



## NEW BIOLOGICAL MARKERS FOR A PROGNOSTIC MODEL FOR ASSESSING THE RISK OF CARDIAC FIBROSIS IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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### Highlights

- The developed prognostic model for assessing the risk of cardiac fibrosis in patients with STEMI with HFmrEF and HFpEF is promising from the point of view of scientific and clinical potential because similar models for predicting the risk of cardiac fibrosis in patients with index MI are not currently validated. The developed scale includes such parameters as age, LVEF, COL-1, BMI, MMP-2. The scale can be used in patients with HFmrEF and HFpEF phenotypes. Identification of patients at high risk of myocardial fibrosis will allow choosing the appropriate treatment method.

<b>Aim</b>	To develop a prognostic model for assessing the risk of cardiac fibrosis (CF) in patients with preserved left ventricular ejection fraction (HFpEF) and mildly reduced ejection fraction (HFmrEF) a year after ST-segment elevation myocardial infarction (STEMI) based on clinical, instrumental and biochemical data.
<b>Methods</b>	The prospective cohort study included 100 STEMI patients with HFmrEF (LVEF 40–49%) and with HFpEF (50% or more). Echo was performed in all patients on the 1 <sup>st</sup> , 10–12 <sup>th</sup> day and a year after onset of STEMI. Upon admission to the hospital and on the 10–12 <sup>th</sup> day after the onset of the disease, the following serum biomarker levels were determined: those associated with changes in the extracellular matrix; with remodeling and fibrosis; with inflammation, and with neurohormonal activation. At the 1-year follow-up visit, 84 patients underwent contrast-enhanced MRI to assess fibrotic tissue percentage relative to healthy myocardium.
<b>Results</b>	The distribution of patients by HFmrEF and HFpEF phenotypes during follow-up was as follows: HFmrEF on the 1 <sup>st</sup> day – 27%, 10th day – 12%, after a year – 11%; HFpEF on the 1st day – 73%, 10 <sup>th</sup> day – 88%, after a year – 89%. According to cardiac MRI at the follow-up visit (n = 84), the median distribution of fibrotic tissue percentage was 5 [1.5; 14]%. Subsequently, the threshold value of 5% was chosen for analysis: CF $\geq$ 5% was found in 38 patients (the 1 <sup>st</sup> group), whereas CF $<$ 5% was noted in 46 patients (the 2 <sup>nd</sup> group). When analyzing the intergroup differences in biological marker concentrations in the in-patient setting and at the annual follow-up, it was determined that the most significant differences were associated with "ST-2" (1st day) that in the "CF $\geq$ 5%" group was 11.4 ng/mL higher on average compared to the "CF $<$ 5%" group (p = 0.0422); "COL-1" (1st day) that in the "CF $\geq$ 5%" group was 28112.3 pg/mL higher on average compared to the "CF $<$ 5%" group (p = 0.0020), and "NT-proBNP" (12th day) that in the "CF $<$ 5%" group was 1.9 fmol/mL higher on average compared to the "CF $\geq$ 5%" group (p = 0.0339). Certain factors (age, LVEF (12th day), collagen-1 (1st and 12th day), body mass index, matrix metalloproteinase-2 (12th day) were determined and included in the prognostic model for assessing the risk of CF a year after the STEMI (AUC ROC 0.90, Chi-square test $<$ 0.0001).
<b>Conclusion</b>	Prognostic model (scale) based on factors such as age, left ventricular ejection fraction (12th day), collagen-1 (1 <sup>st</sup> and 12 <sup>th</sup> day), body mass index, matrix metalloproteinase-2 (12th day) shows high prognostic power and enables identification of patients with HFmrEF and HFpEF phenotypes and at high risk of cardiac fibrosis a year after STEMI.
<b>Keywords</b>	Biomarkers 1 • Myocardial infarction 2 • Heart failure 3 • Prognostic model 4

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## Список сокращений

ACE	– angiotensin-converting enzyme	HFpEF	– HF with preserved EF
BMI	– body mass index	LVEF	– left ventricular ejection fraction
CABG	– coronary artery bypass grafting	MI	– myocardial infarction
CAD	– coronary artery disease	MRI	– magnetic resonance imaging
CCTA	– coronary computed tomography angiography	PCI	– percutaneous coronary intervention
CF	– cardiac fibrosis	STEMI	– myocardial infarction with ST
HF	– heart failure	TIA	– segment elevation
HFmrEF	– HF with mid-range EF		transient ischemic attack

## Introduction

In the last decade the prevalence and mortality associated with myocardial infarction (MI) has decreased in industrialized countries, thanks to the effective healthcare system management and implementation of preventive programs [1]. Nevertheless, complication rates in the early and long-term post-MI period remain high and thus require further study [2, 3]. In this regard, risk stratification in patients with MI is of particular interest for practical medicine, since tools like that improve the prognosis substantially. The long-term prognosis for this category of patients is determined by the course of the disease within the first hours or days, therefore, it is important to carry out timely risk assessment to determine the likelihood of complications in patients, starting with the acute period of MI.

Heart failure (HF) is one of the complications associated with an adverse event in the post-MI period [4]. Currently, the development and progression of HF in patients with coronary artery disease (CAD) is considered from the perspective of “remodeling” of the myocardium – a complex process of structural, geometric and functional changes of the heart which rely upon changes in the cellular-stromal ratio and morpho-functional characteristics of the main cellular elements, including excessive extracellular matrix and collagen proliferation, and, as a consequence, the development of cardiac fibrosis [5, 6]. Thus, modern approaches to studying fibrogenesis involve cohorts of patients with cirrhosis, idiopathic pulmonary fibrosis and renal fibrosis, and, to a lesser extent, patients with cardiovascular diseases [6–9]. Moreover, anti-fibrotic drugs remain understudied, and the available therapeutic strategies are mainly focused on the inflammatory response, not on other pathogenetic components of fibrogenesis. Thus, studying cardiac fibrosis (CF) is somewhat controversial and contradictory, but it is still necessary to study it on patients with MI with ST segment elevation (STEMI) [7]. A multi-marker strategy, along with instrumental methods, can provide significantly more information on risk stratification than any single marker on its own. Moreover, the identification of high-risk patients can assist in making

decisions regarding the optimal treatment of this group of patients [8, 10]. The available traditional approaches to diagnosis, risk assessment and treatment are not suitable for patients with HF with preserved/mildly reduced left ventricular ejection fraction (LVEF), which indicates the need to search for new ways of improving prediction of cardiovascular complications after STEMI [7, 8]. Thus, the research targets are molecular predictors, clinical and instrumental markers associated with pathological remodeling and cardiac fibrosis, as well as the markers associated with early and long-term unfavorable prognosis.

