Garganeeva A. A., Kuzheleva E. A., Tukish O. V.,
Kondratiev M. Yu., Vitt K. N., Andreev S. L., Ogurkova O. N.
Research Institute of Cardiology, Tomsk National Research Medical Center, Tomsk, Russia

Biomarkers of Inflammation in Predicting the Outcomes of Heart Failure of Ischemic Etiology: the Results of Factor Analysis

Aim	To study the prognostic significance of inflammatory biomarkers in patients with chronic heart failure (CHF) and stenotic multivessel coronary atherosclerosis, with determination of the biomarker separate set that reflects subclinical inflammation and is associated with the development of cardiovascular complications during prospective observation.
Material and methods	A prospective observational study was conducted that included 80 patients with CHF and ischemic heart disease who were scheduled for coronary artery bypass grafting (CABG) during their current hospitalization. In addition to routine clinical laboratory tests, coagulation parameters were evaluated and the following inflammatory biomarkers were determined: neutrophil gelatinase-associated lipocalin (NGAL), growth/differentiation factor 15 (GDF-15), fibroblast growth factor 23 (FGF-23), transforming growth factor beta-1 (TGF-β1), and high-sensitivity C-reactive protein. Also, the calculated neutrophil-to-lymphocyte ratio (N LR) was included in the analysis. Follow-up duration was at least 12 months (median 16 [13, 22] months). Statistical analysis of the data was performed with the IBM SPSS Statistics 21 software.
Results	The study presented results of a factor analysis of 10 inflammatory biomarkers in patients who were scheduled for CABG. One of the factors identified by the analysis included the levels of NGAL and GDF-15, N LR, and the level of fibrinogen in the blood in CHF patients with stenotic coronary atherosclerosis and was significantly associated with the death rate during prospective observation. Furthermore, this association remained significant even after adjustments for age, glomerular filtration rate, severity of heart and coronary insufficiency, and the presence of diabetes mellitus.
Conclusion	In patients with CHF and stenotic coronary atherosclerosis, a set of inflammatory markers, including blood NGAL, GDF-15, N LR, and fibrinogen, can be combined into one factor reflecting subclinical inflammation. The value of this factor can be used to predict cardiovascular death in the long term after surgical myocardial revascularization.

Keywords	Chronic heart failure; coronary atherosclerosis; coronary artery bypass grafting; inflammation; biomarkers; factor analysis
For citations	Garganeeva A.A., Kuzheleva E.A., Tukish O.V., Kondratiev M.Yu., Vitt K.N., Andreev S.L. et al. Biomarkers of Inflammation in Predicting the Outcomes of Heart Failure of Ischemic Etiology: the Results of Factor Analysis. Kardiologiia. 2024;64(2):18–26. [Russian: Гарганеева А.А., Кужелева Е.А., Тукиш О.В., Кондратьев М.Ю., Витт К.Н., Андреев С.Л. и др. Биомаркеры воспаления в прогнозировании исходов хронической сердечной недостаточности ишемической этиологии: результаты факторного анализа. Кардиология. 2024;64(2):18–26].

For citations	Kuzheleva E. A. E-mail: kea@cardio-tomsk.ru

Introduction

Chronic heart failure (CHF) is a pandemic with an increasing prevalence as the population ages [1]. Coronary artery disease (CAD) is a major cause of CHF. Its pathological effect on cardiac function is realized in several ways, including loss of viable myocardium during acute myocardial infarction (MI) and stunned and hibernating cardiomyocytes due to chronic coronary insufficiency [2, 3]. The role of inflammatory processes in the development and progression of CHF of ischemic origin is undisputed [4]. It should be recognized that inflammation, a universal protective response of the organism to damage, is an extremely complex process whose individual links are reflected in changes in plasma concentrations of several pro- and anti-inflammatory biomarkers [5]. On the one hand, studying the levels of such biomarkers in patients with CHF is a very promising direction that includes the discovery of new therapeutic targets for this syndrome. On the other hand, the need to consider many parameters simultaneously and the complexity of their mutual interpretation result in the lack of tangible scientific progress in this field.

The specified problem may be solved using modern means of mathematical analysis, which allow simultaneous evaluation of a combination of parameters of interest and drawing a general conclusion.

ISSN 0022-9040. Kardiologiia. 2024;64(2). DOI: 10.18087/cardio.2024.2.n2465

Objective

Investigate the prognostic significance of inflammatory biomarkers in patients with CHF and multivessel coronary artery stenosis and identify a separate set reflecting the processes of subclinical inflammation associated with the development of adverse cardiovascular complications during prospective follow-up.

