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RESEARCH ARTICLE

Circulating FNDC4 levels and 12-month major adverse cardiovascular events in patients with STEMI undergoing PCI: A prospective cohort study

Xiaojun Pu[#], Shengchao Xiao[#], Shanhong Liu, and Liwen Gong[*]

Fibronectin type III domain-containing protein 4 (FNDC4) is a circulating hepatokine with anti-inflammatory and cardioprotective properties, but its prognostic relevance after ST-segment elevation myocardial infarction (STEMI) remains uncertain. We investigated whether admission serum FNDC4 levels were associated with 12-month major adverse cardiovascular events (MACE) in patients with STEMI undergoing primary or urgent percutaneous coronary intervention (PCI). This single-center prospective observational study included 274 patients. Serum FNDC4 was measured before PCI using an enzyme-linked immunosorbent assay, and participants were followed for 12 months. Associations and prognostic performance were assessed using Spearman correlation, receiver operating characteristic, Kaplan–Meier, and Cox proportional hazards analyses. During follow-up, 51 patients (18.6%) experienced MACE. Serum FNDC4 levels were significantly lower in patients with MACE and were inversely correlated with interleukin-6 (IL-6) and N-terminal pro–B-type natriuretic peptide (NT-proBNP). The area under the receiver operating characteristic curve (AUC) for FNDC4 was 0.771 (95% confidence interval [CI], 0.695–0.839). Adding FNDC4 to a clinical model increased the AUC from 0.874 to 0.905 (△AUC, 0.031; 95% CI, 0.009–0.061). After adjustment for age, NT-proBNP, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), and Killip class III/IV, each 10 ng/mL decrease in FNDC4 was associated with a higher risk of MACE (hazard ratio, 1.821; 95% CI, 1.360–2.438; $P < 0.001$). Lower admission FNDC4 levels were independently associated with 12-month MACE after PCI for STEMI and may provide complementary prognostic information; however, multicenter external validation and serial FNDC4 measurements are required before clinical application.

Keywords: ST-segment elevation myocardial infarction, FNDC4, inflammation, major adverse cardiovascular events, percutaneous coronary intervention, prognosis.

Introduction

ST-segment elevation myocardial infarction (STEMI) remains a leading cause of death worldwide, imposing a substantial and growing global health burden despite advances in care [1, 2]. Primary percutaneous coronary intervention (PCI) has revolutionized STEMI management by rapidly restoring epicardial flow and improving survival compared with earlier strategies [3]. Nevertheless, even in the contemporary PCI era, patients experience considerable residual risk of major adverse cardiovascular events (MACE) during follow-up, highlighting the limitations of current risk stratification [4, 5]. Traditional prognostic markers such as N-terminal pro–B-type natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF), and low-density lipoprotein cholesterol (LDL-C) are informative but do not fully capture the heterogeneity in post-PCI outcomes [6–8].

Fibronectin type III domain–containing protein 4 (FNDC4) is a secreted hepatokine with immunomodulatory properties. It binds to and signals in macrophages to dampen inflammatory activation [9]. The soluble, circulating form of FNDC4 (sFNDC4) is detectable in plasma/serum, representing the bioavailable fraction capable of systemic action [10]. Preclinical and translational studies indicate that FNDC4 confers cardioprotection in ischemia–reperfusion (I/R) conditions by promoting hypoxia-inducible factor 1α (HIF-1α)–dependent cardiomyocyte survival and angiogenesis, and circulating/plasma FNDC4 responds to myocardial injury [11]. Beyond the heart, FNDC4 broadly suppresses inflammatory responses and metabolic stress, suggesting its potential relevance to atherosclerosis progression and post-infarction remodeling biology [12]. However, the clinical significance of circulating FNDC4 for predicting MACE specifically in STEMI patients treated with PCI has not been defined.

Therefore, we conducted a single-center prospective study to investigate whether baseline circulating FNDC4 levels were associated with 12-month MACE in STEMI patients undergoing

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primary or urgent PCI. We further explored whether FNDC4 provided additional prognostic information beyond established markers such as NT-proBNP and echocardiographic LVEF in this dataset. Given the single-center observational design, this study aimed to generate preliminary clinical evidence regarding the association between circulating FNDC4 levels and post-PCI outcomes, rather than to establish FNDC4-guided clinical management.

Materials and methods

Study population

This was a single-center, prospective observational study. Between January 2021 and August 2024, we screened 389 STEMI patients undergoing PCI at our hospital. After excluding 28 patients who met exclusion criteria, 64 who declined to participate, and 23 who did not complete follow-up, 274 patients were included in the final analysis (Figure 1). STEMI diagnosis was established according to current European Society of Cardiology (ESC) guidelines [13], requiring: (1) ischemic chest pain lasting ≥20 minutes; (2) new or presumed new ST-segment elevation at the J-point in two or more contiguous leads (≥2.0 mm in men or ≥1.5 mm in women in leads V2–V3, or ≥1.0 mm in other contiguous leads, or new left bundle branch block); and (3) a rise and/or fall in cardiac troponin with at least one value above the 99th percentile upper reference limit.

All enrolled patients underwent primary or urgent PCI by the same experienced interventional cardiology team using standardized procedural techniques and postoperative management protocols. Exclusion criteria included: (1) previous myocardial infarction, PCI, or coronary artery bypass grafting within the preceding three months; (2) administration of thrombolytic therapy before admission; (3) active infection, autoimmune disease, or malignancy; (4) severe hepatic dysfunction (alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal) or renal insufficiency (estimated glomerular filtration rate [eGFR] <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$); (5) chronic inflammatory disorders, hematologic diseases, or current immunosuppressive therapy; (6) use of drugs with potential anti-inflammatory or immunomodulatory effects within the past month; (7) pregnancy or lactation; and (8) inability to provide informed consent or complete follow-up.

This observational study was not registered in a clinical-trial registry as it involved no randomization, treatment allocation, or intervention beyond routine clinical care. The study protocol was approved by the Ethics Committee of our hospital (Approval No. YXLL20230706), and all procedures adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Sample size calculation

The required sample size was calculated to estimate the 12-month incidence of MACE in STEMI patients after PCI with a prespecified absolute precision. The formula used was $n = Z^2 \times p \times (1-p)/d^2$, where p represents the expected 12-month MACE proportion, d represents the allowable absolute error, and Z represents the standard normal deviate for a two-sided 95% confidence level. Based on prior reports and our pilot data [14], the expected 12-month MACE proportion was assumed to be 0.20. With $Z = 1.96$ and $d = 0.05$, the calculated sample size was $n = 1.96^2 \times 0.20 \times 0.80/0.05^2 = 245.86$, rounded up to 246 participants. Allowing for an approximately 10% attrition rate, the final target sample size was 246/0.90 = 273.33. Therefore, at least 274 participants were required.

