Original Research Article: full paper

(2022), «EUREKA: Health Sciences»
Number 5

PREDICTION OF ONE-YEAR ADVERSE CLINICAL OUTCOMES BY MACROPHAGE MIGRATION INHIBITORY FACTOR IN STEMI PATIENTS

***Iryna Vyshnevska*[1]**
[1]Department of Prevention and Treatment of Emergency Conditions
Government Institution "L. T. Malaya Therapy National Institute NAMSU"
2A Liubovi Maloy ave., Kharkiv, Ukraine, 61039

***Tatyana Storozhenko*[1]**

***Mykola Kopytsya*[1]**

Natalia Bila ✉
Department of Propaedeutics of Internal Medicine and Physical Rehabilitation
Medical School
V. N. Karazin Kharkiv National University
4 Svobody sq., Kharkiv, Ukraine, 61022
natory3@gmail.com

✉**Corresponding author**

Abstract

Biomarkers have taken one of the first places as diagnostic and prognostic tools in ST-segment elevation myocardial infarction (STEMI) and are consequently widely used as predictors of short-term and long-term prognosis. One of the promising biomarkers for early cardiovascular outcomes prediction is the pro-inflammatory cytokine macrophage migration inhibitory factor (MIF).

The aim of the study was to elucidate a plausible predictive value of the MIF levels for one-year clinical outcomes in STEMI patients who underwent primary percutaneous coronary intervention (PCI).

Materials and methods. 134 STEMI patients were enrolled in the study after receiving voluntary informed consent. All patients underwent conventional investigations, and additionally, the MIF levels were determined at baseline, directly before and after PCI. During 1-year follow-up, 37 % of patients reached the endpoint, which was composite and included all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, heart failure decompensation, and urgent revascularization.

Results. We have found that pre-PCI MIF levels > 3934 pg/mL (AUC=0.7; 95 % CI 0.578 to 0.753; Youden index=0.31; p=0.008) might be an independent predictor of composite endpoints with sensitivity 54 % and specificity 82 %. A positive correlation between MIF and inflammatory biomarkers was revealed (WBC count r=0.33, p=0.0001; CRP r=0.19, p=0.032). 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 a substantially lower long-term survival rate in patients with a MIF level > 3493 pg/ml compared to a MIF level ≤ 3493 pg/ml (Log rank=0.00025).

Conclusions. The MIF levels exceeding 3934 ng/ml were associated with a higher risk of one-year adverse clinical outcomes in STEMI patients who underwent primary PCI.

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

DOI: 10.21303/2504-5679.2022.002714

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 procedures and a no-reflow phenomenon [3, 4]. Over the past decades, biomarkers of inflammation and fibrosis have been

deeply considered diagnostic and prognostic tools in myocardial infarction [5]. Providing new biomarkers that can predict cardiovascular events at an 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 early adverse outcome prediction in STEMI patients [8]. Furthermore, as a mediator of many acute and chronic inflammatory diseases, MIF 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 who underwent primary percutaneous coronary intervention (PCI).

2. Materials and methods

2. 1. Study population and design

The study prospectively enrolled 134 STEMI patients 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 the 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 for 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. In addition, patients having one more of the following criteria were excluded: liver cirrhosis, acute kidney failure that requires hemodialysis, active malignancy, and chronic inflammatory disease in the acute phase. Twenty-five healthy individuals, comparable in age and gender, without a history of cardiovascular diseases, were enrolled in the control group. During the enrollment process, the study protocol assessed the medical history, physical examination, laboratory, and instrumental investigations. The study flow chart is presented in **Fig. 1.**

