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Prognostic Value of the Endothelial Activation and Stress Index in Patients with Non–ST-Segment Elevation Myocardial Infarction

ABSTRACT

Background: Early risk stratification is essential in patients with non–ST-segment elevation myocardial infarction (NSTEMI). The Endothelial Activation and Stress Index (EASIX) reflects endothelial dysfunction and systemic stress; however, its prognostic value in NSTEMI remains unclear. This study aimed to investigate the association between EASIX and in-hospital mortality in patients with NSTEMI.

Methods: This retrospective, single-center observational study included 1001 consecutive NSTEMI patients hospitalized between January 2015 and August 2025. Endothelial Activation and Stress Index was calculated at admission using lactate dehydrogenase, creatinine, and platelet count. Univariable and multivariable logistic regression analyses were performed to identify independent predictors of in-hospital mortality. Discriminative performance was assessed using receiver operating characteristic analysis and Kaplan–Meier survival analysis.

Results: In-hospital mortality occurred in 41 patients (4.1%). Non-survivors had significantly higher EASIX values than survivors (median 1.76 vs. 0.94, $P < .001$). In multivariable analysis, EASIX (OR 1.66, 95% CI 1.24-2.23; $P = .001$), GRACE score (OR 1.04, 95% CI 1.03-1.06; $P < .001$), and revascularization (OR 0.37, 95% CI 0.15-0.55; $P = .003$) remained independent predictors of in-hospital mortality. EASIX demonstrated good discriminative ability (AUC 0.770), and higher levels were associated with worse survival.

Conclusion: Endothelial Activation and Stress Index is an independent and practical predictor of in-hospital mortality in NSTEMI and may aid early risk stratification using routine laboratory data.

Keywords: Biomarkers, Endothelial Activation and Stress Index, in-hospital mortality, non–ST-segment elevation myocardial infarction, risk stratification

INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide.[1,2] Acute coronary syndrome (ACS) often represent the first clinical manifestation of CVDs and encompass a spectrum of urgent cardiac conditions resulting from an abrupt reduction or complete interruption of coronary blood flow, leading to myocardial ischemia and subsequent cellular injury.[1,2] Clinically, ACSs are classified into 3 main subtypes: ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA).[3]

The NSTEMI accounts for approximately 58%-70% of all ACS cases.[4,5] The formation of a non-occlusive thrombus over an atherosclerotic plaque rupture or erosion constitutes the fundamental pathophysiological mechanism of NSTEMI.[6] In this process, inflammation, oxidative stress, endothelial dysfunction, and microvascular perfusion impairment play critical roles.[6] Endothelial dysfunction and vascular stress are well recognized not only to contribute to the initiation and progression of NSTEMI but also to play a pivotal role in determining its prognosis.[7-9]

Recently, Thomas Luft and colleagues introduced the Endothelial Activation and Stress Index (EASIX), which is considered to reflect systemic endothelial injury and vascular stress.[10] This score is simply calculated using the formula lactate

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dehydrogenase (LDH) × creatinine/platelet count. Although EASIX has previously been investigated as a predictor of mortality in various systemic diseases, its prognostic significance in patients with NSTEMI has not yet been adequately explored.[10-13] The fact that LDH serves as a marker of tissue injury in patients with NSTEMI, that creatinine levels may increase due to impaired renal perfusion and systemic endothelial dysfunction in ACS and have been associated with poor prognosis, and that platelets play a key role in the pathophysiology of NSTEMI suggests that this score may be an important predictor of in-hospital mortality in NSTEMI patients.[6,14,15]

Early risk stratification in ACS is crucial for guiding treatment decisions and predicting prognosis. Therefore, this study aimed to investigate the association between the EASIX score and in-hospital mortality in patients with NSTEMI and to evaluate its potential value as a novel prognostic marker in clinical practice.

METHODS

Study Population

This retrospective observational study included consecutive patients hospitalized with a diagnosis of NSTEMI at a tertiary care center between January 1, 2015, and August 31, 2025.

Patients aged ≥18 years who were admitted with NSTEMI during the study period, had complete clinical records, and for whom in-hospital mortality data were available were included in the analysis. The diagnosis of NSTEMI was established in accordance with the latest guidelines of the European Society of Cardiology.[3] The exclusion criteria were a diagnosis of STEMI or UA; type 2 myocardial infarction (e.g., secondary to sepsis, anemia, or arrhythmia); hematological disorders; liver disease; chronic kidney disease; missing laboratory or clinical data; solid organ malignancy; acute infection or sepsis; a history of cardiac surgery; connective tissue diseases; and age <18 years. Clinical characteristics and laboratory data were obtained from hospital records. The Global Registry of Acute Coronary Events (GRACE) score and the Thrombolysis in Myocardial Infarction (TIMI) score were calculated for all patients at admission according to the original published risk models.[16,17]

HIGHLIGHTS

- Endothelial Activation and Stress Index (EASIX) is a simple biomarker reflecting endothelial dysfunction and systemic stress.
- Endothelial Activation and Stress Index is independently associated with in-hospital mortality in non–ST-segment elevation myocardial infarction.
- Endothelial Activation and Stress Index demonstrates good discriminative performance for predicting in-hospital mortality.
- Higher EASIX levels are associated with worse in-hospital survival.
- Endothelial Activation and Stress Index may aid early risk stratification using routine laboratory data.

As a result of the exclusion criteria, 1001 patients with NSTEMI were included in the study (Figure 1). Baseline measurements obtained within the first 24 hours of admission were compared. The study was approved by the Local Ethics Committee (Date: October 30, 2025; Approval No: 2025/2511). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki for research involving human participants and complied with national ethical standards.

Blood Samples

Biochemical parameters, including LDH and creatinine levels, were measured using an Atellica CH 930 automated chemistry analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). Complete blood count parameters, including platelet count, were analyzed using a Mindray BC-6000 automated hematology analyzer (Mindray Bio-Medical Electronics Co., Shenzhen, China). The EASIX score was calculated as previously described using the formula LDH (U/L) × creatinine (mg/dL) / platelet count (10^9/L).