Material and Methods

A prospective observational study was conducted, which included 80 patients with CHF and CAD who underwent elective coronary artery bypass grafting (CABG) during the index hospitalization (included in 2019–2020). The protocol complies with the Declaration of Helsinki and was approved by the local ethics committee (Minutes No. 188 dated 18/09/2019). All patients signed the voluntary informed consent prior to any study procedures.

Inclusion criteria: presence of CHF, presence of multivessel coronary artery atherosclerosis, elective revascularization by CABG during the current hospitalization up to the cardiac team, patient consent for intervention and participation in the study.

Exclusion criteria: patient refusal to participate in the study, MI, acute cerebrovascular accident (CVA) within the last 6 months, presence of implanted cardiac rhythm control devices and pacemakers, need for additional cardiac surgical procedures other than CABG, severe renal dysfunction (glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2), severe comorbidities: active cancer, infiltrative heart disease, autoimmune diseases, acute infections and exacerbations of chronic somatic diseases. Patients were excluded from the study if they died during hospital stay.

CHF was diagnosed in accordance with the current clinical guidelines [1]. All patients underwent echocardiography and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured. NT-proBNP ≥ 125 pg/mL was considered the threshold for the diagnosis of CHF. However, 16 (20%) patients with clinically significant symptoms and signs of CHF had NT-proBNP levels within the reference range. CHF was confirmed in such patients by the presence of reliable echocardiographic signs of systolic and/or diastolic myocardial dysfunction [1, 6]: decreased left ventricular ejection fraction (LVEF) in 2 patients (38% and 32%); significant (>2-fold) increase in E/A ratio in 4 patients, E/e' ratio > 14 in 4 cases, E/e' > 9 in 10 cases, increased left atrial (LA) volume index >34 mL/m^2 in 9 patients, increased of tricuspid regurgitation rate or elevated pulmonary artery pressure in 8 patients, increased LV mass indexed to body surface area in 7 patients. Diastolic stress testing was performed in patients with borderline values of the CHF criteria.

Multivessel atherosclerotic coronary artery stenosis was diagnosed by invasive coronary angiography using the Cardio-scop-V complex and the ACOM computer system (Siemens, Germany) according to clinical indications. Echocardiography was performed using a Philips HD 15 ultrasound system in accordance with current guidelines for quantitative assessment of heart chamber structure and function [7].