**The aim** of the study was to develop a prognostic model for assessing the risk of CF in STEMI patients with preserved and mildly reduced LVEF a year after onset of the disease based on clinical, instrumental and biochemical factors.

## Material and methods

The prospective cohort study included 100 STEMI patients admitted to the Research Institute for Complex Issues of Cardiovascular Diseases in 2015. The study was conducted in accordance with guidelines for Good Clinical Practice and it complies with the principles of the Declaration of Helsinki. The study protocol received approval by the Institutional Review Board.

## Inclusion criteria:

- signed informed consent;
- age >18 years and <75 years;
- diagnosis of STEMI: angina pectoris lasting  $\geq 20$  minutes or its equivalents, ST segment elevation in at least two consecutive leads, which is estimated at the J point and equal to  $\geq 0.2$  mV in men and  $\geq 0.15$  mV in women, or a left bundle branch block, a diagnostically significant increase in markers of myocardial necrosis [creatine phosphokinase myocardial band fraction (CPK-MV) or troponin T/I];
- successful percutaneous coronary intervention (PCI);
- ejection fraction  $\geq 40\%$ ;

## Exclusion criteria:

- presence of clinically significant concomitant pathology [liver failure, acute or chronic renal failure, chronic obstructive pulmonary disease, acute infectious

disease or exacerbation of chronic infectious disease, mental diseases, autoimmune diseases, cancer, adrenal gland disorders and thyroid disorders];

- STEMI, which occurred as a complication of PCI or coronary artery bypass grafting (CABG);
- age over  $\geq 75$  years;
- Killip class IV HF;
- ejection fraction  $< 40\%$ ;
- the need for subsequent staged revascularization;
- death of the patient on the first day of hospitalization.

Demographic, clinical, and anamnestic data were collected from all patients, and standard examinations, including basic blood chemistry tests, complete blood count, and ECG were performed. Coronary computed tomography angiography (CCTA) was performed in patients with index MI using an INNOVA 3100 cardiovascular imaging system (USA) upon admission and a year later. Echocardiography was performed in all patients on the 1<sup>st</sup> and 10–12<sup>th</sup> day of hospitalization, and a year later using a Sonos 2500 Ultrasound machine

(Hewlett Packard, USA). At the follow-up visit, patients underwent contrast-enhanced (gadolinium) T1-weighted magnetic resonance imaging (MRI), which is the preferred method of assessing cardiac fibrosis, using an Excelart Vantage Atlas 1.5T MRI Machine (Toshiba, Japan).

Upon admission to the hospital and on the 10–12th day from the onset of the disease, the serum concentrations of the following biomarkers were determined: those associated with changes in the extracellular matrix, remodeling and fibrosis; inflammatory markers; and neurohormonal activation markers. The concentrations were determined by quantitative solid-phase enzyme immunoassay using BCM Diagnostics laboratory kits (USA) – Table 1.

The mean age of patients in was 57 (52; 63) years. Out of 100 patients, 74 were men (74%). The prevailing cardiovascular risk factors were as follows: arterial hypertension found in 70 (70.0%) patients, smoking in 56 (56%) patients, type 2 diabetes mellitus in 11 (11%) patients. According to the results of analysis, about half of the patients presented with clinical manifestations of CAD: angina was noted in 31 (31%) patients, MI in 5 (5%) patients, whereas PCI was found in 3 (3%) cases. 12 (12%) patients had an established diagnosis of HF, and 22 (22%) patients had high cholesterol. Most of the patients (71 cases (71%)) were overweight (body mass index (BMI)  $> 25$  kg/m<sup>2</sup>). The average length of stay was 14 (12; 18) days.

The analysis of the prescribed medication revealed that aspirin was prescribed to 9% of patients,  $\beta$ -blockers to 11%, angiotensin-converting enzyme (ACE) inhibitors to 11%, and statins to 4% of patients. In hospital setting all patients received medication according to the Guidelines on Management of Acute MI in Patients Presenting with ST-Segment Elevation [European Society of Cardiology, 2015], which included:  $\beta$ -blockers, disaggregants, ACE inhibitors (if prescribed), diuretics, and calcium channel blockers. Thus, acetylsalicylic acid was prescribed to 99% of patients, clopidogrel to 83% of patients, ticagrelor to 25% of patients,  $\beta$ -blockers to 97% of patients, ACE inhibitors to 77% of patients, and statins were prescribed to 94% of patients. Systemic thrombolytic therapy was prescribed to 11% of patients in prehospital setting. According to the CCTA, the majority of patients (41%) presented with hemodynamically significant lesions (coronary artery stenosis  $> 50\%$ ) of one arterial bed, 33% of patients presented with lesion of two coronary arterial beds, whereas multivessel CAD was diagnosed in 26% of patients. All patients underwent revascularization.

