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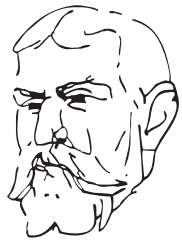

Memory of
dr Władysław
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ORIGINAL ARTICLE

THE ROLE OF BIOMARKER MACROPHAGE MIGRATION INHIBITORY FACTOR IN CARDIAC REMODELING PREDICTION IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT

The aim: To estimate the role of macrophage migration inhibitory factor and soluble ST2 in predicting the left ventricle remodeling six months after ST-segment elevation myocardial infarction.

Materials and methods: The study involved 134 ST-segment elevation myocardial infarction patients. Occurrence of post-percutaneous coronary (PCI) intervention epicardial blood flow of TIMI <3 or myocardial blush grade 0-1 along with ST resolution <70% within 2 hours after PCI was qualified as the no-reflow condition. Left ventricle remodeling was defined after 6-months as an increase in left ventricle end-diastolic volume and/or end-systolic volume by more than 10%.

Results: A logistic regression formula was evaluated. Included biomarkers were macrophage migration inhibitory factor and sST2, left ventricle ejection fraction: Y=exp(-39.06+0.82EF+0.096ST2+0.0028MIF) / (1+exp(-39.06+0.82EF+0.096ST2+0.0028MIF)). The estimated range is from 0 to 1 point. Less than 0.5 determines an adverse outcome, and more than 0.5 is a good prognosis. This equation, with sensitivity of 77 % and specificity of 85%, could predict the development of adverse left ventricle remodeling six months after a coronary event (AUC=0.864, CI 0.673 to 0.966, p<0.05).

Conclusions: A combination of biomarkers gives a significant predicting result in the formation of adverse left ventricular remodeling after ST-segment elevation myocardial infarction.

KEY WORDS: inflammation, prognosis, biomarkers, coronary event

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INTRODUCTION

A sharp decrease in the contractile capacity of instigated cardiomyocytes in ST-segment elevation myocardial infarction (STEMI) leads to changes in the heart architecture [1]. Left ventricle remodeling (LVR) refers to alterations in ventricular function involving both the infarcted and non-infarcted zones leading to a progressive increase in systolic and diastolic LV volumes. Adverse LVR after STEMI treated with primary percutaneous coronary intervention (PCI) is the main determinant for the long-term outcomes. In STEMI, to reduce the area of necrosis and scar formation, inflammation and the neurohumoral system play significant roles [2]. In routine clinical practice, a series of biomarkers use in helping to assess the prognosis in STEMI patients. These are high-sensitive C-reactive protein (C-RP) and N-terminal pro-brain natriuretic peptide, a biomarker of inflammation and hemodynamic stress [3,4]. However, the search for a universal biomarker that can predict the maximum number of possible complications in the early period of the disease continues. The soluble isoform of suppression tumorigenicity 2 (sST2) has a combination of such properties. The level of sST2 increases because of myocardial damage that occurs after STEMI onset, and it is linked with myocardial fibrosis formation. [5-7]. However, the role of sST2 in the development of adverse LVR is not clear. Known that the no-reflow phenomenon takes a role in adverse cardiac remodeling as much as myocardial ischemia due to insufficient myocardial perfusion [8]. Based on the knowledge, we suggest one promising biomarker in this field, macrophage migration inhibitory factor (MIF). MIF functions as a pleiotropic protein, participating in inflammatory and immune responses [9-11].

THE AIM

The aim of the study was to estimate the role of MIF and sST2 in predicting the LVR six months after STEMI.

MATERIALS AND METHODS

The hypothesis of the study is that level of biomarker MIF, sST2 or their combination can help us to determine STEMI patients with high risk of adverse LVR and could help in the decision process regarding the treatment strategy to reduce probability of heart failure formation.

The study involved 134 STEMI patients. Primary PCI was performed in the Department of Interventional Cardiology of the V. T. Zaitseva Institute of General and Emergency Surgery of the National Academy of Medical Sciences of Ukraine 12 hours after the index event. 24-48 hours after the PCI patients have transferred to the emergency department of the L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine. STEMI diagnosis based on European Society of Cardiology guidelines (2017) [12]. The study was approved by the local ethics committee (Protocol №13 of December 19, 2019). All patients signed informed consent before the enrollment procedure.

