

The predictive value of endothelial activation and stress index (EASIX) for major adverse cardiovascular events in patients with coronary slow-flow phenomenon: a retrospective cohort study

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Abstract

Background

Coronary slow flow phenomenon (CSFP), defined by delayed distal opacification of epicardial coronary arteries without any identifiable mechanical cause, is increasingly considered as a manifestation of endothelial and microvascular dysfunction. In this study, we aimed to investigate the prognostic value of the endothelial activation and stress index (EASIX) in patients with CSFP.

Methods

We retrospectively analyzed 517 patients with angiographically confirmed CSFP. EASIX was calculated from lactate dehydrogenase, creatinine, and platelet count. The primary endpoint was major adverse cardiovascular events (MACE), defined as a composite of myocardial infarction (MI), stroke, or all-cause death. Data were analysed using Kaplan–Meier estimation, Cox proportional-hazards regression and receiver operating characteristic analysis.

Results

During a median follow-up of 27 months, MACE occurred in 47 patients (9.1%). MACE occurred in 23.2% of patients with $EASIX > 1.03$ versus 4.0% with $EASIX \leq 1.03$ ($p < 0.001$), with higher rates of MI and stroke. Event-free survival was significantly lower in the high-EASIX group (log-rank $p < 0.001$). After adjustment for age, diabetes mellitus, smoking, estimated glomerular filtration rate, and high-sensitivity C-reactive protein, $EASIX > 1.03$ remained independently associated with MACE (hazard ratio 2.31, 95% confidence interval [CI] 1.06–5.00; $p = 0.034$). EASIX discriminated MACE with an area under the curve of 0.757 (95% CI 0.677–0.829), with 68.1% sensitivity and 77.7% specificity. Mean TIMI frame count and multivessel involvement were not prognostic.

Conclusions

Higher EASIX was independently associated with MACE in patients with CSFP and may provide a simple, readily available indicator for long-term risk stratification.

Background

The coronary slow flow phenomenon (CSFP) is an angiographic entity characterised by delayed distal opacification of the epicardial coronary arteries in the absence of obstructive stenosis, spasm or other identifiable mechanical cause [1]. CSFP was first described by Tambe et al. in patients presenting with angina and angiographically normal coronary arteries [2], and has since been proposed as a specific coronary microvascular disease [3]. Its reported prevalence among patients undergoing diagnostic

coronary angiography ranges from approximately 1% to 7% [4, 5]. Although CSFP was regarded as a benign angiographic finding for many years, subsequent studies have documented its association with acute coronary syndrome (ACS), life-threatening ventricular arrhythmias, and sudden death [5, 6]. Moreover, contemporary cohorts have demonstrated major adverse cardiovascular event (MACE) rates of approximately 9% to 10% during long-term follow-up [7, 8].

The underlying mechanisms of CSFP are not fully clarified; however, current evidence primarily implicates endothelial dysfunction and chronic low-grade inflammation, leading to impaired endothelium-dependent microvascular vasodilatation, enhanced platelet activation, and early subclinical diffuse atherosclerosis [9]. Accordingly, several inflammation-based biomarkers such as high-sensitivity C-reactive protein (hs-CRP), serum soluble adhesion molecules, systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have been shown to be consistently higher in patients with CSFP than in those with normal coronary flow and to correlate with the TIMI frame count [10–13].

The Endothelial Activation and Stress Index (EASIX), derived from serum lactate dehydrogenase (LDH), creatinine, and platelet count, has recently emerged as a simple and readily available inflammatory indicator of endothelial activation and systemic stress. It was originally developed to predict endothelial complications and prognosis in patients undergoing allogeneic hematopoietic stem cell transplantation [14]. Subsequently, EASIX has been shown to predict clinical outcomes in many cardiovascular conditions, including heart failure (HF) [15], coronary artery bypass grafting (CABG) [16], non-ST-segment elevation myocardial infarction (NSTEMI) [17], chronic coronary syndrome (CCS) with prediabetes [18], transcatheter aortic valve implantation (TAVI) [19, 20] and coronary heart disease requiring intensive care [21]. Also, the relationship between EASIX and the no-reflow phenomenon has been demonstrated in patients with ST-segment elevation myocardial infarction (STEMI), NSTEMI, and saphenous vein graft disease undergoing percutaneous coronary intervention (PCI) [22–24]. This phenomenon reflects acute microvascular obstruction, which may represent the procedural analogue of the chronic microvascular impairment that characterises CSFP. However, to our knowledge, EASIX has not been investigated in CSFP. This study aimed to determine whether EASIX is associated with MACE during long-term follow-up in patients with CSFP.

Methods

Study population

This was a retrospective, single-centre observational cohort study conducted at a high-volume tertiary invasive cardiology department. We screened 20,884 consecutive patients who underwent diagnostic coronary angiography for suspected stable ischaemic heart disease between September 2020 and June 2026 and identified those with CSFP in the absence of any significant epicardial stenosis. Patients were excluded if they had obstructive coronary artery disease (CAD) (any epicardial stenosis $\geq 50\%$), hypotension or spasm during the procedure, previous PCI or CABG, coronary ectasia or aneurysm,

moderate or severe valvular heart disease, acute or chronic HF, any type of cardiomyopathy, atrial fibrillation, a known hematological disorder, active or chronic infection, chronic inflammatory or autoimmune disease, malignancy, end-stage renal disease requiring renal replacement therapy, chronic liver or biliary disease, chronic use of steroids or nonsteroidal anti-inflammatory drugs, anticoagulant therapy, or incomplete baseline laboratory data or follow-up. After the application of these inclusion and exclusion criteria, a total of 517 patients with CSFP constituted the final study population.

Demographic information and clinical history such as age, sex, diabetes mellitus, hypertension, dyslipidemia, smoking status, family history of CAD, and medical therapy were collected. Left ventricular ejection fraction (LVEF) was measured with transthoracic echocardiography using the modified Simpson method. All data were obtained from the hospital database records and patient files at the time of the coronary angiography procedure.

