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CIRCULATING EDIL3 AS A NOVEL BIOCHEMICAL INDICATOR OF CORONARY MICROVASCULAR DYSFUNCTION IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

CIRKULIŠUĆI EDIL3 KAO NOVI BIOHEMIJSKI INDIKATOR KORONARNE MIKROVASKULARNE DISFUNKCIJE KOD PACIJENATA SA INFARKTOM MIOKARDA SA ELEVACIJOM ST-SEGMENTA

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Summary

Background: Developmental endothelial locus-1 (EDIL3) is an extracellular matrix-associated glycoprotein involved in endothelial activation, inflammatory regulation, and vascular remodeling. However, the clinical significance of circulating EDIL3 in ST-segment elevation myocardial infarction (STEMI), particularly in relation to coronary microvascular dysfunction, remains unclear. This study aimed to investigate the dynamic changes of serum EDIL3 and evaluate its biochemical and diagnostic value for angiography-derived microvascular resistance (AMR) in STEMI patients.

Methods: In this prospective observational study, 90 consecutive STEMI patients undergoing emergency percutaneous coronary intervention (PCI) and 40 control subjects wit Correlation analysis, receiver operating characteristic (ROC) analysis, and multivariate logistic regression were performed to evaluate the association between circulating EDIL3 and AMR.

Results: Serum EDIL3 levels showed significant temporal alterations after STEMI onset, with peak concentrations observed approximately 30 hours after chest pain onset. STEMI patients exhibited markedly elevated circulating EDIL3 levels compared with controls. Serum EDIL3 was positively correlated with cTnI and AMR values. ROC analysis demonstrated that EDIL3 effectively discriminated

Kratak sadržaj

Uvod: Razvojni endotelni lokus-1 (EDIL3) je glikoprotein povezan sa ekstracelularnim matriksom koji je uključen u aktivaciju endotela, regulaciju zapaljenja i vaskularno remodeliranje. Međutim, klinički značaj cirkulišućeg EDIL3 kod infarkta miokarda sa elevacijom ST-segmenta (STEMI), posebno u vezi sa koronarnom mikrovaskularnom disfunkcijom, ostaje nejasan. Cilj ove studije je bio da se ispitaju dinamičke promene serumskog EDIL3 i proceni njegova biohemijska i dijagnostička vrednost za mikrovaskularnu otpornost (AMR) izvedenu angiografijom kod pacijenata sa STEMI.

Metode: U ovoj prospektivnoj, jednocentričnoj kohortnoj studiji uključeno je 218 pacijenata sa HBB stadijuma 3–4. Na početku studije određene su serumske koncentracije IL-6, IL-1β, TNF-α, TGF-β, Gal-3 i FGF-23. Pacijenti su praćeni 36 meseci u odnosu na primarni kompozitni ishod: smanjenje procenjene brzine glomerulske filtracije (eGFR) ≥40%, progresiju ka bubrežnoj insuficijenciji koja zahteva zamensku terapiju (KFRT) ili veliki neželjeni kardiovaskularni događaj (MACE). Korišćeni su Cox-ovi proporcionalni hazard modeli, Kaplan-Meier analiza i ROC krive.

Rezultati: Nivoi EDIL3 u serumu pokazali su značajne vremenske promene nakon početka STEMI, sa vršnim kon-

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STEMI patients from controls, yielding an area under the curve (AUC) of 0.96, with 90.0% sensitivity and 97.5% specificity at a cutoff value of 2.65 ng/mL. Multivariate logistic regression analysis further identified EDIL3 as an independent biochemical predictor of elevated AMR (OR = 2.54, 95% CI: 1.46–4.90, P = 0.002).
Conclusion: Circulating EDIL3 is significantly associated with coronary microvascular resistance and may serve as a novel biochemical indicator of microcirculatory dysfunction in STEMI patients. Measurement of serum EDIL3 may provide additional value for laboratory-based risk stratification and individualized cardiovascular assessment following myocardial infarction.

Keywords: EDIL3, circulating biomarker, ST-segment elevation myocardial infarction, coronary microvascular dysfunction, angiography-derived microvascular resistance, laboratory medicine

centracijama primećenim približno 30 sati nakon pojave bola u grudima. Pacijenti sa STEMI pokazali su značajno povišene nivoe EDIL3 u cirkulaciji u poređenju sa kontrolnom grupom. EDIL3 u serumu je bio pozitivno koreliran sa vrednostima cTnI i AMR. ROC analiza je pokazala da EDIL3 efikasno razlikuje pacijente sa STEMI od kontrolne grupe, dajući površinu ispod krive (AUC) od 0,96, sa osetljivošću od 90,0% i specifičnošću od 97,5% pri graničnoj vrednosti od 2,65 ng/mL. Multivarijantna logistička regresiona analiza dodatno je identifikovala EDIL3 kao nezavisni biohemijski prediktor povišenog AMR (OR = 2,54, 95% CI: 1,46–4,90, P = 0,002).
Zaključak: Cirkulišući EDIL3 je značajno povezan sa koronarnim mikrovaskularnim otporom i može poslužiti kao novi biohemijski indikator mikrocirkulatorne disfunkcije kod pacijenata sa STEMI. Merenje serumskog EDIL3 može pružiti dodatnu vrednost za laboratorijsku stratifikaciju rizika i individualizovanu kardiovaskularnu procenu nakon infarkta miokarda.