Serum biomarker assessment

For each patient, peripheral venous blood (8–10 mL) was collected within 30 minutes after hospital admission and immediately before PCI, typically upon arrival at the catheterization laboratory, to minimize pre-analytical variability. Samples were collected into serum separator tubes, allowed to clot at room temperature for 30 minutes, then centrifuged at 1,500–2,000 g for 10–15 minutes. The resulting serum was carefully separated, aliquoted into 0.3–0.5 mL cryovials, and stored at −80 °C until analysis. All laboratory measurements were performed in duplicate by investigators blinded to clinical data.

Serum FNDC4 concentrations were determined using a commercially available human FNDC4 enzyme-linked immunosorbent assay (ELISA) kit (MyBioSource, San Diego, CA, USA; catalog No. MBS9332722) according to the manufacturer's protocol. This quantitative sandwich ELISA had a detection range of 31.2–1000 ng/mL and a sensitivity of 5.0 ng/mL. Serum samples were assayed undiluted as observed FNDC4 concentrations were within the detection range. Inflammatory biomarkers were measured using commercial ELISA kits from Nanjing Jiancheng Bioengineering Institute (Nanjing, China), including interleukin-6 (IL-6; catalog No. H007-1-2), interleukin-1β (IL-1β; catalog No. H002-1-2), interleukin-17 (IL-17; catalog No. H014-1), and C-reactive protein (CRP; catalog No. H126-1-2). All biomarker measurements were performed in duplicate. The exact intra- and inter-assay coefficients of variation (CV) values for FNDC4 and other inflammatory biomarkers were not available in the laboratory records. Serum samples were stored at −80 °C from collection until analysis. While the exact storage duration for each individual sample was not recorded due to continuous collection throughout the study period, pre-analytical variability was minimized by aliquoting serum before storage, thawing each aliquot only once for biomarker measurement, and avoiding repeated freeze–thaw cycles. Samples from patients with and without MACE were randomly distributed across plates, and laboratory investigators were blinded to clinical data and outcome status.

Data collection

Clinical and laboratory data were prospectively collected for all enrolled patients at hospital admission using standardized case report forms. Baseline demographic variables included age, sex, body mass index (BMI), smoking status, and medical history of hypertension, diabetes mellitus, and hyperlipidemia. Clinical information included the number of diseased vessels and the use of guideline-directed medical therapy. Medication variables shown in Table 1 referred to prescriptions at discharge after

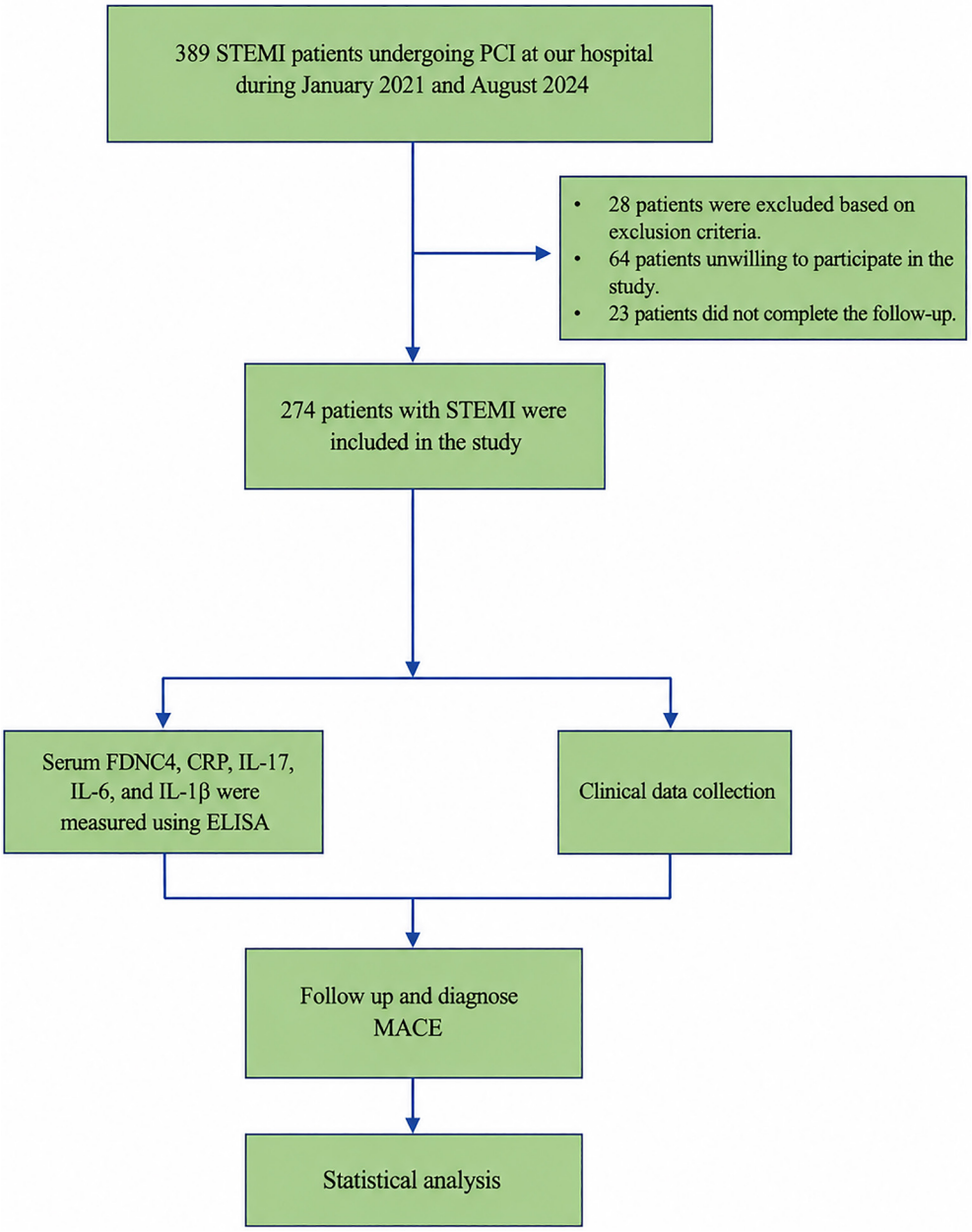


Figure 1. Patient flow diagram. Abbreviations: CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; FNDC4, fibronectin type III domain-containing protein 4; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-17, interleukin-17; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

the index PCI, rather than prior medication use or follow-up adherence.

Venous blood samples were collected immediately upon admission and prior to PCI for biochemical analysis. Laboratory analyses included: (1) cardiac injury markers—high-sensitivity cardiac troponin I (hs-cTnI), creatine kinase-MB (CK-MB), and lactate dehydrogenase (LDH); (2) cardiac function marker—NT-proBNP; and (3) lipid metabolism parameters—total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and LDL-C. All biochemical assays were conducted in the hospital's central laboratory using standardized automated analyzers (Beckman Coulter, Brea, CA, USA) under rigorous internal and external quality control. Procedural and reperfusion-related variables, such as symptom-to-door time, door-to-balloon time, total ischemic time, pre-PCI thrombolysis in Myocardial Infarction (TIMI) flow, and post-PCI TIMI flow, were also recorded.