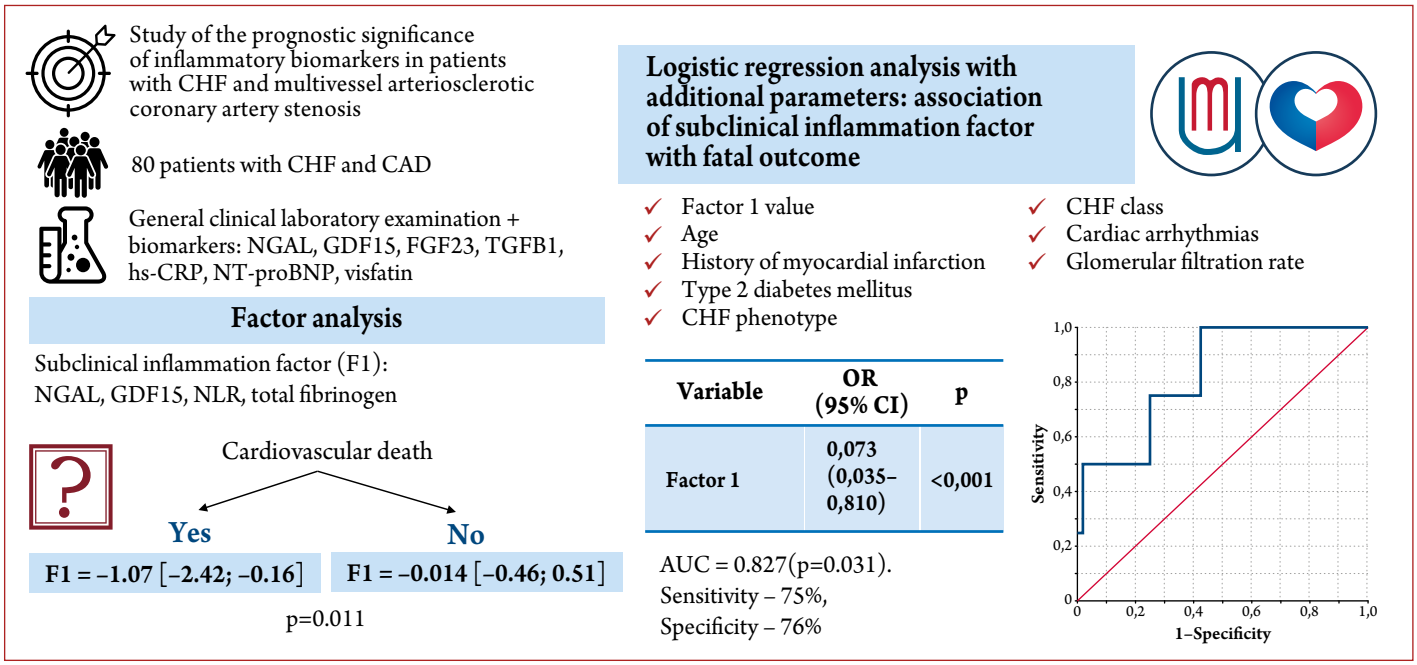
In addition to routine clinical laboratory tests (complete blood count with differential, blood biochemistry, lipid profile), fibrinogen levels were determined using an automated coagulometric analyzer for in vitro diagnosis (ACL TOP750, Instrumentation Laboratory Co, USA), and GFR was calculated using the CKD-EPI formula. Biomarkers were assessed by enzyme immunoassay using diagnostic kits. The following biomarkers were investigated: neutrophil gelatinase-associated lipocalin (NGAL, ng/mL), growth differentiation factor 15 (GDF15, pg/mL), osteoprotegerin (pmol/L), fibroblast growth factor (FGF23), C-terminal peptide (pmol/L), N-terminal pro-brain natriuretic peptide (NT-proBNP, pg/mL), transforming growth factor beta 1 (TGFB1, pg/mL), visfatin (ng/mL), high-sensitivity C-reactive protein (CRP, mg/L). The tests were carried out using the equipment of the Collective Use Center «Medical Genomics» of the Tomsk National Research Medical Center.

Neutrophil-to-lymphocyte ratio (NLR) was also calculated. According to the literature, it also reflects the processes of subclinical inflammation and is associated with the progression of cardiovascular pathology [8].

Fasting blood samples were collected from the ulnar vein in the morning before surgery for CAD and prepared for analysis by centrifugation, serum separation, and freezing at –80°C. Analysis was performed after a single thaw of the blood serum.

Patients were followed for at least 12 months (median 16 [13; 22] months). Postoperative drug therapy was fully consistent with current clinical guidelines and did not differ significantly between patients with and without cardiovascular complications. The following endpoints were reported during prospective follow-up: primary endpoint (cardiovascular death): 4 (5%) events were reported during the follow-up period; secondary endpoint (composite endpoint including cardiovascular death, decompensated CHF or need for intravenous diuretics or doubling of diuretic dose, episode of acute ischemia requiring emergency revascularization, STEMI, progression of clinical symptoms of CAD and/or CHF by one or more functional classes): a total of 22 (27.5%) events were reported during the post-discharge follow-up period. Adherence to medical therapy, as assessed by the Morisky Medication Adherence Scale, was 81% at 12 months and was comparable in patients with and without cardiovascular complications.

Central illustration. Biomarkers of Inflammation in Predicting the Outcomes of Heart Failure of Ischemic Etiology: the Results of Factor Analysis



Statistical processing of data was performed using SPSS Statistics version 21. The normality of the distribution was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as the means and standard deviations (M ± SD) and non-normally distributed variables are expressed as the medians and interquartile ranges (Me [Q1; Q3]). Categorical data is presented as the absolute and relative values (n (%)). The continuous variables of the independent samples were compared using the Student's t-test or the Mann-Whitney U-test, depending on the type of distribution. Spearman's correlation coefficient was calculated to evaluate the correlations. The correlation matrix was displayed as a heat map with color grading of the correlation coefficient values. Pearson's chi-squared test and two-tailed Fisher's exact test were used to determine statistical significance of differences for categorical variables. Factor analysis was used to determine the association between individual inflammatory markers. The adequacy of the sample in terms of the possibility of factor analysis was verified using the Kaiser-Meyer-Olkin test and Bartlett's test of sphericity. We analyzed the scree plot to determine the optimal number of factors. Principal component analysis was used for the analysis procedure. Varimax orthogonal rotation was used to optimize the factor structure. Variables with an absolute factor loading value of less than 0.1 were excluded from the summary table. The rotated factor loading matrix and the quantitative values of the factors were analyzed. The prognostic significance of the factors obtained was determined using the Mann-Whitney test. The values of the obtained factors were tested for association with the development of the endpoints using logistic regression analysis, taking into account additional parameters that may influence the prognosis of patients. The quality of the regression model was assessed using ROC analysis, the area under the curve (AUC) was calculated, and $p<0.05$ was considered statistically significant.