Ključne reči: EDIL3, cirkulišući biomarker, infarkt miokarda sa elevacijom ST-segmenta, koronarna mikrovaskularna disfunkcija, mikrovaskularna rezistencija dobijena angiografijom, laboratorijska medicina

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is one of the most critical clinical types of cardiovascular diseases. Its pathological basis is coronary atherosclerotic plaque rupture leading to thrombosis and complete vessel occlusion, resulting in ischemic necrosis of cardiomyocytes. Despite continuous improvements in reperfusion therapy strategies in recent years, with timely restoration of coronary blood flow, patients with STEMI still face high mortality and adverse prognosis risks (1, 2). Although traditional myocardial injury markers such as cardiac troponin I (1, 3) have high specificity for STEMI diagnosis, they have limitations in assessing microcirculatory function after myocardial infarction. Therefore, identifying novel serum biomarkers that can reflect microcirculatory dysfunction after STEMI has important clinical value.

EDIL3 is a secreted glycoprotein belonging to the extracellular matrix protein family with multiple biological functions. Although EDIL3 has been partially studied in atherosclerosis, aortic diseases, and other fields (4, 5), its role in acute myocardial ischemic injury remains unclear. Previous studies have shown that EDIL3 may affect myocardial ischemia-reperfusion injury by regulating inflammatory responses (6), while participating in ischemic repair by promoting angiogenesis (7). However, the expression of peripheral blood EDIL3 in STEMI patients and its relationship with coronary microvascular resistance remain unclear.

This study aimed to systematically analyze the dynamic changes of serum EDIL3 levels in STEMI patients, explore its correlation with clinical characteristics, traditional myocardial injury markers, and coronary microvascular resistance, and evaluate the diagnostic value of EDIL3 for acute myocardial infarction. These findings are expected to provide a new theoretical basis for individualized treatment of STEMI patients.

Materials and Methods

Study Protocol

This prospective observational study consecutively enrolled 90 patients diagnosed with STEMI who underwent emergency PCI in the Department of Cardiology at Taizhou People's Hospital from January 2024 to December 2024 as the AMI group. Meanwhile, 40 patients who underwent coronary angiography during the same period and were excluded from coronary heart disease were consecutively selected as the control group. This study strictly followed the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of our hospital (KY2024-002-01). All enrolled patients signed informed consent forms.

Inclusion Criteria for AMI Group

Inclusion criteria: Age 18–80 years; meeting the diagnostic criteria for acute ST-segment eleva-

tion myocardial infarction (1, 3); onset time ≤ 12 hours; first occurrence of myocardial infarction; undergoing emergency coronary angiography and stent implantation.

Exclusion criteria: Patients with any of the following conditions were excluded: previous history of myocardial infarction or coronary artery bypass grafting; patients with severe renal insufficiency (eGFR < 30 mL/min/1.73 m^2) or uremia; patients with severe hepatic insufficiency (ALT/AST > 3 times the upper limit of normal); patients with congenital heart disease, dilated cardiomyopathy, severe valvular heart disease, or hypertrophic cardiomyopathy; patients with malignant tumors, hyperthyroidism, autoimmune diseases, or hematological diseases; recent history of acute infection or chronic inflammatory diseases (such as Crohn's disease); recent history of major surgery or trauma; active bleeding or severe bleeding tendency; pregnant or lactating women; acute stroke; severe vessel tortuosity, vessel overlap, or poor angiographic image quality that may prevent accurate AMR calculation.

Inclusion Criteria for Control Group

Inclusion criteria: No history of myocardial infarction; no significant stenosis on coronary angiography; no significant abnormalities on echocardiography.

Exclusion criteria: Same as the exclusion criteria for the AMI group.

Sample Size Calculation

This study adopted a significance level of 0.05 and 80% power, with a two-sided test level (α) of 0.05. Using the sample size calculation formula for comparing two means, and based on preliminary experimental results where the difference between sample means was 2.9 and the standard deviation was 2.69, Cohen's d was calculated as 1.08. The sample size was calculated using the pwr package in R language, resulting in 15 cases per group. To further explore the correlation between EDIL3 and AMR in STEMI patients, based on preliminary experimental results, the expected correlation coefficient was 0.30 (moderate effect size), and the minimum required sample size was calculated as 85 cases. Considering a 20% dropout rate, it was estimated that 102 cases would need to be enrolled. The final enrolled sample size was 130 cases, including 90 STEMI patients and 40 normal controls.

Data Collection

General Data

Research data were independently collected by standardized trained technicians through the hospital electronic medical record system using a blinded design. Data collected included medical history, blood biochemistry test results, echocardiographic parameters, and coronary artery lesion characteristics.

(1) Medical history: including gender, age, smoking history, hypertension, diabetes, hyperlipidemia, etc.

(2) Blood sample collection for biochemistry: For the AMI group, on the morning following emergency PCI, after overnight fasting; for the control group, samples were collected after overnight fasting. Blood samples were drawn from the antecubital vein.

(3) Blood biochemistry tests: including cardiac troponin I (cTnI), Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C), Creatinine (Cre), etc.