Transthoracic echocardiography was performed by experienced sonographers within 24–48 hours post-PCI. LVEF was measured using the modified Simpson's biplane method from apical four- and two-chamber views. Echocardiographic measurements were independently reviewed and verified by two investigators blinded to serum FNDC4 levels and clinical outcomes.

Table 1. Baseline characteristics of patients with and without MACE

Variable	Non-MACE group ($n = 223$)	MACE group ($n = 51$)	*P*
Age, y	63 (55–71)	66 (57–71)	0.259
Male, *n* (%)	131 (58.8)	33 (64.7)	0.433
BMI (kg/m^2)	23.65 (21.35–25.48)	23.02 (21.01–25.10)	0.196
Smoking, *n* (%)	92 (41.3)	19 (37.3)	0.383
Hypertension, *n* (%)	103 (46.2)	27 (52.9)	0.384
Diabetes, *n* (%)	29 (13.0)	8 (15.7)	0.613
Hyperlipidemia, *n* (%)	98 (44.0)	32 (62.7)	0.015
No. of diseased vessels, *n* (%)			0.822
1-vessel disease	93 (41.7)	19 (37.3)	
2-vessel disease	88 (39.5)	21 (41.2)	
3-vessel disease	42 (18.8)	11 (21.6)	
Dual antiplatelet therapy, *n* (%)	218 (97.8)	50 (98.0)	0.901
β-blocker use, *n* (%)	197 (88.4)	43 (84.3)	0.431
ACEI/ARB use, *n* (%)	204 (91.5)	47 (92.2)	0.875
Statin use, *n* (%)	178 (79.8)	41 (80.4)	0.927
Killip class III/IV, *n* (%)	13 (5.8%)	8 (15.7%)	0.036
Symptom-to-door time (min)	95.6 (65.3–123.8)	89.7 (59.3–112.1)	0.106
Door-to-balloon time (min)	67.7 (56.1–78.7)	66.5 (56.5–77.2)	0.852
Total ischemic time (min)	162.3 (129.9–191.1)	146.7 (121.3–178.6)	0.096
Pre-PCI TIMI flow 0–1, *n* (%)	92 (41.3%)	15 (29.4%)	0.160
Post-PCI TIMI flow grade 3, *n* (%)	199 (89.2%)	44 (86.3%)	0.721

Medication variables refer to discharge prescriptions following the index PCI. **Abbreviations:** ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

Follow-up and definition of MACE

This study did not involve intervention in patient management; all treatments adhered to our hospital's clinical practice guidelines. Patients were followed for 12 months post-index PCI via scheduled outpatient visits or structured telephone interviews at 1, 6, and 12 months. Information on hospital readmissions, emergency visits, and survival status was obtained from electronic medical records and confirmed through direct contact with patients or their families. The primary endpoint was the occurrence of MACE within 12 months post-PCI. MACE was defined as a composite of cardiovascular death, nonfatal myocardial infarction, ischemic stroke, unplanned coronary revascularization, or hospitalization for heart failure.

Cardiovascular death was defined as death due to myocardial infarction, heart failure, malignant arrhythmia, sudden cardiac death, stroke, or other vascular causes. Nonfatal myocardial infarction was defined as recurrent ischemic symptoms with new electrocardiographic changes and elevated cardiac biomarkers. Ischemic stroke was defined as a new focal neurological deficit lasting over 24 hours with imaging confirmation of cerebral ischemia. Unplanned coronary revascularization was defined as any non-elective PCI or coronary artery bypass grafting performed due to recurrent ischemia or clinically significant coronary stenosis. Hospitalization for heart failure was defined as an unplanned hospital admission for worsening heart failure symptoms or signs requiring intravenous diuretics, vasodilators, or inotropic therapy. For patients experiencing multiple events during follow-up, only the first MACE event was included in the primary endpoint analysis. Endpoint events were independently reviewed by two cardiologists blinded to baseline FNDC4 levels, with disagreements resolved by discussion with a third investigator.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 26.0; IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test and visual inspection of histograms assessed the distribution of continuous variables. Normally distributed data were expressed as mean ± standard deviation (SD) and compared using the independent-samples *t*-test. Non-normally distributed data were expressed as median (interquartile range, IQR) and compared using the Mann–Whitney *U* test. Categorical variables were presented as counts and percentages and compared using the chi-square (χ^2) test or Fisher's exact test, as appropriate.

Table 2. Laboratory and echocardiographic characteristics of patients with and without MACE

Variable	Non-MACE group ($n = 223$)	MACE group ($n = 51$)	*P*
hs-cTnI (ng/L)	7297.45 ± 2655.32	10268.75 ± 4078.92	<0.001
CK-MB (U/L)	31 (23–41)	37 (26–45)	0.027
LDH (U/L)	273 (228–328)	289 (233–320)	0.945
NT-proBNP (pg/mL)	1268 (815–1710)	1514 (924–2115)	0.006
TC (mmol/L)	4.5 (4.0–5.2)	4.5 (4.0–5.4)	0.511
TG (mmol/L)	1.6 (1.2–1.9)	1.6 (1.2–2.1)	0.316
HDL-C (mmol/L)	1.0 (0.9–1.2)	1.1 (0.9–1.2)	0.707
LDL-C (mmol/L)	2.7 (2.3–3.2)	3.2 (2.5–3.5)	0.001
LVEF (%)	50 (46–55)	49 (45–53)	0.046
FNDC4 (ng/mL)	87.9 (79.7–96.3)	76.0 (66.6–85.5)	<0.001
eGFR (mL/min/1.73 m^2)	96.3 (90.0–102.9)	84.0 (77.2–94.3)	<0.001

Abbreviations: CK-MB, creatine kinase-MB; eGFR, estimated glomerular filtration rate; FNDC4, fibronectin type III domain-containing protein 4; HDL-C, high-density lipoprotein cholesterol; hs-cTnI, high-sensitivity cardiac troponin I; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro–B-type natriuretic peptide; TC, total cholesterol; TG, triglycerides.

Spearman's rank correlation analyzed the relationships between serum FNDC4 levels and laboratory parameters, including inflammatory cytokines (IL-6, IL-1β, IL-17, and CRP) and cardiac injury markers (hs-cTnI, CK-MB, LDH, and NT-proBNP). Receiver operating characteristic (ROC) curve analysis assessed FNDC4's ability to predict 12-month MACE, calculating the area under the curve (AUC) with corresponding 95% confidence intervals (CIs). The optimal FNDC4 cutoff value was derived from the current dataset using the Youden index, thus considered exploratory rather than prespecified. Given that lower FNDC4 levels indicated higher MACE risk, sensitivity, specificity, positive predictive value, negative predictive value, and 2×2 classification counts were calculated at this cutoff.

