

Predictive Value of Macrophage Migration Inhibitory Factor in No-Reflow Phenomenon in STEMI Patients

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ABSTRACT

This study was conducted to determine whether macrophage migration inhibitory factor (MIF) levels predict no-reflow in patients with ST-segment elevation myocardial infarction (STEMI). We included 120 STEMI patients who had received initial PCI therapy. Serial 12-lead ECGs acquired before and after primary PCI within 1-2 hours at 50 mm/sec were used to assess the ST-segment dynamics. When microcirculatory perfusion is compromised, the dynamics of ST-segment elevation resolution (STR) remain at 70% or less. No-reflow was detected using real-time myocardial perfusion imaging by myocardial blush grade assessment. MIF levels were assessed using ELISA before and after PCI. We found that the pre-PCI MIF contents did not significantly differ from the post-PCI MIF levels and that the total population of STEMI patients had higher plasma MIF contents than the group of healthy volunteers (3400 [2089.0-5571.0] pg/mL and 721 [567.3-1104.1] pg/mL, respectively, $P < 0.001$). MIF levels before and after PCI were significantly higher in patients with no-reflow than in those without it. According to ROC characteristics, the pre-PCI MIF levels that predicted the no-reflow condition had a well-balanced cut-off of 3663 pg/mL (sensitivity = 74%, specificity = 72%, 95% CI = 0.585-0.857; $P = 0.0023$). The no-reflow was predicted by pre-PCI MIF levels > 3663 pg/mL, whereas post-PCI MIF levels showed no discriminative potency for it. The no-reflow phenomena were independently predicted by female gender and pre-PCI MIF levels > 3663 pg/mL. Higher pre-PCI MIF levels (> 3663 pg/mL and > 5033 pg/mL, respectively) in STEMI patients were predictive of systolic cardiac dysfunction and the post-procedural no-reflow phenomena.

Keywords: Macrophage migration, ST-segment elevation myocardial infarction, Percutaneous coronary artery intervention, Myocardial hypoperfusion, Prognosis

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Introduction

Even though primary percutaneous coronary intervention (PCI) has significantly improved the cardiovascular (CV) outcomes and short- and long-term prognosis for patients with ST-segment elevation myocardial infarction (STEMI), peri-procedural events (sudden death, cardiac arrest, and cardiogenic shock) continue to be among the leading causes of death for this patient population [1-3]. The median time reduction from hospital admission to primary PCI, the use of drug-eluting stents, dual antiplatelet therapy, an efficient lipid-lowering strategy with statins, ezetimibe, and human monoclonal antibodies against proprotein convertase subtilisin / kexin 9, beta-blockers, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers were among the strategies that demonstrated mild-to-moderate benefits in lowering the in-hospital mortality of STEMI patients with reperfusion damage [4-6]. Furthermore, the increase in the financial strain on the global health system over the past ten years is unquestionably linked to the in-hospital management of post-PCI problems [7].

Numerous pathological processes including downstream embolization by plaque debris, the release of soluble inflammatory and prothrombogenic factors from the culprit lesion, altered endothelial integrity due to increased vascular permeability and oedema of the vascular wall, platelet aggregation, red blood cell and leucocyte adherence, endothelial dysfunction, and vasoconstriction have been caused by ischemia/reperfusion damage of cardiomyocytes and coronary vasculature [8-10]. Ultimately, intramyocardial haemorrhage, microvascular blockage, and eventual no-reflow phenomenon cause structural damage to cardiac myocytes, the vasculature of intramuscular arterioles, and capillary walls, which contributes to persistent myocardial hypoperfusion and unfavorable cardiac remodeling [11]. Furthermore, contemporary biomarker technologies can detect and diagnose myocardial hypoperfusion after PCI, independent of the magnitude of the myocardial infarction [12, 13].

Due to glucocorticoid activation, macrophages and T lymphocytes produce the multifunctional cytokine known as Macrophage Migration Inhibitory Factor (MIF), which has several biological characteristics [14]. MIF plays a role in inflammation and immunological reactivity. It is also thought to be a key component of the stress response to infection and the ensuing tissue damage. At an early stage of myocardial infarction, the MIF level rose sharply and likely had predictive value for both recurrent CV events and all-cause mortality [15]. Among STEMI patients, MIF levels were strongly correlated with unfavorable cardiac remodeling, cerebrovascular events, and N-terminal pro-b-type natriuretic peptide (NT-proBNP) levels [16, 17]. Consequently, the extent of the myocardial infarct as determined by magnetic resonance imaging was linked with the MIF contents in STEMI patients who were admitted urgently to a catheter laboratory [18]. It is uncertain, nevertheless, if inflammatory indicators can forecast the no-reflow phenomenon, myocardial damage linked to PCI. The study speculates as to whether circulating MIF levels in STEMI patients are a sign of reperfusion myocardial damage.

Materials and Methods

Patients' population

Totally 120 patients who presented with a first STEMI and undergone primary PCI were included in the research from an entire cohort of STEMI individuals (n = 341). These patients were urgently admitted to the emergency unit of the Government Institution “L. T. Malaya Therapy National Institute NAMSU” and the Department of Interventional Cardiology of the Government Institution “V.T. Zaitsev Institute of General and Emergency Surgery of the NAMS of Ukraine” with STEMI within two to twelve hours of the onset of the first symptoms between October 2019 and December 2020. Twenty-five healthy volunteers were served in an age-matched control group. The research design flow chart is reported in **Figure 1**.