(4) Blood sample collection for EDIL3 detection: Blood samples were drawn from the antecubital vein at the following time points: before emergency PCI, and on the morning of day 1, day 2, day 3, and day 7 after emergency PCI after overnight fasting. Corresponding cTnI levels were measured at the same time points.

(5) Echocardiographic parameters: Left ventricular Ejection Fraction (LVEF), Left Ventricular Fraction Shortening (LVFS).

(6) Coronary angiography data collection: Coronary angiography assessment included culprit vessel, number of diseased vessels, pre- and post-procedural TIMI flow, etc. Coronary angiography results were independently evaluated by two experienced cardiovascular interventional specialists. In case of disagreement, a third specialist made the final judgment.

Serum EDIL3 Measurement (ELISA Method)

EDIL3 enzyme-linked immunosorbent assay kits were purchased from Jianglai Biotechnology Company, and operations were performed according to the manufacturer's instructions.

ELISA Data Processing

ELISACalc software was used to draw the ELISA standard curve. Logistic curve fitting 2 (four-parameter) was selected to construct the

curve formula. Using the fitted curve formula, the corresponding concentration values were calculated by back-calculation based on the optical density (OD) values of the test samples.

Angio-based Microvascular Resistance (AMR)

Angiographic images were transferred to the AngioPlus system (Pulse Medical Technology, Shanghai, China) through the Picture Archiving and Communication System, which performs AMR and quantitative flow ratio (QFR) calculations using artificial intelligence (8, 9). The optimal angiographic view was selected to minimize vessel overlap, and the coronary lumen contour was automatically measured. Contrast flow velocity (CFV) was calculated by dividing the vessel centerline length by the contrast agent filling time, then converted to hyperemic velocity (Velocityhyp) (10). Quantitative flow ratio (QFR) was calculated by dividing the distal coronary pressure (Pd) by the mean aortic pressure, and AMR was calculated by dividing Pd by Velocityhyp, while Pd can be calculated by multiplying the aortic pressure (Pa) by μQFR (Murray law-based Quantitative Flow Ratio) (11, 12).

$$AMR = Pd/Velocityhyp = (Pa \times \mu QFR) / Velocityhyp$$

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 8 software and R 4.3.1 software. Categorical data were expressed as rates or proportions and compared between groups using χ^2 test or Fisher's exact test. Normally distributed data were expressed as mean ± standard deviation, and independent sample t-test was used for comparison between two groups. EDIL3 was tested and found not to conform to normal distribution. Non-parametric tests were used to analyze the time-dependent changes of EDIL3, described as median (Q1, Q3). Kruskal-Wallis test was used for intergroup comparison, followed by Dunn's test for pairwise comparison with Bonferroni correction. Spearman correlation analysis was used to evaluate the correlation between serum EDIL3 and cTnI as well as AMR, with data expressed as correlation coefficient (r) and 95% confidence interval (CI). Receiver operating characteristic (ROC) curve was used to evaluate the ability of serum EDIL3 to distinguish STEMI patients from controls, and the area under the curve (AUC), sensitivity, specificity, and 95% confidence interval were calculated. To screen predictors of high AMR, univariate Logistic regression analysis was performed on D-Dimer, cTnI, EDIL3, BNP, and CRP; variables with $p < 0.05$ in univariate analysis were included in the multivariate Logistic regression model to determine independent predictors of high AMR. Statistical significance was set at two-sided $p < 0.05$.

Results

Baseline Characteristics of Study Subjects (Table I)

This study was divided into AMI group and Control group, including a total of 90 STEMI patients (AMI group) and 40 subjects with normal coronary arteries (control group).

In the AMI group, there were 57 males (63.3%) and 33 females (36.7%), with a median age of 56.0 years. Comorbidities included hypertension in 43 cases (47.8%), diabetes in 19 cases (21.1%), hyperlipidemia in 17 cases (18.9%), and smoking history in 51 cases (56.7%). There were no statistically significant differences in gender, age, history of hypertension, diabetes, hyperlipidemia, and smoking history between the control group and the AMI group ($p > 0.05$).

Levels ofTC, LDL-C, HbA1c, D-Dimer, ALT, AST, CK-MB, CK, CRP, cTnI, and BNP were significantly higher in the AMI group than in the control group, with statistically significant differences ($p < 0.05$).Meanwhile, AMR values were significantly higher in the AMI group compared with the control group (2.67 (2.37-2.95) vs. 2.00 (1.86-2.13) mmHg·s/cm, $p < 0.001$).

Compared with the control group, the AMI group had significantly increased left ventricular end-diastolic diameter (50.0 (47.0–53.0) vs. 47.0 (45.0–48.7) mm) and left ventricular end-systolic diameter (33.0 (30.0–36.8) vs. 29.0 (27.0–30.0) mm) (both $p < 0.001$), while left ventricular ejection fraction (59.5 (52.0–65.8) vs. 70.0 (66.0–72.5) %) and left ventricular fractional shortening (34.0 (28.2–38.8) vs. 39.0 (36.0–42.0) %) were significantly decreased (both $p < 0.001$). No significant differences were observed in other clinical and biochemical indicators between the two groups.