The incremental predictive value of FNDC4 was primarily evaluated beyond a parsimonious clinical model, not NT-proBNP alone. The clinical model included age, NT-proBNP, LVEF, eGFR, and Killip class III/IV, chosen as clinically relevant prognostic variables given the limited number of MACE events. The extended model additionally included FNDC4. This clinical-model comparison was the main incremental prediction analysis, while comparisons with NT-proBNP alone were secondary exploratory analyses. Model discrimination was compared using AUC, ΔAUC, integrated discrimination improvement (IDI), and continuous net reclassification improvement (NRI). Kaplan–Meier curves compared 12-month MACE-free survival in STEMI patients undergoing PCI, stratified by baseline serum FNDC4 level.

As time-to-event data were available, Cox proportional hazards regression served as the main adjusted analysis for 12-month MACE. Follow-up time was defined as the interval from index PCI to the first MACE event; patients without MACE were censored at 12 months. To mitigate overfitting risk, given 51 MACE events, a parsimonious multivariable model was constructed using *a priori* selected clinically relevant variables. The final model included FNDC4, age, NT-proBNP, LVEF, eGFR, and Killip class III/IV. Continuous variables were rescaled for improved interpretability: FNDC4 per 10 ng/mL decrease, age per 10-year increase, NT-proBNP per 100 pg/mL increase, LVEF per 5% increase, and eGFR per 10 mL/min/1.73 m^2 increase. Results were expressed as hazard ratios (HRs) with 95% CIs. Since the Gensini score was not prospectively recorded, the number of diseased vessels was used as an angiographic indicator of coronary atherosclerotic burden. A sensitivity Cox regression model, additionally adjusting for multivessel disease, was performed. All tests were two-tailed, and a P-value < 0.05 indicated statistical significance.

Ethical statement

The study protocol was approved by the Ethics Committee of First Hospital of Zibo City (Approval No. YXLL20230706), adhering to the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Results

Baseline characteristics of the study population

Table 1 summarizes the baseline clinical and laboratory characteristics of the study population. During the 12-month follow-up, 51 of 274 patients experienced MACE, an incidence of 18.6%. MACE components included cardiovascular death (12 patients), nonfatal myocardial infarction (7 patients), ischemic stroke (3 patients), unplanned coronary revascularization (15 patients), and hospitalization for heart failure (14 patients).

Mean patient age, proportions of male patients, and mean BMI were comparable between the MACE and non-MACE groups. No significant differences were found in smoking

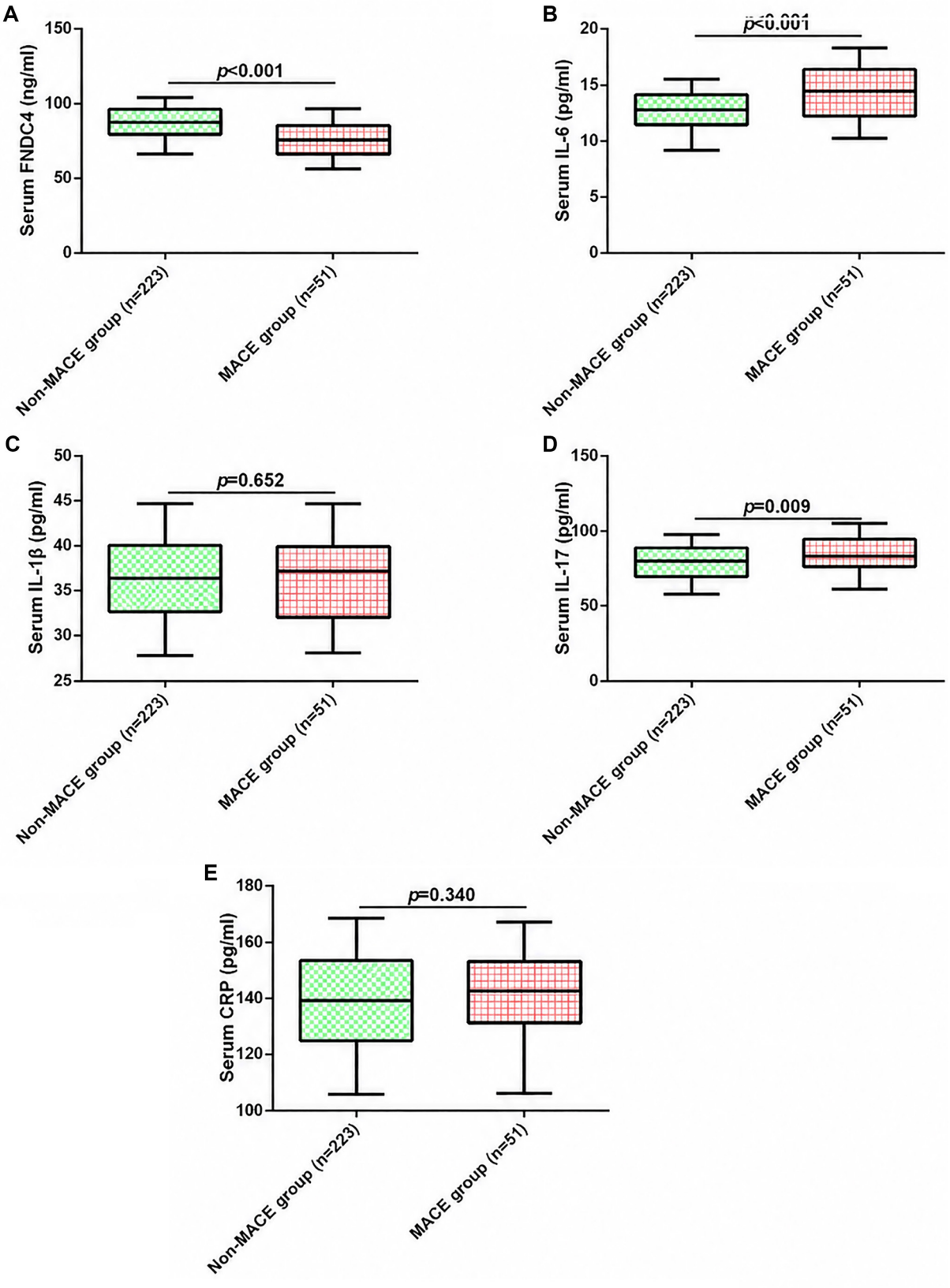


Figure 2. Admission serum FNDC4 and inflammatory biomarker levels according to 12-month MACE status. Box-and-whisker plots compare baseline serum concentrations between patients without MACE (non-MACE group, $n = 223$) and those who experienced MACE during the 12-month follow-up (MACE group, $n = 51$): (A) FNDC4, (B) IL-6, (C) IL-1β, (D) IL-17, and (E) CRP. Serum FNDC4 levels were significantly lower in the MACE group ($P < 0.001$), whereas serum IL-6 ($P < 0.001$) and IL-17 ($P = 0.009$) levels were significantly higher. No significant between-group differences were observed in serum IL-1β ($P = 0.652$) or CRP ($P = 0.340$) levels. *P* values are shown above the comparison brackets. **Abbreviations**: CRP, C-reactive protein; FNDC4, fibronectin type III domain-containing protein 4; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-17, interleukin-17; MACE, major adverse cardiovascular events.