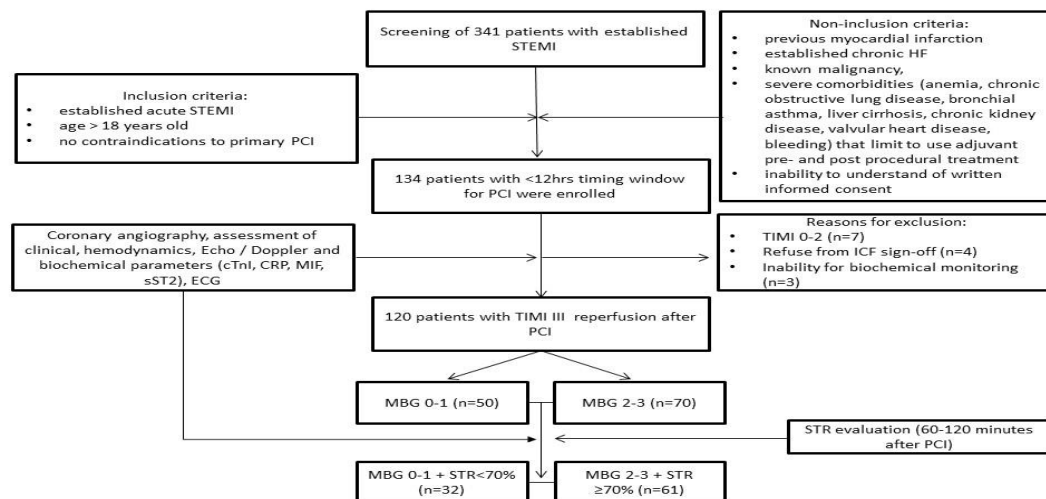


Figure 1. Flow chart of the research design; abbreviations: CRP, C-reactive protein; cTnI, cardiac troponin I; ECG, electrocardiogram; H.F., heart failure; ICF, informed consent form; MBG, myocardial blush grade; MIF, macrophage migration inhibitory factor; PCI, percutaneous coronary intervention; STEMI, ST-segment Elevation Myocardial Infarction; STR, ST-segment resolution; sST2, soluble suppression of tumorigenesis 2 protein;- TIMI, thrombolysis in myocardial infarction flow grade.

STEMI, age over 18 years old, and successfully performed primary PCI with epicardial blood flow that corresponded to TIMI III were the inclusion criteria. Patients with severe comorbidities, including active malignancy, chronic inflammatory disease in its acute phase, and the presence of known psychiatric disorders - have not been included in the research.

STEMI determination

STEMI was diagnosed following the ECS Guideline [19] within the first 12 hours after the onset of the coronary event.

Ethical declaration

The local Ethics Committee of G.I. "L. T. Malaya Therapy National Institute NAMSU" (Kharkiv, Ukraine) confirmed this study following the Helsinki Declaration (Protocol № 5, 26.05.2016). All enrolled patients expressed their agreement in written form to participate in the research.

Coronary angiography

We used the radial approach by the Seldinger technique to provide conventional coronary angiography. Multiple projections of coronary arteries were recorded for each vessel. Automatic contrast injection of 6-10 mL of the "Ultravist-370" (Bayer Pharma GmbH, Germany) was utilized for contrast enhancement. The radiation exposure fluctuated from 20 to 35 mGycm. Two independent assessors analyzed the contrast images visually and quantitatively. Controversial issues were re-examined by the supervisor (MPK). Unclear angiograms were excluded from further analysis.

Primary PCI

Primary PCI was performed within six to twelve hours after the first symptom onset. Integrity bare-metal stent (Boston Scientific, USA) and Resolute Integrity drug-eluting stent (Medtronic, USA) were implanted in 92 and 42 patients. Adjuvant therapy was provided for all examined patients based on current ESC guidelines.

Assessment of successful reperfusion

Assessment of the ST-segment dynamics was performed with serial 12-lead ECGs obtained before and after primary PCI within 1-2 hours at 50 mm/sec. In the case of impaired microcirculatory perfusion, the dynamics of ST-segment elevation Resolution (STR) remain equal to 70% or less [20].

STEMI prognosis determination

To accredit prognostic capacity after STEMI, we utilized the TIMI and the GRACE score [21, 22].

Real-time myocardial perfusion imaging determination

Real-time myocardial perfusion imaging with myocardial blush determination grade (MBG) was used to measure myocardial perfusion [23]. The MBG was scored during angiographic analysis according to the conventional method [24]. MBG was graded as 0, 1, 2, and 3 corresponding to the following criteria: a lack of contrast density of myocardial blush (M.B.), minimal contrast density of M.B., contrast density of M.B. with impaired clearing, and normal M.B. or contrast density, respectively [25]. Occurrence of post-PCI epicardial large coronary artery blood flow of TIMI < 3 or MBG 0-1 along with STR < 70% within 2 hours after PCI was qualified as the no-reflow condition. **Figure 2** illustrates the decision-making performed by the supervisor regarding contrast density and myocardial blush.