A year after STEMI, the response rate was 84% (84 patients). The analysis did not include patients deceased in the hospital setting. Analyzing endpoints at the follow-up visit (survival/death, hospitalization due to unstable angina and decompensated HF, MI, acute

**Table 1.** Markers analyzed in the study

Markers	Reference values
<b>Markers associated with changes in the extracellular matrix, remodeling and cardiac fibrosis</b>	
TGF- $\beta$	4 639.00–14 757.00 pg/mL
MMP-1	2.20–22.90 ng/mL
MMP-2	15.00–72.00 ng/mL
MMP-3	12.00–71.00 ng/mL
TIMP-1	1.10–10000 pg/mL
FGF	0–14.60 pg/mL
COL-1	0.16–21.30 pg/mL
PICP	0.16–10.00 pg/mL
PIIINP	14.70–115.60 pg/mL
Galectin-3	0.0–2.28 ng/mL
sST-2	39.10–28 180.00 pg/mL
<b>Inflammatory markers</b>	
TNF- $\alpha$	100–5 000 pg/mL
IL-6	0–12.70 pg/mL
IL-10	7.9–12.90 pg/mL
IL-12	40.40–150.00 pg/mL
IL-33	1.30–1 140.00 pg/mL
CRP	1.00–5.00 мг/л
<b>Neurohormonal activation markers</b>	
NT-proBNP	21.9–1 400.00 fmol/mL
proANP	78.10–5 000.00 nmol/L

**Note:** COL-1 – collagen; CRP – C-reactive protein; FGF – fibroblast growth factors; IL – interleukin; MMP – matrix metalloproteinase; NT-proBNP – N-terminal pro-B-type natriuretic peptide; PICP – procollagen type I C-terminal propeptide; PIIINP – N-terminal propeptide of procollagen type III; proANP – pro atrial natriuretic peptide; sST-2 – soluble ST-2 receptor; TGF- $\beta$  – transforming growth factor- $\beta$ ; TIMP-1 – tissue inhibitor of metalloproteinase-1; TNF- $\alpha$  – tissue necrosis factor- $\alpha$ .

cerebrovascular accident (stroke)/transient ischemic attack (TIA), including planned and emergency PCI/CABG, we have noted that the adverse events were largely associated with the following factors: repeated MI in 7 patients (8.3%), repeated hospitalizations for unstable angina in 4 patients (4.8%), and hospitalizations for other reasons in 9 patients (10.7%). Hospitalization due to decompensated HF did not occur. Stroke/TIA developed in 2.4% of patients. Death was registered in 3 patients (3.6%) as a result of recurrent MI (stent thrombosis). Throughout the year, 11 planned revascularizations were performed: CABG in 1 patient (1.2%), and PCI in 10 patients (11.9%). 1 emergency PCI was performed in a patient with recurrent MI. The prevalence and functional classification of HF a year after STEMI were analyzed as well: clinical manifestations of HF were found in 100% of patients; class I HF was observed in 12 (14.3%) patients, class II HF in 69 (82.1%), and class III HF in 3 (3.6%).

At the follow-up visit, 84 patients underwent contrast-enhanced MRI, which assessed the fibrotic tissue percentage to healthy myocardium. Thus, the median distribution of fibrotic tissue percentage was 5 [1.5; 14] %. Subsequently, the threshold value of 5% was chosen for analysis:  $CF \geq 5\%$  was noted in 38 patients (the 1st group), whereas  $CF < 5\%$  was noted in 46 patients (the 2<sup>nd</sup> group, Figure 1).

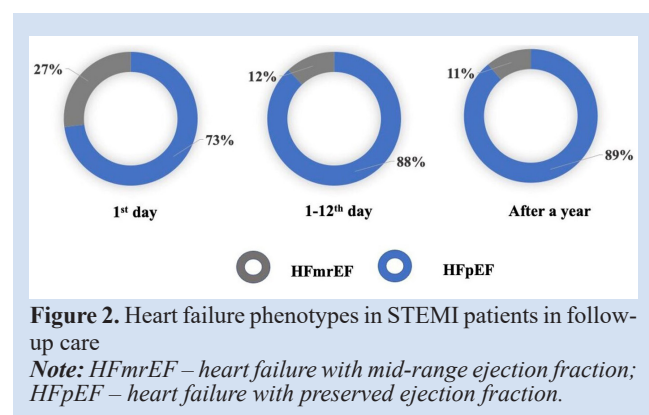
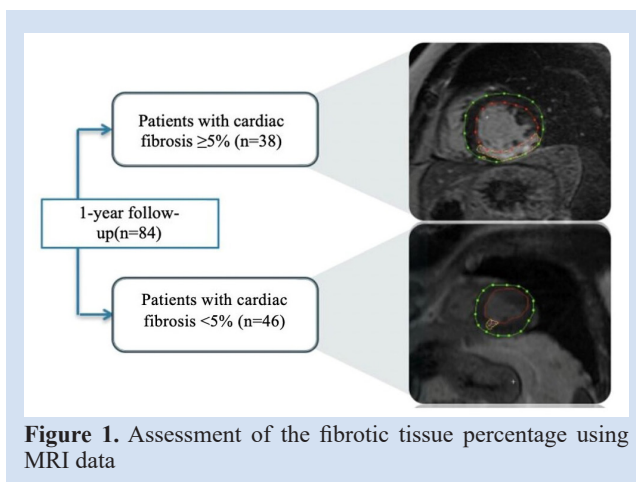
STATISTICA software Version 8.0 (StatSoft, Inc, USA) was used for statistical evaluation. Standard descriptive statistics methods were used in the study. The Shapiro-Wilk test was used to test the normality of the data. Results are expressed as the mean, the standard deviation, the median and interquartile range between the first quartile (25th percentile) and the third quartile (75th percentile) (Me [Q25; Q75]). The Mann-Whitney U test was used to compare differences between two independent groups. The Wilcoxon signed rank test was used to assess the significance of each variable. Spearman's correlation coefficient was used to measure the strength and direction of association between two variables. In all cases,  $p < 0.05$  was considered significant. The null hypothesis was rejected at  $p < 0.05$ . The process of model building

began with the identification of binary variables that statistically significantly affect the dependent variable, which are identified based on risk assessment (cut-off point is identified as well). Out of these candidate predictors, the predictors that included information that preceded the outcome of interest in time and that were believed to predict the outcome of interest were selected. To impute missing data, any variable containing missing value was assigned a value of 0.5 to minimize misclassification. Then, using stepwise logistic regression and factors that contribute most to the model, we obtained scales with different number of factors. Using AUROC curves, the models with the optimal number of variables were chosen based on the highest sensitivity, specificity, and best performance. For the chosen models, a 100-point scale of coefficients was built based on logistic regression (each factor included in the scale is assigned a certain value reflecting the strength of the factor's influence on the dependent variable).