Table 3. Correlations among serum FNDC4 levels and other biomarkers

	FNDC4	
	Spearman's correlation	*P*
IL-6	−0.174	0.004
IL-1β	−0.066	0.274
IL-17	−0.067	0.272
CRP	−0.045	0.457
hs-cTnI	−0.080	0.186
CK-MB	0.029	0.630
LDH	0.034	0.570
NT-proBNP	−0.119	0.048
TC	−0.088	0.147
TG	−0.060	0.320
HDL-C	−0.023	0.709
LDL-C	−0.026	0.670
LVEF	−0.027	0.660

Abbreviations: CK-MB, creatine kinase-MB; CRP, C-reactive protein; FNDC4, fibronectin type III domain-containing protein 4; HDL-C, high-density lipoprotein cholesterol; hs-cTnI, high-sensitivity cardiac troponin I; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-17, interleukin-17; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; TC, total cholesterol; TG, triglycerides.

status, history of hypertension, or diabetes mellitus status ($P > 0.05$). However, the prevalence of hyperlipidemia and Killip class III/IV was significantly higher in patients who developed MACE than in those who did not ($P < 0.05$). The distributions of coronary artery lesions did not significantly differ between the two groups. Furthermore, discharge prescriptions of guideline-directed medical therapy, including dual antiplatelet agents, β-blockers, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), and statins, were similar in both groups ($P > 0.05$).

Laboratory characteristics of patients with and without MACE

Venous blood samples, obtained immediately upon admission and before PCI, underwent biochemical analysis. As shown in Table 2, patients who developed MACE generally exhibited higher serum cardiac injury markers. Specifically, hs-cTnI and CK-MB levels were significantly elevated in the MACE group compared to the non-MACE group ($P < 0.05$), while LDH levels showed no significant difference. The cardiac function marker NT-proBNP was markedly increased in MACE patients ($P < 0.05$), indicating greater myocardial stress and ventricular dysfunction. Regarding lipid metabolism, LDL-C levels were significantly higher in the MACE group ($P < 0.05$); however, TC, TG, and HDL-C levels did not significantly differ between groups. Furthermore, transthoracic echocardiography performed within 24–48 hours post-PCI revealed significantly lower LVEF and eGFR in the MACE group compared to the non-MACE group ($P < 0.05$). Serum FNDC4 levels were also significantly lower in the MACE group than in the non-MACE group ($P < 0.05$).

Serum biomarker levels and correlations

As depicted in Figure 2, circulating FNDC4 levels demonstrated a clear and statistically significant downward trend in the MACE group compared to the non-MACE group ($P < 0.05$). Conversely, inflammatory cytokines IL-6 and IL-17 were significantly elevated in the MACE group ($P < 0.05$). No significant differences were observed in IL-1β or CRP levels between the two groups. Spearman's rank correlation analysis revealed that FNDC4 was negatively correlated with both IL-6 and NT-proBNP (Table 3).

To further investigate whether low FNDC4 levels were preferentially associated with specific components of 12-month MACE, baseline serum FNDC4 levels were compared among patients experiencing different MACE events. As shown in Table 4, baseline serum FNDC4 levels did not significantly differ among patients who died from cardiovascular disease, nonfatal myocardial infarction, ischemic stroke, unplanned coronary revascularization, or hospitalization for heart failure (all $P > 0.05$).

Predictive performance of serum FNDC4 for 12-month MACE

ROC curve analysis was performed to evaluate the predictive value of baseline serum FNDC4 levels for 12-month MACE post-PCI. As shown in Figure 3, ROC analysis indicated that lower baseline serum FNDC4 levels predicted 12-month MACE, with an AUC of 0.771 (95% CI 0.695–0.839). The optimal FNDC4 cutoff, determined by the Youden index, was 80.92 ng/mL. At this exploratory cutoff, FNDC4 ≤80.92 ng/mL indicated a higher MACE risk, demonstrating a sensitivity of 66.7%, specificity of 73.5%, positive predictive value of 36.6%, and negative predictive value of 90.6%. The 2 × 2 classification counts were 34 true positives, 17 false negatives, 59 false positives, and 164 true negatives.

For the main incremental prediction analysis, we compared a parsimonious clinical model with and without FNDC4 to assess whether FNDC4 provided additional predictive information beyond established clinical prognostic variables. The clinical model included age, NT-proBNP, LVEF, eGFR, and Killip class III/IV. The AUC increased from 0.874 (95% CI 0.819–0.932) for the clinical model to 0.905 (95% CI 0.848–0.961) after FNDC4 inclusion. The corresponding ΔAUC was 0.031 (95% CI 0.009–0.061), with an IDI of 0.097 (95% CI 0.035–0.197) and a continuous NRI of 0.741 (95% CI 0.247–1.188), suggesting that FNDC4 provided incremental predictive information in this dataset (Table 5).

In a secondary exploratory comparison, NT-proBNP had an AUC of 0.623 (95% CI 0.531–0.715, $P = 0.006$). The AUC of FNDC4 was significantly higher than that of NT-proBNP according to the DeLong test ($P = 0.014$). When both biomarkers were combined in a logistic regression model, predictive accuracy improved, yielding a combined AUC of 0.803 (95% CI 0.735–0.871, $P < 0.001$).

Table 4. Distribution of first MACE components and baseline serum FNDC4 levels among patients with 12-month MACE

	Cardiovascular death ($n = 12$)	Nonfatal myocardial infarction ($n = 7$)	Ischemic stroke ($n = 3$)	Unplanned coronary revascularization ($n = 15$)	Hospitalization for heart failure ($n = 14$)
FNDC4 (ng/mL)	70.95 ± 11.77	83.01 ± 7.64	69.36 ± 9.98	78.96 ± 8.87	75.69 ± 11.82

Abbreviations: FNDC4, fibronectin type III domain-containing protein 4; MACE, major adverse cardiovascular events.

