Scholars LITERATURE

La Prensa Medica Argentina

Research Article

DOI: https://doi.org/10.47275/0032-745X-160
Volume 105 Issue 6

Macrophage Inhibitory Factor Predicted Late Cardiac Remodeling in Acute Myocardial Infarction Patients Underwent Successful Percutaneous Coronary Intervention

Olga VPetyunina[1], Mykola P Kopytsya[1] and Alexander E Berezin[2]*

[1]Department of prevention and treatment of emergency conditions, Government Institution LT Malaya Therapy National Institute NAMSU, Kharkiv, Ukraine
[2]Department of Internal Medicine, State Medical University of Zaporozhye, Zaporozhye, Ukraine

Abstract

Background: Macrophage inhibitory factor (MIF) plays a pivotal role in late adverse cardiac remodeling in acute ST-segment elevation myocardial infarction (STEMI). The aim of the study was to investigate the predictive role of the circulating MIF in adverse cardiacremodeling in STEMI patients undergoing percutaneous coronary intervention (PCI).

Methods: A total of 73 patients with confirmed acute STEMI successfully treated with PCI were enrolled for participation in the study. Control group was included 20 healthy volunteers. All patients signed informed consent to participate in the study. Echo and Doppler, biomarker assay and MIF determinations were performed at baseline and at 6 month after study entry.

Results: There were significant differences (P<0.001) between the levels of MIF in control group (573.75 ng/mL; 95% CI=397.80 to 1016.75 ng/mL) and entire STEMI patient population (2582.80 ng/mL; 95% CI=1308.40 to 4122.20 ng/mL). The entire STEMI patient population was divided by the median of the MIF level as follow: the first group consisted of STEMI patients with MIF ≤ 2582.80 ng/ mL (n=36), and the second group consisted of STEMI patients with the levels of MIF>2582.80 ng/mL (n=37).We found that cut-offMIF level≥2644.5ng/mlat baseline predicted adverse cardiac remodeling (AUC=0.736, 95% CI=0.515 to 0.956, P=0.0362; sensitivity=72.7%; specificity=81.8%; positive predictive value=52.7%; negative predictive value=32.4%; positive likelihood ratio=0.89 and negative likelihood ratio=0.72).

Conclusion: The MIF level ≥2644.5ng/mLmight be predictor for late adverse cardiac remodeling after STEMI.

Keywords: ST-segment elevation myocardial infarction; Adverse cardiac remodeling; Macrophage inhibitory factor; Prediction

Correspondence to: Alexander E Berezin, Department of Internal Medicine, State Medical University of Zaporozhye, Zaporozhye, Ukraine, Tel: +380612894585; E-mail: aeberezin@gmail.com

Citation: Petyunina OV, Kopytsya MP, Berezin AE (2019) Macrophage Inhibitory Factor Predicted Late Cardiac Remodeling in Acute Myocardial Infarction Patients Underwent Successful Percutaneous Coronary Intervention. Prensa Med Argent, Volume 105:6. 160. DOI: https://doi.org/10.47275/0032-745X-160.

Received: October 16, 2019; **Accepted:** October 29, 2019; **Published:** November 04, 2019

Introduction

Acute myocardial infarction (AMI) and adverse cardiac remodelling that frequently follows remain to be leading causes of cardiovascular (CV) death and heart failure (HF) development worldwide [1]. It has found that final AMI size and post-AMI HF are results of the dynamic immune cell response and inflammation, which comprises an initial pro-inflammatory reaction followed by an anti-inflammatory phase [2].Indeed, inflammation, which are involved numerous cells, such as neutrophils, monocytes/macrophages, lymphocytes, dendritic cells, pericardial lymphoid cells, progenitor precursors, endothelial cells, cardiac myocytes and fibroblasts, promotes turn over early adaptive cardiac remodeling to disadptive remodeling and shaping HF [3]. For instance, myocardial healing and hypertrophy, scar forming and expansion, extracellular matrix accumulation, fibrosis, are under dynamic control of circulating and vesicle-derived inflammatory mediators, growth factors, chemokines, and neurohormons [4-6].

Macrophage inhibitory factor (MIF) is defined as pleotropic multifunctional cytokine with inflammatory chemokine properties, which acts as inflammation regulator and mediator of congenital and acquired immunity, neoangiogenesis, vasculogenesis, and glucose homeostasis [7]. MIF is highly expressed and released from immune cells (macrophages, monocytes, T-lymphocytes, endothelium), cardiac myocytes, fibroblasts in response of hypoxia/ischemia, endotoxins, oxidative stress, and due to direct effect of several pro-inflammatory cytokines, such as interleukin-6, hypoxia induce factor-1 alpha [8]. Elevated serum levels of MIF were found in patients with multifocal atherosclerosis across all stages of plaque formation and rupture, acute coronary syndrome, acute MI [9].