## Results

The distribution of patients by HFmrEF and HFpEF phenotypes during follow-up was as follows: HFmrEF on the 1st day – 27%, 10th day – 12%, after a year – 11%; HFpEF on the 1st day – 73%, 10th day – 88%, after a year – 89% (Figure 2).

The analysis of changes in echocardiographic parameters of STEMI patients with mildly reduced and preserved LVEF on the 1st, 10–12th inpatient day, as well as a year later, resulted in the identification of reliable trends in several parameters: LVEF ( $p = 0.0001$ ), ESD ( $p = 0.0001$ ), ESV ( $p = 0.0001$ ), SV ( $p = 0.0001$ ), ESVI ( $p = 0.0071$ ), MM ( $p = 0.0057$ ), LVM mass index ( $p = 0.0057$ ), IVRT ( $p < 0.001$ ), DT ( $p = 0.0363$ ), ET ( $p < 0.001$ ), systolic pulmonary venous flow ( $p = 0.0084$ ), diastolic pulmonary venous flow ( $p = 0.0375$ ), AR ( $p < 0.001$ ), LVEDP ( $p = 0.0212$ ), Tei index ( $p < 0.001$ ), diastolic stiffness ( $p = 0.0072$ ), Vp ( $p = 0.001$ ) (Table 2). Thus, the parameters such as LVEF, SV, and Vp had the tendency to increase in MI patients by the 10–12th day, whereas EDV, ESV, ESD, DT, ET, Em, Em/Vp – on the contrary, decreased. The assessment of LVEF after a year in comparison with the first days revealed a statistically significant positive



dynamic ( $p < 0.05$ ). LVEF, myocardial mass and LV myocardial mass index, ET, blood flow velocity in the pulmonary veins (systolic and diastolic), Am, and Vp were increasing by the 12th month of follow-up ( $p < 0.05$ ), while ESD, ESV, ESVI, EDD, VpvA, Tei index, and Em/Am were steadily decreasing ( $p < 0.05$ ).

MRI revealed that patients with HFmrEF phenotype are characterized by a larger percentage of fibrotic

tissue ( $CF > 5\%$  in 80.00% of patients), compared to patients with HFpEF (only 35.85%) (Figure 3).

Echo data analysis revealed that patients with  $CF \geq 5\%$  presented with the worst LV systolic and diastolic function (Table 3). EDD (cm) in the  $CF \geq 5\%$  group was 0.4 cm larger compared to the  $CF < 5\%$  group ( $p = 0.0010$ ); EDVI ( $\text{mL}/\text{m}^2$ ) in the  $CF \geq 5\%$  group was  $14.4 \text{ mL}/\text{m}^2$  higher compared to the  $CF < 5\%$  group

**Table 2.** Echocardiographic parameters in patients with myocardial infarction in follow-up care

Parameter	Follow up			p
	1 <sup>st</sup> day	10–12 <sup>th</sup> day	1-year follow-up	
LVEF (%)	42.5 [39.25; 48.0]	46 [43.0; 50.0]	48.5 [43; 55]	0.0001
EDD (cm)	5.5 [5.2; 5.7]	5.4 [5.25; 5.7]	5.5 [5.1; 5.8]	0.9878
ESD (cm)	3.9 [3.6; 4.3]	3.8 [3.5; 4.1]	3.7 [3.3; 4.1]	0.0001
EDV (mL)	141 [124.0; 160.0]	141 [130.0; 160.0]	147 [124; 167]	0.0689
ESV (mL)	66 [54.0; 83.0]	62 [51.0; 74.0]	62 [44; 74]	0.0001
LA (cm)	4.1 [3.9; 4.3]	4.1 [3.9; 4.3]	4.1 [3.9; 4.3]	0.7655
RV (cm)	1.8 [1.8; 1.8]	1.8 [1.8; 1.8]	1.8 [1.8; 1.9]	0.8551
IVS (cm)	1.1 [1.0; 1.2]	1.1 [1.0; 1.2]	1.1 [1.0; 1.2]	0.5971
LVPW (cm)	1.1 [1.0; 1.2]	1.1 [1.0; 1.2]	1.1 [1.0; 1.2]	0.8231
EDVI ( $\text{mL}/\text{m}^2$ )	76 [68.0; 85.5]	75 [68.0; 86.0]	75.72 [66.34; 86.72]	0.7989
ESVI ( $\text{mL}/\text{m}^2$ )	37 [28.0; 42.75]	32 [26.0; 39.0]	30.85 [22.58; 40.54]	0.0071
SV (mL)	79 [70.25; 88.0]	81 [74.25; 90.0]	86.0 [78.25; 93.0]	0.0001
MM (g)	241 [217.5; 271.0]	234 [213.0; 271.0]	299.07 [257.67; 339.10]	0.0057
LVM mass index ( $\text{g}/\text{m}^2$ )	130 [122.0; 140.75]	124 [116.0; 142.0]	155.09 [134.86; 170.99]	0.0057
E (cm/s)	57 [49.25; 70.0]	60 [47.0; 71.5]	55 [43; 68]	0.6898
A (cm/s)	68.5 [59.0; 78.0]	69 [53.5; 78.5]	66.5 [57; 76]	0.8858
E/A	0.78 [0.71; 1.19]	0.79 [0.68; 1.24]	0.795 [0.66; 1.18]	0.3764
IVRT (ms)	111 [104.0; 118.0]	110 [104.0; 118.0]	118 [111.0; 131.0]	<0.001
DT (ms)	202 [170.0; 222.0]	196 [170.0; 221.5]	215 [183; 242]	0.0363
AT (ms)	131 [116.25; 141.75]	131 [111.0; 137.0]	124 [111; 137]	0.3312
ET (ms)	294 [279.75; 307.0]	287 [268.0; 300.0]	529 [437; 614]	<0.001
dE (ms)	242 [228.0; 281.0]	242 [209.7; 275.7]	242 [212; 274]	0.7812
dA (ms)	157 [137.0; 176.0]	157 [137.0; 176.2]	155 [140.5; 170]	0.7838
Systolic pulmonary venous flow (cm/s)	40 [35.0; 46.25]	40.5 [37.0; 47.0]	49 [43; 57]	0.0084
Diastolic pulmonary venous flow (cm/s)	31.5 [28.75; 37.0]	33 [29.0; 38.0]	35.5 [31; 39]	0.0375
AR	26 [24.0; 28.0]	25 [23.0; 28.0]	22 [21; 23]	<0.001
LVEDP (mm Hg)	10.88 [9.9; 11.84]	10.4 [9.44; 11.84]	9 [8; 9]	0.0212
Tei index	0.7 [0.64; 0.76]	0.71 [0.65; 0.77]	0.39 [0.32; 0.47]	<0.001
Diastolic stiffness	0.07 [0.06; 0.08]	0.07 [0.06; 0.08]	0.05 [0.05; 0.055]	0.0072
MAV (cm/s)	7 [6.0; 8.0]	7 [6.0; 8.0]	7.0 [6.0; 8.0]	0.5257
Em	7 [6.0; 8.0]	6 [5.0; 8.0]	6.0 [5.0; 8.0]	0.0535
Am	8 [6.9; 9.0]	7.9 [7.0; 9.0]	9.0 [7.0; 10.0]	0.0675
Em/Am	0.83 [0.7; 1.14]	0.75 [0.67; 1.14]	0.78 [0.60; 0.88]	0.0240
E/e'	8.6 [7.38; 10.22]	9 [7.56; 10.42]	8.2 [6.91; 10.40]	0.0670
Vp (cm/s)	36.85 [29.0; 45.0]	40 [31.0; 48.0]	48.0 [36.0; 56.0]	0.0001