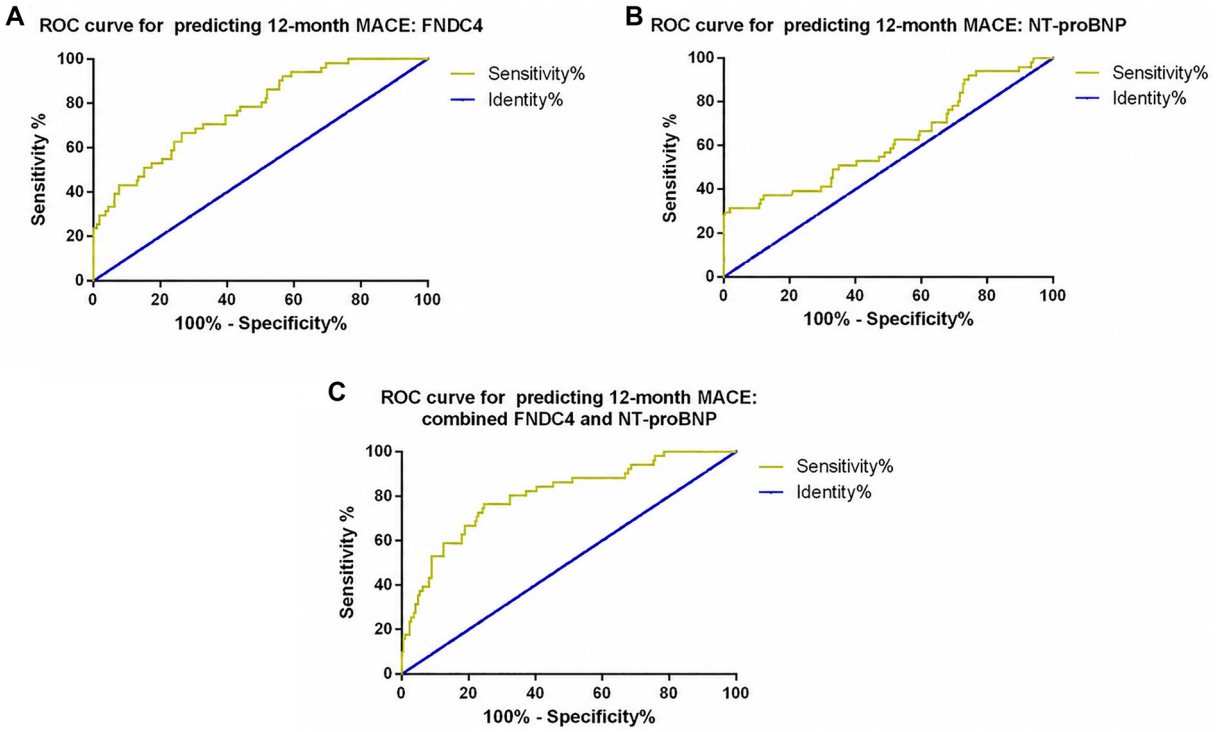


Figure 3. ROC curves for FNDC4, NT-proBNP, and their combination for predicting 12-month MACE in patients with STEMI undergoing PCI. ROC analysis assessed the discriminative performance of baseline serum biomarkers and their combined model for predicting 12-month MACE: (A) FNDC4, (B) NT-proBNP, and (C) the combined FNDC4 and NT-proBNP logistic regression model. FNDC4 yielded an AUC of 0.771 (95% CI, 0.695–0.839), NT-proBNP yielded an AUC of 0.623 (95% CI, 0.531–0.715), and the combined model yielded an AUC of 0.803 (95% CI, 0.735–0.871). The AUC of FNDC4 was significantly higher than that of NT-proBNP (DeLong $P = 0.014$). Yellow curves represent ROC performance, and blue diagonal lines represent the no-discrimination reference. **Abbreviations**: AUC, area under the curve; CI, confidence interval; FNDC4, fibronectin type III domain-containing protein 4; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PCI, percutaneous coronary intervention; ROC, receiver operating characteristic; STEMI, ST-segment elevation myocardial infarction.

Table 5. Incremental predictive value of FNDC4 for 12-month MACE beyond a clinical model

Model	AUC	95% CI	ΔAUC	IDI	Continuous NRI
Clinical model	0.874	0.819–0.932			
Clinical model + FNDC4	0.905	0.848–0.961	0.031	0.097	0.741

Abbreviations: AUC, area under the curve; CI, confidence interval; FNDC4, fibronectin type III domain-containing protein 4; IDI, integrated discrimination improvement; MACE, major adverse cardiovascular events; NRI, net reclassification improvement.

This secondary exploratory analysis evaluated the incremental predictive value of FNDC4 beyond NT-proBNP using IDI. Compared to the NT-proBNP-based model, the addition of FNDC4 significantly improved discrimination for 12-month MACE, with an IDI of 0.172 (95% CI 0.080–0.286, $P = 0.001$).

Kaplan–Meier analysis of 12-month MACE-free survival according to baseline serum FNDC4 level

To further evaluate the prognostic significance of baseline serum FNDC4, Kaplan–Meier survival analysis was performed based on the Youden-derived FNDC4 cutoff value. As shown in Figure 4, patients in the low FNDC4 group exhibited a

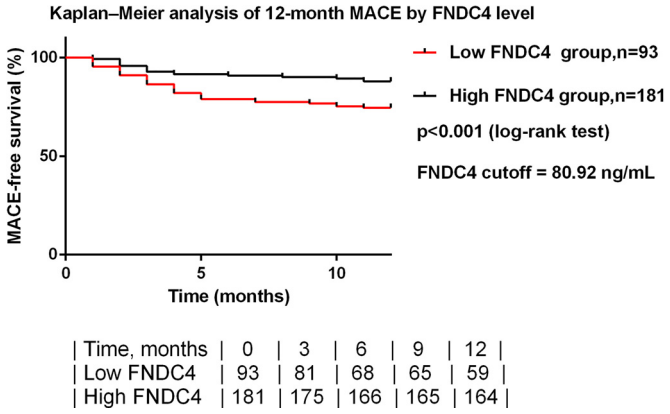


Figure 4. Kaplan–Meier analysis of 12-month MACE-free survival according to baseline serum FNDC4 level in patients with STEMI undergoing PCI. Patients were stratified using the exploratory Youden-derived FNDC4 cutoff of 80.92 ng/mL into the low FNDC4 group (≤80.92 ng/mL; $n = 93$) and the high FNDC4 group (>80.92 ng/mL; $n = 181$). The low FNDC4 group had significantly lower 12-month MACE-free survival than the high FNDC4 group (log-rank $P < 0.001$). During follow-up, MACE occurred in 34 of 93 patients in the low FNDC4 group and in 17 of 181 patients in the high FNDC4 group. Tick marks indicate censored observations, and the numbers at risk at 0, 3, 6, 9, and 12 months are shown below the curves. **Abbreviations**: FNDC4, fibronectin type III domain-containing protein 4; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Table 6. Cox regression analysis of risk factors for 12-month MACE

Variables	HR	95% CI	*P*
FNDC4, per 10 ng/mL decrease	1.821	1.360–2.438	<0.001
Age, per 10-year increase	1.091	0.783–1.520	0.606
NT-proBNP, per 100 pg/mL increase	1.035	0.979–1.094	0.228
LVEF, per 5% increase	0.650	0.494–0.857	0.002
eGFR, per 10 mL/min/1.73 m^2 increase	0.551	0.416–0.730	<0.001
Killip class III/IV	2.559	1.156–5.665	0.021

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FNDC4, fibronectin type III domain-containing protein 4; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

significantly lower 12-month MACE-free survival rate than those in the high FNDC4 group (log-rank $P < 0.001$). MACE occurred in 34 of 93 patients in the low FNDC4 group and in 17 of 181 patients in the high FNDC4 group.