Results

Main clinical and demographic characteristics of subjects are provided in Table 1. The majority of the study group is represented by elderly men with a more severe comorbid background. More than 60% of patients had a history of prior MI, and 25% of patients had type 2 diabetes mellitus (DM). One in five patients had previously undergone coronary stenting. The severity of CHF was class II–III in most cases, and the mean 6-minute walk distance was 340 [280; 380] meters. More than 50% of patients smoked, and multifocal atherosclerosis was found in 25% of patients. Most patients achieved target blood pressure levels at the time of hospitalization. Stage II–III chronic kidney disease was diagnosed in 91% of patients (Table 1).

The groups of patients with a favorable course of the disease and patients with lethal outcome or adverse cardiovascular complications did not differ from each other in terms of the main clinical and anamnestic parameters (Table 2 and Table 3).

The means of the most important laboratory parameters reflecting the activation of the inflammatory processes in the body, which were examined in the patients, are shown in Table 4.

The correlations between the indicators studied were analyzed. The correlation matrix transformed into a heat

ISSN 0022-9040. Kardiologiia. 2024;64(2). DOI: 10.18087/cardio.2024.2.n2465

Table 1. Clinical and anamnestic characteristics and some laboratory and clinical examination findings of the patients included in the study

Parameter	Value
	n (%)
Male	71 (88.8)
Female	9 (11.2)
History of MI	50 (62.5)
DM type 2	20 (25)
Obesity	30 (37.5)
History of CVA	3 (3.8)
History of coronary artery stenting	15 (18.8)
Lower limb atherosclerosis	6 (7.5)
Carotid atherosclerosis (≥40 %)	20 (25)
CHF class (NYHA)	
I	8 (10)
II	41 (51.2)
III	31 (38.8)
Smoking	46 (57.5)
CHF with preserved LVEF	41 (51.2)
CHF with mid-range LVEF	10 (12.5)
CHF with reduced LVEF	29 (36.3)
Cardiac arrhythmias	37 (46.3)
Atrial fibrillation	19 (23.8)
Chronic kidney disease, stage	
II	51 (63.8)
IIIa	19 (23.8)
IIIb	3 (3.8)
M ± SD	
Mean age, years	62 ± 7.3
Body mass index, kg/m^2	28.4 ± 4.5
Heart rate, bpm	70.4 ± 10.9
Left ventricular ejection fraction, %	50 ± 15.6
Creatinine, μmol/L	97.8 ± 22.4
Glomerular filtration rate, mL/min/1.73m^2	68.9 ± 16
Median [Q1; Q3]	
Duration of CAD, years	3 [1; 11]
Duration of hypertension, years	10 [5; 20]
Age at first MI, years	54 [43.5; 60]
Time from last MI to surgery, months	35 [7; 156]
Duration of type 2 DM, years	5 [1; 10.5]
Systolic BP, mm Hg	124 [120; 130]
Diastolic BP, mm Hg	80 [70; 80]
6 minute walk distance, m	340 [280; 380]

CVA, cerebrovascular accident.

Table 2. Clinical and anamnestic characteristics and selected laboratory and clinical examination data of patients with regard to the development of a fatal outcome during the prospective follow-up period