The study protocol was approved by the Kocaeli University Ethics Committee (GOKAEK- 2026/18/21; Project No: 2026/572). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Coronary angiography and definition of coronary slow flow

Coronary angiography was performed by the standard Judkins technique through the femoral or radial access with a Siemens imaging system. Images were acquired at 30 frames per second in at least four projections of the left coronary system and two of the right, using non-ionic low-osmolar contrast medium in all procedures. Coronary flow was evaluated by the Thrombolysis in Myocardial Infarction (TIMI) frame count according to the method defined by Gibson and colleagues [25]: the number of cine frames elapsing between the frame in which contrast fully enters the proximal segment of the vessel and the frame in which it first reaches the standardised distal landmark [the distal bifurcation of the left anterior descending (LAD) artery, the distal bifurcation of the longest obtuse marginal branch of the left circumflex (LCx) artery, and the first lateral branch of the posterolateral artery of the right coronary artery (RCA)]. The TIMI frame count of the LAD and LCx arteries was evaluated in the right anterior oblique projection with caudal angulation and RCA in the left anterior oblique projection with cranial angulation. The normal reference values of the TIMI frame count were 22.2 ± 4.1 for the LCx artery and 20.4 ± 3.0 for the RCA [25]. The frame count of the LAD artery was divided by 1.7 to obtain the corrected TFC (cTFC) value because of its longer length, and cTFC for the LAD artery was 21.1 ± 1.5 frames. The mean TIMI frame count was calculated from the arithmetic mean of the uncorrected frame counts of the three major epicardial vessels. CSFP was diagnosed when the frame count of at least one major epicardial artery exceeded the published normal mean for that vessel by more than two standard deviations [25]. All angiograms were reviewed independently by two experienced interventional cardiologists blinded to the laboratory data and to the clinical outcomes.

Laboratory measurements

All venous blood samples were drawn after an 8–12-hour fasting period within 24 hours before the procedure. Complete blood counts, including hemoglobin, neutrophil, lymphocyte and platelet counts, were measured using an automated blood cell counter. Biochemical parameters, including serum creatinine, LDH, lipid profile, and hs-CRP levels, were measured on an automated clinical chemistry analyser using standard laboratory techniques. EASIX was calculated using the following formula: serum LDH (U/L) × creatinine (mg/dL) / platelet count ($\times 10^9/L$) [14]. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The estimated glomerular filtration rate (eGFR) was derived with the Modification of Diet in Renal Disease formula [26].

Clinical outcomes and follow-up

The primary endpoint was MACE, defined as the composite of myocardial infarction (MI), stroke and all-cause death, with the time to the first component event used in the time-to-event analyses. MI was defined according to the fourth universal definition of MI [27], and stroke as an acute neurological deficit of vascular cause persisting for more than 24 hours and confirmed by a cranial imaging modality. All-cause death was defined as death from any cause during follow-up. The individual components were also analysed separately. Follow-up began at the index coronary angiography and was ascertained from hospital records, the national health information system and, where necessary, structured telephone contact with the patient or first-degree relatives.

Statistical analysis

Statistical analyses were performed in Python, version 3.12 (Python Software Foundation), using pandas 2.3, SciPy 1.18, statsmodels 0.14, lifelines 0.30 and scikit-learn 1.9; figures were drawn with matplotlib 3.11. Normally distributed continuous variables are presented as mean $\pm$ standard deviation (SD), whereas non-normally distributed continuous variables are expressed as median (interquartile range [IQR]). Categorical variables are presented as frequencies and percentages. Comparisons between two groups were performed using the independent samples Student's *t*-test or the Mann–Whitney *U* test, as appropriate. Categorical variables were compared using the Pearson's chi-square test or Fisher's exact test.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of EASIX to predict MACE and to determine the optimal cut-off value using the Youden index. Survival analysis was performed using the Kaplan–Meier method and compared using the log-rank test. The discriminative ability of EASIX and hs-CRP for predicting MACE was evaluated using ROC curve analysis, with the area under the curve (AUC) calculated for both parameters. Cox proportional hazards regression analyses were performed to identify independent predictors of the MACE. Variables that differed significantly between EASIX groups were considered candidate predictors and were included in the Cox proportional hazards regression models. To avoid multicollinearity problem, serum LDH, serum creatinine, neutrophil, lymphocyte, and platelet counts were not included as separate covariates in the Cox regression models. Variables with a *p*-value < 0.05 in the univariable analysis and those considered clinically relevant were

entered into the multivariable models. The results were reported as hazard ratios (HR) with corresponding 95% confidence intervals (CI). All tests were two-sided and a p-value < 0.05 was considered statistically significant.

Results

A total of 517 patients with CSFP were included in the study. The median age of the study population was 53 [44–59] years, 213 patients (41.2%) were male, and the median follow-up duration was 27 [15–44] months. Baseline demographic, clinical and laboratory characteristics stratified by EASIX are presented in Table 1. Patients in the high-EASIX group were older (55 [45–65] vs. 53 [42–59] years, $p = 0.046$), more frequently had diabetes mellitus (34.8% vs. 25.6%, $p = 0.040$) and were more frequently smokers (32.6% vs. 19.0%, $p = 0.001$). The prevalence of hypertension, dyslipidemia and a family history of CAD did not differ between the two groups, nor did the proportion of men (47.8% vs. 38.8%, $p = 0.065$). Patients in the high-EASIX group had higher hs-CRP levels [2.45 (1.10–5.50) vs. 1.40 (1.00–3.40), $p = 0.001$] and neutrophil count [6.77 (5.12–8.91) vs. 5.20 (3.97–7.77), $p < 0.001$], whereas their lymphocyte count [1.88 (1.12–2.33) vs. 2.08 (1.71–2.77), $p < 0.001$] and eGFR [76.8 (55.4–96.1) vs. 100.0 (85.9–111.8), $p < 0.001$] were lower than those of patients in the low-EASIX group. There was no statistically significant difference between the groups in terms of medication use.