The role of MIF in pathogenesis of AMI and post-AMI cardiac remodelling appears to be controversial. MIF showed both tissue

protective ability and direct tissue damage effect in patients with AMI depending on pre-conditioning and post-conditioning period [10, 11]. Indeed, cardiac protective actions of MIFwere accompanied byMAPK and PI3K/Akt/mTOR pathways, and mediated glucoseuptake, oxidative stresss uppression, and apoptosis inhibition that were associated with stem cell proliferation and differentiation of endothelial progenitor cells in myocardium and vasculature around infarct zone [12, 13]. On contrary, MIF was able to influence on migration of inflammatory, antigen-presentingand immune cells into damaged areaand attenuate ischemia-induced adverse cardiac remodeling [14]. In fact, early coronary intervention have been considered as a leading factor for improvement of survival and preventing cardiac remodeling and HF among STEMI patients [15], while there is limiting evidence regarding discriminative value of circulating MIF for cardiac remodeling and HF after successful percutaneous coronary intervention (PCI) in AMI [16]. The aim of the study was to investigate the predictive role of the circulating MIF in adverse cardiacre modeling in patients with acute ST-segment elevation myocardial infarction (STEMI) under going PCI.

Materials and Methods

Patients' population

A total of 268 patients with confirmed acute STEMI were screened for participation in the study. Control group was included 20 healthy volunteers. Flowchart of the study design is shown in Figure1. From the entire population of STEMI (n=268) and according to the inclusion and non-inclusion criteria, 177 individuals who were admitted to intensive care unit of GI "L.T. Malaya TNI NAMSU" with acute STEMI within 2-12 hours of symptoms onset in between August 2016 and July 2018 were enrolled into the study. STEMI was diagnosed according to the ECS Guidelines (2017) [17]. Inclusion criteria included known STEMI, age>18 years old, and lack of contraindication to PCI. Non-inclusion criteria included previous myocardial infarction, established chronic HF, known malignancy, severe comorbidities (anemia, chronic obstructive lung disease, bronchial asthma, liver cirrhosis, chronic kidney disease, valvular heart disease, bleeding), inability to understand of written informed consent. The final study cohort retrospectively included 73 patients with confirmed STEMI after primary or facilitated PCI with successful revascularization of TIMI-III. Primary PCI with bare-metal stent (COMMANDER, "Alvimedica", Turkey) implantation was performed in 43 patients, and 30 patients were previously treated with primary thrombolysis (tenecteplase, alteplase) as a rescue procedure before admission, which was followed by PCI within six to twelve hours after the initial STEMI confirmation. Thrombolysis was done with tenecteplase (Metalise, Boehringer Ingelheim Pharma, Germany), depending on patients weight and was not more than 50 mg iv bolus. Alteplase (Actilyse, Boehringer Ingelheim Pharma, Germany) 100 mg was infused intravenously for two hours. All investigated patients received adjuvant treatment according to the current ESC recommendations.

