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Key words: ST-segment elevation myocardial infarction; Adverse cardiac remodeling; Macrophage inhibitory factor; Prediction.
INTRODUCTION

Acute myocardial infarction (AMI) and adverse cardiac remodeling that frequently follows remain to be leading causes of cardiovascular (CV) death and heart failure (HF) development worldwide[16]. It has been 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[22]. 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 disadaptive remodeling and shaping HF[4]. 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[14-16].

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[3]. 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[9]. 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[8,10,11]. Indeed, cardiac protective actions of MIF were accompanied by MAPK and PI3K/Akt/mTOR pathways, and mediated glucose uptake, oxidative stress suppression, 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-presenting and immune cells into damaged area and 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[14], 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 cardiac remodeling in patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing PCI.

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 Figure 1. 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.

Ethical declaration

The study complied with the Declaration of Helsinki and was approved by the local ethics committee (Protocol №68, 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 mGym). 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[18]. 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 at discharge 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].
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 SPSS for 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-Whitney and Wald-Wolfowitz criteria were used for intergroup differences and quantitative values. The qualitative variables are expressed as percentages, and were analyzed by the χ² test and exact Fisher test. Receiver operating characteristic (ROC) curve was performed for detection of well-balanced cut-off of MIF concentrations. Area under curve (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 follows: the first group consisted of STEMI patients with MIF $\leq$ 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 yielded a significant difference ($p = 0.034$) between both subgroups depending on MIF levels was frequency of stable angina before STEMI (Table 1). Other variables did not differ between patients in both subgroups.

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 found 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, BMI, TC, LDL, HDL, smoking, and T2DM.

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

| Data                        | Entire population ($n=73$) | MIF level $\leq$2582.80 ng/mL ($n=36$) | MIF level $>2582.80$ ng/mL ($n=37$) | $\chi^2$ value $/ \beta$ 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)                             | 1.05 $p = 0.30$                 |
| 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 [69.77-107.47]      | 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, $x10^3$/L | 10.8 ± 8.3-12.3       | 9.8 [8.3-10.3]                        | 11.7 [9.7-12.8]                      | 0.011                           |
| MIF, ng/mL                  | 2582.80 [1308.40-4122.20] | 1277.85 [556.70-1931.80]               | 3954.00 [3076.30-4964.30]            | $<0.001$                        |

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 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) | $\chi^2$ 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 (%)                 | 21 (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        |                           |                                   |                                   |                        |
| PCl, 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)                  | 56 (100)                          | 17 (100)                          | -                     |
| Aspirin, n (%)                    | 73 (100)                  | 56 (100)                          | 17 (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)                           | 0.003 p = 0.513       |

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

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 myocardium probably 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 (39).

Our study has revealed more frequent LAD injury in the group with higher levels of MIF, which indirectly indicates more severe ischemia and subsequent necrosis of anterior LV wall. Our data is comparable with the results received by Chan W et al. (40) (2013). 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 (24, 25), 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 cardioprotective response in the future, while there are controversial issue regarding this assumption (39).

However, we found that the levels of MIF ≥ 2644.5 ng/mL were associated with adverse cardiac remodeling, while there were other co-morbidities (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 asymptom-
Elevated level of MIF might be suggested as predictor for late adverse cardiac remodeling in STEMI patients underwent successful PCI.

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