Table 1
Baseline demographic, clinical and laboratory characteristics of the study population.

Variable	All (n = 517)	EASIX ≤ 1.03 (n = 379)	EASIX > 1.03 (n = 138)	p-value
Age, years	53 [44–59]	53 [42–59]	55 [45–65]	0.046
Male sex, n (%)	213 (41.2)	147 (38.8)	66 (47.8)	0.065
Comorbidities, n (%)				
Diabetes mellitus	145 (28.0)	97 (25.6)	48 (34.8)	0.040
Hypertension	204 (39.5)	150 (39.6)	54 (39.1)	0.927
Dyslipidemia	147 (28.4)	109 (28.8)	38 (27.5)	0.785
Smoking	117 (22.6)	72 (19.0)	45 (32.6)	0.001
Family history of CAD	119 (23.0)	92 (24.3)	27 (19.6)	0.260
Laboratory findings				
hs-CRP, mg/L	2.00 [1.10–4.00]	1.40 [1.00–3.40]	2.45 [1.10–5.50]	0.001
Neutrophil count, ×10 ⁹ /L	5.77 [4.06–8.00]	5.20 [3.97–7.77]	6.77 [5.12–8.91]	< 0.001
Lymphocyte count, ×10 ⁹ /L	2.01 [1.56–2.67]	2.08 [1.71–2.77]	1.88 [1.12–2.33]	< 0.001
Creatinine, mg/dL	1.00 [0.90–1.19]	0.90 [0.80–1.10]	1.20 [1.00–1.50]	< 0.001
eGFR, mL/min/1.73 m ²	96.2 [78.6–108.8]	100.0 [85.9–111.8]	76.8 [55.4–96.1]	< 0.001
LDH, U/L	159 [133–181]	155 [133–176]	171 [150–196]	< 0.001
Platelet count, ×10 ⁹ /L	201 [168–241]	211 [188–265]	155 [122–188]	< 0.001
NLR	2.65 [1.80–4.63]	2.32 [1.63–4.15]	3.71 [2.23–5.98]	< 0.001
EASIX	0.77 [0.60–1.08]	0.67 [0.53–0.80]	1.33 [1.18–1.59]	< 0.001
LVEF, %	63 [60–65]	63 [60–65]	63 [59–65]	0.773
Medications, n (%)				
Antiplatelet agent	442 (85.5)	321 (84.7)	121 (87.7)	0.394
Beta-blocker	115 (22.2)	84 (22.2)	31 (22.5)	0.942
ACEi/ARB	194 (37.5)	146 (38.5)	48 (34.8)	0.437
Calcium-channel blocker	139 (26.9)	108 (28.5)	31 (22.5)	0.171
Statin	184 (35.6)	144 (38.0)	40 (29.0)	0.058
Nitrate	94 (18.2)	75 (19.8)	19 (13.8)	0.116

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; EASIX, endothelial activation and stress index; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; NLR, neutrophil-to-lymphocyte ratio.

Angiographic characteristics and clinical outcomes of the study population are summarized in Table 2. The TIMI frame count of the LAD artery was higher in the high-EASIX group [39 (34–42) vs. 37 (32–40), $p = 0.002$], as was the mean TIMI frame count across the three major epicardial vessels [34.7 (27.7–38.1) vs. 32.0 (26.3–37.3), $p = 0.003$]. Frame counts in the LCx artery and RCA did not differ significantly ($p = 0.555$ and $p = 0.068$, respectively). The number of vessels with CSFP also differed between the two groups ($p = 0.005$). Three-vessel involvement was substantially more common in the high-EASIX group (59.4% vs. 43.3%), while single-vessel involvement was correspondingly less common (26.1% vs. 37.5%).

Table 2
Angiographic characteristics and clinical outcomes of the study population.

Variable	All (n = 517)	EASIX ≤ 1.03 (n = 379)	EASIX > 1.03 (n = 138)	p-value
TIMI frame count, frames				
Left anterior descending artery	37 [33–41]	37 [32–40]	39 [34–42]	0.002
Left circumflex artery	34 [22–38]	34 [21–38]	34 [27–38]	0.555
Right coronary artery	33 [20–38]	33 [20–38]	34 [21–39]	0.068
Mean TIMI frame count	32.7 [26.7–37.7]	32.0 [26.3–37.3]	34.7 [27.7–38.1]	0.003
Number of vessels with CSFP, n (%)				0.005
Single-vessel	178 (34.4)	142 (37.5)	36 (26.1)	
Two-vessel	93 (18.0)	73 (19.3)	20 (14.5)	
Three-vessel	246 (47.6)	164 (43.3)	82 (59.4)	
Clinical outcomes, n (%)				
Myocardial infarction	30 (5.8)	10 (2.6)	20 (14.5)	< 0.001
Stroke	12 (2.3)	3 (0.8)	9 (6.5)	< 0.001
All-cause death	8 (1.5)	4 (1.1)	4 (2.9)	0.219
MACE	47 (9.1)	15 (4.0)	32 (23.2)	< 0.001

MACE was defined as the composite of myocardial infarction, stroke or all-cause death. CSFP, coronary slow flow phenomenon; EASIX, endothelial activation and stress index; MACE, major adverse

cardiovascular events; TIMI, thrombolysis in myocardial infarction.

During follow-up, MACE occurred in 47 patients (9.1%). EASIX was significantly higher among patients who experienced an adverse event than among those who did not ($p < 0.001$; Fig. 1).