Coronary Angiographic Characteristics of AMI Patients

Culprit vessel distribution: left anterior descending artery in 47 cases (52.2%), left circumflex artery in 8 cases (8.89%), right coronary artery in 35 cases (38.9%). Among them, single-vessel disease in 46 cases (51.1%), two-vessel disease in 26 cases (28.9%), three-vessel disease in 18 cases (20%).

Before emergency PCI, there were 75 patients (83.3%) with TIMI flow grade 0, 5 patients (5.56%) with grade 1, 4 patients (4.44%) with grade 2, and

Table I Comparison of clinical data between the two groups (AMI group vs. Control group).

	AMI group (n=90)	Control group (n=40)	p value
Age (year)	56.0 [47.0; 68.0]	60.5 [54.8; 69.2]	0.080
Male	57 (63.3%)	22 (55.0%)	0.482
Hypertension history	43 (47.8%)	18 (45.0%)	0.918
Diabetes history	19 (21.1%)	4 (10.0%)	0.199
Smoking history	51 (56.7%)	18(45.0%)	0.289
Hyperlipemia history	17 (18.9%)	12 (30.0%)	0.239
BMI (kg/m^2)	25.5 ± 4.06	25.0 ± 3.53	0.533
HR (bpm)	78.0 [67.2; 91.0]	72.5 [69.8; 85.2]	0.230
SBP (mmHg)	118 [100; 132]	130 [122; 137]	0.001
DBP (mmHg)	75.6 ± 15.9	79.3 ± 11.2	0.135
CRE (μmol/L)	70.0 [59.1; 83.1]	67.0 [57.0; 78.1]	0.197
UA (μmol/L)	352 [302; 412]	326 [288; 372]	0.066
TC (mmol/L)	4.60 ± 0.88	4.03 ± 0.78	<0.001
TG (mmol/L)	1.71 [1.08; 2.27]	1.56 [1.13; 2.50]	0.830
HDL-C (mmol/L)	1.04 [0.85; 1.19]	1.04 [0.89; 1.16]	0.696
LDL-C (mmol/L)	3.02 ± 0.68	2.50 ± 0.74	<0.001
HbA1c (%)	6.20 [5.80; 7.30]	5.90 [5.60; 6.22]	0.004
CRP (mg/L)	2.24 [0.96; 6.26]	1.32 [0.50; 2.43]	0.002
HB (g/L)	147 [132; 156]	140 [130; 148]	0.067
D-Dimer (mg/L)	0.72 [0.57; 1.00]	0.53 [0.44; 0.63]	<0.001
ALB (g/L)	38.6 [36.3; 42.5]	40.1 [38.8; 42.7]	0.171
ALT (U/L)	44.0 [26.5; 59.5]	23.0 [14.8; 32.1]	<0.001
AST (U/L)	165 [48.2; 228]	22.2 [19.0; 27.0]	<0.001
CK-MB (U/L)	111 [31.5; 174]	12.0 [10.4; 14.0]	<0.001
CK (U/L)	1192 [274; 2260]	84.5 [57.3; 134]	<0.001
cTnI (ng/mL)	24.3 [12.0; 46.8]	0.00 [0.00; 0.00]	<0.001
BNP (pg/mL)	192 [38.6; 710]	5.00 [5.00; 10.1]	<0.001
AMR (mmHg*s/cm)	2.67 [2.37; 2.95]	2.00 [1.86; 2.13]	<0.001
LVEDD (mm)	50.0 [47.0; 53.0]	47.0 [45.0; 48.7]	<0.001
LVESD (mm)	33.0 [30.0; 36.8]	29.0 [27.0; 30.0]	<0.001
LVEF (%)	59.5 [52.0; 65.8]	70.0 [66.0; 72.6]	<0.001
LVFS (%)	34.0 [28.2; 38.8]	39.0 [36.0; 42.0]	<0.001

Note: BMI, Body Mass Index; HR, Heart Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; CRE, Creatinine; UA, Uric Acid; TC, Total Cholesterol; TG, Triglycerides; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; HbA1c, Glycated Hemoglobin; CRP, C-Reactive Protein; HB, Hemoglobin; ALB, Albumin; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; CK-MB, Creatine Kinase-MB; CK, Creatine Kinase; cTnI, Cardiac Troponin I; BNP, B-type Natriuretic Peptide; AMR, Angio-based Microvascular Resistance; LVEDD, Left Ventricular End-Diastolic Diameter; LVESD, Left Ventricular End-Systolic Diameter; LVEF, Left Ventricular Ejection Fraction; LVFS, Left Ventricular Fractional Shortening.