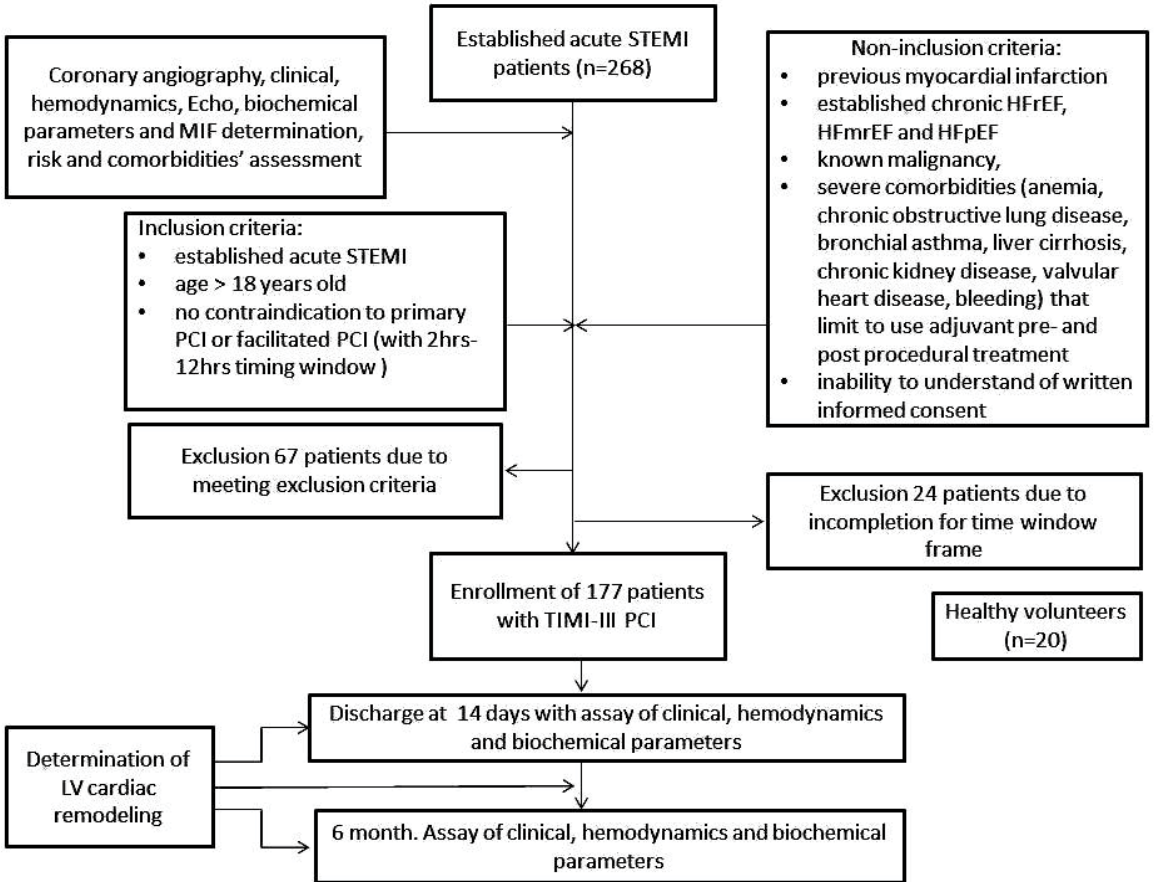

Figure 1: The flow chart for study design. Abbreviations: STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; HF, heart failure; HFrEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; HFmrEF, HF with mid-range ejection fraction; CAD, coronary artery disease; LV, left ventricular.

Ethical declaration

The study complied with the Declaration of Helsinki and was approved by the local ethics committee in the Government Institution "L.T. Malaya Therapy National Institute NAMSU", Kharkiv, Ukraine (Protocol №8, 29.08.2016). All patients signed informed consent to participate in the study.

Coronary angiography

Conventional coronary angiography was performed using Digital X-Ray system "Integris Allura" (Philips Healthcare, Best, The Netherlands) and managed by radial or femoral vascular access. Coronary arteries were visualized with two-to-three orthogonal projections. In this study, the contrast "Ultravist-370" (Bayer Pharma GmbH, Germany) and automatic contrast injector were used. The contrast amount used in coronary angiography in each injection was 8 – 10 mL at 4 mL/s for the left coronary artery and 6 mL at 3 mL/s for the right coronary artery (radiation exposure 20 to 35 mGycm). The number of views obtained was decided by the operator depending on coronary anatomy. The coronary arteries were divided into segments according to the American Heart Association classification

Determination of risk factors and comorbidities

Hypercholesterolemia (HCE) was diagnosed if the total cholesterol (TC) level was above 5.2 mmol/L, and/or the low-density lipoprotein cholesterol (LDL) level was above 3.0 mmol/L, and/or the level of triglycerides (TG) was above 1.7 mmol/L according to the European Cardiology Society dyslipidemia guideline (2016) [18]. Hypertension was diagnosed if the systolic blood pressure (SBP) was >140 mm Hg, and/or the diastolic blood pressure (DBP) >90 mm Hg according to the European guideline on diagnostics and treatment of arterial hypertension, 2018 [19]. Newly diagnosed HF was verified according to ESC guidelines (2016) [20]. Type 2 diabetes mellitus was determined according to the new ADA statement (2017) [21].

Echo and Doppler examination

Echo-CG was performed on "Sono Ace X6" ultrasound station (Medison, South Korea) by using a phase probe with an ultrasound frequency of 3.5 MHz atdischarge and at six-month post-PCI. Left ventricular (LV) end diastolic volume (EDV), LV end systolic volume (ESV), left atrium volume (LAV), LV ejection fraction (EF) were measured according to Simpson's biplane method [22].

Determination of late adverse cardiac remodeling

Late adverse cardiac remodeling was defined as increased LVEDV (>10% from baseline) and/or LVESV (>10% from baseline) over next six months afteracute STEMI managed by PCI or occurrence of newly diagnosed HF [23].

Physical exercise examination

6-minute walking test was performed at 6-month to identify clinical significance of cardiac remodeling and identify severity of HF according to ESC guidelines (2016) [20].

Sample size calculation

The sample size was calculated through the effect size estimated (0.99), the type of present study, providing study power of 80% and type I error 5% [24]. The sample size is at least 170 individuals.

Calculation of glomerular filtration rate

Glomerular filtration rate (GFR) was calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [25].

Blood samples

Blood samples were drawn immediately before PCI at baseline and at six month of post-PCI period. Blood samples were centrifuged, serum was isolated within 30 minutes of sample acquisition, and then they were stored in plastic tubes and frozen at -70 C until being shipped to the laboratory of immunechemical and molecular-genetic researches of GI "L.T. Malaya TNI NAMSU".

Troponin I (Tn I) level was measured by chemo luminescent immuno assay (Humalyzer 2000, HUMAN GmbH, Germany) according to the manufacturers' recommendations. The average of Tn I level was 0.5-50 ng/mL.

Total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG) were measured by direct enzymatic method (Roche P800 analyzer, Basel, Switzerland). The intra-assay and inter-assay coefficients of variation were <5%.

Fasting glucose level was measured by double-antibody sandwich immunoassay (Elecsys 1010 analyzer, F. Hoffmann-La Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficients of variation were <5%.