**Note: Here and further in Table 2:** A – late LV diastolic filling velocity; Am – late diastolic mitral annular velocity; AR – atrial reversal phases of pulmonary venous flow; AT – acceleration time of early filling; DT – deceleration time of early filling; E – early LV diastolic filling velocity; E/A – ratio of early to late transmitral flow velocity; E/e' – ratio of early mitral inflow velocity to early diastolic mitral annular velocity; EDD – end diastolic dimension; EDV – end diastolic volume; EDVI – end diastolic volume index; Em – early diastolic mitral annular velocity; Em/Am – ratio of early to late diastolic mitral annular velocity; ESD – end systolic dimension; ESV – end systolic volume; ESVI – end systolic volume index; ET – ejection time; IVRT – isovolumic relaxation time; IVS – interventricular septum; LA – left atrium; LVEDP – left ventricular end diastolic pressure; LVEF – left ventricular ejection fraction; LVM mass index – left ventricular myocardial mass indexed to body surface area; LVPW – left ventricular posterior wall; MAV – mitral annulus velocity; MM – myocardial mass; RV – right ventricle; SV – stroke volume; Vp – flow propagation velocity of early transmitral flow.

( $p = 0.0008$ ); ESD (cm) in the  $CF \geq 5\%$  group was 0.5 cm larger compared to the  $CF < 5\%$  group ( $p = 0.0006$ ).

When analyzing the intergroup differences in biological marker concentrations in the in-patient setting and at the annual follow-up, it was determined that the most significant differences were associated with “ST-2” (1st day) that in the “ $CF \geq 5\%$ ” group was 11.4 ng/mL higher on average compared to the “ $CF < 5\%$ ” group ( $p = 0.0422$ ); “COL-1” (1st day) that in the “ $CF \geq 5\%$ ” group was 28112.3 pg/mL higher on average compared to the “ $CF < 5\%$ ” group ( $p = 0.0020$ ), and “NT-proBNP” (12th day) that in the “ $CF < 5\%$ ” group was 1.9 fmol/mL higher on average compared

to the “ $CF \geq 5\%$ ” group ( $p = 0.0339$ ) (Figure 4). Certain factors (age, LVEF (12th day), collagen-1 (1st and 12th day), body mass index, matrix metalloproteinase-2 (12th day) were determined and included in the prognostic model for assessing the risk of CF a year after the STEMI (AUROC 0.90, Chi-square test  $< 0.0001$ ).

Despite the absence of significant intergroup differences in MMP-2 and IL-18, their influence on the risk of CF (target variable) was revealed during multivariate analysis. To build a prognostic model for assessing the risk of CF a year after STEMI, alongside markers, clinical and echocardiographic parameters were also included in the multivariate regression