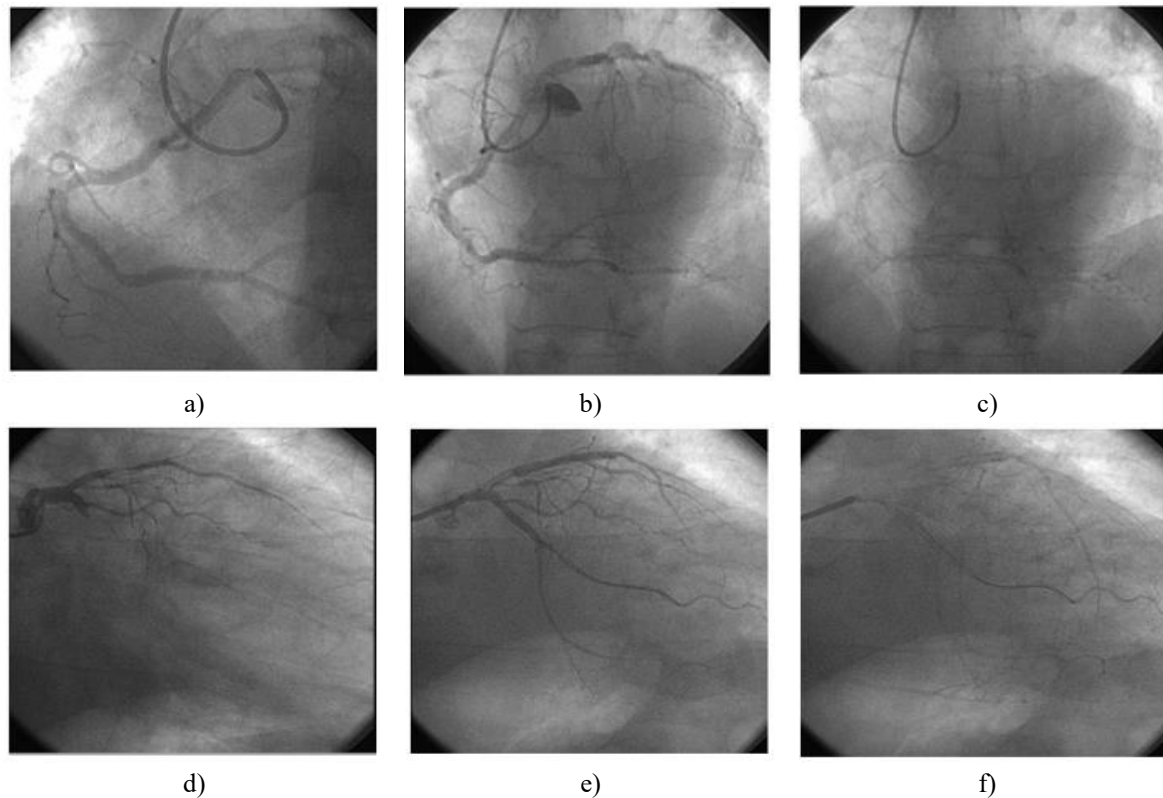


Figure 2. Determination of contrast density and myocardial blush in STEMI patients undergoing primary PCI; a) inferior infarction with severe proximal and mid-RCA occlusion, b) final angiographic image after stent implantation with TIMI 3 flow in RCA, c) lack of myocardium staining in the infarct area, MBG 0 grade, d) anterior infarction with stenosis of both LAD and LCX, e) final angiographic result after revascularization with TIMI 3 Flow in LAD, as well as LCX, and f) MBG 0 grade adjusted by supervisor

Notes: The skilled operator performed the MBG right after PCI and was based on a visual evaluation of the contrast density in the myocardium's infarcted zone. Without myocardial flush, MBG was rated as zero in the first scenario.

The supervisor verified the MBG 0 grade on the recorded angiograms during the angiographic study. In the second instance, the supervisor assigned MBG a score of 0 due to the minimal myocardial blush. The following acronyms are used: STEMI, or ST-segment elevation myocardial infarction; RCA, or right coronary artery; PCI, or percutaneous coronary intervention; MBG, or myocardial blush grade; LCX, or left circumflex artery; and LAD, or left anterior descending artery.

Comorbidities and risk factors determination

A questionnaire was used to assess the patient's medical history, including recent transient ischaemic attacks and strokes, malignancy, hypertension, and use of medications (such as lipid-lowering, antihypertensive, and hypoglycemic medications). During the interview, anthropometric parameters were measured by trained investigators. A body mass index (BMI) of kg/m² was calculated. The European Society of Cardiology's (ESC) 2019 dyslipidemia guideline [26] was used to determine dyslipidemia. Hypertensive patients were defined according to the 2018 ESC guideline on diagnosis and management of arterial hypertension [27]. A new diagnosis of H.F. was made following the ESC criteria [28]. According to the 2017 ADA statement, type 2 diabetes was identified [29].

Transthoracic echocardiography and Doppler

Twenty-four hours after being admitted to the intensive cardiac care unit (ICCU), all STEMI patients underwent transthoracic conventional B-mode echocardiography and Doppler using a Toshiba TUS-A500 (Aplio 500, Japan) equipped with a 3.5 MHz phase probe. Left ventricular end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV mass (LVM), and LV ejection fraction (LVEF) were automatically measured using Simpson's

biplane method. Following the current recommendation, diastolic function was evaluated by impulse Doppler using early to late diastolic transmitral flow velocity (E/A) [30].

Calculation of the sample size

The sample size was determined using the study's prospective design, which provided a design effect of 1.0, 95% confidence intervals, and an error of 5% [31].

Glomerular filtration rate calculation

The glomerular filtration rate (GFR) was calculated using the CKD-EPI (chronic kidney disease epidemiology collaboration) algorithm [32].

Blood samples

According to the following plan, blood samples were taken at admission before PCI (MIFI, CRPI, sST2) and following PCI for the analysis of biomarkers and other standard laboratory analyses: Peak cardiac TnI levels were monitored every six hours for 24 hours following the surgery, and post-PCI MIF levels were assessed 24 hours later. Before being delivered to G.I. "L. T. Malaya TNI NAMSU's" immunochemical and molecular-genetic research lab, blood samples were carefully centrifuged, separated within 30 minutes, and frozen in plastic tubes at -70 °C.