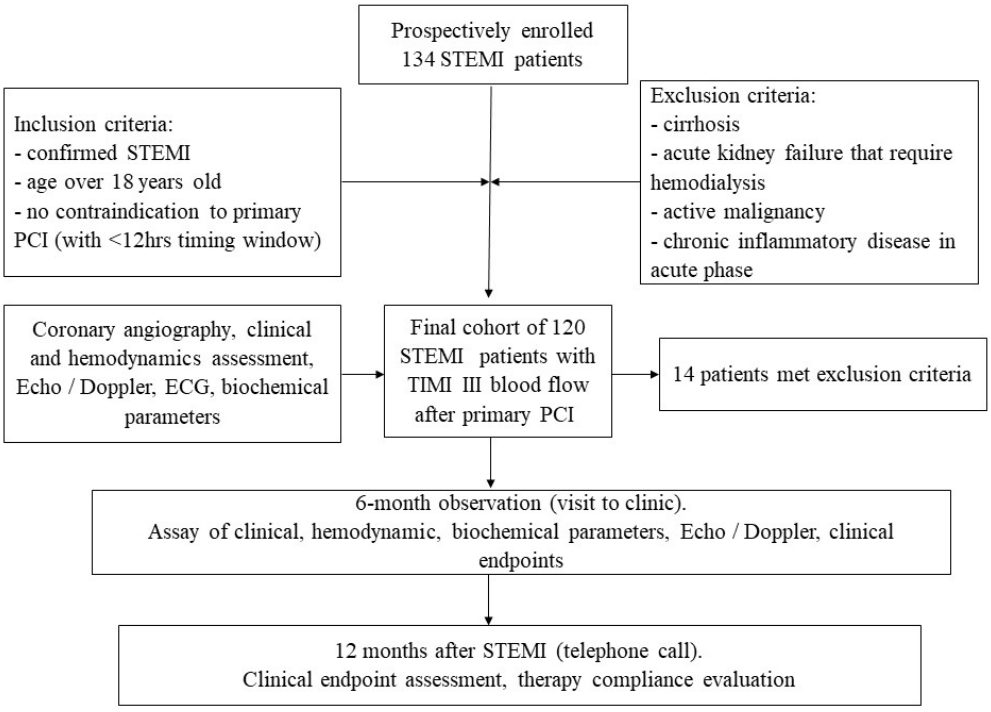

Fig. 1. The study design: Flow chart: ECG, electrocardiogram; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction flow grade

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" following the Helsinki Declaration (Protocol No. 5, 26.05.2016). Furthermore, all enrolled patients gave informed written consent to participate in the study.

2. 3. Risk factors and comorbidities

Information on the previous history of the disease, including stroke, hypertension and medication use, were 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 the current ADA statement (2020) [15].

2. 4. Combined endpoint of the study

During the 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, 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 the Digital X-Ray system "Integris Allura" (Philips Healthcare, The Best, The Netherlands) through radial or femoral vascular access. The final cohort successfully restored blood flow with TIMI-III and residual stenosis <50 %. 134 patients underwent primary PCI, and 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 % of patients, left anterior descending artery stenosis was diagnosed in 70 % of individuals, and left circumflex artery was found in 35 % of 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 study's prospective design, providing the design effect of 1.0, confidence intervals of 95 % and an error of 5 % [17].

2. 7. Estimation of glomerular filtration rate

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

2. 8. Echocardiography

The only operator under the supervisor's control performed transthoracic echocardiography on Toshiba TUS-A500 (Aplio 500, Japan) days 3–5 after STEMI. We measured left ventricular (LV) end-diastolic volume (EDV), LV end-systolic volume (LVESV), LV mass (LVM), and LV ejection fraction (LVEF), according to Simpson's biplane method. There are gender differences in parameters; these were accounted entirely for once indexed to body surface area. Early to late dia-

stolic transmitral flow velocity (E/A) was used to assess diastolic function by impulse transmitral Doppler regime [19].

2. 9. Blood samples and biomarkers

Blood samples for biomarkers' measures were collected prior to and after PCI. First, blood samples were thoroughly centrifuged and isolated within 30 minutes of sample acquisition. Then they were stored in plastic tubes and frozen at -70 C until they were transported to the immunochemical and molecular-genetic research laboratory 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 a direct enzymatic method (Roche P800 analyzer, Basel, Switzerland). The intra- and inter-assay coefficients of variation were <5 %.