PERCUTANEOUS CORONARY INTERVENTION

Within 12 h after the first symptoms, primary PCI was performed. There are two types of stents: bare-metal and drug-eluting stents (Resolute Integrity (Medtronic, USA), Integrity (Boston Scientific, USA, respectively)). Coronary angiography was undertaken on an Integris Allura digital X-ray system (Philips Healthcare, Best, The Netherlands). Several projections of coronary arteries have been recorded during coronary angiography. Ultravist-370 (Bayer Pharma GmbH, Germany) was used to increase contrast. All patients received standard treatment [12].

Using serial electrocardiography in 12 leads obtained before and 60-90 minutes after primary PCI evaluation of ST-segment dynamics was performed [13].

REAL-TIME MYOCARDIAL PERFUSION IMAGING

We used real-time myocardial perfusion imaging with Myocardial Blush Grade (MBG) determination to measure myocardial perfusion [14, 15]. The MBG was scored during angiographic analysis using the Van't Hof method [16]. MBG graded as 0, 1, 2, and 3 that corresponded to the following criteria: a lack of myocardial blush or contrast density, minimal myocardial blush or contrast density, myocardial blush or contrast density with impaired clearing, and unchanged myocardial blush or contrast density, respectively [17]. Occurrence of post-PCI epicardial blood flow of TIMI <3 or MBG 0-1 along with STR <70% within 2 hours after PCI was qualified as the no-reflow condition.

DETERMINATION OF RISK FACTORS AND COMORBIDITIES

The trained investigator measured anthropometric parameters during the interview and assessed anamnesis vitae by questionnaire. Body mass index (kg/m2) calculated. Hypercholesterolemia diagnosed according to the guidelines of the European society of cardiology for dyslipidemia [18], hypertension [19], chronic heart failure following the recommendations of the European Society of Cardiology [20].

A combined primary endpoint was determined as all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, chronic heart failure decompensation with or without hospitalization, unscheduled revascularization. Patients had *excluded* if they *had* a prior history of ischemic events.

TRANSTHORACIC ECHOCARDIOGRAPHY AND DOPPLER

Transthoracic Doppler echocardiography with Toshiba TUS-A500 (Aplio 500, Japan) was performed 24-48 hours after PCI and after a 6-months follow-up. LV end-diastolic and end-systolic volume (LVEDV and LVESV, relatively), LV myocardial mass (LVM), LV ejection fraction (LVEF), and left atrial volume (LAV) determined by Simpson's biplane method. To assess the diastolic function of the left ventricle by pulse Doppler mode diastolic transmitral velocity (E / A) from the beginning to the late period, the ratio of peak mitral inflow rate to an early diastolic velocity of the mitral ring (E / e ') used. Right ventricular function was assessed as TAPSE [21]. LV remodeling was defined after 6-months as an increase in LVEDV and/or ESV by more than 10%.

SAMPLE SIZE CALCULATION

The sample size was calculated through the prospective design of the study, providing the design effect of 1.0, confidence intervals of 95%, and the error of 5% [22].

BLOOD SAMPLES

Blood samples for biomarker analysis have collected before PCI and 24 hours after. Peak troponin I (TnI) levels were measured every six hours for 24 h after hos-

