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The macrophage migration inhibitory factor as a predictive biomarker of one-year adverse clinical outcomes in ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention

Tatyana Y. Storozhenko[1], Iryna R. Vyshnevska[1], Mykola P. Kopytsya[1], Alexander E Berezin[2]

[1]Department of Prevention and Treatment of Emergency Conditions, Government Institution "L.T.Malaya Therapy National Institute NAMSU", Ukraine
[2]Internal Medicine Department, State Medical University of Zaporozhye, Ukraine

Abstract— The aim of the study was to elucidate a plausible predictive value of the macrophage migration inhibitory factor (MIF) levels for one-year clinical outcomes in ST-segment elevation myocardial infarction (STEMI) patients underwent primary percutaneous coronary intervention (PCI). Materials and methods: 134 STEMI patients underwent PCI were enrolled in the study. The MIF levels were determined at baseline, directly prior and after PCI along with conventional observations. Results. During 1-year follow-up 37% of patients has reached the compositeendpoint (all-cause mortality, non-fatal STEMI, and non-fatal stroke, hospitalization for unstable angina, heart failure decompensation, and PCI). We have found that pre-PCI MIF levels > 3934 pg/mL might be an independent predictor of composite endpoints with sensitivity 54% and specificity 82%. Positive correlation between MIF and inflammatory biomarkers was revealed. Adverse outcomes associated with higher pre- and post-PCI MIF levels (OR 1.0, 95% CI 1.0001–1.0008; p=0.013 and OR 1.0, 95% CI 1.0001–1.0009; p=0.019) and CRP that determined during the first week after the event (OR 1.0, 95% CI 1.005–1.2, p=0.03). Kaplan-Meier analysis has shown substantially lower long-term survival rate in patients with the MIF level > 3493 pg/ml when compared with the MIF level ≤ 3493 pg/ml.
Conclusions:The MIF levels exceeded 3934 ng/ml were associated with the higher risk of one-year adverse clinical outcome in STEMI patients underwent primary PCI.

Keywords: macrophage migration inhibitory factor, ST-segment elevation myocardial infarction, primary percutaneous coronary intervention, prognosis.

1. Introduction

Previous clinical studies have revealed that early reperfusion with primary percutaneous coronary intervention (PCI) substantially decreases in-hospital mortality in ST-segment elevation myocardial infarction (STEMI) patients [1, 2]. However, the rate of long-term adverse clinical events in STEMI individuals after PCI remains significant due to delaying procedure and occurrence of no-reflow phenomenon [3, 4]. Over the past decades, biomarkers of inflammation and fibrosis have been deeply considered as diagnostic and prognostic tools in myocardial infarction [5]. Providing of new biomarkers that have ability to predict cardiovascular events at exceedingly early stage of STEMI to routine clinical practice will improve the further outcome [6, 7].

Pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) is one of the promising biomarkers for the early adverse outcome prediction in STEMI patients [8]. MIF as a mediator of many acute and chronic inflammatory diseases has several unique biological effects, including cardioprotection in the acute phase of ischemia and modulating inflammatory responses in prolonged myocardial ischemia [9-11]. The aim of the study was to elucidate a plausible predictive value of the MIF levels for one-year clinical outcomes in STEMI patients underwent primary percutaneous coronary intervention (PCI).

2. Materials and methods

2.1 Study populationand design: The study prospectively enrolled 134 STEMI patients, who were admitted to the intensive care unit of the Government Institute “LT Malaya Therapy National Institute of the NAMS of Ukraine” from October 2018 to December 2020. The revascularization of infarct-related artery was urgently performed at the department of interventional cardiology of the GI "VT Zaitsev Institute of General and Emergency Surgery of the NAMS of Ukraine". Inclusion criteria were established acute STEMI with <12 hours timing window for PCI, age > 18 years old. According to inclusion and exclusion criteria, the final cohort consisted of 120 patients. Patients having one more of the following criteria were excluded: liver cirrhosis, acute kidney failure that require hemodialysis, active malignancy, chronic inflammatory disease in acute phase. Twenty-five healthy individuals, comparable in age and gender, without history of cardiovascular diseases were enrolled in the control group.During the enrollment process the medical history, physical examination, laboratory, and instrumental investigations were assessed by the study protocol. The study flow chart is presented in Figure 1.