MIF levels were measured using Humalyzer 2000 (HUMAN GmbH, Germany) by the enzyme linked immunoassay method (RayBio® Human MIF ELISA KIT, USA)

Statistics

Statistical analyses were performed using SPSSfor Windows v. 23 (IBM, USA). Continuous variables are presented as mean± standard deviation and mean and 95% confidence interval (CI) when they were normally distributed, or median and interquartile range if otherwise. Categorical variables are presented as frequencies and percentages. Mann-Whitneyand Wald-Wolfowitz criteria were used for intergroup differences and quantitative values. The qualitative variables are expressed as percentages, and were analyzed by the χ^2 test and exact Fisher test. Receiver operating characteristic (ROC)curve was performed for detection of well-balanced cut-offof MIF concentrations. Areaundercurve (AUC), sensitivity and specificity were calculated for cut-off point. All differences were considered statistically significant with 2-tailed P<0.05.

Results

Entire STEMI patient population was consisted male and female (72.6%/27.4%) with hypertension (69.9%), hypercholesterolemia (72.6%), obesity (35.6%), and stable angina prior to STEMI (30.1%). At least 67% of patients included in the study were smokers. Table 1 is reported clinical characteristic of included patients with STEMI.

There were significant differences (P<0.001) between the levels of MIF in control group (573.75 ng/mL; 95% CI=397.80 to 1016.75 ng/mL) and entire STEMI patient population (2582.80 ng/mL; 95% CI=1308.40 to 4122.20 ng/mL) (Figure 2). The entire STEMI patient population was divided by the median of the MIF level as follow: the first group consisted of STEMI patients with MIF ≤ 2582.80 ng/ mL (n=36), and the second group consisted of STEMI patients with the levels of MIF>2582.80 ng/mL (n=37). The only variable that was yielded a significant difference (P=0.034)between both subgroups depending on MIF levels was frequency of stable angina before STEMI (Table 1).

Table 1: Basic clinical characteristic of researched patients with acute STEMI.

Data	Entire population (n=73)	MIF level ≤2582.80 ng/mL (n=36)	MIF level >2582.80 ng/mL (n=37)	χ^2 value / P value
Age, years	58.37± 10.34	57.44± 9.37	59.03± 11.48	0.521
Male, n (%)	53 (72.6)	24 (66.7)	29 (78.2)	1.26 p=0.262
Female, n (%)	20 (27.4)	12 (33.3)	8 (21.8)	
Hypertension, n (%)	51 (69.9)	28 (77.8)	23 (62.2)	2.11 p=0.146
T2DM, n (%)	5 (6.8)	4 (11.1)	1 (2.7)	0.92 p=0.338
BMI>30,kg/m^2	26 (35.6)	15 (46.7)	11 (29.7)	1.13 p=0.287
HCE, n (%)	53 (72.6)	26 (72.2)	27 (73.0)	0.01 p=0.943
Smoking, n (%)	49 (67.1)	23 (63.8)	26 (70.3)	0.34 p=0.562
Stable angina before STEMI	22 (30.1)	15 (41.7)	7 (18.9)	4.48 p=0.034
GFR, ml/min/1.73 m^2	83.22 [69.77-107.41]	85.35 [72.05-106.92]	82.14 [66.36-107.46]	0.566
TC, mmol/l	5.25± 1.26	5.41± 1.33	5.17± 1.21	0.425
HDL, mmol/l	1.05± 0.30	1.06± 0.31	1.05± 0.30	0.999
LDL, mmol/l	3.18± 1.24	3.07± 1.43	3.32± 1.06	0.403
Troponin I, ng/ml	27 [11-38]	23 [10-31]	27 [14-36]	0.043
Peripheral blood leucocytes, *10^9/l	10.8 [8.3-12.3]	9,8 [8.3-10.3]	11.7 [7.9-12.8]	0.011
MIF, ng/ml	2582.80 [1308.40-4122.20]	1277.85 [556.70-1931.80]	3954.00 [3076.30-4964.30]	<0.001

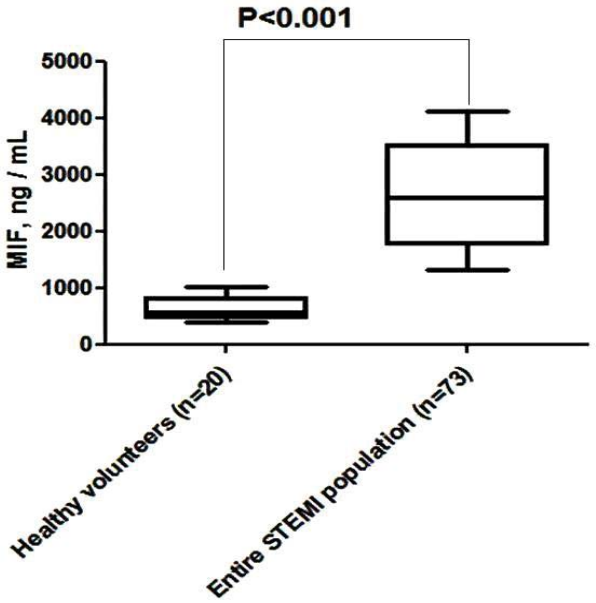

Figure 2: Circulating levels of MIF in healthy volunteers and patients with known STEMI.

Other variables did not differ between patients in both subgroups.

Where: BMI – body mass index; T2DM – type 2 diabetes mellitus; GFR – glomerular filtration rate; HCE – hypercholesterolemia; HDL – high density cholesterol; MI – myocardial infarction; MIF – macrophage inhibitory factor; TC - total cholesterol; LDL - low-density lipoprotein; HDL -high-density lipoprotein.