Biochemical studies (level of glucose) were carried out on a biochemical analyzer "Humalyser" ("Human", Germany), head. No. 18300-5397. The glucose level was determined by the glucoseoxidase method.

The levels of MIF were determined before PCI (MIFI), 24 hours after PCI (MIFII) and 5–7 days 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 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 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, the Kaplan-Mayer survival curve was constructed. Statistical significance was defined as $p<0.05$.

3. Results

The clinical characteristic of STEMI patients and the levels of biomarkers are reported in **Table 1** and **Table 2**. Patients who reached the primary endpoint were predominantly male and had a history of stable angina before the index event (62 %); patients in this group corresponded to the group of intermediate risk of an unfavourable outcome according to GRACE and TIMI risk scores. The group of patients who reached the primary endpoint during further 12 months had a higher incidence of complications in the acute period of STEMI, including acute heart failure, cardiac aneurysm, new 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 haemoglobin 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 unfavourable outcome. The level of CRP has not shown any significant differences before PCI or 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), the 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).

Table 1

Comparison of patients who reached the endpoint and those who did not: demographics, STEMI risks, STEMI complications, hemodynamic parameters

Parameters	All patients with STEMI (n=134)	Patients who did not reach an endpoint (n=89)	Patients who reach an 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 months)	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 the 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/m^2	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/m^2	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

Note: 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 did not reach an endpoint (n=89)	Patients who reach an 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
Haemoglobin, 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/1.73m^2	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

Note: 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 the concentration of biomarker MIF determent before and after PCI might predict the formation of combined endpoint 12 months after the event. Pre-PCI MIF level of more than 3493 pg/mL with a sensitivity of 54 % and specificity 82 % was associated with adverse outcomes (AUC=0.7; 95 % CI 0.578 to 0.753; Youden index=0.31; p=0.008) (**Fig. 2**).

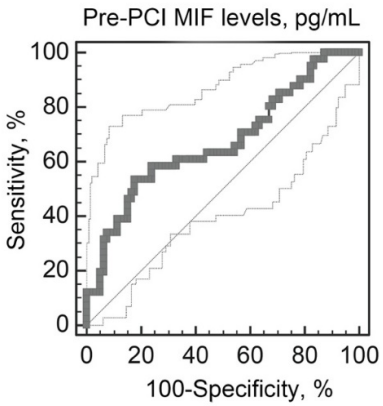

Fig. 2. Predictive value of circulating pre-PCI MIF levels for 1-year endpoints after STEMI: The ROC curve analysis

Post-PCI MIF level of more than 5353 pg/mL with a sensitivity of 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 (**Fig. 3**).

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

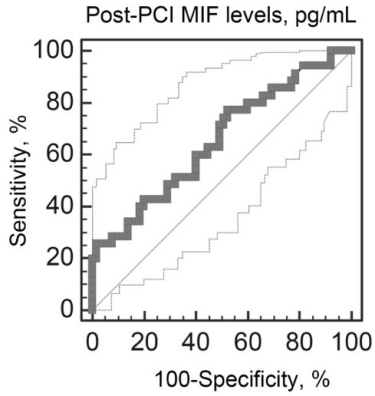

Fig. 3. Predictive value of circulating post-PCI MIF levels for 1-year endpoints after STEMI: The ROC curve analysis