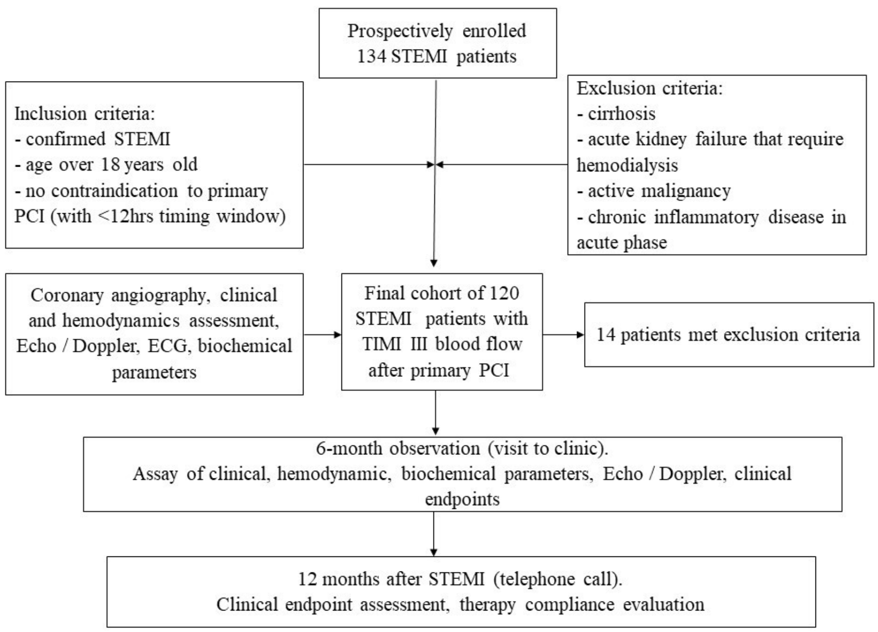

Figure 1. The study design: Flow chart.

Abbreviations: ECG, electrocardiogram; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction flow grade

2.2 Ethical declaration: This study was approved by the local Ethics Committee of the Government Institute “LT Malaya Therapy National Institute of the NAMS of Ukraine”in accordance to the Helsinki Declaration (Protocol №5, 26.05.2016). All enrolled patients gave their informed written consent to participate in the study.

2.3 Risk factors and comorbidities: Information on previous history of disease including stroke, hypertension and medication use was assessed via questionnaire. Trained investigators measured anthropometric parameters. Body mass index (BMI) was calculated (kg/m^2). 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

(2019) [12]. 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 [13]. Newly HF was diagnosed according to ESC guidelines (2016) [14]. Type 2 diabetes mellitus was determined according to current ADA statement (2020) [15].

2.4 Combined end-pointof the study: During one-year follow-up period, 45 STEMI patients have reached the combined endpoints, which included all-cause mortality, non-fatal myocardial infarction and non-fatal stroke, the hospitalization for unstable angina, heart failure decompensation, and recurrent non-planned revascularization.

2.5 Reperfusion therapy: Percutaneous coronary intervention (PCI) was carried out within the first 12 hours after the onset of the first symptoms with Integrity bare-metal stent (Boston Scientific, USA) and Resolute Integrity drug-eluting stent (Medtronic, USA). Coronary angiography was performed using Digital X-Ray system "IntegrisAllura" (Philips Healthcare, The Best, The Netherlands) through radial or femoral vascular access. The final cohort had successful restoration of blood flow with TIMI-III and residual stenosis <50%. 134 patients underwent primary PCI, 14 patients were treated with thrombolytic therapy followed by PCI. Stenosis of one coronary artery was observed in 55 patients (main right coronary artery stenosis was determined in 63% patients, left anterior descending artery stenosis was diagnosed in 70% individuals, left circumflex artery was found in 35% patients), multiple vessels injury - in 79 patients (two vessel injury - 30%, three and more vessel injury- 29%). All examined patients received treatment according to current ESC recommendations 2017 [16].

2.6 Sample size calculation: The sample size was estimated through the prospective design of the study, providing the design effect 1.0, confidence intervals of 95% and the error 5% [17].