Statistical Analysis

All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation (SD) for normally distributed data or as median (25^{th}-75^{th} percentiles) for skewed data, and categorical variables as counts and percentages. Normality was assessed using the Kolmogorov–Smirnov test. Differences between survivors and non-survivors were evaluated using the Student's *t*-test or Mann–Whitney *U*-test for continuous variables and the chi-square test for categorical variables.

Baseline characteristics were compared across EASIX percentile groups (≤25^{th}, 25^{th}-75^{th}, and ≥75^{th} percentiles). One-way ANOVA with Tukey post-hoc tests was applied for normally distributed variables, whereas the Kruskal–Wallis test with Bonferroni-adjusted pairwise comparisons was used for skewed variables. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate.

Univariable binary logistic regression analysis was performed to identify predictors of in-hospital mortality. Variables with $P < .05$ in the univariable analysis and those considered clinically relevant were initially entered into the multivariable binary logistic regression model. Multicollinearity was assessed using the variance inflation factor (VIF). A backward stepwise (likelihood ratio) binary logistic regression method was then applied, whereby the statistical software (SPSS) automatically removed variables that did not contribute significantly to the model at each step. Only the variables retained in the final step of the backward stepwise procedure are presented in Table 1. Results were reported as odds ratios (ORs) with 95% CIs.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminative performance of EASIX, GRACE score, TIMI score, and Killip class for predicting in-hospital mortality. The optimal cut-off values were determined using Youden's index. Pairwise comparisons

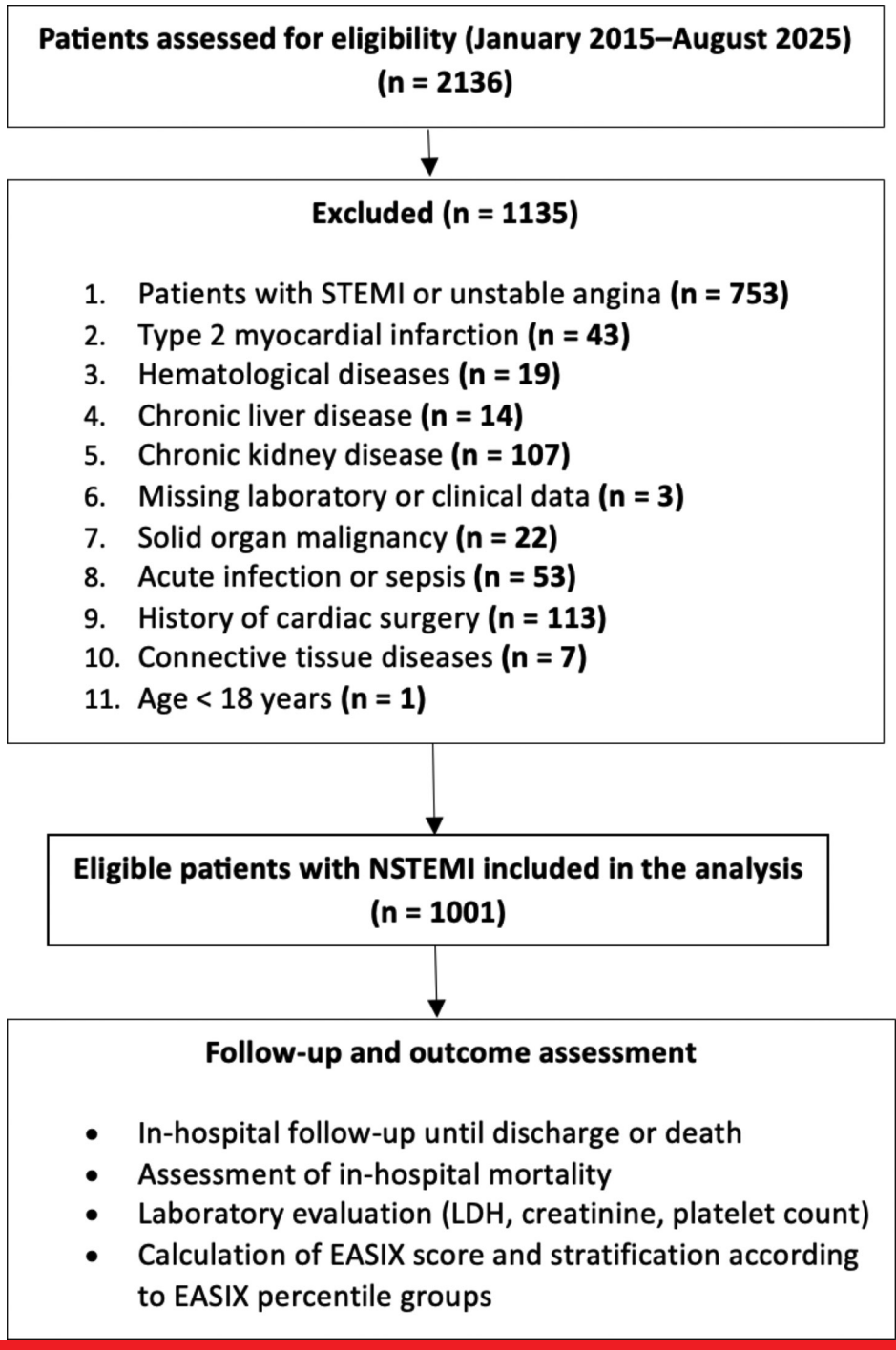

Figure 1. Flow diagram illustrating patient selection and inclusion in the final analysis.

of the areas under the ROC curves (AUCs) were performed using the DeLong test. For survival analysis, patients were first categorized into two groups based on the ROC-derived cut-off value (1.31), and Kaplan–Meier survival curves were generated; differences between curves were evaluated using the log-rank test. For Kaplan–Meier survival analysis, the time-to-event variable was defined as the duration of hospitalization (in days). In-hospital death was considered the event of interest, whereas patients who were discharged alive were treated as censored observations at the time of discharge. In addition, Kaplan–Meier survival analysis was performed across EASIX percentile groups, and pairwise comparisons between percentile groups were assessed using Bonferroni-adjusted log-rank tests. There were no missing data for variables included in the primary analyses. A probability value of $P < .05$ was considered statistically significant.