Independent predictors of 12-month MACE

Given the availability of exact follow-up time to the first MACE event, multivariable Cox proportional hazards regression was performed using a parsimonious model. After adjusting for age, NT-proBNP, LVEF, eGFR, and Killip class III/IV, lower baseline FNDC4 remained independently associated with a higher risk of 12-month MACE. Each 10 ng/mL decrease in FNDC4 was associated with an increased MACE risk (HR = 1.821, 95% CI 1.360–2.438, $P < 0.001$). LVEF, eGFR, and Killip class III/IV were also independently associated with 12-month MACE (Table 6).

In a sensitivity Cox regression model, additionally adjusting for multivessel disease, lower FNDC4 remained independently associated with 12-month MACE risk. Each 10 ng/mL decrease in FNDC4 was associated with increased MACE risk (HR = 1.812, 95% CI 1.356–2.423, $P < 0.001$), while multivessel disease was not significantly associated with MACE in this model (HR = 0.704, 95% CI 0.398–1.244, $P = 0.227$).

Discussion

Despite timely PCI, STEMI patients face a substantial residual risk for MACE, highlighting the need for improved post-infarction risk stratification [15]. In our prospective cohort, baseline circulating FNDC4 levels were significantly lower in patients who developed 12-month MACE compared to event-free patients. FNDC4 levels also demonstrated an inverse correlation with IL-6 and NT-proBNP. ROC analysis indicated moderate discriminatory ability for 12-month MACE, and in Cox regression, lower FNDC4 remained an independent predictor after adjusting for NT-proBNP, LVEF, and eGFR. Collectively, these results suggest that lower circulating FNDC4 levels are associated with 12-month MACE and specific markers of inflammation and myocardial stress following STEMI-PCI.

Our observation that lower circulating FNDC4 correlates with a higher 12-month MACE risk after STEMI-PCI aligns with human data showing reduced plasma FNDC4 in

systemic inflammatory states like morbid obesity, where it is linked to adverse metabolic profiles [16, 17]. This supports the view that diminished FNDC4 reflects an unfavorable inflammatory–metabolic milieu. Furthermore, experimental and translational research has identified FNDC4 as an anti-inflammatory, tissue-protective factor, consistent with our finding that lower FNDC4 levels coexist with higher IL-6 levels and increased myocardial stress, as indicated by elevated NT-proBNP [9]. Beyond epidemiological associations, a previous experimental study reported that FNDC4 attenuates inflammatory injury and enhances cell survival through adenosine monophosphate-activated protein kinase (AMPK)-related metabolic signaling, suggesting a potential biological link between FNDC4 and inflammatory regulation [17]. Additional evidence from immunology and bone-marrow models indicates that FNDC4 inhibits proinflammatory activation/polarization, further supporting its role as a counter-inflammatory signal *in vivo* [18]. While these observations from human cohorts and experimental systems provide mechanistic background for the present findings, they do not establish FNDC4 as a direct marker of residual inflammatory risk after STEMI-PCI.

Lower FNDC4 levels in patients with MACE following STEMI may reflect a broader inflammatory and metabolic disturbance rather than a single pathway-specific change. Acute myocardial infarction (AMI) triggers an early inflammatory response, initiated by plaque rupture, coronary occlusion, and subsequent reperfusion, leading to the activation of neutrophils, monocytes, and pro-inflammatory mediators like IL-6 [19]. Clinical data in STEMI patients reveal that elevated IL-6 levels correlate with larger infarct size, reduced LVEF, and adverse clinical outcomes [20]. In our study, MACE patients also exhibited higher IL-6 and IL-17 levels, with FNDC4 showing a negative correlation with IL-6. These findings suggest that diminished FNDC4 may link to heightened IL-6-related inflammatory activity. However, this correlation was weak, and causality cannot be inferred from observational data.

Oxidative stress during primary PCI may also play a role, as AMI patients undergoing reperfusion demonstrate early oxidative stress and inflammatory responses post-PCI [21]. Furthermore, metabolomic profiling in STEMI has revealed significant metabolic shifts associated with ischemia-reperfusion injury and infarct size [22]. Consistent with this metabolic context, our MACE group displayed higher LDL-C levels and a greater prevalence of hyperlipidemia. Therefore, decreased circulating FNDC4 might indicate a systemic response involving inflammation, oxidative stress, and lipid-metabolic dysregulation after STEMI. This hypothesis requires validation through serial FNDC4 measurements and mechanistic experiments.

Previous phenotype-based research in PCI patients underscores the clinical relevance of inflammatory status for long-term prognosis. Galimzhanov et al. identified three distinct phenotypic clusters among PCI patients: an inflammatory cluster (characterized by elevated white blood cell counts, CRP, and neutrophil-to-lymphocyte ratio), a high-erythrocyte sedimentation rate (ESR) cluster, and a non-inflammatory cluster. These inflammatory phenotypes were linked to recurrent cardiovascular events [23]. Our findings extend this concept from conventional inflammatory markers to FNDC4, a circulating protein with reported anti-inflammatory properties. In our STEMI-PCI cohort, lower admission FNDC4 levels correlated with an increased 12-month MACE risk and were negatively associated with IL-6. This suggests FNDC4 may offer complementary information regarding inflammatory vulnerability, rather than simply duplicating traditional inflammatory markers. However, as FNDC4 was measured only once pre-PCI, we cannot ascertain whether low FNDC4 signifies a chronic pre-existing inflammatory phenotype, an acute response during early STEMI, or both. Consequently, FNDC4 should currently be interpreted as an admission biomarker associated with adverse prognosis, with serial measurements needed to clarify its role as a chronic or acute inflammatory-prognostic marker.