Table 2 is reported angiographic and clinical data among STEMI patients. Anterior myocardial infarction and LAD injury observed more frequently in the second group, with the level of MIF higher median (P=0.047; P=0.016 respectively) and together with significantly higher troponin I level indicates a direct connection with MI size.

Hemodynamic status in STEMI patients at baseline and at 6-month observation has shown in Table 3. There was not significant differences between subgroups of STEMI patients with up and bottom mean levels of MIF in majority of hemodynamic characteristics and distance of 6-minute walking, but significant increase in LVEDV was defined in patients with MIF level >2582.80 ng/mL. Additionally, serum levels of MIF in STEMI patients were significantly (P=0.017) higher in patients with 6-month post-STEMI LV dilation (4122.16 ng/mL; 95% CI = 2869.10 to 5399.70 ng/mL) versus not having it (2044.65 ng/mL; 95% CI = 585.50 to 2644.50 ng/mL).

We also determined positive linear relation between serum levels of MIF, and concentrations of troponin I (r=0.33; P=0.045), peripheral blood leukocytes (r=0.36; P=0.039), T2DM (r=0.31; P=0.048), and appearance of 6-month post-STEMI LV dilation (r=0.44; P=0.044). The inverse relation was fond between MIF levels and GFR (r=-0.32; P=0.044). There were not significant associations between serum levels of MIF, and age, sex, HCE, hypertension, smoking, and medical therapies.

ROC-analysis was performed to find MIF level, which could predict adverse remodeling at 6-month observation period in STEMI patient underwent PCI (Figure 3). We found that cut-off MIF level≥2644.5 ng/mL at baseline predicted adverse cardiac remodeling (AUC = 0.736, 95% CI = 0.515 to 0.956, P=0.0362; sensitivity=72.7%; specificity =81.8%; positive predictive value = 52.7%; negative predictive value = 32.4%; positive likelihood ration = 0.89 and negative likelihood ration = 0.72).

Discussion

The results of our study have demonstrated that elevated levels of MIF had predictive ability to late adverse cardiac remodeling in STEMI patients underwent successful PCI. This fact can be interpreted as pre- and post-conditioned impact on myocardiumprobably through collateral development and prevention of remote ischemic/reperfusion injury.Indeed, it has been found that AMI with good developed collateral vasculature around infarct area had less infarct size and lower mortality compared with those who had poor collateralization [26]. Our study has revealed more frequent LAD injury in the group with higher levels of MIF, which indirectly indicates more severe is chemia and subsequent necrosis of anterior LV wall. Our data is comparable with

Table 2: Angiographic and clinical data of the STEMI patients.

Data	Entire population (n=73)	MIF level ≤2582.80 ng/mL (n=36)	MIF level>2582.80 ng/mL (n=37)	χ^2 value / P value
STEMI localization				
Anterior, n (%)	39 (53.4)	15 (41.6)	24 (64.9)	3.95 p=0.047
Posterior, n (%)	32 (43.8)	19 (52.7)	13 (35.1)	2.31 p=0.129
Amount of injured coronary arteries				
One, n (%)	37 (50.7)	19 (52.7)	18 (48.6)	0.12 p=0.724
Two, n (%)	21 (28.8)	9 (25.0)	12 (32.7)	0.49 p=0.483
Three and more, n (%)	14 (19.2)	7 (19.4)	7 (18.9)	0.06 p=0.810
Amount of coronary artery stenosis				
One artery, n (%)	31 (42.5)	16 (44.4)	15 (40.5)	0.11 p=0.736
Two and more stenotic arteries, n (%)	42 (56.2)	20 (52.8)	22 (59.5)	0.33 p=0.565
Injured coronary arteries				
Left main, n (%)	4 (5.5)	2 (3.2)	2 (5.4)	0.682 p=0.520
LAD, n (%)	52 (71.2)	21 (58.3)	31 (83.8)	5.77 p=0.016
RCA, n (%)	41 (56.2)	24 (66.7)	17 (45.9)	3.18 p=0.075
Circumflex, n (%)	28 (38.4)	14 (38.9)	14 (37.8)	0.01 p=0.926
Complications of STEMI				
General amount, n (%)	17 (23.3)	9 (25.0)	8 (21.6)	0.12 p=0.949
Killip II-III, n (%)	5 (6.8)	2 (5.6)	3 (8.1)	0.003 p=0.513
Killip IV, n (%)	2 (2.7)	1 (2.8)	1 (2.7)	0.0001 p=0.747
Adverse cardiac remodeling after 6 month	29 (39.7)	12 (33.3)	17 (45.9)	5.45 p=0.02
Procedures and medications				
PCI, n (%)	43 (58.9)	17 (47.2)	25 (67.6)	2.31 p=0,129
TLT+PCI, n (%)	30 (41.1)	19 (52.8)	12 (32.4)	3.13 p=0,077
ACEi/ARAII, n (%)	59 (80.82)	34 (94.44)	25 (67.57)	6.82 p=0,009
β-blockers, n (%)	61 (83.6)	27 (83.3)	34 (94.6)	0.052 p=0,050
Statin, n (%)	73 (100)	36 (100)	37 (100)	-
Aspirin, n (%)	73 (100)	36 (100)	37 (100)	-
Clopidogrel, n (%)	48 (65.8)	22 (61.1)	26 (70.3)	0.68 p=0,410
Ticagrelor, n (%)	25 (34.2)	12 (33.3)	13 (35.1)	0.03 p=0,871
MKRA, n (%)	5 (6.8)	2 (5.6)	3 (8.1)	0.003p=0,513