RESULTS

A total of 1001 patients with NSTEMI were included in the study, and in-hospital mortality occurred in 41 patients (4.1%)

Table 1. Univariable and Multivariable Binary Logistic Regression Analysis for Predictors of In-hospital Mortality

	Univariable Regression		Multivariable Regression		
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**VIF**
EASIX	1.458 (1.236-1.721)	<.001	1.663 (1.237-2.234)	.001	1.222
GRACE score	1.042 (1.033-1.051)	<.001	1.043 (1.030-1.055)	<.001	1.443
TIMI score	1.277 (1.042-1.565)	.019			1.191
EF	0.941 (0.917-0.965)	<.001			1.217
AF	4.162 (1.529-11.331)	.005			1.018
Revascularization	0.470 (0.249-0.887)	.020	0.374 (0.145-0.554)	.003	1.165
Troponin	1.020 (1.007-1.033)	.003			1.132
Sodium	0.867 (0.786-0.957)	.005			1.114
CRP	1.070 (1.002-1.143)	.043			1.176
AST	1.001 (1.000-1.002)	.091			

AF, atrial fibrillation; AST, aspartate aminotransferase; CRP, C-reactive protein; EASIX, endothelial activation and stress index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; Killip class, Killip classification; SBP, systolic blood pressure; TIMI, Thrombolysis in Myocardial Infarction; VIF, variance inflation factor.

Table 2. Baseline Demographic, Clinical, Laboratory, and Treatment Characteristics of Survivors And Non-survivors with NSTEMI During Index Hospitalization

Variables	**Survivors (n = 960)**	**Non-survivors (n = 41)**	***P***
Demographics and comorbidities			
Age, (years)	62.50 ± 12.75	71.48 ± 13.61	**<.001**
Gender (male), n (%)	642 (66.9)	29 (70.7)	.607
Current smoker, n (%)	599 (66)	22 (57.9)	.304
DM, n (%)	239 (24.9)	10 (24.4)	.936
HT, n (%)	574 (62.8)	26 (68.4)	.482
AF, n (%)	31 (3.2)	5 (12.2)	**.003**
Chronic heart failure, n (%)	40 (4.4)	8 (21.1)	**<.001**
PAD, n (%)	59 (6.5)	3 (7.9)	.733
COPD, n (%)	53 (5.8)	5 (13.2)	.066
Family history of cardiovascular disease, n (%)	211 (23.2)	8 (21.1)	.754
History of myocardial infarction, n (%)	274 (30)	17 (42.5)	.093
Laboratory values			
Troponin, (ng/mL)	0.81 (0.11-4.45)	4.10 (1.75-17.27)	**<.001**
HbA1c, %	6.81 ± 1.71	6.36 ± 0.97	.090
Glucose, (mg/dL)	121 (101-179)	138 (105-184)	.182
WBC, $\times 10^9$/L	9.40 (7.8-11.5)	11.0 (6.8-12.7)	.290
Neutrophil, $\times 10^9$/L	6.0 (4.6-7.8)	6.0 (4.55-8.25)	.821
Lymphocyte, $\times 10^9$/L	2.20 (1.6-3)	2.50 (2-3.15)	.172
Hemoglobin, (g/dL)	13.52 ± 2.09	13.06 ± 2.77	.309
Platelet, $\times 10^9$/L	235.78 ± 72.10	217.95 ± 72.85	.121
Creatinine, (mg/dL)	1.00 ± 0.31	1.39 ± 0.43	**<.001**
eGFR, (mL/min/1.73 m^2)	80.11 ± 22.60	59.64 ± 23.74	**<.001**
Sodium, (mEq/L)	139.19 ± 2.98	137.60 ± 3.32	**.004**
Potassium, (mEq/L)	4.39 ± 0.51	4.54 ± 0.93	.136
Total protein (g/dL)	6.62 ± 0.64	6.36 ± 0.95	.149
CRP, (mg/L)	0.70 (0.22-2.3)	3.35 (1.52-5.22)	**<.001**
ALT, (U/L)	20 (15-30)	40 (24-72)	**<.001**
AST, (U/L)	23 (17-33)	89 (65-114)	**<.001**
LDH, (U/L)	217 (185-274)	285 (204-358)	**.002**

(*Continued*)

Table 2. Baseline Demographic, Clinical, Laboratory, and Treatment Characteristics of Survivors And Non-survivors with NSTEMI During Index Hospitalization (*Continued*)

Variables	Survivors (n = 960)	Non-survivors (n = 41)	*P*
Total cholesterol, (mg/dL)	189.24 ± 50.19	178 ± 57.95	.336
LDL, (mg/dL)	115 (88-142)	112 (77-136)	.516
HDL, (mg/dL)	35 (29-41)	36 (24-45)	.951
Triglyceride, (mg/dL)	149 (107-223)	99 (84-176)	.065
Medications			
Antiplatelet, n (%)	343 (35.7)	9 (22)	.070
Anticoagulant, n (%)	21 (2.2)	3 (7.3)	**.035**
ACE inhibitor/ARB, n (%)	368 (38.3)	18 (43.9)	.473
Beta-blocker, n (%)	299 (31.1)	16 (39)	.287
Statin, n (%)	186 (19.4)	9 (22)	.683
Oral antidiabetic, n (%)	176 (18.3)	7 (17.1)	.838
On admission, clinical characteristics			
EASIX	0.94 (0.67-1.41)	1.76 (1.19-2.63)	**<.001**
GRACE score	120.85 ± 31.83	200.73 ± 59.16	**<.001**
TIMI score	2.81 ± 1.33	3.31 ± 1.23	**.018**
EF, %	50.25 ± 10.77	41.14 ± 13.41	**<.001**
Heart rate, per min	87.34 ± 24.79	99.11 ± 25.26	**.004**
SBP, mmHg	150.71 ± 28.78	132.65 ± 31.33	**<.001**
DBP, mmHg	83.70 ± 16.69	75.71 ± 18.25	**.007**
Killip class, n (%)	Class I: 872 (90.9) Class II: 39 (4.1) Class III: 46 (4.8) Class IV: 2 (0.2)	Class I: 23 (56.1) Class II: 3 (7.3) Class III: 12 (29.3) Class IV: 3 (7.3)	**<.001**
In-hospital treatments/procedures			
In-hospital hemodialysis, n (%)	30 (3.1)	5 (12.2)	**.002**
Multivessel coronary disease, n (%)	383 (41.5)	9 (47.4)	.610
Revascularization, n (%)	577 (60.1)	17 (41.5)	**.017**
Outcomes			
Length of hospital stay, days	6 (4-10)	6 (4-10)	.872