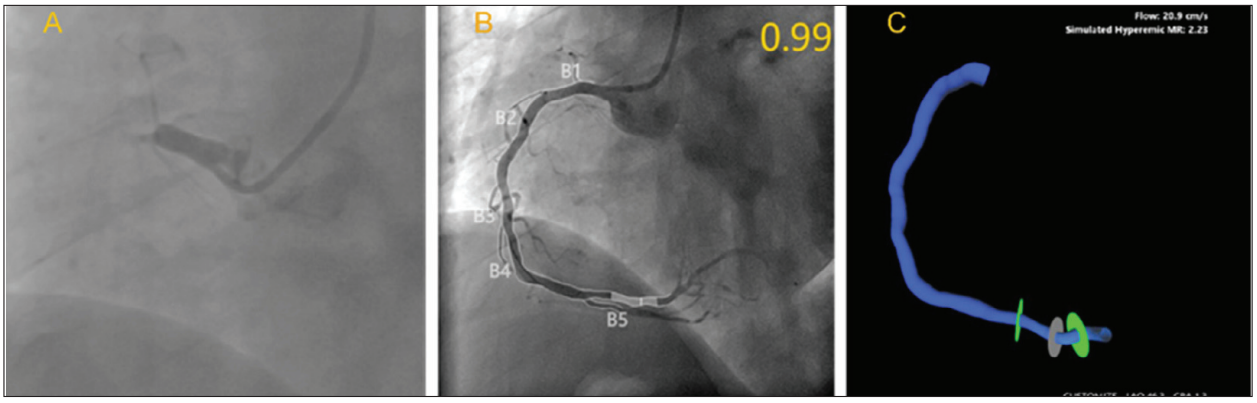

Figure 1 Representative image of AMR. (A) Angiogram before right coronary artery recanalization, (B) Automatic measurement of coronary lumen contour after right coronary artery recanalization, (C) Simulated three-dimensional coronary lumen contour.

Table II Baseline data at each time point.

	Chest pain time (h)	EDIL3 (ng/mL)	cTnI (ng/mL)
Day0	5.50 (3.25,7)	4.16 (3.14,4.69)	3.77 (0.04,17.35)
Day1	29.5 (27.2,31)	4.90 (4.27,5.58)	38.3 (23.3,67.75)
Day2	53.5 (51.2,55)	3.71 (2.81,3.91)	13.6 (7.51,22.73)
Day3	77.5 (75.2,79)	3.08 (2.76,3.18)	2.99 (2.53,6.40)
Day7	174 (171,175)	2.41 (2.32,2.46)	0.29 (0.12,0.65)

Note: Day 0 represents before emergency PCI; Day 1, Day 2, Day 3, Day 7 represent day 1, day 2, day 3, and day 7 after emergency PCI, respectively.

6 patients (6.67%) with grade 3 flow. Postoperative flow reached TIMI grade 3 in all patients.

Temporal Changes of Serum EDIL3 Levels

To explore the temporal changes of serum EDIL3 after myocardial infarction in STEMI patients, antecubital venous blood was collected from 6 STEMI patients before emergency PCI (Day 0), and on the morning of day 1, day 2, day 3, and day 7 after emergency PCI after overnight fasting, labeled as Day 1, Day 2, Day 3, and Day 7, respectively. The results showed that serum EDIL3 levels showed a significant increasing trend within 20–40 hours after chest pain onset, reaching a peak at approximately 30 hours after chest pain. After 72 hours, EDIL3 concentration decreased to a relatively low level, showing a gradual decreasing trend over time, with the lowest EDIL3 level on day 7 after PCI (*Table II*, *Figure 2A-B*). Kruskal-Wallis test evaluated the overall difference in EDIL3 levels at different time points and showed statistical significance ($\chi^2 = 14.112$, df = 4, p = 0.006). Dunn's pairwise comparison showed that the serum EDIL3 concentration on the first day after emergency PCI was significantly higher than that on the seventh day (median: 4.90 vs. 2.41 ng/mL, Bonferroni-adjusted p = 0.0018) (*Figure 2C*).

Differential Analysis of Serum EDIL3 Levels Between STEMI Patients and Controls

Comparison of EDIL3 levels at each time point between STEMI patients and Control group showed that serum EDIL3 levels before emergency PCI and on day 1 and day 2 after PCI were significantly higher than the Control group, with corrected $p < 0.05$; while after day 3, there was no significant difference in serum EDIL3 levels compared with the control group, with corrected $p > 0.05$ (*Figure 2D*). Among all enrolled cases, the median serum EDIL3 concentration on day 1 after PCI in all STEMI patients was 3.63 (2.92–5.13) ng/mL, which was significantly higher than 2.18 (1.93–2.37) ng/mL in the control group ($p < 0.001$) (*Figure 2E*); ROC curve analysis showed that the AUC of EDIL3 level on day 1 after PCI for distinguishing STEMI patients from controls was 0.96 (95% CI: 0.93–0.99), with an optimal cut-off value of 2.65 ng/mL, sensitivity of 90.0%, and specificity of 97.5% (*Figure 2F*).