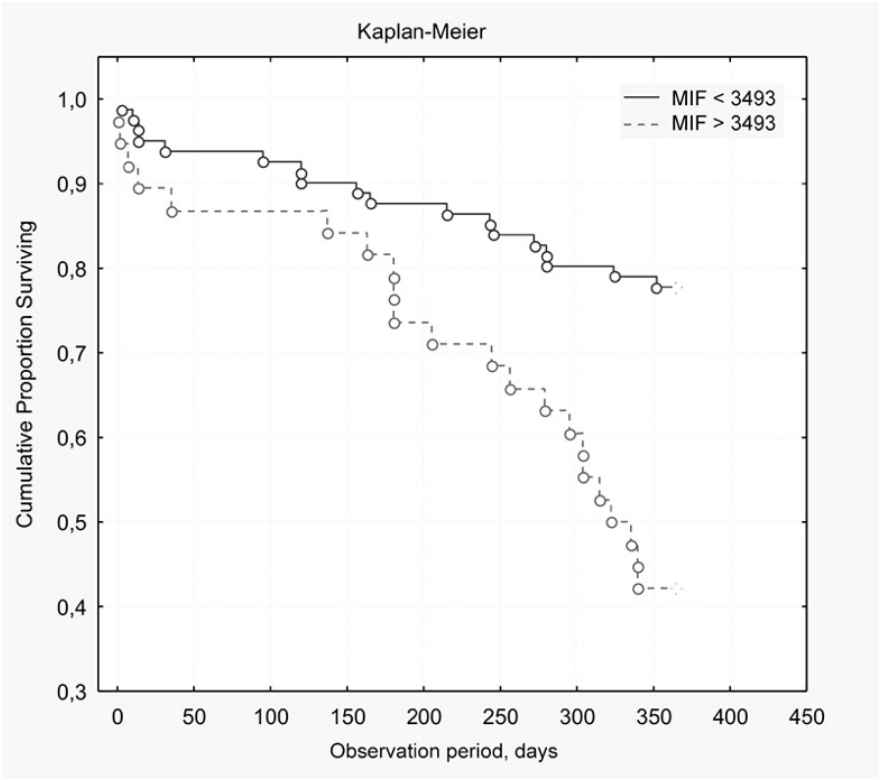

Fig. 4. Kaplan-Meier survival curve in STEMI patients depending on MIF levels and 1-year adverse event prediction

When the outcomes were analyzed using the multivariable logistic regression model, reaching the endpoints was 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
1	2	3	4	5		6		
sST2	0.01	1.01	0.9–1.0	0.141		–		

Continuation of Table 3

1	2	3	4	5	6			
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

Note: 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

4. Discussion

The study's results confirmed that plasma MIF level rapidly increased and showed its predictive properties after the onset of STEMI. Furthermore, the MIF level was significantly higher in patients who reached endpoints than in the favourable course of the disease. Our findings correspond to the evidence that had been received by other 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 signalling, inhibiting pro-apoptotic cascades, and reducing 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 remodelling, and the formation of fibrosis after myocardial infarction since the above processes are important factors that determine the severity of ventricular myocardial remodelling and the state of cardiac function.

The relationship between a high level of the biomarker and an unfavourable 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 restore damaged myocardium after a cardiac event. 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, which is against the 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 investigated patients. Our results look ambiguous considering the literature data that MIF can exhibit anti-inflammatory and cardioprotective properties. 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 significantly increased at the early stages of STEMI and was associated with increased susceptibility to ventricular arrhythmias [21, 27, 30]. Thus, an increase in the level of MIF in the blood serum was already noted in the first 12–24 hours after the index event formation.

Even though a high level of MIF can initiate an increase in CRP and acute myocardial infarction is the cause of its increase, our CRP study level did not increase significantly, even if admission MIF level was initially higher in the group of patients with adverse outcomes. However, a correlation between the levels of MIF and inflammatory markers WBC and CRP was found. Furthermore, CRP affected the 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 a large risk of mortality and the 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 inhibiting the antihypertrophic effects of IL-33. Therefore, 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 periods 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. However, recent studies have exhibited conflicting results [31, 34, 36]. Probably, it might tackle a presentation of co-existing HF in these studies, whereas our study population had not 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 %. 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 likely to need more intensive care.

Study limitations. The study had several limitations: the single-centre design and the small sample size. Despite this, the study allowed us to analyze the discriminative value of MIF levels for predicting post-STEMI adverse events.

Prospects for further research. However, a large clinical study is required to obtain more information regarding MIF as a predictor for clinical outcomes. As we could demonstrate, a correlation exists between MIF, CRP and WBC; the further task will be to analyze the link between MIF and additional inflammatory markers, cardiac remodelling and dysfunction.