Non-normally distributed continuous variables are presented as median (25^{th}-75^{th} percentiles).
ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; EASIX, endothelial activation and stress index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HT, hypertension; Killip class, Killip classification; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; NSTEMI, non–ST-segment elevation myocardial infarction; PAD, peripheral arterial disease; SBP, systolic blood pressure; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell.

during the index hospitalization. Baseline clinical and laboratory characteristics of survivors and non-survivors are presented in Table 2. Patients who died were significantly older and had lower left ventricular ejection fraction; moreover, the prevalence of atrial fibrillation and chronic heart failure was significantly higher compared with survivors (all $P < .05$). In these patients, higher levels of creatinine, troponin, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and LDH, along with lower estimated glomerular filtration rate (eGFR) and serum sodium levels, were observed. Admission Killip class strongly discriminated mortality, and advanced Killip classes were significantly more frequent among non-survivors ($P < .001$). EASIX values were also significantly higher in patients who died compared with survivors (median 1.76 vs. 0.94; $P < .001$). Similarly, GRACE score ($P < .001$) and TIMI score ($P = .018$) were significantly higher in non-survivors than in survivors.

When patients were evaluated according to EASIX percentile groups, a stepwise deterioration in age, comorbidities, inflammatory markers, and indicators of tissue injury was observed with increasing EASIX levels, accompanied by progressively higher GRACE and TIMI scores and a progressive increase in in-hospital mortality rates (Table 3).

In univariable logistic regression analysis, age, EASIX, GRACE score, TIMI score, ejection fraction, atrial fibrillation, Killip class, systolic blood pressure, revascularization, troponin, estimated glomerular filtration rate, sodium, and CRP were associated with in-hospital mortality. In multivariable analysis, EASIX (OR 1.66; 95% CI 1.24-2.23; $P = .001$), GRACE score

Table 3. Baseline Demographic, Clinical, and Laboratory Characteristics of Patients Stratified According to EASIX Percentile Groups (≤25th, 25th-75th, and ≥75th Percentiles)

Variables	EASIX ≤25th (<0.676)	EASIX 25th–75th (0.676–1.452)	EASIX ≥75th (>1.452)	*P*
Demographics and comorbidities				
Age, (years)	58.06 ± 12.14[a]	62.85 ± 12.55[b]	67.66 ± 12.63[c]	**<.001**
Gender (male), n (%)	139 (56.3)[a]	354 (70.1)[b]	178 (71.5)[b]	**<.001**
Current smoker, n (%)	158 (67.8)	308 (64.6)	155 (65.7)	.694
DM, n (%)	60 (24.3)	121 (24.1)	68 (27.3)	.603
HT, n (%)	134 (57.3)[a]	293 (61.3)[a]	173 (72.1)[b]	**.002**
AF, n (%)	6 (2.4)	15 (3)	15 (6)	.056
Chronic heart failure, n (%)	5 (2.1)[a]	22 (4.6)[a]	21 (8.9)[b]	**.003**
PAD, n (%)	15 (6.4)	25 (5.2)	22 (9.4)	.111
COPD, n (%)	8 (3.4)[a]	28 (5.9)[a,b]	22 (9.4)[b]	**.027**
Family history of cardiovascular disease, n (%)	73 (31.3)[a]	108 (22.6)[b]	38 (16.1)[c]	**<.001**
History of myocardial infarction, n (%)	56 (24)[a]	140 (29.2)[a]	95 (39.6)[b]	**.001**
Laboratory values				
Troponin, (ng/mL)	0.37 (0.10-80)[a]	0.81 (0.10-63) [a]	3 (0.10-189) [b]	**<.001**
HbA1c, %	6.67 ± 1.66	6.85 ± 1.72	6.86 ± 1.70	.430
Glucose, (mg/dL)	110 (57-496)[a]	120 (37-640) [b]	133 (51-544) [c]	**<.001**
WBC, ×10^9/L	9.40 (4.10-20.10)[a,b]	9.17 (2.5-30.40)[a]	9.90 (3.10-37.60)[b]	**.021**
Neutrophil, ×10^9/L	5.7 (2.4-14.5)[a]	5.9 (1.1-26.2)[a]	6.7 (1.9-35.8)[b]	**<.001**
Lymphocyte, ×10^9/L	2.60 (0.12-9.50)[a]	2.30 (0.06-7.90)[a]	1.70 (0.20-13.20)[b]	**<.001**
Hemoglobin, (g/dL)	13.64 ± 1.79[a]	13.68 ± 2.05[a]	12.99 ± 2.46[b]	**<.001**
Platelet, ×10^9/L	284.05 ± 77.97[a]	230.64 ± 56.59[b]	195.40 ± 66.80[c]	**<.001**
Creatinine, (mg/dL)	0.79 ± 0.11[a]	0.98 ± 0.25[b]	1.32 ± 0.37[c]	**<.001**
eGFR, (mL/min/1.73 m^2)	93.27 ± 14.77[a]	81.02 ± 20.67[b]	61.35 ± 22.86[c]	**<.001**
Sodium, (mEq/L)	139.64 ± 2.60[a]	139.25 ± 2.99[a]	138.43 ± 3.26[b]	**<.001**
Potassium, (mEq/L)	4.26 ± 0.42[a]	4.35 ± 0.44[a]	4.60 ± 0.71[b]	**<.001**
Total protein (g/dL)	6.72 ± 0.65[a]	6.61 ± 0.58[a,b]	6.50 ± 0.74[b]	**.003**
CRP (mg/L)	0.50 (0.20-21)[a]	0.70 (0.20-22.20)[a]	1.80 (0.20-31.50)[b]	**<.001**
ALT (U/L)	20 (7-89)[a]	20 (6-195)[a]	24 (6-2239)[b]	**.005**
AST (U/L)	20 (7-93)[a]	22 (6-172)[a]	34 (5-3978)[b]	**<.001**
LDH (U/L)	185 (86-387)[a]	219 (121-876)[b]	305 (166-1226)[c]	**<.001**
LDL (mg/dL)	116 (44-239)	117 (18-297)	111 (25-372)	.063
HDL (mg/dL)	36 (19-88)[a]	35 (14-85)[a,b]	34 (5-74)[b]	**.038**
Triglyceride (mg/dL)	155 (50-1629)[a]	149 (38-960)[a]	138 (38-1366)[b]	**.015**
Medications				
Antiplatelet, n (%)	82 (33.2)	169 (33.5)	101 (40.6)	.120
Anticoagulant, n (%)	2 (0.8)	14 (2.8)	8 (3.2)	.159
ACE inhibitor/ARB, n (%)	80 (32.4)	205 (40.6)	101 (40.6)	.072
Beta-blocker, n (%)	67 (27.1)	164 (32.5)	84 (33.7)	.224
Statin, n (%)	50 (20.2)	91 (18)	54 (21.7)	.460
Oral antidiabetic, n (%)	49 (19.8)	88 (17.4)	46 (18.5)	.721
On admission, clinical characteristics				
EF, %	53.15 ± 9.62[a]	50.32 ± 10.81[b]	45.74 ± 11.68[c]	**<.001**
Heart rate, per min	84.76 ± 24.06[a]	86.43 ± 24.06[a]	93.74 ± 26.51[b]	**<.001**
SBP (mm Hg)	147.19 ± 28.58	150.41 ± 27.70	151.67 ± 32.08	.274
DBP (mm Hg)	83.02 ± 14.97	83.26 ± 16.20	83.89 ± 19.57	.862
Killip class, n (%)	Class I: 230 (93.1)[a] Class II: 9 (3.6)[a] Class III: 7 (2.8)[a] Class IV: 1 (0.4)[a]	Class I: 463 (91.7)[a] Class II: 18 (3.6)[a] Class III: 23 (4.6)[a] Class IV: 1 (0.2)[a]	Class I: 202 (81.5)[b] Class II: 15 (6)[a] Class III: 28 (11.3)[b] Class IV: 3 (1.2)[a]	**<.001**