2.7 Estimation of glomerular filtration rate: The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used to calculate glomerular filtration rate (GFR) [18].

2.8 Echocardiography: The only operator under supervisor's control performed transthoracic echocardiography on Toshiba TUS-A500 (Aplio 500, Japan) on day 3-5 after STEMI. We measured left ventricular (LV) end diastolic volume (EDV), LV end systolic volume (LVESV), LV mass (LVM), LV ejection fraction (LVEF), according to Simpson's biplane method. There are gender differences in parameters; these were completely accounted for once indexed to body surface area. Early to late diastolic transmitral flow velocity (E/A) was used to assess diastolic function by impulse transmitral Doppler regime [19].

2.9Blood samples and biomarkers: Blood samples for biomarkers' measures were collected prior and after PCI. Blood samples were thoroughly centrifuged, isolated within 30 minutes of sample acquisition, and then they were stored in plastic tubes and frozen at -70 C until being transported to the laboratory of immunochemical and molecular-genetic research of GI "LT Malaya Therapy National Institute of the NAMS of Ukraine".

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- 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 levels of MIF were determined before PCI (MIFI), in 24 hours after PCI (MIFII) and on 5-7 day after the PCI (MIFIII). The troponin I (TnI) levels were measured before PCI and every 6 hours after

PCI with the determination of the peak value of this biomarker. The C-reactive protein (CRP) was determined before PCI (CRPI) and on 5-7 day after occurred coronary event (CRPII).

Determination of biomarkers was performed by enzyme-linked immunosorbent assay using commercial kits. MIF levels were measured using Humalyzer 2000 (HUMAN GmbH, Germany) by «Human MIF ELISA» (RayBio, USA) kit with the upper reference limits 6000.0 pg/mL.sST2 levels were measured by «The Presage ST2 Assay» (Critical Diagnostics, CA, USA) kit with the limits of 0 - 200.0 ng/mL according to the manufacturers' recommendations. The levels of troponin I (TnI) and C-reactive protein (CRP) were determined by «Troponin I-ELISA» (Xema, Russia) kit with the limits of 0-10.0 ng/mL and «CRP-ELISA» (Xema, Russia) kit with the upper limit of 25.0 mg/L, respectively.

2.10 Statistics: Statistical analysis was performed using Statistica 10.0 (Stat Soft Inc, Tulsa, OK, USA). Data are presented as mean ± standard deviation or median and interquartile ranges depending on a type of distribution. The Mann-Whitney U-test was used to assess intergroup quantitative differences. Categorical data are presented as numbers and percentages. Multiple logistic regression analysis was used to predict the onset of endpoints. The approach of the endpoint is represented as a binary variable. The Hosmer-Lemeshow test was used to determine the goodness of fit of the predictive model. The receiver operational characteristic (ROC) curve analysis was used to assess the discrimination capacity of the biomarker. For the patient's survival analysis, Kaplan-Mayer survival curve was constructed. Statistical significance was defined as $p<0.05$.

2. Results

The clinical characteristic of STEMI patients and the levels of biomarkers are reported Table 1 and Table 2. Patients who reached the primary endpoint were predominantly male, had a history of stable angina before the index event (62%); patients in this group corresponded to the group of intermediate risk of an unfavorable outcome according to GRACE and TIMI risk scores. The group of patients who reached the primary endpoint during further 12 months had higher incidence of complications in the acute period of STEMI, including acute heart failure, cardiac aneurysm, newly atrial fibrillation / flatter and sustainable ventricular tachycardia (p=0.019) (Table 1).

The level of MIF, determined before and after PCI, was significantly higher in the group of patients who reached the endpoint, than those who did not (3623.0 [1711.0-5664.0] pg/mL and 2405.0 [1324.0-3231.0]pg/mL respectively, p=0.002, respectively, and 3232.0 [1899.0-5473.0] pg/mL and 2110.0 [1215.0-3640.0] pg/mL respectively, p=0.012, respectively) (Table 2). The level of hemoglobin was significantly lower (p=0.015), and the level of leukocytes (p=0.0015), sST2 (p=0.05), total cholesterol (p=0.042), low-density lipoprotein (p=0.032) were significantly higher in the group of patients with an unfavorable outcome. The level of CRP has not showed any significant differences neither before PCI nor after (p=0.288, p=0.179, respectively).