Our finding that lower serum FNDC4 levels correlate with higher IL-6, elevated NT-proBNP, and poorer clinical outcomes post-STEMI is supported by previous mechanistic studies. Experimental research demonstrates FNDC4's role as an intrinsic cardioprotective molecule, promoting myocardial survival and recovery under stress. In murine I/R models, cardiac and circulating FNDC4 levels rise in a HIF-1α–dependent manner. Cardiac-specific FNDC4 overexpression facilitated cardiomyocyte survival and promoted angiogenesis via paracrine release of fibroblast growth factor 1 (FGF1), while FNDC4 knockdown worsened myocardial injury. Administration of recombinant FNDC4 protein alleviated I/R damage and improved cardiac function, highlighting its therapeutic potential in acute ischemic injury [11]. In aging models, a progressive decrease in FNDC4 expression coincided with cardiac dysfunction. Restoring FNDC4 expression activated the adenosine monophosphate-activated protein kinase catalytic alpha subunit (AMPKα)–peroxisome proliferator-activated receptor alpha (PPARα) pathway, enhanced mitochondrial biogenesis, and reduced lipotoxicity, thereby preserving myocardial metabolic homeostasis [24]. Similarly, studies in myocardial infarction and I/R models showed that FNDC4 deficiency exacerbated cardiomyocyte apoptosis and increased infarct size, whereas FNDC4 overexpression promoted antioxidative and antiapoptotic effects via the extracellular signal-regulated kinases 1 and 2 (ERK1/2)–nuclear factor erythroid 2-related factor 2 (Nrf2) signaling cascade [25]. These mechanistic observations align with our clinical findings, where lower circulating FNDC4 levels accompanied elevated IL-6 and increased myocardial stress markers. However, whether reduced FNDC4 directly reflects impaired cardioprotective signaling requires further mechanistic validation. Collectively, the evidence suggests FNDC4's involvement in metabolic and inflammatory regulation related to cardiac structure and function. FNDC4 may be associated with adaptive processes, including mitochondrial activity, angiogenesis, and oxidative stress responses, contributing to cardiovascular resilience. In our cohort, lower serum FNDC4 alongside increased inflammatory and myocardial stress markers supports its potential clinical relevance as a circulating marker associated with adverse inflammatory and myocardial stress profiles. Consistent with reviews emphasizing FNDC4's role in metabolic

and inflammatory adaptation, these observations further support its potential as a circulating biomarker of residual cardiac risk [26].

Beyond FNDC4-related inflammatory signaling, routinely available inflammatory and nutritional biomarkers also contribute to cardiovascular risk assessment. Serum albumin, a nutritional marker, also reflects systemic inflammation, oxidative stress, and physiological reserve. A meta-analysis in acute coronary syndrome patients demonstrated that low serum albumin correlated with increased all-cause mortality, supporting its prognostic relevance in coronary artery disease [27]. Similarly, the prognostic nutritional index, combining serum albumin and lymphocyte count, has been reported to predict mortality and major adverse cardiovascular events in coronary artery disease patients [28]. More recently, combined assessment of inflammation and malnutrition in acute coronary syndrome patients undergoing PCI improved long-term risk prediction beyond conventional clinical risk assessment [29]. These findings suggest that future post-STEMI risk-stratification models could benefit from integrating circulating biomarkers like FNDC4 with simple inflammatory-nutritional indices.

From a clinical perspective, our findings suggest that circulating FNDC4 may serve as a candidate biomarker for predicting 12-month MACE risk in STEMI patients treated with PCI. FNDC4, a secreted circulating protein measurable by conventional ELISA, showed an inverse correlation with adverse outcomes in this cohort; lower FNDC4 levels were associated with a higher risk. However, as this was a single-center observational study, these results should be interpreted as exploratory. FNDC4 should not yet be considered a standalone marker for treatment decisions or a basis for FNDC4-guided management. Larger multicenter studies with external validation and serial FNDC4 measurements are essential to determine its utility in improving post-STEMI risk stratification.

Beyond circulating biomarkers, emerging evidence indicates that noninvasive structural and anthropometric phenotyping can complement cardiovascular risk assessment. For instance, in a community-based cohort, mitral valve prolapse (MVP) was linked to generally low rates of adverse clinical sequelae. Affected individuals typically exhibited a leaner body habitus and mostly trace or mild mitral regurgitation, suggesting that specific structural phenotypes may carry distinct prognostic implications [30]. Modified thoracic morphometric assessments, such as the modified Haller index, have also been applied in patients with suspected coronary artery disease, potentially offering additional insights into stress echocardiographic findings and clinical outcomes [31]. These observations suggest that future cardiovascular risk-stratification strategies could benefit from integrating circulating biomarkers, imaging findings, and anthropometric or thoracic morphometric parameters.

A crucial question is whether low circulating FNDC4 signifies a pre-existing chronic phenotype before STEMI or an acute biomarker response during the early phase of STEMI. Since FNDC4 was measured only once at admission before PCI, this study cannot differentiate between these possibilities. Lower FNDC4 levels might reflect a chronic inflammatory-metabolic background predisposing patients to worse outcomes, an early acute response to myocardial ischemia and reperfusion injury, or a combination of both. Therefore, in this study, FNDC4 should be interpreted as an admission biomarker associated with poor prognosis rather than a definitively chronic or acute marker. Future studies incorporating pre-event samples, serial measurements during hospitalization, and post-discharge follow-up are needed to clarify FNDC4's temporal profile.

Several study limitations warrant acknowledgment. First, this was a single-center prospective study conducted in a Chinese population with a relatively modest sample size, which may limit the generalizability of our findings to other ethnic groups, regions, and healthcare settings. Second, FNDC4 levels were measured only once at admission before PCI, precluding assessment of dynamic changes during hospitalization or follow-up. Consequently, we could not determine if low FNDC4 represented a pre-existing chronic phenotype, an acute STEMI-related biomarker change, or both. Serial FNDC4 measurements could offer additional information regarding its temporal relationship with post-infarction inflammation, myocardial remodeling, and MACE. Third, despite multivariate analysis adjusting for several clinical and biochemical variables, residual confounding by unmeasured or incompletely assessed factors cannot be excluded. The Gensini score was not prospectively recorded, and coronary atherosclerotic burden was assessed using the number of diseased vessels; thus, more detailed angiographic scoring should be considered in future studies. Notably, hepatic function, which can influence circulating biomarker levels and cardiovascular prognosis, was not fully incorporated into the adjusted model. Fourth, mechanistic pathways linking FNDC4 to inflammation, metabolic stress, and myocardial injury were inferred from correlation analyses and previous experimental studies rather than directly verified in this cohort. Future studies with larger multicenter populations, serial biomarker measurements, and more comprehensive adjustment for renal and hepatic function are needed to validate these findings and determine FNDC4's clinical utility in post-STEMI risk stratification. Additionally, established risk scores like Global Registry of Acute Coronary Events (GRACE) and Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) were not prospectively recorded in this study. While several conventional prognostic variables, including age, renal function, Killip class, NT-proBNP, LVEF, and angiographic TIMI flow, were incorporated where available, we could not reliably evaluate FNDC4's incremental value across GRACE or SYNTAX risk strata. Future studies should validate whether FNDC4 provides additional prognostic information beyond established risk scores and across different clinical risk categories.

Conclusion

This prospective study demonstrated that circulating FNDC4 levels were significantly lower in STEMI patients who experienced MACE within 12 months after PCI. Furthermore, lower circulating FNDC4 levels were associated with a higher

12-month MACE risk in STEMI patients. These findings suggest that FNDC4 may serve as a candidate complementary biomarker for post-STEMI risk after revascularization. Further multicenter studies with serial FNDC4 measurements and external validation are necessary before its clinical utility can be established.

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