrative review. *Metab. Target Organ Damage* **2025**, *5*, 54. https://doi.org/10.20517/mtod.2025.71
5. Ziogos, E.; Chelko, S.P.; Harb, T.; Engel, M.; Vavuranakis, M.A.; Landim-Vieira, M.; Walsh, E.M.; Williams, M.S.; Lai, S.; Halushka, M.K.; Gerstenblith, G.; Leucker, T.M. Platelet activation and endothelial dysfunction biomarkers in acute coronary syndrome: The impact of PCSK9 inhibition. *Eur.*

Heart J. Cardiovasc. Pharmacother. **2023**, *9*, 636–646. https://doi.org/10.1093/ehjcvp/pvad051

6. Finke, D.; Hund, H.; Frey, N.; Luft, T.; Lehmann, L.H. EASIX (endothelial activation and stress index) predicts mortality in patients with coronary artery disease. *Clin. Res. Cardiol.* **2025**, *114*, 1008–1018. https://doi.org/10.1007/s00392-024-02534-y
7. Sang, M.; Ma, X.; Zhu, F.; Zhu, C.; Ying, Z. Association between endothelial activation and stress index and 30-day mortality risk in acute myocardial infarction patients: A study based on the Medical Information Mart for Intensive Care-IV database. *BMC Cardiovasc. Disord.* **2024**, *24*, 699. https://doi.org/10.1186/s12872-024-04353-5
8. Karauzum, K.; Tanık, V.O.; Taş, A.; Mirzamidinov, D.; Şimşek, U.; Gencer, E.; Çelik, F.; Badalova, N.; Büyükbaş, F.C.; Yılmaz, I.; et al. The role of endothelial activation and stress index (EASIX) for predicting contrast-induced nephropathy and in-hospital mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Diagnostics* **2026**, *16*, 1123. https://doi.org/10.3390/diagnostics16081123
9. Şahin, Y.B.; Tanık, V.O.; Boz, S.; Akdoğan, M.; Tunca, Ç.; Seçkin, Ö.; Taş, A.; Özlek, B. Admission EASIX score predicts coronary no-reflow and in-hospital mortality in STEMI patients undergoing primary PCI. *J. Clin. Med.* **2026**, *15*, 1063. https://doi.org/10.3390/jcm15031063
10. Faideci, E.M.; Hancıoğlu, E.; Ziyrek, M.; Özcan, S.; Güzel, S.; Alak, M.E.; Aslan, R.; Ardahanlı, İ.; Ertan, Ç.; Şahin, İ.; Okuyan, E. Endothelial activation and stress index (EASIX) as a novel index associated with no-reflow phenomenon in STEMI: A bi-center retrospective study. *BMC Cardiovasc. Disord.* **2026**, *26*, 363. https://doi.org/10.1186/s12872-026-05719-7
11. Tekin, I.; Büber, İ.; Avcı, E. Endothelial stress indices in acute coronary syndrome: Comparative prognostic performance of EASIX and its variants. *J. Lab. Med.* **2026**, *50*, 120–127. https://doi.org/10.1515/labmed-2025-0275
12. Wu, H.; Wu, Z.; Xin, Y.; Jiang, X.; Guo, C. Lactate dehydrogenase-to-albumin ratio for the severity of coronary artery disease in acute myocardial infarction: A retrospective study. *J. Int. Med. Res.* **2026**, *54*, 3000605251409694. https://doi.org/10.1177/03000605251409694
13. Libby, P. The changing landscape of atherosclerosis. *Nature* **2021**, *592*, 524–533. https://doi.org/10.1038/s41586-021-03392-8
14. Ajoolabady, A.; Pratico, D.; Lin, L.; Mantzoros, C.S.; Bahijri, S.; Tuomilehto, J.; Ren, J. Inflammation in atherosclerosis: Pathophysiology and mechanisms. *Cell Death Dis.* **2024**, *15*, 817. https://doi.org/10.1038/s41419-024-07166-8
15. Henein, M.Y.; Vancheri, S.; Longo, G.; Vancheri, F. The Role of Inflammation in Cardiovascular Disease. *Int. J. Mol. Sci.* 2022, *23*, 12906. https://doi.org/10.3390/ijms232112906
16. Arnold, N.; Koenig, W. Inflammation in atherosclerotic cardiovascular disease: From diagnosis to treatment. Eur. J. Clin. Invest. 2025, 55, e70020. https://doi.org/10.1111/eci.70020
17. Ridker, P.M. Residual inflammatory risk: Addressing the obverse side of the atherosclerosis prevention coin. *Eur. Heart J.* **2016**, *37*, 1720–1722. https://doi.org/10.1093/eurheartj/ehw024
18. Lin, Q.; Zhao, W.; Zhang, H.; Chen, W.; Lian, S.; Ruan, Q.; Qu, Z.; Lin, Y.; Chai, D.; Lin, X. Predicting the risk of heart failure after acute myocardial infarction using an interpretable machine learning model. *Front. Cardiovasc. Med.* **2025**, *12*, 1444323. https://doi.org/10.3389/fcvm.2025.1444323
19. Zhang, H.; Kang, K.; Chen, S.; Su, Q.; Zhang, W.; Zeng, L.; Lin, X.; Peng, F.; Lin, J.; Chai, D. High serum lactate dehydrogenase as a predictor of cardiac insufficiency at follow-up in elderly patients with acute myocardial infarction. *Arch. Gerontol. Geriatr.* **2024**, *117*, 105253. https://doi.org/10.1016/j.archger.2023.105253