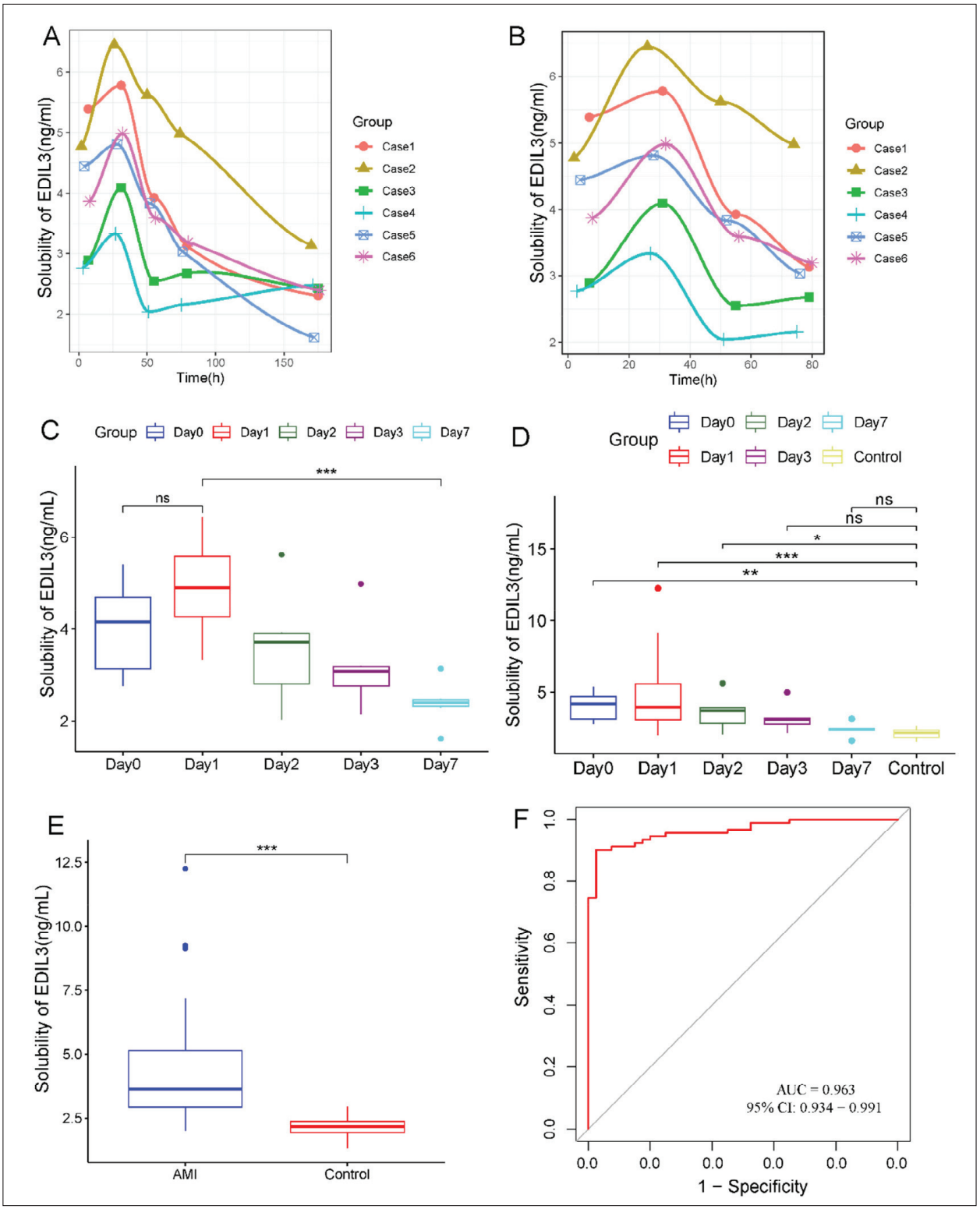

Figure 2 (A) Evolution of serum EDIL3 within 7 days in STEMI patients, (B) Evolution of serum EDIL3 within 3 days in STEMI patients, (C) Box plot showing EDIL3 evolution in STEMI patients, (D) EDIL3 levels at each time point compared with controls, (E) Serum EDIL3 level significantly elevated on day 1 after PCI, (F) ROC curve showing the ability of EDIL3 level on day 1 after PCI to identify STEMI patients. Note: Day 0 represents before emergency PCI, Day 1, Day 2, Day 3, Day 7 represent day 1, day 2, day 3, and day 7 after emergency PCI, respectively, Control represents control group; for all figures in this paper, * represents $p < 0.05$, ** represents $p < 0.01$, *** represents $p < 0.001$, ns represents no significant difference.

Table III Univariate and multivariate analysis of high AMR.

	Univariate			Multivariate		
Characteristic	OR	95% CI	p-value	OR	95% CI	p-value
cTnI (ng/mL)	1.06	1.03, 1.08	<0.001	1.01	0.98, 1.04	0.67
CK-MB (U/L)	1.01	1.00, 1.01	<0.001	1.00	1.00, 1.01	0.10
D-Dimer (mg/L)	1.04	0.95, 1.19	0.41			
EDIL3 (ng/mL)	3.49	2.31, 5.79	<0.001	2.54	1.46, 4.90	0.002
CRP (mg/L)	1.23	1.10, 1.43	0.002	1.05	0.92, 1.24	0.62
BNP A(pg/mL)	1.00	1.00, 1.00	0.003	1.00	1.00, 1.00	0.31