Using commercial kits, the enzyme-linked immunosorbent assay was used to determine the serum biomarkers. Humalyzer 2000 (HUMAN GmbH, Germany) used a "Human MIF ELISA" (RayBio, USA) kit with upper reference limits of 6000.0 pg/ml to assess MIF levels. According to the manufacturer's instructions, the "The Presage ST2 Assay" (Critical Diagnostics, CA, USA) kit was used to measure the sST2 contents, with limits of 0–200.0 ng/ml. The troponin I (TnI) and C-reactive protein (CRP) levels were measured using the "Troponin I-ELISA" kit from Xema, Russia, which had limits of 0–10.0 ng/ml and the "CRP-ELISA" kit from Xema, Russia, which had an upper limit of 25.0 mg/L. Total cholesterol (T.C.), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (T.G.) were measured using the direct enzymatic method (Roche P800 analyzer, Basel, Switzerland). The coefficients of variation within and between assays were less than 5%.

The double-antibody sandwich immunoassay (Elecsys 1010 analyzer, F. Hoffmann-La Roche Diagnostics, Mannheim, Germany) was used to measure the fasting glucose level.

Statistics

For statistical analysis, we utilized Statistica version 10.0 (Stat Soft Inc., Tulsa, OK, USA). Means (S.D.s) and counts (percentages) were used to represent continuous and categorical variables, respectively. If the data showed a skewed distribution, it would be assumed that it was distributed normally or shown as medians (interquartile ranges [IQR]).

Data distribution was tested using the Shapiro-Wilk test. Student's t-test, one-way ANOVA, or non-parametric tests (Kruskal-Wallis or Mann-Whitney) were used to compare continuous variables between groups. The chi-square test was used to compare categorical variables. The Spearman test was used to examine correlations between variables.

A well-balanced cut-off of biomarker concentration was found using the receiver operational characteristic (ROC) curve analysis. The Youden technique was used to calculate the cut-off point's area under the curve (AUC), specificity, and sensitivity [33]. The relationship between several variables and myocardial perfusion disruption was examined using logistic regression. For every component influencing the no-reflow phenomenon, the odds ratio (OR), β -coefficient, and 95% confidence interval (CI) were performed. A P-value of 0.05 or less was regarded as statistically significant.

Results and Discussion

Table 1 displays the baseline clinical characteristics of the individuals who participated in the study. With a broad spectrum of cardiovascular risk factors, such as type 2 diabetes mellitus (33.6%), hypertension (78.4%), mild-to-moderate obesity (42.5%), smoking (45.8%), and a family history of coronary artery disease (44.8%), the majority of patients (70.9%) are male.

Table 1. Baseline specifications of the research patients

	Entire STEMI patients' cohort (n = 134)	Patients with post-PCI no-reflow condition (MBG 0-1, STR < 70%, n = 32)	Patients without post-PCI no-reflow condition (MBG 2-3, STR >70%, n = 61)	P-value
Clinical data, previous medical history				
Age (years)	61.36 ± 10.43	65.31 ± 10.03	62.25 ± 9.67	0.066*
Male (n (%))	95 (70.9%)	23 (71.9%)	41 (67.2%)	0.645
Female (n (%))	39 (29.1%)	9 (28.1%)	20 (32.8%)	
Systolic blood pressure (mm Hg)	133.90 ± 30.51	125.22 ± 34.85	139.05 ± 26.49	0.110
Diastolic blood pressure (mm Hg)	80.12 ± 14.97	76.66 ± 15.43	81.93 ± 15.41	0.321
Heart rate (beats/min)	79.22 ± 16.74	84.38 ± 23.29	77.18 ± 15.41	0.104
Hypertension (n (%))	105 (78.4%)	28 (87.5%)	48 (78.7%)	0.226
Type 2 diabetes mellitus (n (%))	45 (33.6%)	12 (37.5%)	17 (27.9%)	0.341
Smoking (n (%))	65 (48.5%)	12 (37.5%)	28 (45.9%)	0.437
BMI > 30 kg/m ² (n (%))	57 (42.5%)	6 (18.8%)	13 (21.3%)	0.771
Stable angina before STEMI (n (%))	63 (47.0%)	18 (56.3%)	30 (49.2%)	0.517
Unstable angina before STEMI (n (%))	24 (17.9%)	9 (28.1%)	8 (13.1%)	0.134
Family history of CAD (n (%))	60 (44.8%)	12 (37.5%)	31 (50.8%)	0.221
Echocardiographic parameters				
LVEDV (mL)	126.03 ± 30.35	131.59 ± 15.01	125.74 ± 28.42	0.663
LVEDV index (mL/m ²)	64.35 ± 15.03	68.31 ± 16.36	65.21 ± 14.50	0.440
LVESV (mL)	60.84 ± 22.26	65.73 ± 24.27	62.32 ± 21.07	0.690
LVM (g)	221.29 ± 77.88	227.09 ± 60.34	209.22 ± 76.75	0.266
LVM index (g/m ²)	109.41 ± 41.42	118.04 ± 30.96	103.21 ± 41.64	0.144
LVEF (%)	49.72 ± 8.66	45.00 ± 6.95	49.79 ± 7.81	0.018*
E/A	1.08 ± 0.38	0.99 ± 0.44	1.09 ± 0.33	0.221
STEMI risk scores				
GRACE risk score (in-hospital) (points)	140.38 ± 35.31	162.00 ± 48.67	138.05 ± 27.74	0.023*
GRACE risk score (admission - 6-month) (points)	115.83 ± 30.73	135.72 ± 39.30	114.27 ± 24.83	0.009*
TIMI risk score (points)	3.82 ± 2.40	5.25 ± 2.63	3.44 ± 2.14	0.001*
STEMI localization				
Anterior (n (%))	64 (47.8%)	23 (71.9%)	24 (39.3%)	0.006*
Posterior (n (%))	70 (52.2%)	9 (28.1%)	37 (60.7%)	0.003
LMCA (n (%))	10 (7.5%)	2 (5.4%)	4 (6.6%)	0.662
LAD (n (%))	94 (70.1%)	27 (84.4%)	38 (62.3%)	0.022*
RCA (n (%))	85 (63.4%)	18 (56.3%)	39 (63.9%)	0.588
LCX (n (%))	47 (35.1%)	17 (53.1%)	21 (34.4%)	0.081
The number of injured coronary vessels				
One-vessel injury (n (%))	55 (41.0%)	12 (37.5%)	26 (42.6%)	0.633
Two-vessel injury (n (%))	40 (29.9%)	8 (25.0%)	20 (32.8%)	0.437
Three and multiple vessel injury (n (%))	39 (29.1%)	12 (37.5%)	15 (24.6%)	0.193
Biomarkers				
Peak TnI (ng/mL)	9.06 ± 4.27	10.74 ± 3.45	9.01 ± 4.21	0.106
MIFI (pg/mL)	2501.0 [1409.0-3896.5]	3262.0 [2260.5-5951.5]	2261.0 [1324-3400]	0.004
MIFII (pg/mL)	2395.5 [1252.0-4140.5]	3287.0 [1927.0-4303]	2008.5 [1202.0-3507.0]	0.015