The composite was driven predominantly by MI, which occurred in 30 patients (5.8%); stroke occurred in 12 patients (2.3%) and all-cause death in 8 patients (1.5%). MACE occurred in 32 of the 138 patients (23.2%) with $EASIX > 1.03$ compared with 15 of the 379 patients (4.0%) with $EASIX \leq 1.03$ ($p < 0.001$). Similar results were observed for MI (14.5% vs. 2.6%, $p < 0.001$) and stroke (6.5% vs. 0.8%, $p < 0.001$). All-cause death was numerically more frequent in the high-EASIX group, but the difference did not reach significance given the small number of events (4 patients, 2.9%, vs. 4 patients, 1.1%; $p = 0.219$) (Fig. 2).

Results of the univariable and multivariable Cox regression models are presented in Table 3. On univariable analysis, $EASIX > 1.03$ (HR 5.845, 95% CI 3.164–10.798, $p < 0.001$), age (HR 1.114, 95% CI 1.078–1.151, $p < 0.001$), diabetes mellitus (HR 5.676, 95% CI 3.065–10.511, $p < 0.001$), smoking (HR 6.535, 95% CI 3.538–12.071, $p < 0.001$), male sex (HR 3.360, 95% CI 1.797–6.281, $p < 0.001$), hs-CRP (HR 1.151, 95% CI 1.104–1.200, $p < 0.001$), NLR (HR 1.110, 95% CI 1.054–1.169, $p < 0.001$), and eGFR (HR 0.969, 95% CI 0.960–0.978, $p < 0.001$) were associated with MACE. Notably, the mean TIMI frame count, frame count of the LAD artery, and three-vessel CSFP involvement were not statistically significant on univariable analysis ($p = 0.519$, $p = 0.422$ and $p = 0.083$, respectively). In the multivariable analysis, $EASIX > 1.03$ remained independently associated with MACE (HR 2.306, 95% CI 1.065–4.996, $p = 0.034$), alongside age (HR 1.065, 95% CI 1.029–1.102, $p < 0.001$), diabetes mellitus (HR 2.859, 95% CI 1.504–5.433, $p = 0.001$), smoking (HR 2.220, 95% CI 1.081–4.561, $p = 0.030$), and hs-CRP (HR 1.093, 95% CI 1.036–1.152, $p = 0.001$), whereas eGFR was no longer significant (HR 0.991, 95% CI 0.980–1.002, $p = 0.105$).

Table 3
Cox proportional-hazards regression for major adverse cardiovascular events in patients with CSFP.

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.114 (1.078–1.151)	< 0.001	1.065 (1.029–1.102)	< 0.001
Diabetes mellitus	5.676 (3.065–10.511)	< 0.001	2.859 (1.504–5.433)	0.001
Smoking	6.535 (3.538–12.071)	< 0.001	2.220 (1.081–4.561)	0.030
eGFR	0.969 (0.960–0.978)	< 0.001		
EASIX > 1.03	5.845 (3.164–10.798)	< 0.001	2.306 (1.065–4.996)	0.034
hs-CRP	1.151 (1.104–1.200)	< 0.001	1.093 (1.036–1.152)	0.001
NLR	1.110 (1.054–1.169)	< 0.001	—	—
Male gender	3.360 (1.797–6.281)	< 0.001	—	—
LAD TIMI frame count	1.015 (0.979–1.052)	0.422	—	—
Three-vessel CSFP	1.684 (0.935–3.033)	0.083	—	—

CI, confidence interval; CSFP, coronary slow flow phenomenon; EASIX, endothelial activation and stress index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LAD, left anterior descending artery; NLR, neutrophil-to-lymphocyte ratio; TIMI, thrombolysis in myocardial infarction.

Kaplan–Meier analysis confirmed that event-free survival was significantly worse in the high-EASIX group for the composite endpoint ($p < 0.001$), for MI ($p < 0.001$), and for stroke ($p < 0.001$). For all-cause death the curves separated in the expected direction but the difference was not statistically significant ($p = 0.138$), consistent with the eight deaths observed. The Kaplan–Meier curves for all four endpoints, with the numbers at risk, are shown in Fig. 3.

ROC analysis for the prediction of MACE is presented in Fig. 4. EASIX showed good discriminative ability, with an AUC of 0.757 (95% CI 0.677–0.829; $p < 0.001$), a sensitivity of 68.1%, and a specificity of 77.7%. In comparison, hs-CRP demonstrated lower discriminative ability, with an AUC of 0.701 (95% CI 0.611–0.789; $p < 0.001$).

Discussion

To our knowledge, this is the first study to evaluate the relationship between EASIX and MACE in patients with CSFP. There are three principal findings in the present study. First, EASIX > 1.03 was associated with a nearly six-fold higher incidence of MACE, and it remained independently associated with the endpoint

after adjustment for age, diabetes, smoking, eGFR and hs-CRP. Second, EASIX discriminated MACE with an AUC of 0.757, numerically higher than that of hs-CRP, although the difference was not statistically significant. Third, EASIX was not merely an indicator of comorbidity but tracked the angiographic severity of the disease itself, being associated with higher LAD and mean TIMI frame counts and with more extensive multivessel involvement.

The event rate of 9.1% observed in our study is consistent with the range published in previous CSFP studies [7, 8, 28]. In a long-term CSFP cohort, 201 patients followed for a mean of 66 months experienced 3 MI (1.5%) and 5 cardiovascular deaths (2.5%) [29], compared with 30 MI (5.8%) and 8 all-cause deaths (1.5%) in our cohort. Part of this difference may be explained by outcome definitions, as we included all-cause death and stroke; however, the MI rate was approximately four-fold higher despite less than half the follow-up duration. Among 250 diabetic patients with CSFP, MACE rates did not differ significantly from those with normal flow, with 6 STEMI and 4 NSTEMI events occurring in the CSFP group during one-year follow-up [28]. However, the relatively short follow-up and the restriction to diabetic patients limit its value for evaluating long-term risk, and its findings should not be interpreted as evidence of safety. In a cohort of 143 patients with coronary artery ectasia, in which the comparison group was also angiographically abnormal, concomitant slow flow predicted hospitalization but not MACE or cardiovascular death over 57 months [30]. Our findings suggest substantial risk heterogeneity within CSFP, with MACE occurring in 4.0% of patients with $EASIX \leq 1.03$ and 23.2% of those with $EASIX > 1.03$. This may partly explain the differences in event rates across previous cohorts, reflecting differences in patient selection.