Parameter	Fatal outcome – (n = 76)	Fatal outcome + (n = 4)	p
Male, n (%)	68 (89.5)	3 (75)	0.372
Female, n (%)	8 (10.5)	1 (25)	
History of MI, n (%)	48 (63.2)	2 (50)	0.597
DM type 2, n (%)	18 (23.7)	2 (50)	0.237
Obesity, n (%)	29 (38.2)	1 (25)	0.597
History of CVA, % (n)	3 (3.9)	0	0.686
History of coronary artery stenting, n (%)	14 (18.4)	1 (25)	0.743
Lower limb atherosclerosis, n (%)	6 (7.9)	0	0.560
Carotid atherosclerosis (≥40 %), n (%)	20 (26.3)	0	0.237
CHF class (NYHA), n (%)			
I	4 (10.5)	0	
II	39 (51.3)	2 (50)	0.915
III	29 (38.2)	2 (50)	
Smoking, n (%)	44 (58)	2 (50)	0.756
CHF with preserved LVEF, n (%)	39 (51.3)	2 (50)	0.692
CHF with mid-range LVEF, n (%)	10 (13.2)	0	
CHF with reduced LVEF, n (%)	27 (35.5)	2 (50)	
Cardiac arrhythmias, n (%)	35 (46.1)	2 (50)	0.878
Atrial fibrillation, n (%)	18 (23.7)	1 (25)	0.952
Chronic kidney disease stage II-III, n (%)	25 (32.9)	1 (25)	0.743
Age, years (Me [Q1; Q3])	63 [58; 68]	65.5 [60; 71]	0.341
Left ventricular ejection fraction, % (Me [Q1; Q3])	50 [35; 63]	49 [21; 71]	0.773
Glomerular filtration rate, mL/min/1.73m2 (Me [Q1; Q3])	70 [59; 80]	73.5 [61; 74]	0.932
NT-proBNP, pg/mL (Me [Q1; Q3])	170 [135; 469]	177 [140; 983]	0.715

CVA, cerebrovascular accident; NT-proBNP, N-terminal pro-brain natriuretic peptide.

map is shown in Figure 1. Correlation coefficients greater than 0.2 or less than –0.2 were statistically significant. According to the data obtained, almost all biomarkers studied showed weak or moderate correlations with each other, confirming their involvement in a single pathogenetic process in patients with CHF and CAD. NT-proBNP also correlated with markers of inflammation, in particular, it had moderate positive correlations with GDF15 and weak positive correlations with CRP.

Factor analysis was the next step in the statistical processing of the results. FGF23 was not included in further calculations because the distribution of its levels was not normal. Therefore, the following markers were used for factor analysis: GDF15, NGAL, TGFB1, visfatin,

white blood cell count, NLR, osteoprotegerin, erythrocyte sedimentation rate, CRP, and fibrinogen. The optimal number of factors was found to be 2 in the analysis of the scree plot. The final results were obtained after excluding the markers with insufficient strength of influence on the factor and the Varimax orthogonal rotation. They are presented in Table 5.

This allowed us to obtain 2 new factors using factor analysis. The first factor included NGAL, NLR and total fibrinogen. The second factor included CRP. GDF15 had a significant effect on both factors, but more so on the former. Therefore, it was included in this factor. Sampling adequacy determined by the Kaiser-Meyer-Olkin test was 0.717 and the level of significance by Bartlett's test of sphericity was 0.045, indicating acceptable sampling adequacy and the possibility of applying factor analysis to these parameters. The cumulative percentage of total variance for this factor solution was 64.8%. This is also an acceptable result.

Based on the functional significance of individual markers, we interpreted the resulting table as follows: Factor 1 characterizes the processes of subclinical inflammation, and Factor 2, considering the biological role of CRP, better reflects clinically manifested inflammation.

The quantitative values of the factors obtained were further analyzed. The values of the factors were normally distributed in the study sample and were 0.05 ± 0.97 (M ± SD) for Factor 1 and 0.15 ± 0.8 for Factor 2.

We analyzed whether these factors were associated with primary and secondary endpoints (Table 6). According to the data obtained, the magnitude of Factor 1 was statistically significantly associated with the development of cardiovascular death during the follow-up period.

It should be noted that the association of individual biomarkers with the development of primary and secondary endpoints was additionally tested, and no statistically significant relationship was observed (Table 7).

Given the result obtained, we evaluated the presence of an independent influence of the magnitude of Factor 1 on the development of cardiovascular death using logistic regression analysis, taking into account additional parameters such as patients' age, presence of type 2 DM and history of MI, CHF phenotype (reduced, mid-range, and preserved LVEF), CHF class (NYHA), presence of arrhythmias, and GFR. The degree of coronary bed involvement, the volume of cardiac surgery, and the clinical course in the early postoperative period did not differ between groups, as these factors were taken into account at the time of patient inclusion.