sST2 (ng/mL)	24.36 [17.59-30.38]	42.1 [30.69-135.74]	33.08 [20.15-56.6]	0.045
CRPI (mg/L)	18.90 ± 9.53	19.02 ± 9.77	19.24 ± 9.53	0.863
CRPII (mg/L)	23.23 ± 8.80	23.37 ± 9.55	22.64 ± 8.32	0.763
Serum creatinine (μmol/L)	104.01 ± 29.46	109.99 ± 32.49	104.96 ± 31.84	0.363
GFR (CKD-EPI) (ml/min/1.73m ²)	66.22 ± 20.23	62.52 ± 22.26	64.36 ± 18.99	0.685
Blood glucose (mmol/L)	9.59 ± 4.78	10.74 ± 5.67	8.78 ± 4.30	0.171
Hemoglobin (g/L)	140.02 ± 16.60	138.13 ± 15.01	139.23 ± 17.50	0.937
WBC (10 ⁹ /L)	10.44 ± 3.80	12.24 ± 3.96	10.36 ± 3.74	0.025
TC (mmol/L)	5.03 ± 1.33	4.53 ± 1.41	5.39 ± 1.33	0.007
LDL (mmol/L)	3.13 ± 1.25	2.82 ± 1.27	3.35 ± 1.31	0.062
HDL (mmol/L)	1.05 ± 0.34	1.01 ± 0.26	1.06 ± 0.35	0.948
TG (mmol/L)	1.87 ± 1.12	1.55 ± 0.69	2.06 ± 1.43	0.044
In-hospital complications				
Total number of in-hospital complications (acute heart failure, cardiac aneurysm, new atrial fibrillation / flutter and sustainable ventricular tachycardia) (n (%))	29 (21.6%)	15 (46.9%)	9 (14.8%)	0.002
II-III Killip class of HF (n (%))	18 (13.4%)	7 (21.9%)	7 (11.5%)	0.304
IV Killip class of HF (n (%))	10 (7.5%)	6 (18.6%)	3 (4.9%)	0.041
Out-hospital complications				
Combined endpoints (n (%))	43 (32.1%)	17 (53.1%)	16 (26.2%)	0.010
Concomitant medication				
Aspirin (n (%))	134 (100%)	32 (100%)	61 (100%)	1.0
Clopidogrel (n (%))	44 (32.8%)	12 (37.5%)	22 (36.1%)	0.892
Ticagrelor (n (%))	89 (66.4%)	19 (59.4%)	39 (63.9%)	0.666
Statins (n (%))	134 (100%)	32 (100%)	61 (100%)	1.0
β-blockers (n (%))	119 (88.8%)	28 (87.5%)	53 (86.8%)	0.94
ACEI/ARBs	112 (83.5%)	30 (93.7%)	55 (90.1%)	0.96
MRA	8 (6.0%)	3 (9.4%)	3 (4.9%)	0.338

Abbreviations: CAD, chronic stable angina pectoris; ARBs, angiotensin II receptor blockers; ACEI, angiotensin-converting-enzyme inhibitors; CRP, C-reactive protein; BMI, body mass index; GFR, glomerular filtration rate; E/A, early to late diastolic transmitral flow velocity; HDL, high-density lipoprotein; H.F., heart failure; LAD, left anterior descending artery; LDL, low-density lipoprotein; LCX, left circumflex artery; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVPWs, left ventricle posterior wall thickness; MIF, macrophage migration inhibitory factor; LMCA, left main coronary artery; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; sST2, soluble suppression of tumorigenesis 2 protein; T.C., total cholesterol; T.G., triglycerides; TnI, troponin I; MRA, mineralocorticoid receptor antagonists.

These patients had mild-to-moderate risk based on GRACE and TIMI risk scores, the majority had posterior localization of STEMI, nearly 60% had two-vessel and multiple vessel injury, and the mean LV ejection fraction was 49.7% (95% interquartile range was from 40.2% to 49.5%). Their left ventricle (LV) was not severely dilated. Consequently, over 22% of STEMI patients experienced in-hospital sequelae, including acute heart failure, cardiac aneurysm, spontaneous atrial fibrillation/flutter, and prolonged ventricular tachycardia. ACE inhibitors/angiotensin-II receptor antagonists, statins, mineralocorticoid receptors, beta-blockers, antiplatelets, and antagonists were among the concurrent drugs.