CSFP is considered a disorder of the coronary microcirculation involving increased microvascular resistance, small-vessel structural and endothelial dysfunction, diffuse subclinical atherosclerosis, and an imbalance between endothelin-1 and nitric oxide, resulting in delayed epicardial contrast transit in the absence of obstructive coronary disease [9]. EASIX was developed as a biomarker of endothelial activation and microangiopathic injury, with its components reflecting cellular injury (LDH), renal microvascular dysfunction (creatinine), and platelet consumption associated with endothelial activation [14]. Its correlation with soluble thrombomodulin, angiopoietin-2, and soluble ST2 further supports EASIX as a surrogate indicator of endothelial dysfunction rather than merely an empirical risk score [31]. Accordingly, EASIX has shown consistent prognostic value across several cardiovascular settings. EASIX independently predicted mortality in 1,283 patients undergoing coronary catheterization, regardless of age, gender, severity of the stenosis, LVEF, hypertension, and diabetes, with consistent findings in an external validation cohort [32]. Also, Estler and colleagues showed that EASIX was a predictor of 5-year mortality in patients with chronic HF across all aetiologies and functional classes [15]. Among 1,084 patients undergoing TAVI, $EASIX \geq 1.65$ was associated with increased 3-year mortality (45.8% vs. 27.7%) [19]. Our threshold of 1.03 is lower than the 1.65 derived in the TAVI cohort, as would be expected in a younger, less comorbid population with a median age of 53 years. In 1,036 patients with acute MI, higher EASIX was associated with increased 30-day mortality [33]. EASIX also predicts MACE and all-cause mortality in patients with CCS and prediabetes [18]. In 38,713 NHANES participants, each $\log_2$ increase in EASIX was associated with a 54% higher risk of cardiovascular mortality [34]. Of particular relevance

to CSFP, EASIX has been linked to angiographic no-reflow during PCI [22–24], another manifestation of coronary microvascular dysfunction. Our findings extend this association from an acute procedural setting to the long-term prognosis of a chronic microvascular phenotype.

The association between EASIX and TIMI frame count is particularly relevant because it suggests that EASIX may reflect disease severity rather than simply associated comorbidity. Patients with high EASIX had higher LAD and mean TIMI frame counts and were more likely to have three-vessel involvement. Similar relationships have been reported for inflammatory indices, including hs-CRP, SII, PLR, and NLR, which correlate with mean frame count and the number of affected vessels [10–13]. Reduced eGFR has also been independently associated with CSFP, while platelet count and platelet indices differ between patients with CSFP and those with normal flow [35, 36]. EASIX may therefore integrate several renal, inflammatory, and platelet-related features previously described separately in CSFP.

Limitations

This study has several limitations. First, it is a retrospective, single-centre analysis with no normal-flow comparison group, so it can describe risk stratification within CSFP but cannot address whether CSFP itself confers excess risk. Second, the multivariable models contained 6 covariates for 47 events, an events-per-variable ratio of 7.8; the adjusted hazard ratios are consequently imprecise, as their wide confidence intervals show, and the models may be overfitted. Also, EASIX was calculated from a single sample at the index admission; a value measured during an intercurrent illness would be transiently elevated, biasing the association away from the null if such patients were over-represented in the high-EASIX stratum. The analysis of all-cause death rested on 8 events and the vessel-distribution comparison involved several sparse cells; both are underpowered and hypothesis-generating. Finally, this is an observational study and the relationships described are associations; they do not establish that endothelial stress causes the events observed. A prospective multicentre CSFP cohort with pre-specified continuous modelling of EASIX, blinded independent event adjudication and a normal-flow comparison group would resolve most of these limitations.

Conclusions

In this retrospective cohort of 517 patients with CSFP, an EASIX above 1.03 was associated with a MACE rate of 23.2% against 4.0% below the threshold over a median of 27 months, and remained independently associated with MACE after adjustment for age, diabetes mellitus, smoking, renal function and hs-CRP (HR 2.31, 95% CI 1.06–5.00). Within the population studied, EASIX is best regarded as an inexpensive laboratory index whose principal value is a high negative predictive value (96.1%) at the 1.03 threshold (Table 4). External validation using a pre-specified continuous parameterisation is required before it is used to guide management.

Abbreviations

ACEi
angiotensin-converting enzyme inhibitor
ACS
acute coronary syndrome
ARB
angiotensin receptor blocker
AUC
area under the receiver operating characteristic curve
CABG
coronary artery bypass grafting
CAD
coronary artery disease
CCS
chronic coronary syndrome
CI
confidence interval
CSFP
coronary slow flow phenomenon
cTFC
corrected TIMI frame count
EASIX
endothelial activation and stress index
eGFR
estimated glomerular filtration rate
HF
heart failure
HR
hazard ratio
hs-CRP
high-sensitivity C-reactive protein
IQR
interquartile range
LAD
left anterior descending artery
LCx
left circumflex artery
LDH
lactate dehydrogenase
LVEF
left ventricular ejection fraction

MACE
major adverse cardiovascular events
MI
myocardial infarction
NHANES
National Health and Nutrition Examination Survey
NLR
neutrophil-to-lymphocyte ratio
NPV
negative predictive value
NSTEMI
non-ST-segment elevation myocardial infarction
PCI
percutaneous coronary intervention
PLR
platelet-to-lymphocyte ratio
PPV
positive predictive value
RCA
right coronary artery
ROC
receiver operating characteristic
SD
standard deviation
SII
systemic immune-inflammation index
STEMI
ST-segment elevation myocardial infarction
TAVI
transcatheter aortic valve implantation
TFC
TIMI frame count
TIMI
thrombolysis in myocardial infarction

Declarations

Ethics approval and consent to participate

The study protocol was approved by the local ethics committee (GOKAEK- 2026/18/21; Project No: 2026/572). The study was conducted in accordance with the ethical principles of the Declaration of

Helsinki. Informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

K.K. and I.Y. contributed to the methodology, software, validation, formal analysis and investigation. D.M. and H.R. performed data curation. K.K and D.M. wrote the original draft and reviewed and edited the manuscript. K.K. supervised the study. All authors read , reviewed and approved the final manuscript.