**Table 3.** Echocardiography results (at follow-up visit) by fibrotic tissue percentage

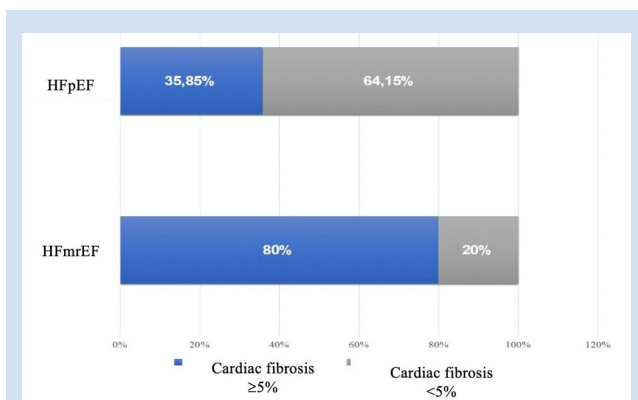
Parameter	Comparison groups		p
	Cardiac fibrosis $< 5\%$ , n = 46	Cardiac fibrosis $\geq 5\%$ , n = 38	
LVEF (%)	64 [61; 66.5]	56.5 [48; 62.75]	0.0027
EDD (cm)	5.3 [5; 5.4]	5.7 [5.425; 5.9]	0.0010
ESD (cm)	3.4 [3.15; 3.8]	4.05 [3.625; 4.375]	0.0006
EDV (mL)	135 [118; 141]	160 [142.5; 173]	0.2625
ESV (mL)	47 [41; 62]	72 [55; 86.75]	0.0011
LV (cm)	4 [3.9; 4.1]	4.2 [3.925; 4.375]	0.0484
RV (cm)	1.8 [1.8; 1.85]	1.8 [1.8; 1.9]	0.8542
IVS (cm)	1 [1; 1.2]	1.1 [1; 1.2]	0.5827
LVPW (cm)	1 [1; 1.15]	1.05 [1; 1.2]	0.9552
Ascending aorta (cm)	3.5 [3.3; 3.5]	3.5 [3.3; 3.6]	0.4349
SV (mL)	83 [77; 87.75]	89 [80.25; 93.5]	0.0616
EDVI	68 [64; 72]	85 [76; 92.5]	0.0008
ESVI	22 [20; 29]	40 [29; 45.5]	0.0013
LVM mass index	112 [99; 127]	129 [114; 136]	0.0077
PMax AV (mm Hg)	7 [6; 8]	6 [6; 8]	0.2617
mPAP (mm Hg)	24 [21; 28]	25.5 [24; 28]	0.1504
E (cm/s)	55 [46.75; 72.5]	51 [40; 61.75]	0.2271
A (cm/s)	69.5 [57; 75]	71.5 [60; 78]	0.4922
E/A	0.805 [0.69; 1.12]	0.69 [0.5225; 0.825]	0.0958
IVRT (ms)	116 [104; 124]	121 [118; 135.5]	0.0595
DT (m/s)	212 [185.75; 228]	209 [183; 242]	0.9028
AT (m/s)	127.5 [124; 131]	131 [104; 143]	0.8519
ET (m/s)	512.5 [485; 561.5]	529 [405; 542]	0.9511
dE (m/s)	231.5 [213.75; 259.5]	242 [196; 268]	0.8539
dA (m/s)	147 [138.75; 165.75]	157 [150; 170]	0.1534
IVCT (m/s)	91 [72; 98]	98 [91; 98]	0.5192
Systolic pulmonary venous flow (cm/s)	49 [44; 60]	56 [47; 57]	0.7386
Diastolic pulmonary venous flow (cm/s)	33 [31; 36]	35 [34; 42]	0.2038
Tei index	0.41 [0.3425; 0.4525]	0.34 [0.34; 0.62]	0.9023
Diastolic stiffness	0.06 [0.0525; 0.06]	0.05 [0.05; 0.053]	0.1158
MAV (cm/s)	7 [6; 7]	8 [7; 9]	0.1084
Em	8 [8; 8]	6 [5; 7]	0.0678
Am	8 [7; 11]	8 [8; 9]	1.0000
Em/Am	0.82 [0.73; 1.14]	0.71 [0.62; 0.88]	0.5296
E/Em	10.2 [5.44; 10.25]	7.385 [6.77; 8.75]	0.8065
Vp (cm/s)	52.5 [44.25; 59.75]	55 [34; 64]	0.8985

*Note:* IVCT – isovolumic contraction time; mPAP – mean pulmonary artery pressure.

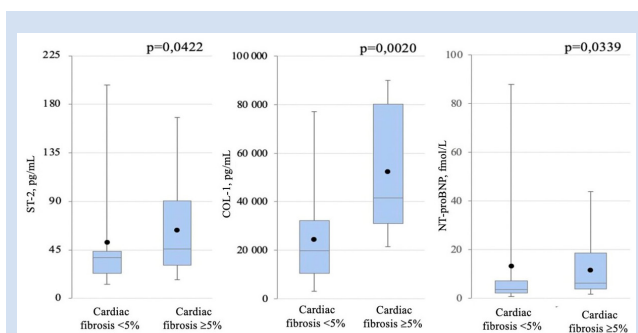
analysis, with the selection of factors of the most significant influence on the target variable (risk of CF). The selection of variables (factors) was carried out on the basis of expediency over time (the variables should be measured earlier or throughout the prediction of an event, but not later) and rationality for medical practice (Table 4). Based on logistic regression, the factors with the highest impact on the target variable were chosen. The results of the stepwise logistic regression are presented in Table 5.

The 2<sup>nd</sup> step of model building is obtaining point scales in order to select the optimal number of factors to include in the model. Based on the identified factors, a scale with factors affecting the target variable (risk of CF) was developed (Table 6). Each factor included in the scale is assigned 1 or 0 points, depending on whether the condition is met or not. If the condition is met, 1 point is assigned, if not – 0 points. The exception would be the missing data, in that case 0.5 points are assigned (but only for one factor). The sensitivity, specificity and performance of the prediction model is presented in Table 7.

A 100-point scale of coefficients was built based on logistic regression. This model allowed us to take into account the influence of each factor on the target variable (the risk of CF). This model takes into account the degree of influence of each factor. Thus, in the other scales each factor can be assigned 1 or 0 points, but in the regression model different factors can be assigned 7 and 26 points out of 100, thus increasing the



**Figure 3.** Fibrotic tissue percentage in patients with different heart failure phenotypes  
 Note: HFmrEF – heart failure with mid-range ejection fraction; HFpEF – heart failure with preserved ejection fraction.



**Figure 4.** Biomarkers in the groups by percentage of fibrotic tissue

**Table 4.** Factors (with cut-off point) selected for building predictive model for assessing the “Risk of cardiac fibrosis”

Time frame	Factor	Cut-off point	HR (95 % CI)	p
1 <sup>st</sup> day	COL-1 $\geq 29\ 930.0$ pg/mL	29 930.0	9.39 (1.40; 63.07)	0.0004
1 <sup>st</sup> day	ST-2 $\geq 45.9$ pg/mL	45.9	1.92 (1.18; 3.12)	0.0095
1 <sup>st</sup> day	MM $\geq 246.0$ g	246.0	1.69 (1.05; 2.72)	0.0307
1 <sup>st</sup> day	IL-18 $\geq 94.8$ pg/mL	94.8	2.19 (1.21; 3.96)	0.0309
12 <sup>th</sup> day	LVEF $< 57.0\%$	57.0	2.82 (1.63; 4.90)	$< 0.0001$
12 <sup>th</sup> day	NT-proBNP $\geq 3.6$ fmol/L	3.6	2.1 (1.02; 4.29)	0.0190
12 <sup>th</sup> day	COL -1 $\geq 30\ 368.0$ pg/mL	30 368.0	2.29 (1.17; 4.48)	0.0201
12 <sup>th</sup> day	IL-18 $\geq 53.9$ pg/mL	53.9	2.44 (0.88; 6.77)	0.0394
12 <sup>th</sup> day	IVRT $\geq 96.0$ m/s	96.0	3.88 (0.62; 24.15)	0.0404
12 <sup>th</sup> day	MMP-2 $\geq 235.6$ ng/mL	235.6	3.84 (0.98; 7.96)	0.0424
–	Age $< 50.0$ years	50.0	1.76 (1.19; 2.62)	0.0317
–	BMI $\geq 29.4$ kg/m <sup>2</sup>	29.4	1.61 (1.05; 2.45)	0.0472
–	Gender (Male)	Male	1.25 (0.68; 2.31)	0.4359

Note: BMI – body mass index; COL – collagen; HR – heart failure; IL – interleukin; IVRT – isovolumic relaxation time; LVEF – left ventricular ejection fraction; MM – myocardial mass; MMP – matrix metalloproteinase; NT-proBNP – N-terminal pro-B-type natriuretic peptide.