Compared to those without this phenomenon, STEMI patients with post-PCI no-reflow state (MBG = 0-1, STR < 70%) exhibited higher levels of sST2 ($P = 0.045$), TC ($P = 0.025$), TG ($P = 0.007$), and white blood cells ($P = 0.044$) and a worse LV ejection percentage ($P = 0.018$). Furthermore, compared to patients without the post-PCI no-reflow condition, those with it had superior anterior STEMI localization ($P = 0.006$) and a left anterior descending artery lesion ($P = 0.022$). Creatinine, TnI, C-reactive protein, and concurrent medicines were among the other biomarkers whose levels did not significantly change between cohorts.

Determination of MIF levels in STEMI patients

The MIF levels in STEMI patients are shown in **Figure 3** along with the differences in this biomarker between STEMI groups and healthy volunteers. When compared to the group of healthy volunteers, the total population of STEMI patients had higher plasma MIF levels (3400 [2089.0-5571.0] pg/mL and 721 [567.3-1104.1] pg/mL, respectively, $P < 0.001$) (**Figure 3a**). Twenty-four hours after the procedure, the pre-PCI MIF levels did not significantly differ from the post-PCI MIF levels (3400 [2089.0-5571.0] pg/mL and 3563 [2283.0-4311.0] pg/mL, respectively, $P = 0.647$), as shown in **Figure 3b**. However, no-reflow condition patients had significantly higher pre-PCI and post-PCI MIF levels (3262.0 [2260.5-5951.5] pg/mL and 2261.0 [1324-3400] pg/mL, respectively, $P = 0.004$ and 3287.0 [1927.0-4303] pg/mL and 2008.5 [1202.0-3507.0] pg/mL, respectively, $P = 0.015$) than those who did not exhibit the no-reflow phenomenon (**Figure 3c**).

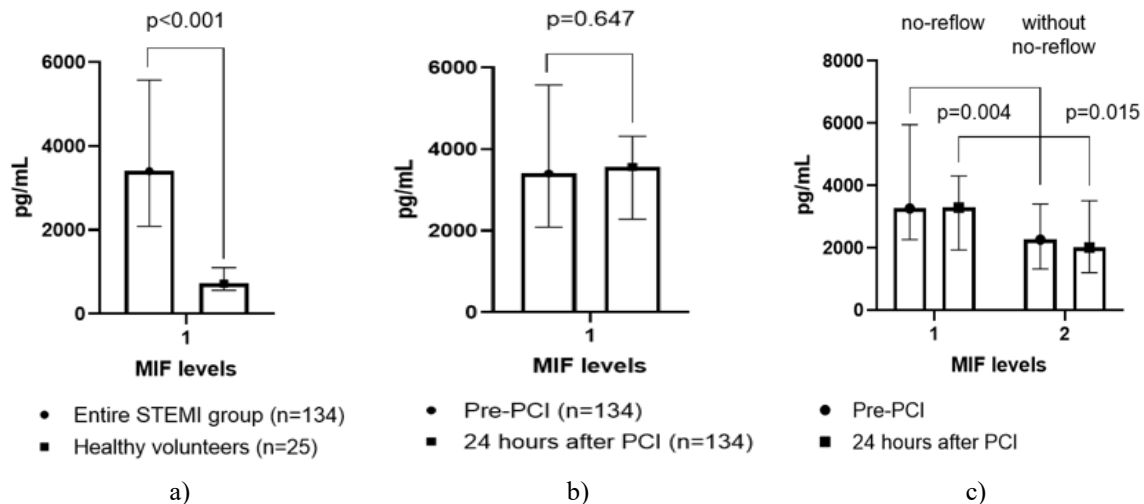


Figure 3. The levels of MIF in STEMI patients and healthy volunteers; a) the comparison of the MIF levels in the entire STEMI patients' population and healthy volunteers' group, b) the comparison of pre-and post-PCI MIF levels in the entire STEMI patients' population, and c) the comparison of pre-and post-PCI MIF levels in STEMI cohorts

Spearman correlations between MIF levels, other circulating biomarkers, cardiac hemodynamics' parameters, risk factors and comorbidities

Spearman's rank correlation test revealed that there were positive relationships between MIF contents and LV mass index ($r = 0.75$; $P = 0.007$), LVEDV ($P = 0.001$), LVESV ($P = 0.02$), peak TnI levels ($r = 0.44$; $P = 0.002$), white blood cells count ($r = 0.33$, $P = 0.0001$), C-reactive protein ($r = 0.19$, $P = 0.032$), but not with sST2 levels, T2DM, and GRACE score. Pre-PCI levels of sST2 positively correlated with GRACE score ($r = 0.42$; $P = 0.001$), T2DM ($r = 0.41$; $P = 0.001$), acute heart failure Killip class ($r = 0.40$; $P = 0.001$), age ($r = -0.36$; $P = 0.001$), peak TnI levels ($r = 0.33$; $P = 0.001$), and inversely correlated with LV ejection fraction ($r = -0.40$; $P = 0.001$), LDLP cholesterol ($r = -0.33$; $P = 0.007$). Pre-PCI LV ejection fraction was associated with GRACE risk score ($r = -0.40$; $P = 0.001$), T2DM ($r = 0.38$; $P = 0.001$), age ($r = 0.32$; $P = 0.002$), male gender ($r = 0.31$; $P = 0.001$), several culprit coronary arteries ($r = -0.31$; $P = 0.002$), and peak TnI ($r = 0.38$; $P = 0.003$).

MIF as predictor for no-reflow condition: receive operation curve analysis

The no-reflow condition was predicted by a well-balanced cut-off of pre-PCI MIF levels of 3663 pg/mL (sensitivity = 74%, specificity = 72%, AUC = 0.74; 95% CI = 0.585-0.857; $P = 0.0023$), according to our findings from the ROC analysis (**Figure 4a**). 2380 pg/mL was found to be the post-PCI MIF level cut-off point (sensitivity = 48%, specificity = 89%, AUC = 0.65; 95% CI = 0.500 to 0.791; $P = 0.07$); (**Figure 4b**).