Acknowledgement

The authors used AI to write the statistical analysis code, to assist with drafting and language editing of parts of the manuscript, and to check and format the references, as described in the Methods. The authors reviewed all output and take full responsibility for the content of this publication.

Data Availability

The datasets generated and analysed during the current study are not publicly available because they contain patient-level clinical data obtained from the hospital records of Kocaeli University Hospital, and public sharing is restricted by patient confidentiality and the conditions of the ethics committee approval (GOKAEK-2026/18/21). De-identified data are, however, available from the corresponding author (Kurtulus Karauzum, kurtuluskarauzum@yahoo.com) on reasonable request and with the permission of the Kocaeli University Ethics Committee

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Figures

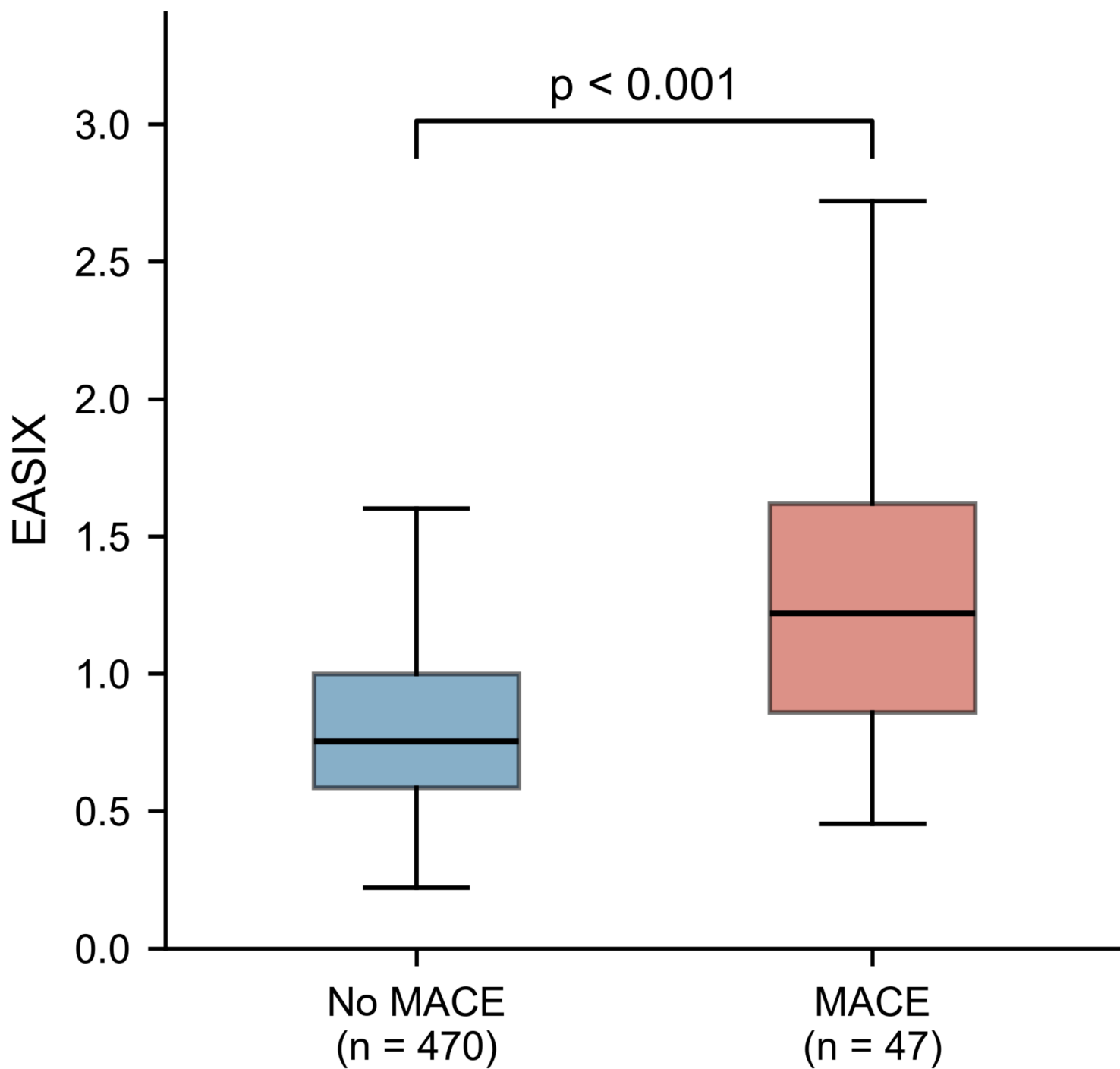


Figure 1

EASIX in patients with and without major adverse cardiovascular events

EASIX, endothelial activation and stress index.