**Table 5.** Results of stepwise logistic regression model for prediction of “Risk of cardiac fibrosis”

Factor	Time frame	AUC ROC	AUC ROC changes	p
LVEF $< 57.0\%$	12 <sup>th</sup> day	0.779	0.279	0.0249
COL-1 $\geq 29\ 930.0$ pg/mL	1 <sup>st</sup> day	0.863	0.084	0.0037
BMI $\geq 29.4$	–	0.919	0.056	0.0095
MMP-2 $\geq 235.6$ ng/mL	12 <sup>th</sup> day	0.922	0.003	0.0380
COL-1 $\geq 30\ 368.0$ pg/mL	12 <sup>th</sup> day	0.932	0.010	0.0681
Age $< 50.0$ years	–	0.936	0.004	0.2273

Note: BMI – body mass index; MMP – matrix metalloproteinase; LVEF – left ventricular ejection fraction.

**Table 6.** Prognostic scale for prediction of “Risk of cardiac fibrosis”

Factor	Condition	Score	
		Condition is met	Condition is not met
LVEF, %	LVEF, % $< 57,0$	1 point	0 points
COL-1 (1 <sup>st</sup> day), pg/mL	COL 1 (1 <sup>st</sup> day), pg/mL $\geq 29\ 930.0$	1 point	0 points
BMI	BMI $\geq 29.4$	1 point	0 points
MMP-2, ng/mL	MMP-2, ng/mL $\geq 235.6$	1 point	0 points
COL-1 (12 <sup>th</sup> day), pg/mL	COL-1 (12 <sup>th</sup> day), pg/mL $\geq 30\ 368.0$	1 point	0 points
Age	Age $< 50.0$	1 point	0 points

Note: BMI – body mass index; HR – heart failure; IL – interleukin; IVRT – isovolumic relaxation time; LVEF – left ventricular ejection fraction; MM – myocardial mass; MMP – matrix metalloproteinase; NT-proBNP – N-terminal pro-B-type natriuretic peptide.

accuracy and sensitivity of prediction. The regression 100-point scale model is presented in Table 8, each factor is assigned a certain number of points, any variable containing missing value is assigned a value of 0.5 to minimize misclassification (but for one factor only). The corresponding values are multiplied by coefficients and summed over all factors. The cut-off point of 53 indicates that variables with higher scores are on average 4 times more likely to lead to cardiac fibrosis than those with lower scores.

Based on Table 9, the model with logistic regression has the highest prognostic potential (predicting performance was 84.02, Chi-square) (Figure 5).

The presented prognostic scale was patented (Pecherina T.B., (2022). Method for assessing the risk of developing cardiac fibrosis in patients with ST segment elevation MI and preserved left ventricular ejection fraction. No. 2773452, Federal Service for Intellectual Property of the Russian Federation).

### Clinical case

Patient P., 65 years old, was admitted to the Regional Vascular Center with a diagnosis of ACS with ST segment elevation. ECG showed subepicardial injury (elevation of the ST segment) in the III, and avF leads. Successful PCI was performed 30 minutes later. The timing and modality of ACS treatment at the prehospital stage and in hospital setting corresponded to the national and European clinical guidelines. After further examination, the diagnosis of STEMI was established.

**Table 8.** Prognostic model with logistic regression for prediction of “Risk of cardiac fibrosis”

Factor	Condition	Score	
		Condition is met	Condition is not met
LVEF, %	LVEF (%) <57.0	16	0
COL-1 (1 <sup>st</sup> day), pg/mL	COL-1 (1 <sup>st</sup> day), pg/mL ≥29 930.0	26	0
BMI	BMI ≥29.4	7	0
MMP-2, ng/mL	MMP-2, ng/mL ≥235.6	9	0
COL-1 (12 <sup>th</sup> day), pg/mL	COL-1 (12 <sup>th</sup> day), pg/mL ≥30 368.0	17	0
Age	Age <50.0	9	0

**Note:** BMI – body mass index; COL – collagen; LVEF – left ventricular ejection fraction; MMP – matrix metalloproteinase.

**Table 7.** Results of the ROC analysis of the prognostic scale for prediction of “Risk of cardiac fibrosis”

Factor	Cut-off point	AUC ROC	Sensitivity	Specificity	Performance	Chi-square
Prognostic model ≥2.5	2.5	0.88	85.71	71.88	78.79	<0.0001

**Table 9.** Comparison of the scales for prediction of “Risk of cardiac fibrosis”

Factor	Cut-off point	AUC ROC	Sensitivity	Specificity	Performance	Chi-square
Regressive model ≥53.0	53.0	0.90	74.29	93.75	84.02	<0.0001
Prognostic model ≥2.5	2.5	0.88	85.71	71.88	78.79	<0.0001

According to Echo, LVEF was 50%.

BMI was 30.2 kg/m<sup>2</sup>

Biomarker concentration at admission:

COL-1 (on admission) = 30 002.1 pg/mL

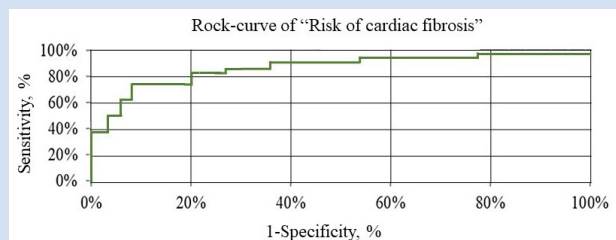
COL-1 (12<sup>th</sup> day) = 32,545.1 pg/mL

MMP-2 (on admission) = 365.1 ng/mL (Table 10).