Table I. Parameters of echocardiography in studied patients

Parameters	Period	Group with LV remodeling n=47	Group without LV remodeling n=86	p*
Heart rate, per minute	At admission	77,28±13,14	80,40±18,46	0,527
	6 months after	67.49±1074	66.26±10.19	0,8403
	p	0.00004*	0.000006*	
SBP, mm Hg	At admission	141,43±22,73	130,64±32,72	0,072
	6 months after	131.34±14.99	125.54±14.66	0,0787
	p	0.009*	0.1457	
DBP, mm Hg	At admission	84,21±13,54	78,35±14,84	0,038*
	6 months after	81.49±8.66	78.43±9.68	0,0641
	p	0.170	0.7080	
LV EDV, ml	At admission	115,77±24,40	135,37±32,23	0,001*
	6 months after	148.71±40.57	129.77±34.05	0,0123*
	p	0.000001*	0.3167	
Index EDV	At admission	58,24±10,98	69,74±16,18	0,0002*
	6 months after	73.79±16.77	67.15±17.11	0,0624
	p	0.000001*	0.3780	
LV ESV, ml	At admission	53,43±21,08	67,33±21,63	0,001*
	6 months after	76.28±26.74	64.24±22.88	0,0102*
	p	0.000002*	0.3053	
Index ESV	At admission	26,83±9,83	34,62±10,87	0,0002*
	6 months after	38.13±11.73	33.17±11.17	0,0401*
	p	0.000001*	0.3167	
Stroke volume, ml	At admission	31,41±6,45	35,12±9,93	0,079
	6 months after	35.59±9.57	33.98±8.10	0,2859
	p	0.004*	0.7107	
LV EDD, cm	At admission	4,97±0,43	5,25±0,51	0,006*
	6 months after	5.45±0.55	5.17±0.56	0,0125*
	p	0.000001*	0.4227	
Index EDD	At admission	2,51±0,26	2,71±0,32	0,002*
	6 months after	2.75±0.30	2.68±0.34	0,2991
	p	0.0002*	0.7862	
ESD, cm	At admission	3,54±0,54	3,91±0,52	0,001*
	6 months after	4.09±0.56	3.82±0.56	0,0200
	p	0.000003*	0.3492	
Index ESD	At admission	1,79±0,29	2,02±0,29	0,0005*
	6 months after	2.07±0.28	1.98±0.30	0,1596
	p	0.00003*	0.4992	
IVS, cm	At admission	1,22±0,18	1,16±0,22	0,019*
	6 months after	1.18±0.16	1.16±0.16	0,4729
	p	0.2336	0.6724	
LV posterior wall, cm	At admission	1,16±0,15	1,11±0,16	0,116
	6 months after	1.17±0.12	1.12±0.12	0,1699
	p	0.9540	0.5985	
RWT	At admission	0,48±0,07	0,43±0,07	0,001*
	6 months after	0.43±0.06	0.52±0.43	0,4908

Table I. (cont.)

	p	0.001*	0.3555	
LA1, cm	At admission	3,61±0,41	3,62±0,41	0,997
	6 months after	3.86±0.43	3.67±0.42	0,0470*
	p	0.003*	0.4752	
LA2, cm	At admission	3,92±0,48	4,02±0,59	0,445
	6 months after	4.23±0.41	4.09±0.52	0,1567
	p	0.0005*	0.4509	
LA index	At admission	1,98±0,24	2,07±0,29	0,168
	6 months after	2.14±0.23	2.11±0.28	0,3970
	p	0.001*	0.3245	
LA volume, ml	At admission	27,65±9,63	28,71±10,86	0,779
	6 months after	33.89±9.92	29.79±10.09	0,0515
	p	0.001*	0.4320	
LA volume, index	At admission	13,82±4,10	14,69±5,24	0,594
	6 months after	16.91±4.30	15.33±5.11	0,0807
	p	0.0003*	0.3631	
LV EF, %	At admission	51,61±9,28	48,36±7,93	0,075
	6 months after	47.69±6.54	50.34±5.90	0,0365*
	p	0.036*	0.1358	
E/A	At admission	1,07±0,39	1,10±0,37	0,795
	6 months after	1.17±0.46	1.01±0.39	0,1554
	p	0.7129	0.2799	
LV mass, g	At admission	218,87±66,07	225,92±84,97	0,802
	6 months after	217.88±62.32	194.85±75.15	0,0759
	p	0.6582	0.0720	
LV mass index, g/м2	At admission	107,74±35,45	112,14±45,88	0,770
	6 months after	109.62±34.02	100.62±38.31	
	p	0.9367	0.1246	0,1222

SBP – systolic blood pressure; DBP – diastolic blood pressure; LV – left ventricle; EDV – end-diastolic volume, ESV – end-systolic volume; EDD – end-diastolic dimension; ESD – end-systolic dimension; IVS – interventricular septum; RWT – relative wall thickness; LA – left atrium; EF – ejection fraction.

pitalization. Determination of the level of biomarkers performed by enzyme-linked immunosorbent assay following the recommendations of manufacturers using kits «Human MIF ELISA» (RayBio, USA), «Presage ST2 Assay» (Critical Diagnostics, CA, USA), «Troponin I-ELISA» (Xema, Russia) and CRP-ELISA (Xema, Russia).