5. Conclusion

We found that a MIF level of more than 3493 pg/mL, determined during the first 12 hours after STEMI before PCI, could predict one-year major adverse clinical events. Pre-PCI level of C-RP did not show any significant prevalence over the MIF biomarker. The routine use of the biomarker might be considered in clinical practice.

Conflicts of interest

The authors declare that there is no conflict of interest in relation to this paper, the published research results, the financial aspects of conducting the research, obtaining and using its results, and any non-financial personal relationships.

Funding

This research is a fragment of the project entitled “To study the biochemical, genetic mechanisms of reperfusion damage of the myocardium and to assess the cardioprotective effect of antiplatelet therapy in acute myocardial infarction” and was supported by the Government Institutions “LT Malaya Therapy National Institute of the NAMS of Ukraine” (Kharkiv, Ukraine, State Registration No. 0117U003028/Ukraine).

References

[1] Feistritzer, H.-J., Jobs, A., de Waha-Thiele, S., Eitel, I., Freund, A., Abdel-Wahab, M. et. al. (2020). Multivessel versus culprit-only PCI in STEMI patients with multivessel disease: meta-analysis of randomized controlled trials. Clinical Research in Cardiology, 109 (11), 1381–1391. doi: https://doi.org/10.1007/s00392-020-01637-6

[2] Cohen, M., Boiangiu, C., Abidi, M. (2010). Therapy for ST-Segment Elevation Myocardial Infarction Patients Who Present Late or Are Ineligible for Reperfusion Therapy. Journal of the American College of Cardiology, 55 (18), 1895–1906. doi: https://doi.org/10.1016/j.jacc.2009.11.087

[3] Jung, C., Elsässer, A. (2018). Update ESC-Leitlinie 2017 – Akuter Myokardinfarkt (STEMI). DMW - Deutsche Medizinische Wochenschrift, 143 (11), 797–801. doi: https://doi.org/10.1055/a-0494-0341

[4] Konijnenberg, L. S. F., Damman, P., Duncker, D. J., Kloner, R. A., Nijveldt, R., van Geuns, R.-J. M., Berry, C., Riksen, N. P., Escaned, J., van Royen, N. (2019). Pathophysiology and diagnosis of coronary microvascular dysfunction in ST-elevation myocardial infarction. Cardiovascular Research, 116 (4), 787–805. doi: https://doi.org/10.1093/cvr/cvz301

[5] Vogel, B., Claessen, B. E., Arnold, S. V., Chan, D., Cohen, D. J., Giannitsis, E. et al. (2019). ST-segment elevation myocardial infarction. Nature Reviews Disease Primers, 5 (1). doi: https://doi.org/10.1038/s41572-019-0090-3

[6] Berezin, A. E., Berezin, A. A. (2020). Adverse Cardiac Remodelling after Acute Myocardial Infarction: Old and New Biomarkers. Disease Markers, 2020, 1–21. doi: https://doi.org/10.1155/2020/1215802

[7] Kulasingam, A., Hvas, A.-M., Grove, E. L., Funck, K. L., Kristensen, S. D. (2018). Detection of biomarkers using a novel proximity extension assay in patients with ST-elevation myocardial infarction. Thrombosis Research, 172, 21–28. doi: https://doi.org/10.1016/j.thromres.2018.10.011

[8] Dayawansa, N. H., Gao, X.-M., White, D. A., Dart, A. M., Du, X.-J. (2014). Role of MIF in myocardial ischaemia and infarction: insight from recent clinical and experimental findings. Clinical Science, 127 (3), 149–161. doi: https://doi.org/10.1042/cs20130828

[9] Ruze, A., Chen, B.-D., Liu, F., Chen, X.-C., Gai, M.-T., Li, X.-M. et al. (2019). Macrophage migration inhibitory factor plays an essential role in ischemic preconditioning-mediated cardioprotection. Clinical Science, 133 (5), 665–680. doi: https://doi.org/10.1042/cs20181013