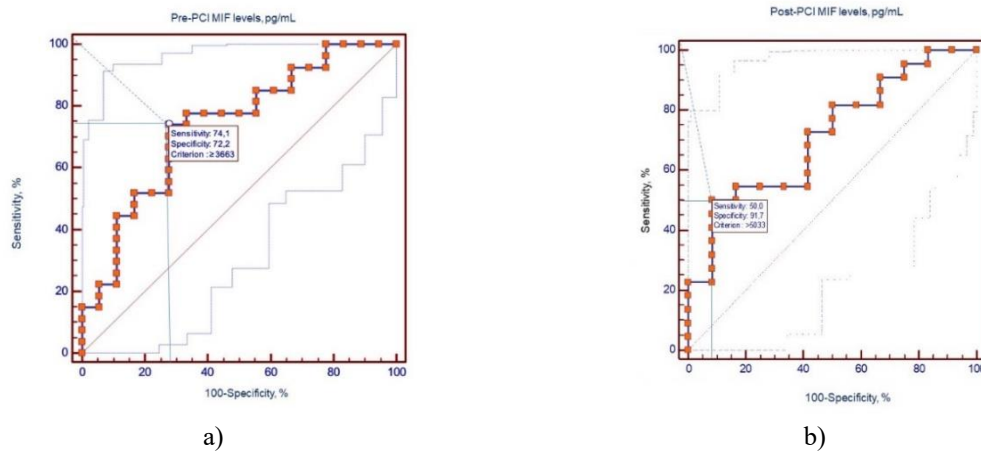


Figure 4. Predictive value of circulating pre-PCI MIF levels for the no-reflow phenomenon in STEMI patients: The ROC analysis; a) predictive value of pre-PCI MIF levels, b) predictive value of post-PCI MIF levels

MIF levels as predictor for reduced left ventricular ejection fraction: receive operation curve analysis

The results of ROC analysis showed that whether or not post-PCI MIF levels independently predicted LV systolic dysfunction, which was defined as a reduced (< 40%) LV ejection fraction (sensitivity = 50.0%; specificity = 91.7%, AUC = 0.716; 95% CI = 0.536-0.857, P = 0.0189) (**Figure 5**).

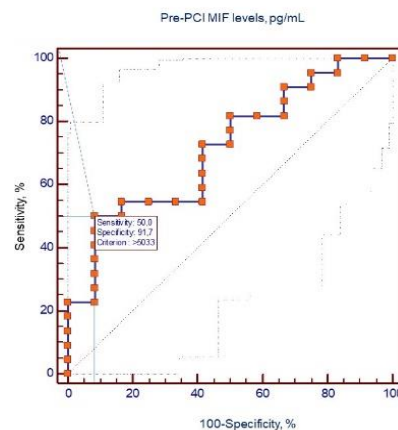


Figure 5. MIF levels as predictor for reduced left ventricular ejection fraction: receive operation curve analysis

Predictive factors for post-PCI no-reflow phenomenon: the results of univariate and multivariate regressions

Using univariate and multivariate regressions, we identified the factors related to the post-PCI no-reflow phenomenon in STEMI patients (**Table 2**).

Table 2. The factors related to Post-PCI no-reflow phenomenon in STEMI patients: univariate and multivariate regressions

Variables	Univariate analysis				Multivariate analysis			
	β - Coefficient	OR	95% CI	P-value	β - Coefficient	OR	95% CI	P-value
Age (years)	-1.1	0.3	0.0-29.3	0.627	-	-	-	-
Gender (female)	15.1	3.9	0.0-5.3	0.684	2.8	17.7	0.9-327.2	0.053
Smoking	2.7	15.6	0.0-31.7	0.658	-	-	-	-
T2DM	-51.6	0.0	-	0.982	-	-	-	-
Number of culprit's vessels	-10.6	0.0	0.0-0.0	0.697	-	-	-	-
STEMI localization	-16.0	0.0	0.0-0.0	0.649	-	-	-	-

CRP	0.6	1.8	0.2-12.0	0.521	-	-	-	-
Pre-PCI MIF > 3663 pg/mL	0.0033	1.0	0.9-1.0	0.664	0.1	1.1	1.0-1.2	0.036
Post-PCI MIF > 2380 pg/mL	-0.001	0.9	0.9-1.0	0.779	-	-	-	-
sST2	-0.2	0.8	0.3-1.9	0.631	-	-	-	-
Peak TnI level	-0.1	0.8	0.0- 9.7	0.894	-	-	-	-

Abbreviations: MIF, macrophage migration inhibitory factor; CRP, C-reactive protein; OR, odds ratio; sST2, soluble suppression of tumorigenesis 2 protein; CI, confidential interval; TnI, troponin I; T2DM, type 2 diabetes mellitus

Pre-PCI MIF levels > 3663 pg/mL and female gender were independent predictors for the no-reflow phenomenon (β -coefficient = 0.1, OR = 1.1, 95% CI = 1.0-1.2, P = 0.036; and β -coefficient = 2.9, OR = 17.7, 95% CI = 0.9-327.2, P = 0.053, respectively).