OR = Odds Ratio, per 1 ng/mL increase , CI = Confidence Interval

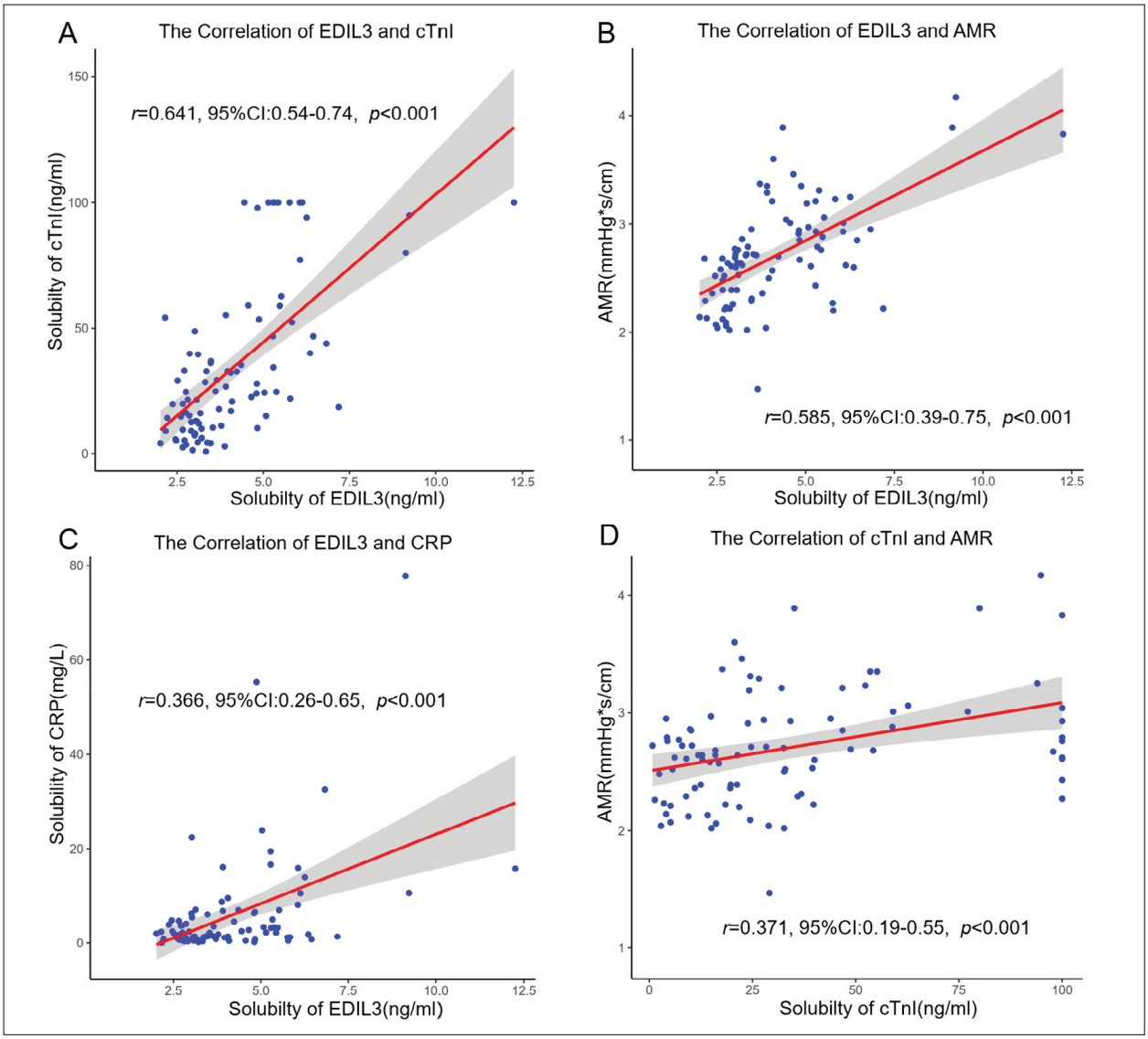

Figure 3 (A) Correlation analysis between serum EDIL3 and cTnI; (B) Correlation analysis between serum EDIL3 and AMR; (C) Correlation analysis between serum EDIL3 and CRP; (D) Correlation analysis between serum cTnI and AMR.

Correlation Analysis Between Serum EDIL3 Levels and cTnI

Spearman correlation analysis was performed between serum EDIL3 levels on day 1 after emergency PCI and serum cTnI levels at the same time point. The results showed that serum EDIL3 levels were significantly positively correlated with cTnI concentration ($r = 0.64$, 95% CI: 0.54-0.74, $p < 0.001$) (*Figure 3A*).

Correlation Analysis Between Serum EDIL3 Levels and AMR

This study evaluated the final hyperemic coronary microvascular resistance at the end of emergency PCI and performed Spearman correlation analysis with serum EDIL3 levels on day 1 after PCI. The results showed that serum EDIL3 levels were moderately positively correlated with AMR ($r = 0.585$, 95% CI: 0.39-0.75, $p < 0.001$) (*Figure 3B*).

Univariate and Multivariate Logistic Regression Analysis of AMR

Patients were divided into high AMR group and low AMR group using 2.5 mmHg·s/cm as the cutoff value (8, 12). First, univariate Logistic regression analysis was performed on indicators such as cTnI, CK-MB, BNP, D-Dimer, EDIL3, and CRP. The results showed that cTnI, CK-MB, BNP, EDIL3, and CRP were significantly associated with high AMR ($p < 0.01$). The above significant variables were further included in multivariate Logistic regression analysis. The results showed that EDIL3 was an independent predictor of high AMR (OR = 2.54, 95%CI: 1.46–4.90, $p = 0.002$) (*Table III*).