[10] Deng, F., Zhao, Q., Deng, Y., Wu, Y., Zhou, D., Liu, W. et al. (2018). Prognostic significance and dynamic change of plasma macrophage migration inhibitory factor in patients with acute ST-elevation myocardial infarction. Medicine, 97(43), e12991. doi: https://doi.org/10.1097/md.0000000000012991

[11] Chan, W., White, D. A., Wang, X., Bai, R., Liu, Y., Yu, H. et al. (2013). Macrophage Migration Inhibitory Factor for the Early Prediction of Infarct Size. Journal of the American Heart Association, 2 (5). doi: https://doi.org/10.1161/jaha.113.000226

[12] Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L. et al. (2019). 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis, 290, 140–205. doi: https://doi.org/10.1016/j.atherosclerosis.2019.08.014

[13] Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M. et al. (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal, 39 (33), 3021–3104. doi: https://doi.org/10.1093/eurheartj/ehy339

[14] Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S. et al. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal, 37 (27), 2129–2200. doi: https://doi.org/10.1093/eurheartj/ehw128

[15] 2. Classification and Diagnosis of Diabetes:Standards of Medical Care in Diabetes – 2020 (2019). Diabetes Care, 43 (Supplement_1), S14–S31. doi: https://doi.org/10.2337/dc20-s002

[16] Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H. et al. (2017). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal, 39 (2), 119–177. doi: https://doi.org/10.1093/eurheartj/ehx393

[17] Kirby, A., Gebski, V., Keech, A. C. (2002). Determining the sample size in a clinical trial. Medical Journal of Australia, 177 (5), 256–257. doi: https://doi.org/10.5694/j.1326-5377.2002.tb04759.x

[18] Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. (Lucy), Castro, A. F., Feldman, H. I. et al. (2009). A New Equation to Estimate Glomerular Filtration Rate. Annals of Internal Medicine, 150 (9), 604–612. doi: https://doi.org/10.7326/0003-4819-150-9-200905050-00006

[19] Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L. 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. Journal of the American Society of Echocardiography, 28 (1), 1–39.e14. doi: https://doi.org/10.1016/j.echo.2014.10.003

[20] Fan, F., Fang, L., Moore, X., Xie, X., Du, X., White, D. A. et. al. (2016). Plasma Macrophage Migration Inhibitor Factor Is Elevated in Response to Myocardial Ischemia. Journal of the American Heart Association, 5 (7). doi: https://doi.org/10.1161/jaha.115.003128

[21] Rassaf, T., Weber, C., Bernhagen, J. (2014). Macrophage migration inhibitory factor in myocardial ischaemia/reperfusion injury. Cardiovascular Research, 102 (2), 321–328. doi: https://doi.org/10.1093/cvr/cvu071

[22] 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, 2019, 1–9. doi: https://doi.org/10.1155/2019/8276180

[23] Koga, K., Kenessey, A., Powell, S. R., Sison, C. P., Miller, E. J., Ojamaa, K. (2011). Macrophage Migration Inhibitory Factor Provides Cardioprotection During Ischemia/Reperfusion by Reducing Oxidative Stress. Antioxidants & Redox Signaling, 14 (7), 1191–1202. doi: https://doi.org/10.1089/ars.2010.3163

[24] Luedike, P., Hendgen-Cotta, U. B., Sobierajski, J., Totzeck, M., Reeh, M., Dewor, M. et al. (2012). Cardioprotection Through S-Nitros(yl)ation of Macrophage Migration Inhibitory Factor. Circulation, 125 (15), 1880–1889. doi: https://doi.org/10.1161/circulationaha.111.069104

[25] Yu, C.-M., Lai, K. W.-H., Chen, Y.-X., Huang, X.-R., Lan, H. Y. (2003). Expression of Macrophage Migration Inhibitory Factor in Acute Ischemic Myocardial Injury. Journal of Histochemistry & Cytochemistry, 51 (5), 625–631. doi: https://doi.org/10.1177/002215540305100508

[26] Peet, C., Ivetic, A., Bromage, D. I., Shah, A. M. (2019). Cardiac monocytes and macrophages after myocardial infarction. Cardiovascular Research, 116 (6), 1101–1112. doi: https://doi.org/10.1093/cvr/cvz336