For statistical analysis of the obtained results, we used the software package "Statistica" version 10.0 (Stat Soft Inc, USA). Data has been given as the arithmetic mean ± standard deviation (M ± SD) or median and the quartile interval between the 25th and 75th percentiles (Q3 – Q1) (Me [LQ; UQ]) depending on the type of distribution. The Mann – Whitney U-test was used to estimate intergroup quantitative differences. Spearman's Rank-Order Correlation used to identify the correlation between the parameters. The logistic regression analysis has been used to predict LV remodeling. Value determination, sensitivity, and specificity were performed according to the ROC analysis. The differences were considered statistically significant at $p < 0.05$.

RESULTS

In our study, most patients were male (73.3%), average age is 60,64±10,42 years. Among concomitant diseases, hypertension was in 76.7% of cases, type 2 diabetes mellitus in 28.6% of patients, history of ischemic heart disease — in 42,5%, unstable angina in 18,3% and obesity — in 23.3%. Distribution according to localization of myocardial infarction was equal, 47,5% is anterior and 52,5% posterior wall. In 67,5% patients the left anterior descending artery was injured, 61,7% – right coronary artery, other were circumflex artery and main left coronary artery, 32,5 and 6,7%, relatively. Among all 134

Table II. Parameters of echocardiography in studied patients with or without "no-reflow"

		MBG 0-1, pST<70% (n=32)	MBG 2-3, pST>70% (n=61)	p
LV EDV	At admission	132,75±32,16	126,15±27,39	0,7514
	6 months after	141,38±35,44	143,39±34,57	0,7297
	p	0,4472	0,009*	
Index EDV	At admission	65,12±15,19	64,54±14,56	0,8673
	6 months after	71,94±12,94	73,48±15,34	0,7199
	p	0,1207	0,0057*	
LV ESV	At admission	64,45±23,97	59,95±21,72	0,3484
	6 months after	69,95±25,49	73,62±23,66	0,4359
	p	0,5092	0,0050*	
Index ESV	At admission	32,76±10,35	30,68±11,21	0,4190
	6 months after	34,83±10,22	38,08±11,08	0,3052
	p	0,5167	0,0022*	
LV EDD	At admission	5,24±0,51	5,13±0,44	0,9360
	6 months after	5,37±0,57	5,39±0,51	0,8310
	p	0,4732	0,0115*	
Index EDD	At admission	2.62±0,26	2,62±0,30	0,9832
	6 months after	2,77±0,25	2,80±0,29	0,7353
	p	0,0654	0,0053*	
ESV	At admission	3,89±0,54	3,71±0,54	0,2642
	6 months after	3,98±0,57	4,05±0,51	0,4318
	p	0,6383	0,0026*	
Index ESV	At admission	1,97±0,26	1,90±0,32	0,3529
	6 months after	2,04±0,21	2,11±0,27	0,3543
	p	0,3564	0,0015*	
LA volume, index	At admission	14,82±9,07	13,93±4,52	0,3047
	6 months after	20,70±10,97	16,86±5,08	0,4430
	p	0,0977	0,004*	
LV EF, %	At admission	45,42±7,32	50,03±8,86	0,4921
	6 months after	48,17±8,30	48,39±5,69	0,9803
	p	0,2939	0,3099	
E/A	At admission	0,96±0,42	1,08±0,36	0,3914
	6 months after	1,17±0,50	1,17±0,43	0,7053
	p	0,2364	0,3498	
RV TAPSE	At admission	22,00±4,00	21,23±2,85	0,6749
	6 months after	23,62±4,25	21,69±2,42	0,1015
	p	0,6015	0,6398	
E/e'.	At admission	11,61±6,04	11,95±5,60	0,3914
	6 months after	13,06±6,35	14,70±6,04	0,4033
	p	0,7823	0,3611	

LV – left ventricle; EDV – end-diastolic volume, ESV – end-systolic volume; EDD – end-diastolic dimension; ESD – end-systolic dimension; IVS – interventricular septum; TAPSE – tricuspid annular plane systolic excursion; LA – left atrium; EF – ejection fraction.

patients enrolled in the present study, 99,9 % of patients completed the follow-up. After a 6-months follow-up, 28 (20,9%) patients reached a combined primary endpoint.