Where:ACEi– angiotensin converting enzyme inhibitors, ARAII – antagonist of receptors to angiotensin II,MKRA– antagonist of mineralocorticoid receptor, PCI – percutaneous coronary intervention, RCA – right coronary artery; LAD – left artery descending; TLT – thrombolytic therapy.

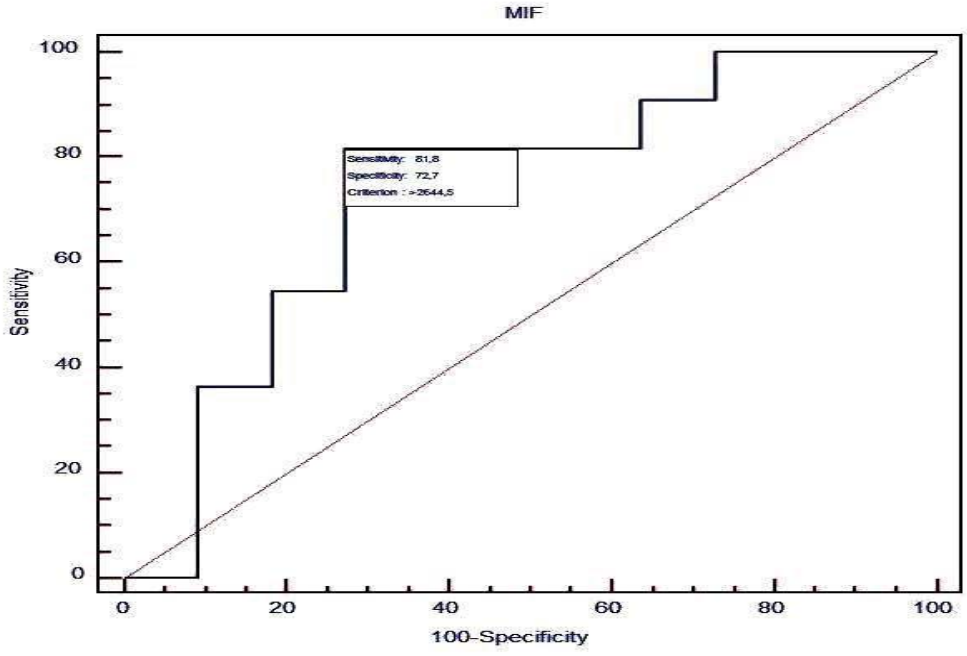

Figure 3: The 6-month predictable power of serum MIF in adverse left ventricular remodeling in STEMI patients underwent PCI. The results of ROC-analysis.

Table 3: Hemodynamic variables in STEMI patients at baseline and at 6-month of observation period.

Data	Period of observation	Entire population (n=73)	MIF level ≤2582.80 ng/mL (n=36)	MIF level >2582.80 ng/mL (n=37)	P value
SBP, mmHg	Baseline	129.22 ± 19. 93	131.33 ± 19.47	127.16 ± 20.43	0.363
SBP, mmHg	6 month	133.96 ± 16. 48	134.29 ± 17.42	129.00 ± 15.06	0.169
P value		0.120	0.499	0.662	
DBP, mmHg	Baseline	78.18 ± 10. 35	80.08 ± 9.36	76.32 ± 11.04	0.087
DBP, mmHg	6 month	80.50 ± 10. 13	80.71 ± 9.32	80.00 ± 11.56	0.774
P value		0.173	0.776		
HR, bpm	Baseline	75.01 ± 13. 99	72.83 ± 13.20	77.14 ± 14.57	0.297
HR, bpm	6 month	71.71 ± 11. 57	68.29 ± 10.36	72.53 ± 13.03	0.129
P value		0.123	0.109	0.156	
LVEDV, mL	Baseline	133.09 ± 30. 68	132.16 ± 33.33	134.00 ± 28.31	0.877
LVEDV, mL	6 month	139.43 ± 21. 92	119.41 ± 23.75	143.88 ± 26.59	0.006
P value		0.153	0.066	0.047	
LV ESV, mL	Baseline	61.51 ± 24. 42	59.23 ± 23.32	63.72 ± 25.57	0.477
LV ESV, mL	6 month	68.79 ± 34.22	61.30 ± 18.53	69.25 ± 21.05	0.092
P value		0.141	0.678	0.313	
Mitral regurgitation I-II, n (%)	Baseline	38 (52.05%)	22 (61.11%)	16 (43.24%)	0.131
Mitral regurgitation I-II, n (%)	6 month	41 (56.2%)	23(63.9%)	18 (48.6%)	0.192
P value		0.616	0.800	0.647	
LVMM, g	Baseline	225.49 ± 56. 48	221.48 ± 55.02	229.50 ± 58.41	0.521
LVMM, g	6 month	227.51 ± 38.42	223.87 ± 41.56	231.41 ± 36.84	0.415
P value		0.801	0.836	0.867	
LAV, mL	Baseline	60.41 ± 19.28	59.17 ± 23.27	61.15 ± 17.42	0.681
LAV, mL	6 month	61.12 ± 20.37	60.32 ± 19.48	62.52 ± 21.54	0.649
P value		0.829	0.821	0.764	
LVEF, %	Baseline	52.15 ± 9. 32	53.39 ± 7.00	50.94 ± 11.09	0.380
LVEF, %	6 month	53.25 ± 10. 10	55.24 ± 6.97	54.84 ± 11.60	0.859
P value		0.495	0.265	0.144	
6-minute walking test, meters	6 month	428.4 ± 100. 6	446.3 ± 64. 6	416.5 ± 120. 1	0.193