(*Continued*)

Table 3. Baseline Demographic, Clinical, and Laboratory Characteristics of Patients Stratified According to EASIX Percentile Groups (≤25th, 25th-75th, and ≥75th Percentiles) (*Continued*)

Variables	EASIX ≤25th (<0.676)	EASIX 25th–75th (0.676–1.452)	EASIX ≥75th (>1.452)	*P*
GRACE score	107.91 ± 29.0[a]	124.28 ± 33.87[b]	139.90 ± 42.62[c]	**<.001**
TIMI score	2.52 ± 1.19[a]	2.86 ± 1.37[b]	3.06 ± 1.33[b]	**<.001**
In-hospital treatments/procedures				
In-hospital hemodialysis, n (%)	0 (0)[a]	10 (2)[b]	25 (10)[c]	**<.001**
Multivessel coronary disease, n (%)	91 (38.2)[a]	184 (38.7)[a]	117 (51.3)[b]	**.003**
Revascularization, n (%)	208 (84.2)[a]	280 (55.4)[b]	106 (42.6)[c]	**<.001**
Outcomes				
In-hospital mortality, n (%)	1 (0.4)[a]	15 (3)[b]	25 (10)[c]	**<.001**
Length of hospital stay, days	6 (1-59)	6 (1-59)	6 (1-46)	.169

Superscript letters (a, b, c) denote statistically significant differences between groups in the same row ($P < .05$).
ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; EASIX, endothelial activation and stress index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HT, hypertension; Killip class, Killip classification; LDL, low-density lipoprotein; PAD, peripheral arterial disease; SBP, systolic blood pressure; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell.

(OR 1.04; 95% CI 1.03-1.06; $P < .001$), and revascularization (OR 0.37; 95% CI 0.15-0.55; $P = .003$) remained independent predictors of in-hospital mortality (Table 1).

Receiver operating characteristic analysis demonstrated that the GRACE score had the highest discriminative performance for predicting in-hospital mortality (AUC 0.870; 95% CI 0.798-0.941; $P < .001$), followed by EASIX (AUC 0.770; 95% CI 0.700-0.840; $P < .001$). According to Youden's index, the optimal EASIX cut-off value was 1.31, yielding a sensitivity of 73% and a specificity of 72%. Pairwise comparisons using the DeLong test showed that the AUC of the GRACE score was significantly higher than that of EASIX ($P = .029$), whereas EASIX demonstrated a significantly higher AUC than the TIMI score ($P < .001$). No significant difference was observed between EASIX and Killip class ($P = .064$) (Table 4, Figure 2). Kaplan–Meier analysis showed significantly reduced survival among patients with EASIX values ≥1.313, with early separation of the survival curves that remained consistently separated throughout hospitalization (log-rank $P < .001$) (Figure 3). In analyses based on EASIX percentile groups, mortality rates increased progressively across the percentile groups; the highest percentile group demonstrated the worst survival, whereas the lowest percentile group exhibited the most favorable survival (log-rank $P < .001$) (Figure 4).

DISCUSSION

This study evaluated the role of the EASIX score in predicting short-term mortality in patients with NSTEMI and demonstrated that EASIX is independently associated with in-hospital mortality. Higher EASIX values were associated with lower survival rates and clear separation of Kaplan–Meier survival curves; moreover, ROC analysis demonstrated that the GRACE score exhibited the highest discriminative performance, while EASIX showed significantly better discriminative performance than the TIMI score and comparable performance to Killip class. Given the lack of previous studies linking EASIX to mortality in NSTEMI populations, these findings provide novel evidence regarding the prognostic value of EASIX in the context of ACS. Importantly, the findings extend the potential clinical application of EASIX from systemic diseases to the risk stratification of patients with NSTEMI.