[27] Voss, S., Krüger, S., Scherschel, K., Warnke, S., Schwarzl, M., Schrage, B. ry. Al. (2019). Macrophage Migration Inhibitory Factor (MIF) Expression Increases during Myocardial Infarction and Supports Pro-Inflammatory Signaling in Cardiac Fibroblasts. Biomolecules, 9 (2), 38. doi: https://doi.org/10.3390/biom9020038

[28] Pohl, J., Hendgen-Cotta, U. R., Rammos, C., Luedike, P., Mull, E., Stoppe, C. et al. (2016). Targeted intracellular accumulation of macrophage migration inhibitory factor in the reperfused heart mediates cardioprotection. Thrombosis and Haemostasis, 115 (1), 200–212. doi: https://doi.org/10.1160/th15-05-0436

[29] Prabhu, S. D., Frangogiannis, N. G. (2016). The Biological Basis for Cardiac Repair After Myocardial Infarction. Circulation Research, 119 (1), 91–112. doi: https://doi.org/10.1161/circresaha.116.303577

[30] Lyu, J., Huang, J., Wu, J., Yu, T., Wei, X., Lei, Q. (2021). Lack of Macrophage Migration Inhibitory Factor Reduces Susceptibility to Ventricular Arrhythmias During the Acute Phase of Myocardial Infarction. Journal of Inflammation Research, 14, 1297–1311. doi: https://doi.org/10.2147/jir.s304553

[31] Jenkins, W. S., Roger, V. L., Jaffe, A. S., Weston, S. A., AbouEzzeddine, O. F., Jiang, R. et al. (2017). Prognostic Value of Soluble ST2 After Myocardial Infarction: A Community Perspective. The American Journal of Medicine, 130 (9), 1112.e9–1112.e15. doi: https://doi.org/10.1016/j.amjmed.2017.02.034

[32] Dimitropoulos, S., Mystakidi, V. C., Oikonomou, E., Siasos, G., Tsigkou, V., Athanasiou, D. et al. (2020). Association of Soluble Suppression of Tumorigenesis-2 (ST2) with Endothelial Function in Patients with Ischemic Heart Failure. International Journal of Molecular Sciences, 21 (24), 9385. doi: https://doi.org/10.3390/ijms21249385

[33] Zhang, T., Xu, C., Zhao, R., Cao, Z. (2021). Diagnostic Value of sST2 in Cardiovascular Diseases: A Systematic Review and Meta-Analysis. Frontiers in Cardiovascular Medicine, 8. doi: https://doi.org/10.3389/fcvm.2021.697837

[34] Mzoughi, K., Chouaieb, S., Zairi, I., Fredj, S., Ben Kilani, M., Berriri, S. et al. (2019). Prognostic value of ST2 in myocardial infarction. Tunis Med, 97 (2), 335–343.

[35] Homsak, E., Gruson, D. (2020). Soluble ST2: A complex and diverse role in several diseases. Clinica Chimica Acta, 507, 75–87. doi: https://doi.org/10.1016/j.cca.2020.04.011

[36] Sabatine, M. S., Morrow, D. A., Higgins, L. J., MacGillivray, C., Guo, W., Bode, C. et al. (2008). Complementary Roles for Biomarkers of Biomechanical Strain ST2 and N-Terminal Prohormone B-Type Natriuretic Peptide in Patients With ST-Elevation Myocardial Infarction. Circulation, 117 (15), 1936–1944. doi: https://doi.org/10.1161/circulationaha.107.728022

Received date 09.08.2022
Accepted date 15.09.2022
Published date 30.09.2022

How to cite: *Vyshnevska, I., Storozhenko, T., Kopytsya, M., Bila, N. (2022). Prediction of one-year adverse clinical outcomes by macrophage migration inhibitory factor in stemi patients. EUREKA: Health Sciences, 5, 19–29. doi: http://doi.org/10.21303/2504-5679.2022.002714*