Where:DBP – diastolic pressure; SBP - systolic pressure;LAV – left atrium volume; LV EDV– left ventricular end diastolic volume; LV ESV- left ventricular end systolic volume; LVEF- left ventricular ejection fraction.

the results received by Chan W, et al. (2013) [14]. Authors have found positive correlation between the MIF level and MI size, heart chambers and negative relation to LVEF at 3rd day and 3rd month after index event. Therefore, elevated levels of MIF become independent predictor of multiple coronary artery stenosis and presence of vulnerable plaque in patients with acute coronary syndrome [27]. In this way, positive correlation between MIF and number of circulating leucocyte in peripheral blood that was established in our study clarifies that late inflammatory response can be important modulator of adverse cardiac remodeling in STEMI even after successful PCI. Although previously it has been determined the fact of strong positive association between elevated levels of MIF and poor clinical outcomes in STEMI patients [28,29], we first reported that similar relation could be determined in STEMI patients underwent successful reperfusion procedure. In this context, we can agree that MIF might become a target molecule for cardio protective response in the future, while there are controversial issue regarding this assumption [30].

However, we found that thelevels of MIF ≥2644.5 ng/mL were associated with adverse cardiac remodeling, while there were other co-comorbidities (hypertension, T2DM, obesity) that could influence on the result. This is study limitation, which should be solved in the future in the larger clinical study with greater sample size. The findings might have serious clinical significant, because asymptomatic adverse cardiac remodeling in STEMI patients in remote period is associated with newly HF manifestation. Moreover, complete revascularization frequently prevents HFrEF, but did not HFpEF due to presentation of metabolic comorbidities, such as T2DM and abdominal obesity. However, negative impact on survival of both HF phenotypes is similar. Indeed, Luedike P, et al. (2018, 2018) [31,32] have showna strong positive association between serum levels of MIF with 180-day HF clinical outcomes, all-cause death and hospitalization in patients with HFpEF. Interestingly, MIF has been also found as independent from conventional cardiovascular risk factors the predictor of impaired cardiac function and long-term prognosis in patients with AMI and HF [33]. Yet, there was suggestion regarding cardio protective role of elevated MIF in acute phase of STEMI. It has assumed that pre-conditioning effect can be mediated by MIF over expression and that collateral vascularization, myocardial fibrosis and extracellular matrix accumulation in area around infarct zone are under direct control of MIF. In this case, elevation of MIF is favorable response directed to prevention of adverse cardiac remodeling and remote HF manifestation. Large clinical studies are required to understand the role of MIF at various stage of nature evolution of STEMI, especially in patients with complete successful revascularization.

In conclusion, elevatedlevel of MIF might be suggested as predictor for late adverse cardiac remodeling in STEMI patients underwent successful PCI.

References

1. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, et al. (2017) Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. Eur Heart J 38:3056-3065.

2. Andreadou I, Cabrera-Fuentes HA, Devaux Y, Frangogiannis NG, Frantz S, et al. (2019) Immune cells as targets for cardioprotection: new players and novel therapeutic opportunities. Cardiovasc Res 115:1117-1130.

3. Ong SB, Hernández-Reséndiz S, Crespo-Avilan GE, Mukhametshina RT, Kwek XY. et al. (2018) Inflammation following acute myocardial infarction: Multiple players, dynamic roles, and novel therapeutic opportunities. Pharmacol Ther 186:73-87.

4. Mantovani A, Cassatella MA, Costantini C, Jaillon S (2011) Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol11:519-531.

5. Montecucco F, Braunersreuther V, Lenglet S, Delattre BM, Pelli G, et al. (2012) CC chemokine CCL5 plays a central role impacting infarct size and post-infarction heart failure in mice. Eur Heart J 33:1964-1974.

6. Mezzaroma E, Toldo S, Farkas D, et al. (2011) Theinflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. ProcNatlAcadSci USA108:19725-19730.

7. Asare Y, Schmitt M, Bernhagen J (2013) The vascular biology of macrophage migration inhibitory factor (MIF) Expression and effects in inflammation, atherogenesis and angiogenesis. Thromb Haemost 109:391-398.