The Spearman's rank correlation test showed that there were positive correlations between the MIF levels and sST2 levels (r=0.33; p=0.0016), peak TnI levels (r=0.23; p=0.013), white blood cells count (r=0.33; p=0.0001), C-reactive protein levels (r=0.19; p=0.032), serum creatinine levels (r=0.22; p=0.015), smoking (r=-0.33; p=0.022), age (r=0.18; p=0.044), LVM (r=-0.22; p=0.024), LVM index (r=-0.20; p=0.039), left atrial area (r=0.37; p=0.027). Therefore, sST2 levels correlated with stable angina before STEMI (r=0.30; p=0.004), white blood cells count (r=0.44; p=0.00001), pre-PCI and post-PCI MIF levels (r=0.32; p=0.0017; r=0.33; p=0.0044, respectively), peak TnI levels (r=0.33; p=0.0032), LVEF (r=-0.24; p=0.02), LVEDV (r=0.29; p=0.009), LVESV (r=0.29; p=0.009).

Table1. Comparison of patients, who reached endpoint and whose, who did not: demographics, STEMI risks, STEMI complications, hemodynemic parameters

Parameters	All patients with STEMI (n=134)	Patients, who didn't reach endpoint (n=89)	Patients, who reach endpoint (n=45)	P value
General parameters				
Age, years	61.36±10.43	60.31±10.54	63.42±10.11	0.124
Male, n (%)	95 (70.9)	70 (78.7)	25 (55.6)	0.005
Female, n (%)	39 (29.1)	19 (21.3)	20 (44.4)	
Smoking, n (%)	65 (48.5)	47 (52.8)	18 (40.0)	0.161
BMI>30 kg/m2, n (%)	33 (24.6)	21 (23.6)	12 (26.7)	0.697
Stable angina before the event, n (%)	63 (47.0)	35 (39.3)	28 (62.2)	0.012
Hypertension, n (%)	105 (78.4)	66 (74.2)	39 (86.7)	0.098
Type 2 diabetes mellitus, n (%)	45 (33.6)	25 (28.1)	20 (44.4)	0.064
Family history of CAD, n (%)	60 (44.8)	40 (44.9)	20 (44.4)	0.956
STEMI risk scores				
GRACE risk score (points, in-hospital)	140.38±35.31	133.97±25.42	153.40±46.67	0.047
GRACE risk score (points, admission - 6-month)	115.83±30.73	110.65±23.85	127.40±39.08	0.033
TIMI risk score, points	3.82±2.40	3.34±1.94	4.67±2.96	0.022
STEMI localization				
Anterior, n (%)	64 (47.8)	41 (46.1)	23 (51.1)	0.581
Posterior, n (%)	70 (52.2)	48 (53.9)	22 (48.9)	
STEMI complications during hospital period				
The incidence of complications in the acute period of the disease, n (%)	29 (21.6)	14 (15.7)	15 (33.3)	0.019
Hemodynamic parameters				
Systolic BP, mm Hg	133.90±30.51	134.56±31.34	132.58±29.09	0.546
Diastolic BP, mm Hg	80.12±14.97	80.66±13.42	79.04±17.76	0.646
Heart rate, beats/min	79.22±16.74	77.54±14.81	82.56±19.79	0.214
LVEDV, mL	126.03±30.35	125.85±28.27	126.44±34.99	0.769
LVEDV index, mL/m2	64.35±15.03	63.91±14.61	65.31±16.28	0.854
LVESV, mL	60.84±22.26	60.55±21.03	61.49±25.10	0.788
LVM, g	221.29±77.88	222.08±80.92	219.55±71.86	0.843
LVM index, g/m2	109.41±41.42	109.58±42.29	109.05±41.06	0.854
LVEF, %	49.72±8.66	50.60±8.43	47.79±8.99	0.070
E/A	1.08±0.38	1.11±0.33	1.03±0.46	0.265

Abbreviations: BMI, body mass index; CAD, chronic stable angina; E/A, early to late diastolic transmitral flow velocity; GFR, glomerular filtration rate; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVM, left ventricular mass; STEMI, ST-segment elevation myocardial infarction.