All patients were split into two groups according to developing LVR, 35% developed adverse cardiac remodeling (Table I). Hemodynamic parameters did not

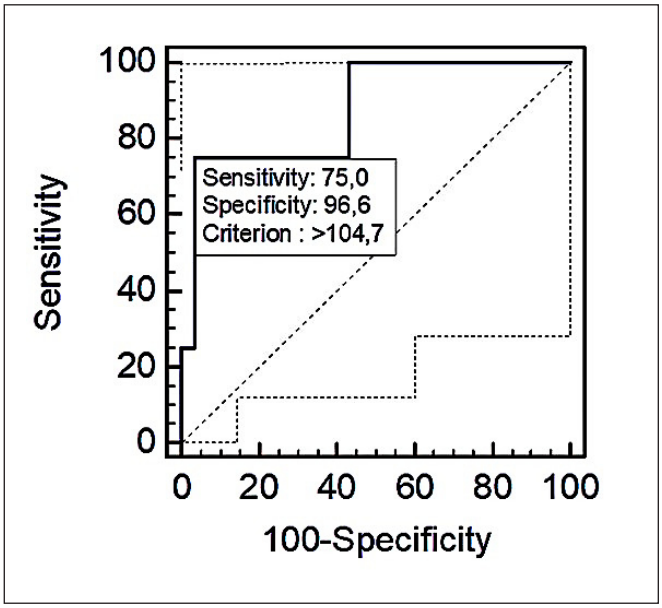

Fig. 1. Level of sST2 biomarker as a predictor of left ventricle ejection fraction deterioration (ROC-analysis).

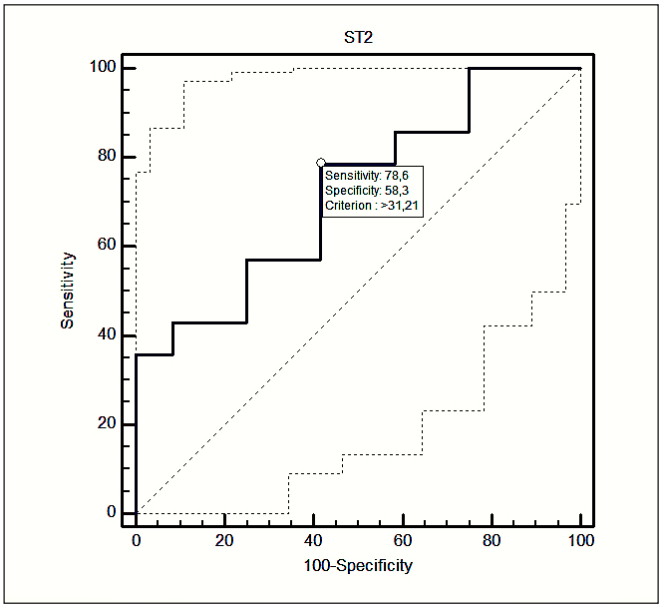

Fig. 2. Level of sST2 biomarker as a predictor of left ventricle remodeling after STEMI (ROC-analysis).

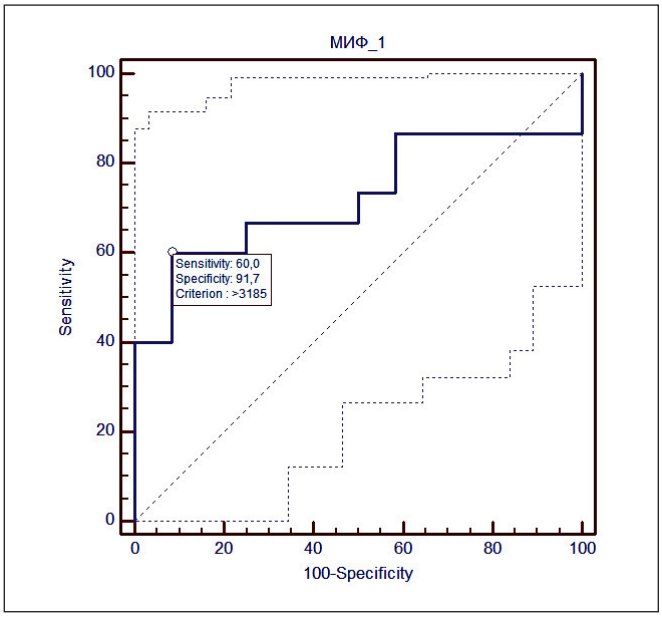

Fig. 3. Level of MIF biomarker as a predictor of left ventricle remodeling after STEMI (ROC-analysis).