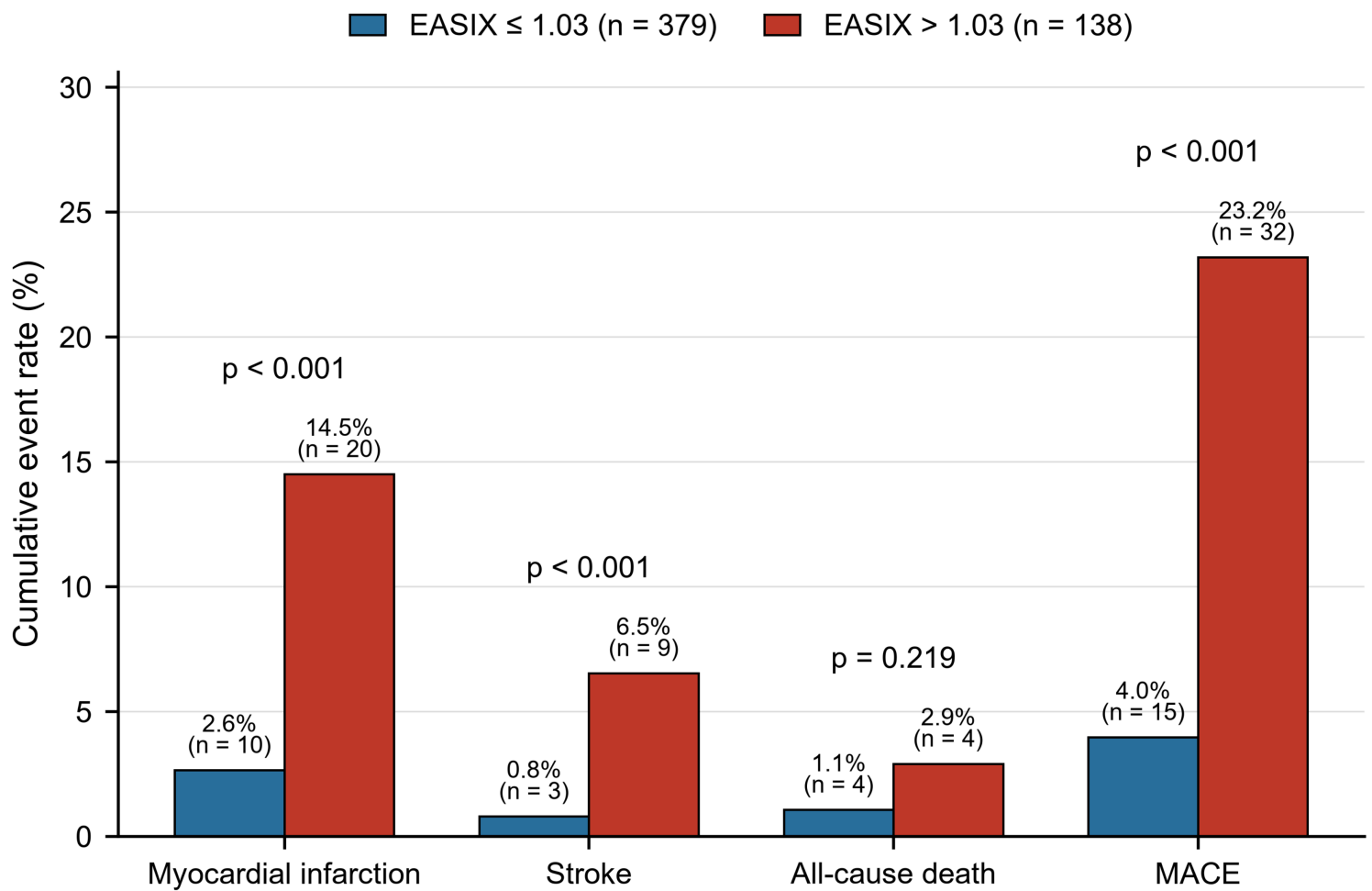


Figure 2

Cumulative event rates during follow-up according to EASIX stratum

EASIX, endothelial activation and stress index; MACE, major adverse cardiovascular events.