Table 2: The levels of biomarkers in patients' study population

Parameters	All patients with STEMI (n=134)	Patients, who didn't reach endpoint (n=89)	Patients, who reach endpoint (n=45)	P value
TnI peak, ng/mL	9.06±4.27	8.87±4.69	9.62±3.49	0.345
MIF_I, pg/mL	2501.0[1409.0-3896.5]	2405.0[1324.0-3231.0]	3623.0[1711.0-5664.0]	0.002
MIF_{II}, pg/mL	2395.5[1252.0-4140.5]	2110.0[1215.0-3640.0]	3232.0[1899.0-5473.0]	0.012
sST2, ng/mL	24.36 [17.59-30.38]	31.21[21.14-45.68]	51.20[21.93-23.25]	0.050
CRP_I mg/L	18.90±9.53	18.25±9.46	20.13±9.64	0.288
CRP_{II} mg/L	23.23±8.80	22.52±8.63	24.53±9.06	0.179
Hemoglobin, g/L	140.02±16.60	142.64±16.61	134.96±15.56	0.015
WBC, 10^9/L	10.44±3.80	9.68±3.38	11.99±4.16	0.0015
Blood glucose, mmol/L	9.59±4.78	9.03±4.30	10.79±5.45	0.065
Serum creatinine, μmol/L	104.01±29.46	101.35±23.15	109.27±38.85	0.749
GFR, ml/min/1.73m2	66.22±20.23	68.04±18.39	62.68±23.25	0.171
Total cholesterol, mmol/L	5.03±1.33	4.75±1.10	5.23±1.29	0.042
HDL, mmol/L	1.05±0.34	1.06±0.35	0.99±0.24	0.352
LDL, mmol/L	3.13±1.25	2.92±0.99	3.35±1.22	0.032
Triglycerides, mmol/L	1.87±1.12	1.88±1.18	1.75±0.76	0.833

Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MIF, macrophage migration inhibitory factor; sST2, soluble suppression of tumorigenesis 2 protein; TnI, troponin I; WBC, white blood cells.

The ROC curve analysis showed that concentration of biomarker MIF determent before and after PCI might predict formation of combined endpoint 12 months after the event. Pre-PCI MIF level more than 3493 pg/mL with sensitivity 54% and specificity 82% was associated with adverse outcome (AUC = 0.7; 95% CI 0.578 to 0.753; Youden index=0.31; p=0.008) (Figure 2).

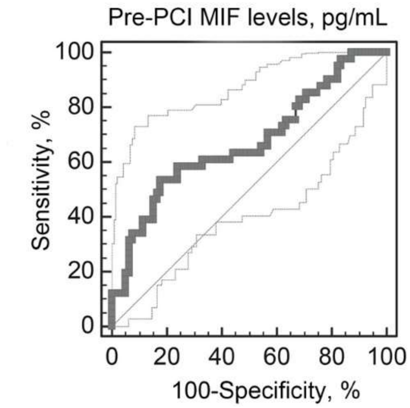

Figure 2. Predictive value of circulating pre-PCI MIF levels for 1-year endpoints after STEMI: The ROC curve analysis.

Post-PCI MIF level more than 5353 pg/mL with sensitivity 25% and specificity 98% was also significantly (AUC = 0.65; 95% CI 0.551 to 0.745; Youden index=0.24; p=0.009) associated with adverse outcome (Figure 3).

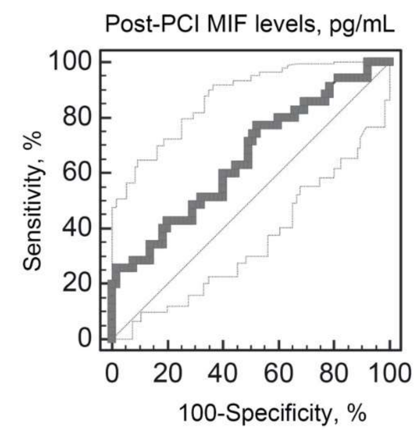

Figure 3. Predictive value of circulating post-PCI MIF levels for 1-year endpoints after STEMI: The ROC curve analysis

The Kaplan–Meier curves have demonstrated a prominent divergence by the end of the first month and further (Figure 4). MIF level >3493 pg/mL was associated with the worst survival and the accumulation of endpoints in cohort with MIF level <3493 pg/mL was lower (Log rank=0.00025). The tendency has been kept by the end of the first year.