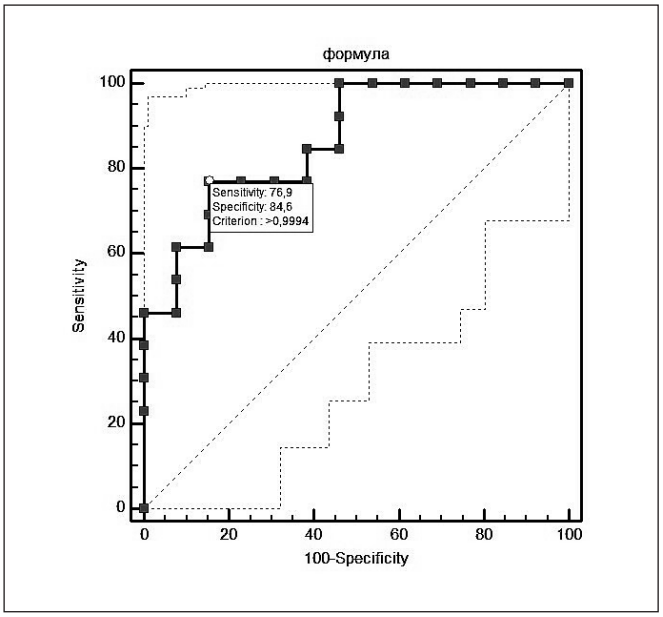

Fig. 4. ROC-curve of the formula that predicts left ventricle remodeling after STEMI.

vary significantly. In the LVR group, EDV was lower initially, but 6-months later, the indicator was significantly higher. The EDV index did not differ significantly after six months, although, at admission was higher in the group without LVR. ESV and its index were also initially lower at admission at the end of the 6th month of observation, and the parameter significantly increased. Stroke volume remained unchanged in both groups. At admission, RWT in the group of adverse LVR was higher than in another group. RWT 6-months after did not differ significantly. LV end-diastolic and end-systolic diameters (EDD) in the first group were initially lower in comparison to the second group but six months after this parameter changed significantly in the group of adverse remodeling. Their indexes did not show crucial changes. In the remodeling group, the left atrium size significantly increased six months after and worsened within the group over time. LVEF parameters deteriorated in the group of adverse remodeling after six months and reached statistical importance among two groups only after the observation period. LV mass and its index did not significantly.

We also divided studied patients according to MBG and compared groups with insufficient and normal MBG. Upon admission, echocardiography parameters

did not differ significantly in both groups, with and without "no-reflow" phenomenon. However, six months after the index event, in the "no-reflow" group, a significant increase in ESV and EDV was noted, while the LV EF remained unchanged (Table II).

A ROC analysis curves served to determine the optimal cut-off point of sST2 and MIF biomarkers for identifying patients with very high risk of adverse cardiac remodeling formation. ROC analysis showed that the serum level of sST2 > 104.7 ng/ml with a sensitivity (Sen) of 75%, a specificity (Spe) of 97% (area under curve (AUC) = 0.875, 95% confidential interval (CI) – 0.766–0.945, p = 0.0001) (Fig 1) could prognosticate reduced LVEF.

After that we tested both biomarkers If they have a predictive power in LVR six months after the event. ROC analysis demonstrated that the sST2 (Fig 2) and MIF (Figure 3) have a predictive potential for LVR. The cut-off for sST2 was > 31.21 ng/ml (Sen – 80%, Spe – 60%, AUC – 0.720, 95% CI – 0.511 – 0.877, p=0.0305), for MIF more than 3185 pg/ml (Sen – 60%, Spe – 92%, AUC – 0.722, 95% CI – 0.518 – 0.876, p=0.0318).