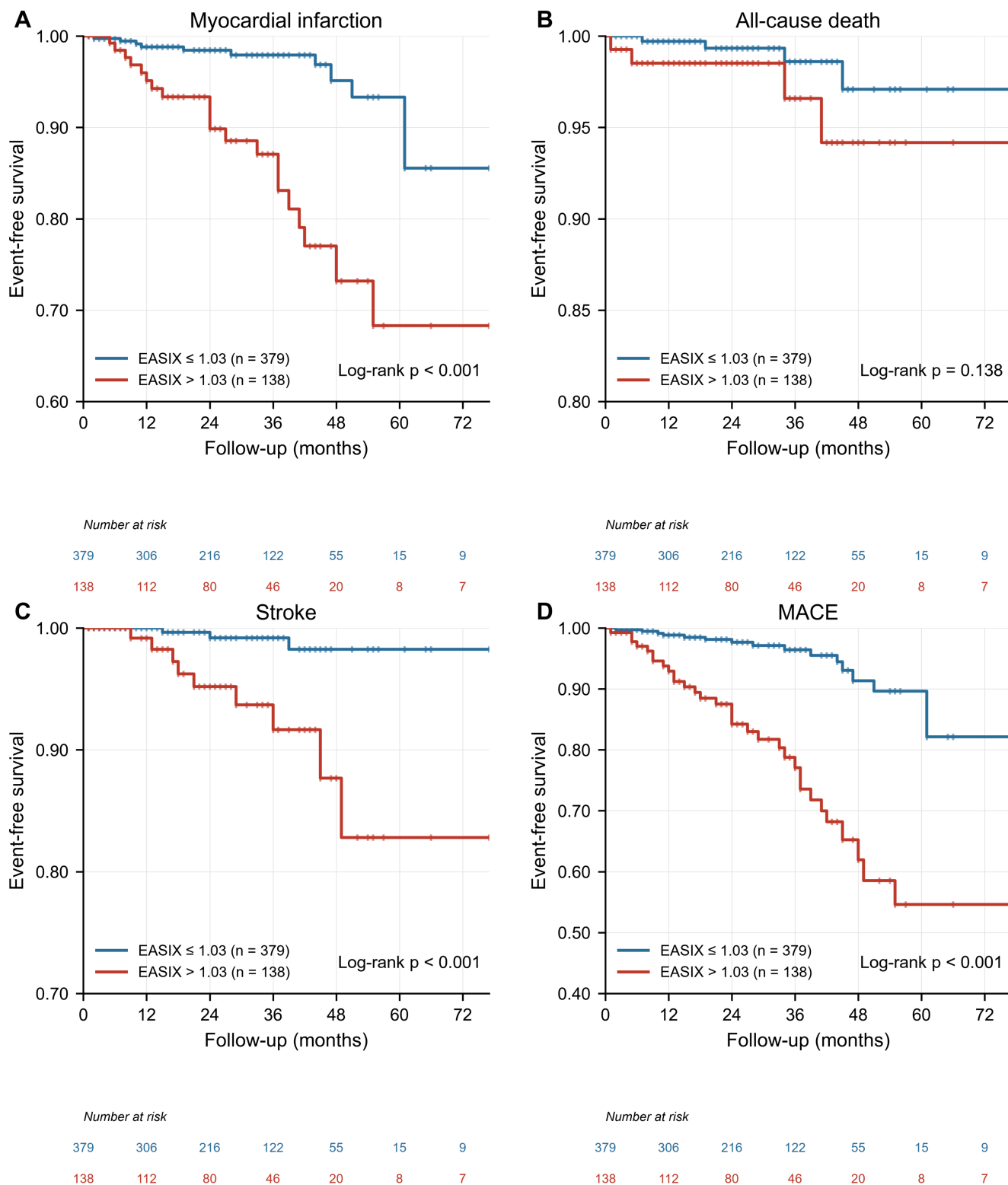


Figure 3

Kaplan–Meier event-free survival according to EASIX stratum

(A) Myocardial infarction, (B) all-cause death, (C) stroke and (D) MACE. EASIX, endothelial activation and stress index; MACE, major adverse cardiovascular events.

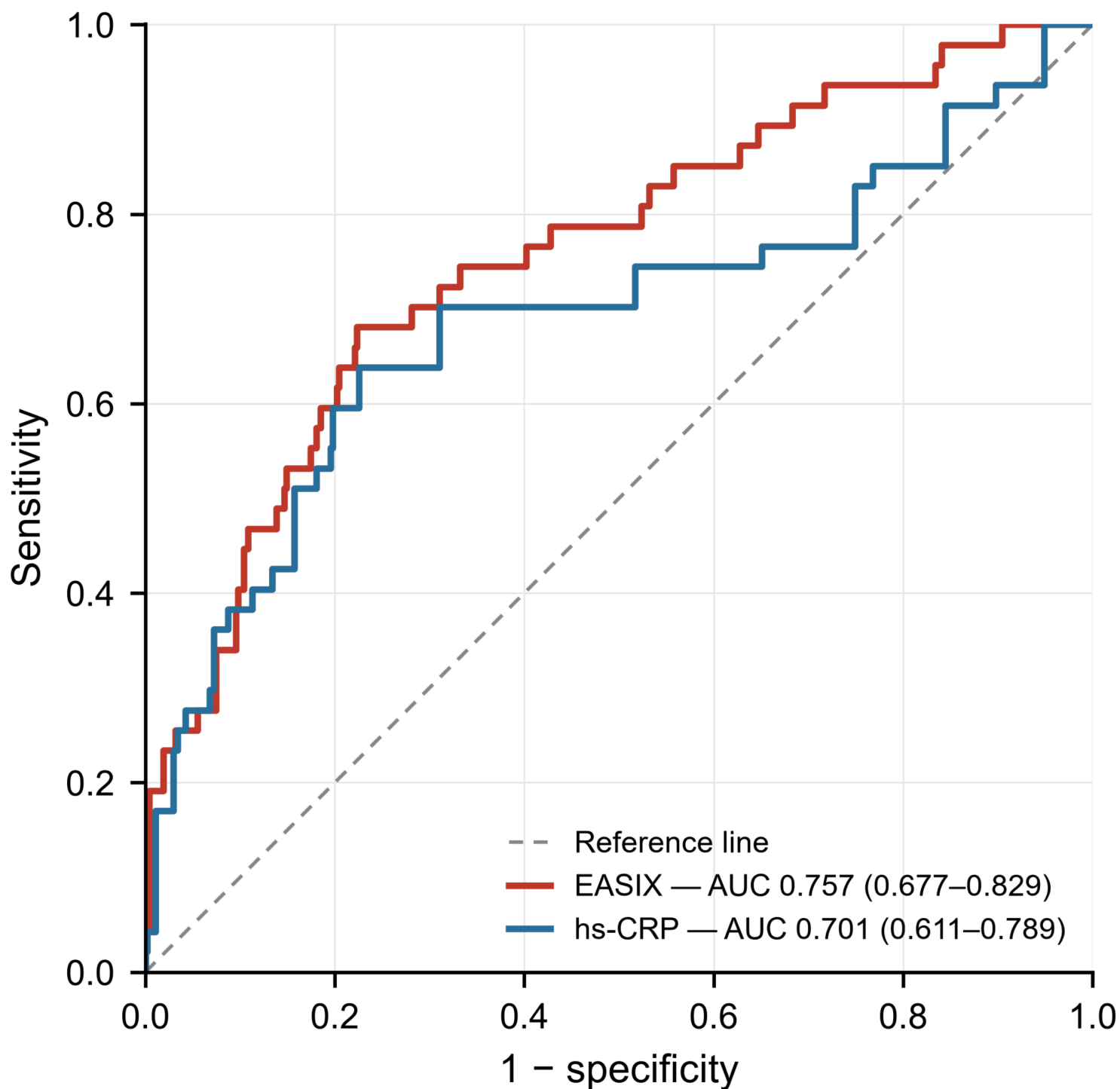


Figure 4

Receiver operating characteristic curves for the prediction of major adverse cardiovascular events

EASIX, endothelial activation and stress index; hs-CRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular events.