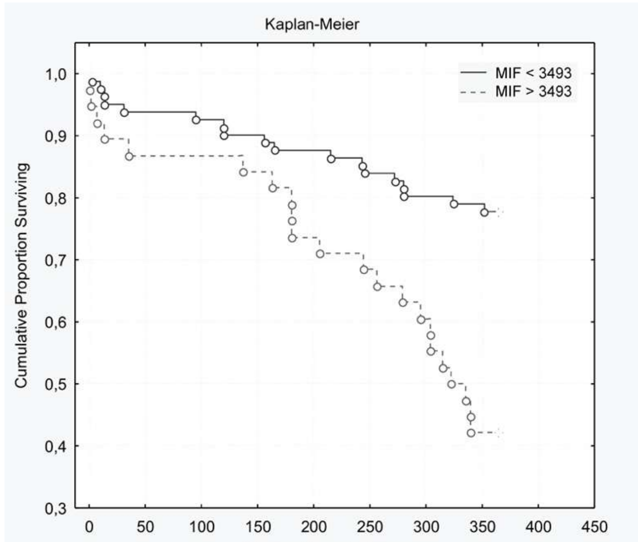

Figure 4. Kaplan–Meier survival curve in STEMI patients depending on MIF levels and 1-year adverse event prediction.

When the outcomes were analyzed using the multivariable logistic regression model, reaching the endpoints were associated with higher pre- and post-PCI MIF levels (OR 1.0, 95% CI 1.0001–1.0008; p=0.013 and OR 1.0, 95% CI 1.0001–1.0009; p=0.019) and CRP that determined during the first week after the event (OR 1.0, 95% CI 1.005–1.2, p=0.03) (Table 3).

Table 3: The factors associated with adverse outcomes in STEMI patients: Univariate and multivariate regressions

Variables	Univariate analysis				Multivariate analysis			
	β-coefficient	OR	95% CI	p	β-coefficient	OR	95% CI	p
sST2	0.01	1.01	0.9-1.0	0.141	-			
Glucose	0.1	1.1	0.9-1.3	0.190	-			
WBC count	-0.03	0.9	0.7-1.1	0.751	-			
STEMI localization	-1.1	0.3	0.06-1.7	0.187	-			
Peak TnI level	-0.05	0.9	0.7- 1.1	0.651	-			
Pre-PCI MIF>3493 pg/mL	0.0003	1.0	0.9-1.0	0.097	0.0004	1.0	1.0001-1.0008	0.013
Post-PCI MIF>5353 pg/mL	-0.0003	1.0	0.9-1.0	0.084	0.0004	1.0	1.0001-1.0009	0.019

Pre-PCI CRP	0.07	1.0	0.9-1.1	0.129	-			
CRP the first week after MI	0.09	1.0	0.9-1.2	0.126	0.09	1.0	1.005-1.2	0.03

Abbreviations: CI, confidential interval; CRP, C-reactive protein; MIF, macrophage migration inhibitory factor; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction; sST2, soluble suppression of tumorigenesis 2 protein; TnI, troponin I; WBC, white blood cells

3. Discussion

The results of the study confirmed that plasma MIF level rapidly increased and showed its predictive properties after the onset of STEMI. The MIF level was significantly higher in patients who reached endpoints than in the favorable course of the disease. Our findings correspond to the evidence that had been receivedother investigators [20-22]. The additional role of MIF in the prognosis of myocardial infarction is probably explained by the cardioprotective functions of this biomarker [23]. MIF contributes to receptor-mediated regulation of cardioprotective adenosine monophosphate-activated protein kinase signaling, inhibition of pro-apoptotic cascades, and the reduction of oxidative stress in the post-ischemic heart. Moreover, the cardioprotective properties of the MIF are modulated by S-nitrosylation [24,25].

We observed that an increased level of MIF at an early stage of the disease indicates the state of cardiac function in the long-term period and the prognosis in STEMI patients. This is due to the MIF participation in an acute inflammatory reaction, regulation processes of cardiac remodeling and the formation of fibrosis after myocardial infarction, since the above processes are important factors that determine the severity of ventricular myocardial remodeling and the state of cardiac function.