The multivariate Cox regression analysis was conducted. The results were assessing the independent predictive value of following parameters for late cardiac remodeling revealed that biomarker MIF (odd ratio (OR)=1,0028, p=0.0289) before revascularization, sST2 (OR=1,1008, CI 1,0032 to 1,2079, p=0.04), and the ejection fraction of LV (OR=2,2712, CI 1,0787 to 4,7818, p=0.03) were independent predictors of LVR in patients who underwent PCI after STEMI.

Although, these results were significant, but CI was not satisfactory. We combined these parameters, and a logistic regression formula was evaluated. Included parameters were MIF, sST2 and LVEF:

Y=exp(39.06+0.82EF+0.096ST2+0.0028MIF)/(1+exp(39.06+0.82EF+0.096ST2+0.0028MIF))

This equation, with Sen of 77 % and Spe of 85% predicts the development of adverse LVR six months after the coronary event (AUC=0.864, CI 0.673 to 0.966, z statistic=5.17, p=0.0001) (Fig 4).

The estimated range is from 0 to 1 point. Less than 0.5 determines the adverse outcome formation, and more than 0.5 corresponds to a good prognosis.

DISCUSSION

On the one hand, post-myocardial infarction remodeling should be considered an adaptive process, on the other hand, too many studies have shown that an increase in the ESV index and a decrease in ejection fraction are valuable predictors of heart failure development and all-cause mortality. The magnitude of adverse remodeling is related to the infarct size and insufficient myocardial perfusion, the "no-reflow" phenomenon. In our study, ESV and EDV significantly changed. However, in the remodeling group, they were lower than in patients of the second group at admission. T*he statistical difference* between the two-group estimated six months after the event to be significant. Accordingly, it is not worth focusing on these indicators in the early period of the disease. That is why the issue of the search for the ideal biomarker is so sharp. An ideal biomarker should have high Sen, which will diagnose as early as possible, and high Spe, which will exclude a non-cardiac origin of the marker and must have prognostic properties.

We evaluated the role of two biomarkers in predicting the development of adverse LVR six months after STEMI. The biomarker MIF was compared with sST2 since the latter is more discovered in the heart failure development in patients after acute myocardial infarction. ST2 is a cardiac biomarker associated with stress and the fibrosis process, with significant dynamics in patients with myocardial infarction or acute heart failure. Because of its lack of cardiac specificity, it had been ruled out as a diagnostic tool for myocardial infarction, but other studies have shown promising results on its prognostic value related to mortality and heart failure development [23]. Our result showed that sST2 predicted a decrease in LV EF in the acute phase. However, the biomarker had low specificity in predicting LVR six months after the event.

In turn, the MIF biomarker looked more promising. MIF, a pleiotropic protein with inflammatory properties, has already been proven in STEMI patients to predict infarct size and adverse outcomes.

We observed that high levels of MIF in the first hours of the disease indicated the state of cardiac function in the long term and the prognosis in patients with STEMI. This relationship was probably obtained due to the direct involvement of MIF in the inflammatory response, regulation of cardiac remodeling, and formation of fibrosis after myocardial infarction. The severity of the inflammatory response and fibrosis induced after infarction are important determinants of the severity of LVR and the progression of heart failure. [24, 25].

With the development of ischemia is accompanied by myocardial necrosis, MIF promotes the accumulation of macrophages in necrotic tissue, enhances the inflammatory response, and induces the production of other inflammatory factors, such as C-RP, interleukin-6, which exacerbates myocardial damage [26, 27]. There is evidence, MIF can also affect interstitial fibrosis in non-infarct areas after myocardial infarction [28], which allows us to consider this biomarker important in predicting adverse LVR.

Biomarker MIF did not show high sensitivity, and sST2 did not have high specificity. So, we attempted to combine them to improve the accuracy of the prognosis. Analysis of logistic regression equation

with continuous predictor applying derivatives helps choose optimal thresholds that provide maximally effective discriminative functions with priority sensitivity or specificity.

RESEARCH LIMITATIONS

A small sample size of patients and a short follow-up period were the main limitations of this study.

CONCLUSIONS

In our study, we have shown that the biomarkers MIF and sST2 exhibit prognostic properties in adverse cardiac remodeling formation. However, a combination of biomarkers gives a more significant predicting result in the formation of adverse left ventricular remodeling after STEMI. To implement these results in routine clinical practice future investigations needed.

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The Authors declare no conflict of interest.

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