8. Fan F, Dart AM (2015) GW26-e1326 Exercise induced myocardial but not peripheral muscle ischemia is associated with rise in plasma macrophage migration inhibitory factor (MIF). Journal of the American College of Cardiology 66: 131-132.

9. Sinitski D, Kontos C, Krammer C, Asare Y, Kapurniotu A, et al.(2019) Macrophage migration inhibitory factor (mif)-based therapeutic concepts in atherosclerosis and inflammation. Thromb Haemost 119: 553-566.

10. White DA, Su Y, Kanellakis P, Kiriazis H, Morand EF, et al. (2014) Differential roles of cardiac and leukocyte derived macrophage migration inhibitory factor in inflammatory responses and cardiac remodelling post myocardial infarction. J Mol Cell Cardiol 69: 32-42.

11. Dayawansa NH, Gao XM, White DA, Dart AM, Du XJ (2014) Role of MIF in myocardial ischaemia and infarction: insight from recent clinical and experimental findings. Clin Sci Lond 127: 149-161.

12. Cui J, Zhang F, Wang Y, et al.(2016) Macrophage migration inhibitory factor promotes cardiac stem cell proliferation and endothelial differentiation through the activation of the PI3K / Akt / mTOR and AMPK pathways. Int J Mol Med 37: 1299-309.

13. Chan W, White DA, Wang X-Y, Bai R-F, Liu Y, et al.(2013) Macrophage migration inhibitory factor for the early prediction of infarct size. J Am Heart Assoc 2:e000226.

14. Cahill TJ, Kharbanda RK (2017) Heart failure after myocardial infarction in the era of primary percutaneous coronary intervention: Mechanisms, incidence and identification of patients at risk. World J Cardiol 9:407-415.

15. Yu H, Wang X, Deng X, Zhang Y, Gao W(2019) Correlation between plasma macrophage migration inhibitory factor levels and long-term prognosis in patients with acute myocardial infarction complicated with diabetes. Mediators of inflammation 8276180: 1-9.

16. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, et al. (2018) ESC Scientific Document Group ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 39: 119-177.

17. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, et al. (2016) ESC scientific document group.2016 ESC/EAS guidelines for the management of dyslipidemias: the task force for the management of dyslipidemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 253: 281-344.

18. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, et al. (2018) ESC Scientific Document Group.2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 39: 3021-3104.

19. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, et al. (2016) ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18: 891-975.

20. Standards of medical care in diabetes-2017: summary of revisions (2017) Diabetes Care 40:S4-S5.

21. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, et al. (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 28: 1-39.

22. Quiñones MA, Douglas PS, Foster E, Gorcsan J 3rd, Lewis JF,et al. (2003) ACC/AHA clinical competence statement on echocardiography: a report of the American College of Cardiology/American Heart Association/American College of Physicians-American Society of Internal Medicine Task Force on Clinical Competence.J Am CollCardiol 107:1068-1089.

23. Kirby A, Gebski V, Keech AC (2002) Determining the sample size in a clinical trial. Med J Aust177:256–257.

24. Levey AS1, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, et al. (2009)A new equation to estimate glomerular filtration rate. Ann Intern Med 150: 604-612.

25. Di Serafino L, Bartunek J, Heyndrickx G, Dierickx K, Scognamiglio G, et al. (2018) Macrophage migration inhibitory factor (MIF) is associated with degree of collateralization in patients with totally occluded coronary arteries. Int J Cardiol 262: 14-19.

26. Müller II, Müller KA, Schönleber H, Karathanos A, Schneider M, et al.(2012) Macrophage migration inhibitory factor is enhanced in acute coronary syndromes and is associated with the inflammatory response. PLoS One 7: e38376.

27. Deng XN, Wang XY, Yu HY, Chen SM, Xu XY, et al. (2018) Admission Macrophage Migration inhibitory factor predicts long-term prognosis in patients with ST-segment elevation myocardial infarction. JACC 77: 240.

28. Deng X, Wang X, Zhang Y, Dart A, Du X, et al. (2018) Higher macrophage migration inhibitory factor levels identify reperfusion inefficiency in patients with acute myocardial infarction. JACC 71: 62.

29. Rassaf T, Weber C, Bernhagen J (2014) Macrophage migration inhibitory factor in myocardial ischaemia/reperfusion injury. Cardiovasc Res 102:321-328.

30. Luedike P, Alatzides G, Papathanasiou M, Heisler M, Pohl J, et al. (2018) Circulating macrophage migration inhibitory factor (MIF) in patients with heart failure. Cytokine110:104-109.

31. Luedike P, Alatzides G, Papathanasiou M, Heisler M, Pohl J, et al. (2018) Predictive potential of macrophage migration inhibitory factor (MIF) in patients with heart failure with preserved ejection fraction (HFpEF). Eur J Med Res 23:22.

32. Zernecke A, Bernhagen J, Weber C (2008) Macrophage migration inhibitory factor in cardiovascular disease. Circulation 117: 1594-1602.

33. Zhou B, Ren C, Zu L, Zheng L, Guo L, et al. (2016) Elevated plasma migration inhibitory factor in hypertension-hyperlipidemia patients correlates with impaired endothelial function. Medicine (Baltimore) 95: e5207.