The relationship between a high level of the biomarker and an unfavorable prognosis is explained by the fact that with exacerbation of ischemia and the development of a heart attack, the production of the MIF biomarker promotes the accumulation of macrophages in the necrotic myocardium, enhances the inflammatory response and induces the production of other inflammatory factors, which aggravates myocardial damage and increases the zone of necrosis [26, 27].

It is also widely known that macrophages are the initial cells that are involved in the restoration of damaged myocardium after a cardiac event, and their deficiency slows down these processes and worsens the course of the disease [28]. Our results show that the level of MIF was associated with worse outcomes during the follow-up, that is against of a protective role of this biomarker in STEMI patients. The survival analysis suggested the incremental effect of elevated MIF level on the prediction of combined endpoint in the cohort of patients that were investigated. Considering the literature data that MIF can exhibit anti-inflammatory and cardioprotective properties, our results look ambiguous. However, these conflicting results most likely indicate that inflammatory responses are necessary for successful myocardial healing, but they can become harmful if continued for too long [29]. The results of other studies have yielded that the expression of the MIF biomarker was found to be significantly increased at the early stages of STEMIand was associated with increased susceptibility to ventricular arrhythmias [21, 27, 30]. Thus, an increase in the level of MIF in the blood serum was noted already in the first 12-24 hours after the index event formation.

Even though a high level of MIF itself can initiate an increase in CRP and acute myocardial infarction itself is the cause of its increase, in our CRP study level, did not increase significantly, even if admission MIF level was initially higher in the group of patients with adverse outcome. However, a correlation between the levels of MIF and inflammatory markers WBC and CRP was found. CRP affected 1-year prognosis of myocardial infarction. Pre-PCI values of CRP were not significantly elevated in contrast to MIF, and only CRP levels 1 week after STEMI showed predictive power.

Therefore, the biomarker MIF has an advantage over CRP as an earlier predictor of adverse events. Several studies have shown that higher levels of sST2 were associated with large risk of mortality and development of heart failure [31, 32]. However, this biomarker has been yet insufficiently studied in STEMI, while its diagnostic and predictive values in heart failure patients appear to be interested [33, 34]. The main function of sST2 is to potentiate the effects of interleukin 33 (IL-33), which has an antihypertrophic, antifibrotic effect on cardiomyocytes [35]. However, a rapid increase of sST2 in myocardial injury is accompanied by inhibition of antihypertrophic effects of IL-33. We hypothesized that the determination of sST2 may have prognostic value for STEMI patients, as it will allow us to assess short- and long-term period and the possibility of complications. The elevated levels of sST2 did not show prognostic values to predict major adverse cardiac events in STEMI patients in our study, although recent studies have exhibited conflicting results in this matter [31, 34, 36]. Probably, it might tackle with a presentation of co-existing HF in these studies, whereas our study population had not been included individuals with known symptomatic HF.

To sum up, we can suggest MIF is associated with the inflammatory response as much as CRP but is a more specific biomarker in this situation, which has been confirmed by the results of the ROC curve analysis, where the specificity of the MIF was about 98%. There are several reasons why a biomarker that could predict final infarct size might be desirable in the clinical management of patients presenting with STEMI. Early changes in circulating levels of this biomarker would facilitate decision-making about the timeliness of reperfusion, particularly in regions of the world where healthcare resources are limited. It would also facilitate appropriate resource allocation for specific patients who are likely to need more intensive care.

4. Study limitations

The study had several limitations: the single-center design and the small sample size. Despite, the study allowed us to analyze the discriminative value of MIF levels for prediction of post-STEMI adverse events. However, a large clinical study is required to obtain more information regarding MIF as a predictor for clinical outcomes. As we could clearly demonstrate, that correlation exists between MIF, CRP and WBC, the further task will be to analyze link of MIF and additional inflammatory markers, cardiac remodeling and dysfunction.

5. Conclusion

We found that the increased MIF levels, which have been determined during the first 12 hours after occurred STEMI treated with primary PCI, predictedone-year adverse clinical events.

6. Acknowledgement

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Conflicts of Interest: Authors declare that the article entitled does not infringe any copyrights or any other proprietary rights of third parties.

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