NSTEMI is the most common presentation among all ACS cases.[4,5] It is of major clinical importance, as it represents one of the leading causes of death worldwide.[4,5] Its pathophysiology is primarily based on the formation of a thrombus overlying a ruptured or eroded atherosclerotic plaque.[6] Inflammation, endothelial dysfunction, oxidative stress, and microvascular perfusion impairment emerge as key triggers

Table 4. Receiver Operating Characteristic (ROC) Curve Analysis for Prediction of In-hospital Mortality

			Asymptotic 95% CI					
Variables	AUC	*P*	Lower Bound	Upper Bound	Cut off	Sensitivity	Specificity	DeLong p
EASIX	0.770	<.001	0.700	0.840	1.31	73	72	
GRACE score	0.870	<.001	0.798	0.941	147.5	82	81	0.029*
TIMI score	0.613	.014	0.534	0.692	2.5	75	44	<0.001**
Killip class	0.682	<.001	0.581	0.781	2.5	65	67	0.064***

AUC, area under the curve; EASIX, endothelial activation and stress index; GRACE, Global Registry of Acute Coronary Events; ROC, receiver operating characteristic; TIMI, Thrombolysis in Myocardial Infarction.
*DeLong test for comparison of EASIX and GRACE score.
**DeLong test for comparison of EASIX and TIMI score.
***DeLong test for comparison of EASIX and Killip class.

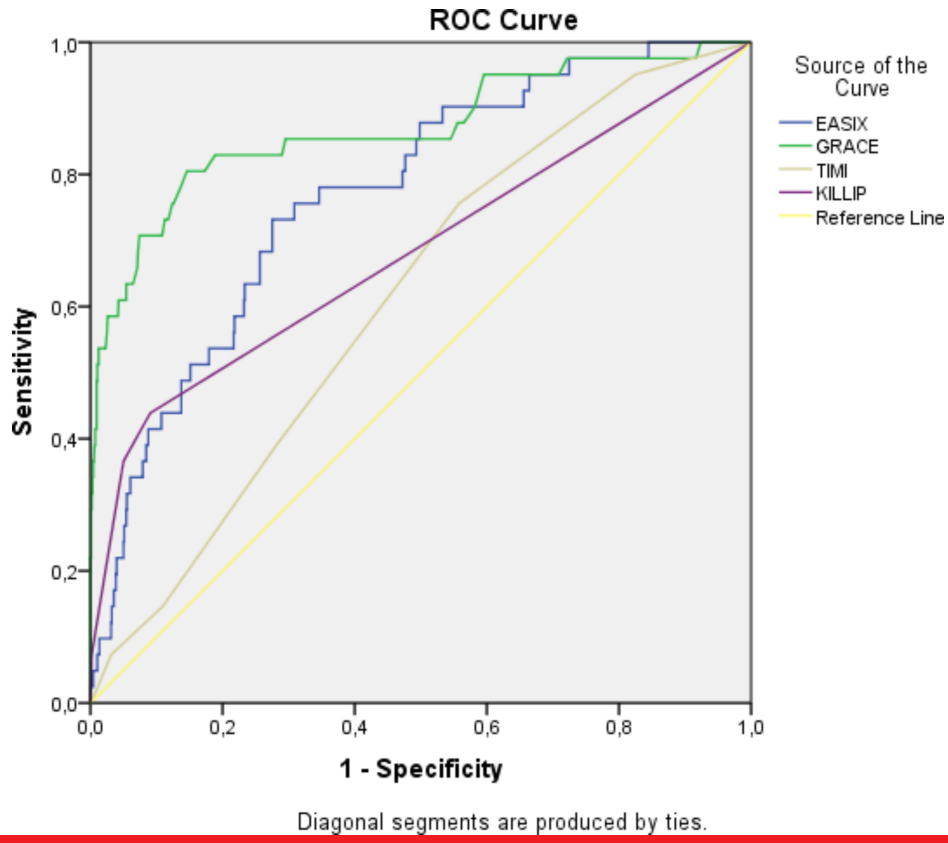

Figure 2. Receiver operating characteristic curves comparing the discriminative performance of the EASIX, GRACE score, TIMI score, and Killip class for predicting in-hospital mortality.

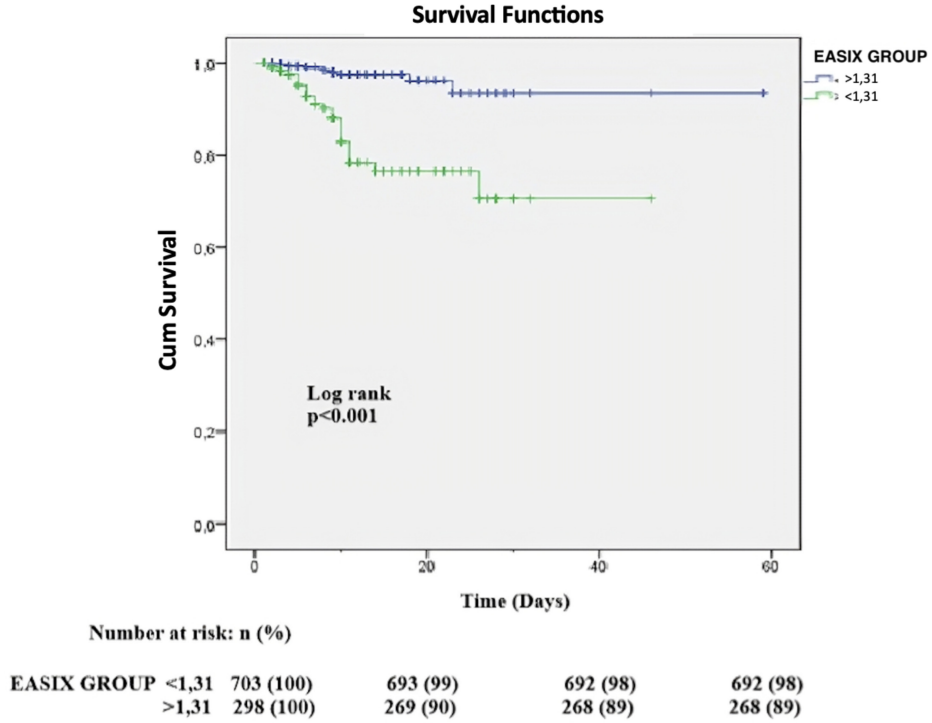

Figure 3. Kaplan–Meier survival analysis based on receiver operating characteristic–derived EASIX cut-off.