Discussion

This study found that serum EDIL3 showed significant dynamic changes in STEMI patients, with its peak appearing approximately 30 hours after acute myocardial infarction. This temporal pattern suggests that EDIL3 does not merely reflect myocardial necrosis (as the cTnI peak typically occurs 12–24 hours after infarction), but may instead participate in the inflammatory repair phase of ischemia-reperfusion injury. Previous studies have shown that EDIL3 can be secreted by vascular endothelial cells and macrophages under hypoxic conditions, participating in the regulation of inflammatory responses and tissue remodeling (13, 14). Based on these findings, we speculate that oxidative stress and the inflammatory cascade induced by reperfusion after STEMI may stimulate the synthesis and release of EDIL3. Its delayed peak pattern at around 30 hours is consistent with the time course characteristics of inflammatory mediators (15). In addition, this study found that EDIL3 was positively correlated with CRP (*Figure 3C*), further confirming that EDIL3 participates in the inflammatory response after acute myocardial infarction.

AMR is a non-invasive method for detecting coronary microvascular resistance based on coronary angiography, which has good correlation with the index of microcirculatory resistance (IMR) (16, 17). No-reflow is a clinical manifestation of poor myocardial perfusion after STEMI reperfusion. Compared with the no-reflow phenomenon that relies on visual judgment, AMR, as a continuous quantitative indicator, can more sensitively reflect changes in microcirculatory resistance (18, 19). Previous studies have shown that although troponin can indirectly reflect microcirculatory function status (20), its predictive value for microcirculatory dysfunction is affected by confounding factors such as the degree of myocardial necrosis, making it difficult to independently predict high AMR. This study also found that cTnI was only weakly positively correlated with AMR ($r = 0.371$, 95% CI: 0.19–0.55, $p < 0.001$) (*Figure 3D*). After adjusting for confounding factors in multivariate Logistic regression analysis, cTnI had no statistical significance for predicting high AMR ($p = 0.87$), supporting the above viewpoint. In contrast, serum EDIL3 levels were significantly positively correlated with AMR ($r = 0.585$, $p < 0.001$), and after adjusting for clinical confounding factors, EDIL3 remained an independent predictor of high AMR (OR=2.54, $p = 0.002$). This suggests that EDIL3 may more directly reflect microcirculatory dysfunction compared with traditional myocardial injury markers.

The potential mechanism by which EDIL3 participates in microcirculatory dysfunction after STEMI is not fully understood, but existing evidence supports several possibilities. First, after acute coronary occlusion, extensive extracellular matrix deposition occurs in the infarcted area. Excessive extracellular matrix accumulation increases cardiac stiffness and exacerbates microvascular resistance through multiple effects such as pro-inflammatory, pro-thrombotic, and pro-fibrotic actions (21, 22). This study found that EDIL3, as an extracellular matrix protein, was significantly positively correlated with AMR, providing new clinical evidence for the hypothesis of extracellular matrix-mediated microcirculatory dysfunction. Second, EDIL3 can affect ischemia-reperfusion injury by regulating inflammatory responses (23), and inflammation is an important driver of microcirculatory dysfunction (24, 25). Third, EDIL3 may be released by endothelial cells or activated platelets in ischemic and hypoxic tissues, improving myocardial perfusion by promoting angiogenesis. However, its overexpression may also exacerbate vascular permeability and edema (26, 27), increas-

ing microcirculatory resistance. Nevertheless, these mechanisms are mainly based on basic research speculations, and the causal relationship between EDIL3 and microcirculatory resistance requires further functional experimental verification.

Although the results showed that EDIL3 had high sensitivity and specificity for distinguishing STEMI patients from healthy controls, since this result is based on the extreme comparison between STEMI patients and healthy controls, important factors that may affect EDIL3 baseline levels were not fully adjusted, such as inflammatory diseases, liver and kidney function status, connective tissue diseases, tumors, and other factors (27–29). These confounding factors may lead to decreased specificity of EDIL3 in real-world non-selective populations. Furthermore, high sensitivity is not equivalent to high positive predictive value, especially in outpatient or emergency screening scenarios with low STEMI incidence. Therefore, EDIL3 is currently more suitable as an auxiliary tool for exclusion diagnosis rather than an independent confirmatory diagnostic biomarker.

This study has certain limitations: First, the sample size is relatively small and it is a single-center design. The selection of the healthy control group may have selection bias, and validation in an external independent cohort is needed. Second, comprehensive stratified analysis of potential confounding factors that may affect EDIL3 test results was not performed. Third, the diagnostic cutoff value of this study was calculated only based on this group of data, and its generalizability in different detection platforms and different populations requires calibration.

Conclusion

In conclusion, circulating EDIL3 levels were markedly elevated following reperfusion in patients with ST-segment elevation myocardial infarction and demonstrated significant positive associations with angiography-derived microvascular resistance. After adjustment for potential clinical confounders, serum EDIL3 remained an independent biochemical predictor of elevated coronary microvascular resistance. These findings suggest that EDIL3 may serve as a novel circulating biomarker reflecting endothelial injury, inflammatory activation, and microcirculatory dysfunction after STEMI. As a laboratory-based indicator, EDIL3 may provide additional value for cardiovascular risk stratification and individualized clinical assessment in patients undergoing reperfusion therapy. Further multicenter prospective investigations and mechanistic studies are warranted to validate its clinical applicability and clarify the underlying pathophysiological mechanisms.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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