Thus, according to the prognostic scale, the total score was 87 points. Which corresponds to a high risk of developing cardiac fibrosis a year after STEMI.

### Discussion

Cardiac fibrosis leads to changes in the structure of myocardium, violating its integrity and affecting mechanical, electrical and vasomotor functions, thus contributing to the progression of HF [11–14]. Focusing on the diagnosis and search for markers that can predict the risk of developing cardiac fibrosis should improve the existing algorithms for managing patients with MI and HF. The multinational academic and industrial consortium “FIBROTARGETS” has directed its efforts towards systematic search for potential targets in the development of CF and the transformation of these mechanisms into diagnostic



**Figure 5.** Rock-curve of “Risk of cardiac fibrosis”

**Table 10.** Prognostic scale for assessing the risk of cardiac fibrosis in the STEMI patient with HFpEF (presented clinical case)

Factor	Time frame	Condition	Condition is met	Condition is not met
LVEF, %	12 <sup>th</sup> day	LVEF <57.0	16 points	–
COL -1, pg/mL	1 <sup>st</sup> day	COL-1 ≥29 930.0	26 points	–
BMI, kg/m <sup>2</sup>	–	BMI ≥29.4	7 points	–
MMP-2, ng/mL	12 <sup>th</sup> day	MMP-2 ≥235.6	9 points	–
COL-1, pg/mL	12 <sup>th</sup> day	COL-1 ≥30 368.0	17 points	–
Age, years	–	Age <50.0	–	0 points

**Note:** BMI – body mass index; COL – collagen; LVEF – left ventricular ejection fraction; MMP – matrix metalloproteinase.



tools and specific therapeutic and pharmacological treatment modalities for HF [11–13]. The severity of CF is associated with higher long-term mortality in patients with cardiovascular diseases (CVD), especially with HF [15, 16]. In this regard, the detection, prevention and reduction of CF have become important goals in the improvement of treatment and prognosis of patients with HF [17, 18].

To build an optimal prognostic model, alongside laboratory and instrumental diagnostic parameters, it is important to include biomarkers of various pathophysiological processes, and instrumental and genetic research methods. In the last decade, there have been attempts to create multi-marker panels to assess the risk of adverse events in different cohorts of CVD patients. However, at the moment, prognostic models for assessing the risk of CF have not been implemented into clinical practice. Few studies are focused on searching for tools of CF risk assessment [19, 20]. Moreover, most of them are not very specific and are aimed at a certain group of patients. Thus, Bayes-Genis et al [21] measured serum concentrations of NT-proBNP, hs-TnT and ST2 in 891 consecutive outpatients with HF. Using negative binomial regression, an independent association was revealed between the multi-biomarker panel and repeated hospitalizations. The overall frequency of repeated hospitalizations for all causes, cardiovascular diseases and HF was significantly higher in patients with concentrations above the threshold value (hs-TnT >14 ng/L, NT-proBNP >1000 ng/L and ST-2 >35 ng/mL –  $p < 0.001$  for all values). Another experience of building prognostic models using neural networks and classification trees was presented by other authors, they aimed to assess the risk of CF in patients with primary Sjogren syndrome without clinical symptoms assessed using MRI [22]. The use of laboratory (ESR, rheumatoid factor, IgG, glycated hemoglobin/HbA1c, NT-proBNP) and clinical parameters (gender, age, BMI, etc.) enabled them to build a mathematical model for identifying patients with primary Sjogren syndrome and CF. In the study by Frank Gommans [23], highly sensitive cardiac troponin T (hs-cTnT), NT-proBNP, growth differentiation factor-15 (GDF-15), Galectin-3, carboxyterminal propeptide procollagen type I (CICP) were studied as candidate predictors for a prognostic model for assessing the risk of CF in patients with hypertrophic cardiomyopathy. Out of all biomarkers, only hs-cTnT was associated with CF according to MRI. The diagnostic accuracy of the model with hs-cTnT and clinical factors, made it possible to exclude the diagnosis of CF in half of the cases – sensitivity 100%, specificity 54%.

## Conclusion

Patients with HFmrEF phenotype are characterized by higher fibrotic tissue percentage ( $\geq 5\%$ ) after STEMI, while patients with HFpEF phenotype by a smaller percentage ( $< 5\%$ ). The study results revealed that in the acute period of the disease, patients with higher fibrotic tissue percentage (estimated a year after STEMI) present with higher values of COL-1 (1st day) and ST-2 (1st day), and these markers significantly prevailed in patients with CF  $\geq 5\%$ , while NT-proBNP (12th day) prevailed in the CF  $< 5\%$  group. Evaluation of parameters (age, LVEF, COL-1, BMI, MMP-2) in the acute period of STEMI using the developed prognostic scale will assist in identifying patients at high risk of CF a year after STEMI.

Using the developed prognostic model for assessing the risk of CF in STEMI patients with HFmrEF and HFpEF seems highly promising in terms of scientific and clinical potential because similar models for predicting the risk of CF in patients with index MI are not currently validated. Moreover, using risk assessment scale facilitates accurate prediction of the target variable occurrence (risk of CF). Successfully identifying patients at high risk of CF means that appropriate treatment modality will be chosen for these patients. Another important fact is the possibility of using the developed scale in patients needing a complex assessment of cardiovascular risk, such as patients with HFmrEF and HFpEF phenotypes.

## Conflicts of Interest

T.B. Pecherina declares no conflict of interest. V.N. Karetnikova and V.V. Kashtalap are the members of the Editorial Board of the journal “Complex Issues of Cardiovascular Diseases”. E.V. Dren’ declares no conflict of interest. J.S. Ignatova declares no conflict of interest. S.Yu. Shuster declares no conflict of interest. A.V. Yurkina declares no conflict of interest. Yu.I. Gusel’nikova declares no conflict of interest. O.L. Barbarash is the deputy editor-in-chief of the journal “Complex Issues of Cardiovascular Diseases”.

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