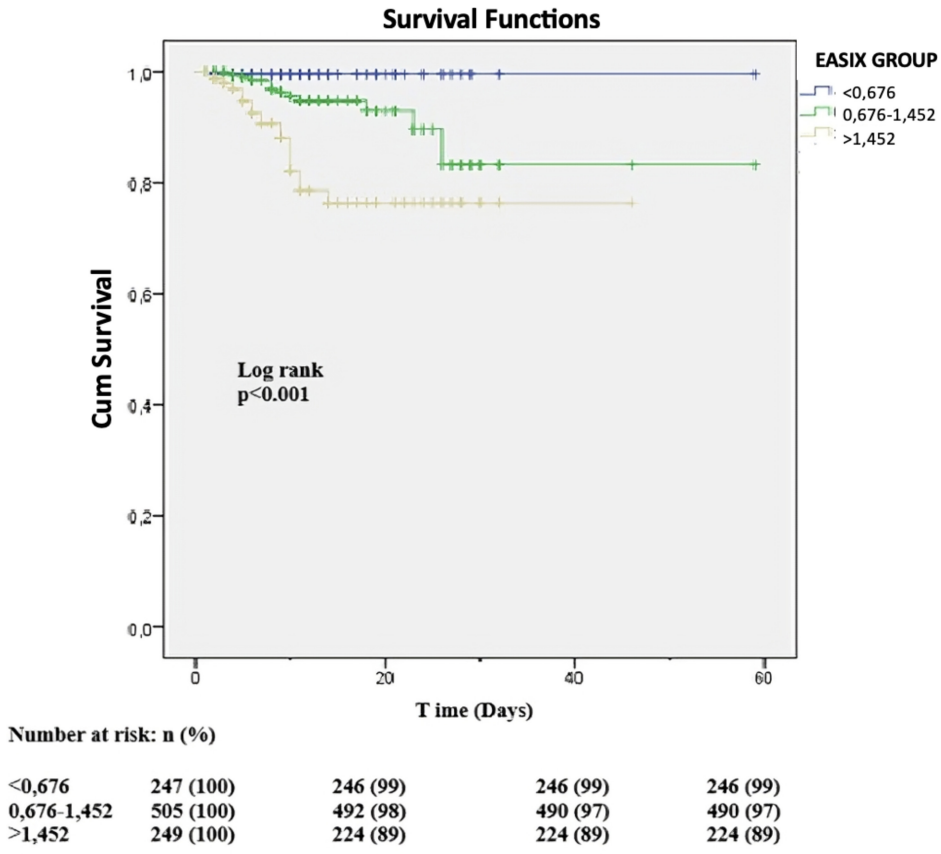

Figure 4. Kaplan–Meier curves for mortality according to EASIX percentile groups.

of this process.[6] Endothelial dysfunction and vascular stress have been shown to contribute to the early phase of NSTEMI by promoting atherosclerotic plaque instability; to exacerbate ischemia during disease progression through thrombus formation and vasoconstriction; and to adversely affect prognosis by impairing microvascular perfusion and increasing the risk of mortality.[7-9]

In NSTEMI, myocardial ischemia–induced cellular injury and necrosis lead to the release of cytoplasmic enzymes into the circulation.[14] The LDH, one of the key biochemical markers of this process, is a protein expressed in all living cells, with particularly high enzymatic activity in the myocardium.[14] Previous studies have demonstrated that LDH reflects the severity of myocardial injury and ischemic burden and is associated with systemic inflammation.[18-20] In acute myocardial infarction, elevated baseline LDH levels have been associated with adverse cardiac remodeling and poor prognosis.[21] As a consequence of all these mechanisms, elevated LDH levels have been associated with poor prognosis and an increased risk of mortality in patients with NSTEMI.[22] Consistent with this biological background, LDH levels were found to be significantly higher in NSTEMI patients who experienced mortality compared with survivors in the study. Moreover, a stepwise increase in LDH values was observed with rising EASIX levels, with the most pronounced LDH elevation detected in the highest EASIX percentile group. This finding supports the notion that increased myocardial tissue injury and systemic stress burden are closely associated with poor short-term prognosis.

In addition to LDH as a marker of myocardial tissue injury, another important parameter influencing prognosis in NSTEMI is creatinine, one of the key indicators of renal function.[15] Hemodynamic instability, sympathetic activation, and endothelial dysfunction occurring during NSTEMI impair renal perfusion, leading to elevated creatinine levels, and additionally predispose patients to the development of contrast-associated nephropathy following coronary angiography.[15] An increase in creatinine due to impaired renal function may develop in the setting of ACS, and elevated creatinine levels may also be present at the time of admission in these patients.[23] Indeed, in the study, creatinine levels were found to be statistically significantly higher in patients who experienced mortality compared with survivors. The higher prevalence of advanced age, atrial fibrillation, and heart failure among patients who experienced mortality suggests that the observed elevation in creatinine reflects both the hemodynamic burden of ACS and underlying comorbidities. Even in the absence of overt chronic kidney disease, mild elevations in creatinine have been shown to be associated with atherosclerosis through mechanisms including microvascular dysfunction, endothelial dysfunction, oxidative stress, and reduced nitric oxide bioavailability, and to constitute an independent risk factor for mortality.[24] It has also been reported to be an important predictor of morbidity and mortality following ACS.[23]

These findings indicate that renal dysfunction in NSTEMI is not merely a biochemical abnormality but also leads to tangible consequences that worsen the clinical course. Indeed, the development of acute kidney injury following ACS and the subsequent need for renal replacement therapy have been reported to be strongly associated with in-hospital mortality.[25] In this study, the significantly higher requirement for in-hospital hemodialysis among patients who experienced mortality is consistent with these findings and further supports the clinical severity of renal dysfunction in this setting. This finding suggests that, in the context of NSTEMI, acute renal dysfunction may not merely represent an accompanying abnormality, but rather may constitute a key determinant of poor short-term prognosis associated with systemic hemodynamic deterioration and multiorgan dysfunction.[25,26]