Pre-PCI MIF values were found to be predictive of the no-reflow phenomenon and the decline in left ventricular pump function following PCI. In STEMI patients, no-reflow is conventionally described as myocardial hypoperfusion related to PCI that is strongly linked to poor clinical outcomes (increased death rate and repeated short-term hospitalization), unfavorable cardiac remodeling, and the development of heart failure [34, 35]. High levels of these inflammatory cytokines in STEMI patients are believed to be a clear indicator of advanced oxidative stress recurrent ischemia-reperfusion injury to the myocardium and vasculature because MIF stimulates the inflammatory response by inducing the release of multiple inflammatory cytokines and forming NLRP3 inflammasomes from circulating leukocytes [36, 37]. Conversely, MIF inhibits the death of cardiac myocytes and endothelial cell progenitors and promotes reparative angiogenesis/neovascularization, cardiomyocyte survival, and endothelial progenitor cell differentiation/proliferation [38]. Since its peak levels remarkably reflect an adaptive response against the severity of microvascular inflammation, endothelial dysfunction, cardiac dysfunction, and remodeling, MIF can be considered an adaptive multifunctional cytokine with the ability to protect the heart and vessels and promote collateral development. It also predicts poor clinical outcomes in patients with STEMI [16, 39].

Even though several clinical investigations have documented a negative correlation between MIF levels and the left ventricular ejection fraction, contingent on the presence of T2DM and other cardiovascular comorbidities [15, 39], we were unable to establish conclusive evidence for these prior concerns in this investigation. The GRACE score, LV systolic and diastolic dimensions, LV ejection fraction, and peak troponin level were all linked with the pre-PCI MIF levels. These results were consistent with those of other researchers [17, 40]. Furthermore, we observed that elevated pre-PCI concentrations of MIF > 5033 pg/mL had a strong discriminative potency for impaired LV systolic function following PCI and that pre-PCI MIF levels > 3663 pg/mL predicted post-procedural no-reflow phenomenon. It is noteworthy that post-PCI MIF levels did not exhibit strong discriminative potency for left ventricular systolic dysfunction and had a weak ability to predict no-reflow. However, increased levels of other biomarkers, including sST2, TnI, and CRP, did not produce predictive values that might have predicted the no-reflow at all. According to Zhao *et al.* [41], the majority of patients with STEMI treated with PCI had elevated MIF levels at admission, which predicted in-hospital CV mortality and major adverse cardio-and/or cerebrovascular events (MACCE) during the hospital stay and long-term follow-up. On the other hand, there was no solid proof of any post-PCI problems using traditional biomarkers. Nonetheless, there is proof that pre-PCI sST2 might accurately predict STEMI no-reflow [42, 43]. We proposed that sST2 and MIF can predict no-reflow and MACCE in PCI-treated STEMI patients in various ways since sST2 concentrations in STEMI patients at admission were positively correlated with the degree of major coronary artery stenosis. While MIF may represent ischemia-induced preconditioning conditions in CAD patients, sST2, which is significantly linked to multivessel major coronary disease, independently predicts reperfusion damage and microvascular inflammation. However, the results of the previously published meta-analysis of 27 retrospective and prospective studies on PCI-induced myocardial dysfunction showed that high thrombus burden and primary TIMI flow ≤ 1 had a significant impact on STEMI patients' survival [44]. As a result, delayed complete reperfusion of ischaemic stenosis may be a significant co-factor that interferes with the predictive capacity of inflammatory biomarkers on no-reflow following successful PCI.

By suppressing the ischemia-induced salvage kinase pathway, the CD74/AMP-activated protein kinase signal system, and its constituents, MIF, which is crucial for ischaemic preconditioning-induced myocardial protection, may improve compromised cardiac function and adverse cardiac remodeling [40, 45]. Furthermore, MIF promotes

CXCR2 in resident cells to maintain cardiac function and decrease myocardial repair, having protective effects [46]. Eventually, MIF can prevent revascularisation damage by reducing the amount of apoptosis of injured cardiac myocytes and circulating mature and progenitor endothelial cells [46]. These findings, however, enable us to explain the likely molecular mechanisms through which pre-PCI MIF affected the recovery of coronary blood flow and the maintenance of myocardial function.

Notably, our study indicated that pre-PCI MIF and female gender were risk factors for no-reflow following primary PCI. A signature of comorbidities, such as type 2 diabetes mellitus, chronic kidney disease, and hypertension, has been proposed as a critical component to fully characterize the role of female gender in prognosis following STEMI, even though prior research has produced contradictory findings regarding the short-term, not long-term, mortality rate and adverse clinical outcomes among women following primary PTCA for STEMI [47]. We hypothesized that sex hormones and cytokines linked to white adipose tissue regulate pre-PCI levels of circulating MIF, which may have varying effects on reperfusion injury. The protective function of MIF may be mediated by sex and sex hormones that affect ectopic fat deposition and surrogate inflammatory markers [47]. However, a substantial clinical trial in the future will need to go deeper into this premise.

Study limitations

There were various restrictions on the study. Although the study's methodology enabled us to examine the discriminative value of MIF levels for post-PCI no-reflow, the first limitation was its small size. The infarct and microvascular blockage were not assessed by cardiac magnetic resonance imaging. Nevertheless, we assessed a peak value of troponin, angiographic TIMI, MBG, and ST-segment resolution during PCI, and we did not examine any other inflammatory biomarkers, aside from CRP, that could connect the rise in MIF to inflammatory responses. A selection bias might have existed, though, because the study was only carried out in one location. Nonetheless, we think that the research findings would not be sufficiently impacted by the study limitations.

Conclusion

The findings of our investigation indicate that no-reflow following primary successful PCI may be predicted by an early rise in MIF levels in STEMI.

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Conflict of Interest: None

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Ethics Statement: Following the Helsinki Declaration, this study was authorized by the local Ethics Committee of G.I. “L. T. Malaya TNI NAMSU” (Kharkiv, Ukraine) (Protocol № 5, 26.05.2016). Every patient who was included provided written, informed consent to take part in the trial.

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