Renal dysfunction aside, the thrombotic process underlying NSTEMI and the associated platelet dynamics also play a decisive role in prognosis. Atherosclerotic plaque rupture or erosion leads to platelet activation.[6] As a consequence, thrombus formation is triggered through platelet adhesion, activation, and aggregation.[6] In the setting of NSTEMI, a greater thrombus burden is associated with increased distal embolization and more pronounced microvascular obstruction.[27] This condition is associated with the coronary no-reflow phenomenon, a larger ischemic burden, more severe left ventricular dysfunction, and an increased risk of mortality.[27] In NSTEMI, the more aggressive the thrombotic process, the greater the thrombus formation, which may lead to a reduction in platelet counts due to increased platelet consumption.[6]

In ACS, thrombocytopenia may be present at admission or develop during hospitalization as a result of increased platelet consumption, systemic inflammation, invasive procedures, and antithrombotic therapies.[28,29] Previous studies have shown that baseline thrombocytopenia is associated with increased mortality and adverse cardiovascular outcomes in patients with ACS, particularly after percutaneous coronary intervention.[30,31] Consistent with these literature findings, platelet counts were found to be lower in NSTEMI patients who experienced mortality compared with survivors in the study. In addition, platelet counts showed a stepwise decline across increasing EASIX percentile groups, with the lowest platelet levels observed in the highest EASIX percentile group. This observation suggests that the platelet component of EASIX may indirectly reflect thrombotic burden and disease severity.

Mortality was associated with lower revascularization rates, suggesting that these patients may have had a more fragile clinical profile. Indeed, previous studies have reported that ACS patients with higher levels of frailty are less likely to undergo invasive treatment and revascularization, and that this is associated with worse clinical outcomes.[32] However, revascularization remained independently associated with lower in-hospital mortality in the multivariable analysis, suggesting that both timely revascularization and the underlying systemic biological burden contribute to patient prognosis.

The EASIX score has the potential to reflect the clinical severity of NSTEMI in a more comprehensive manner by integrating multiple biological axes that have been shown to be associated with mortality into a single composite measure. In this study, increasing EASIX levels were accompanied by a marked rise in LDH values reflecting myocardial tissue injury, a higher frequency of renal dysfunction and indicators of hemodynamic stress, as well as a progressive decline in platelet counts. These findings suggest that EASIX may represent the combined effects of endothelial dysfunction, microvascular stress, and thrombo-inflammatory burden rather than alterations in a single organ system. This integrated biological reflection is consistent with previous studies demonstrating that EASIX reflects endothelial dysfunction and microvascular stress and can predict mortality related to systemic endothelial activation across different clinical populations.[10-13,33]

The findings that EASIX remained an independent predictor of in-hospital mortality together with the GRACE score and revascularization in multivariable analysis, and demonstrated good discriminative performance in ROC analysis, suggest that this score reflects more than the patient's current clinical status. Rather, EASIX appears to provide additional prognostic information by identifying a high-risk phenotype early in the course of NSTEMI. Although the GRACE score demonstrated the highest discriminative performance, EASIX significantly outperformed the TIMI score despite being derived exclusively from three routinely available laboratory parameters. Moreover, the clear and early separation of survival curves according to EASIX levels in Kaplan–Meier analyses supports the ability of this score to capture the acute clinical trajectory. Given the absence of prior studies specifically evaluating EASIX in NSTEMI populations, these findings indicate that EASIX may represent an easily calculable prognostic tool based on routine laboratory parameters, with potential value for early risk stratification in patients with NSTEMI.

In light of these results, the EASIX score may be integrated into clinical decision-making as a rapid and practical risk assessment tool at the time of admission in patients with NSTEMI. Its objective and cost-effective nature makes EASIX particularly attractive for routine clinical practice, especially in resource-limited settings. Because it relies on routinely obtained laboratory parameters, EASIX can facilitate the early identification of high-risk patient phenotypes without the need for additional testing or time-consuming procedures. Particularly when used in conjunction with clinical assessment and established risk stratification methods, EASIX may aid in distinguishing patients who require closer monitoring or who may benefit from more aggressive therapeutic strategies. In this regard, EASIX can be considered a feasible and complementary tool to existing clinical and laboratory-based prognostic markers in the management of NSTEMI.

Study Limitations

This study has several limitations. First, its single-center and retrospective design may limit the generalizability of the

findings. The exclusion of patients with incomplete data may have partially reduced the representativeness of the study sample. In addition, differences in medical therapies, percutaneous coronary intervention strategies, and antithrombotic treatment approaches are potential confounders that may affect clinical outcomes, and the effects of these variables could not be entirely excluded.

The EASIX score was calculated using laboratory parameters obtained at admission, and dynamic changes in these parameters during hospitalization were not evaluated. In addition, the fact that EASIX does not include parameters that directly reflect hemodynamic status (such as blood pressure, cardiac output, or cardiac index) may be considered a factor that could limit risk assessment, particularly in patients in whom acute hemodynamic instability is prominent. Similarly, because EASIX is based exclusively on laboratory parameters, it should be interpreted together with clinical findings rather than used as a standalone risk assessment tool.

Moreover, since the study focused solely on in-hospital mortality, data on long-term mortality and MACE could not be analyzed. Furthermore, the study was limited to the NSTEMI population, and the prognostic value of EASIX in other cardiac populations, such as STEMI or stable coronary artery disease, was not evaluated. Finally, the findings were not externally validated in an independent cohort. Therefore, larger prospective, multicenter studies with external validation are needed to confirm the generalizability of the findings.

CONCLUSION

This study demonstrates that EASIX is independently associated with in-hospital mortality in patients with NSTEMI. Given its simplicity, routine laboratory-based structure, and consistent prognostic performance, EASIX may serve as a practical tool for early risk stratification in NSTEMI.

Ethics Committee Approval: This study was approved by the Ethics Committee of Karabük University, (Approval No: 2025/2511, Date: October 30, 2025).

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

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