Therefore, the above parameters were included in the logistic regression model. The regression results are shown in Table 8. The statistical significance of the model was p=0.012, Nigelkerk' R2 was 0.368 (insufficient). Coefficient of concordance (percentage of correctly classified results) was 92.9%.

Table 3. Clinical and anamnestic characteristics and selected laboratory and clinical examination data of patients with regard to the development of the secondary composite endpoint during the prospective follow-up period

Parameter	Composite endpoint – (n = 58)	Composite endpoint + (n = 22)	p
Male, n (%)	51 (87.9)	20 (90.9)	0.707
Female, n (%)	7 (12.1)	2 (9.1)	
History of MI, n (%)	33 (56.9)	17 (77.3)	0.093
DM type 2, n (%)	13 (22.4)	7 (31.8)	0.386
Obesity, n (%)	23 (39.7)	7 (31.8)	0.518
History of CVA, % (n)	2 (3.4)	1 (4.5)	0.818
History of coronary artery stenting, n (%)	10 (17.2)	5 (22.7)	0.575
Lower limb atherosclerosis, n (%)	5 (8.6)	1 (4.5)	0.537
Carotid atherosclerosis (≥40 %), n (%)	16 (27.6)	4 (18.2)	0.386
CHF class (NYHA), n (%)			
I	6 (10.3)	2 (9.1)	
II	30 (51.7)	11 (50)	0.933
III	22 (37.9)	9 (40.9)	
Smoking, n (%)	34 (65.4)	12 (54.5)	0.742
CHF with preserved LVEF, n (%)	32 (55.2)	9 (40.9)	0.293
CHF with mid-range LVEF, n (%)	8 (13.8)	2 (9.1)	
CHF with reduced LVEF, n (%)	18 (31)	11 (50)	
Cardiac arrhythmias, n (%)	31 (53.4)	6 (27.3)	0.046
Atrial fibrillation, n (%)	16 (27.6)	3 (13.6)	0.191
Chronic kidney disease stage II-III, n (%)	16 (27.6)	10 (45.5)	0.128
Age, years (Me [Q1; Q3])	54 [43; 61.7]	54 [46; 59]	0.294
Left ventricular ejection fraction, % (Me [Q1; Q3])	54.5 [37; 64]	41 [27; 63]	0.161
Glomerular filtration rate, mL/min/1.73m^2 (Me [Q1; Q3])	72.5 [59; 80]	68 [55.7; 77]	0.374
NT-proBNP, pg/mL (Me [Q1; Q3])	157.5 [133; 397]	225 [114; 625]	0.372

CVA, cerebrovascular accident;
NT-proBNP, N-terminal pro-brain natriuretic peptide.

Thus, Factor 1, which characterizes subclinical inflammation in patients with CHF and atherosclerotic coronary artery stenosis, was an independent predictor of cardiovascular mortality within 16 [13; 22] months after CABG. The significance of the resulting model was evaluated by means of ROC analysis. The ROC curve was

ISSN 0022-9040. Kardiologiia. 2024;64(2). DOI: 10.18087/cardio.2024.2.n2465

Table 4. Values of key laboratory indicators

Parameter	Value M ± SD
WBCs, 10^9/L, M ± SD	7.42 ± 2.3
ESR, mm/h, M ± SD	11.4 ± 3.8
Fibrinogen, g/L, M ± SD	3.5 ± 0.58
Lymphocytes, 10^9/L, M ± SD	2.7 ± 0.83
Neutrophils, 10^9/L, M ± SD	3.5 ± 1.1
NLR, M ± SD	1.37 ± 0.43
NGAL, ng/mL, M ± SD	44.9 ± 14.6
GDF15, pg/mL, M ± SD	2,623.7 ± 843.5
TGFB1, pg/mL, M ± SD	57,638.9 ± 19,165
Visfatin, ng/mL, M ± SD	11.8 ± 3.5
Osteoprotegerin, pmol/L, M ± SD	11.1 ± 0.7
C-reactive protein, mg/L, M ± SD	4.7 ± 1.42
FGF23, pmol/L (Me [Q1; Q3])	0.64 [0.31; 0.96]
NT-proBNP, pg/mL (Me [Q1; Q3])	170.1 [132; 469.4]

NLR, neutrophil-to-lymphocyte ratio; NGAL, neutrophil gelatinase-associated lipocalin; GDF15, growth/differentiation factor type 15; TGFB1, transforming growth factor beta-1; FGF23, fibroblast growth factor type 23; NT-proBNP, N-terminal pro-brain natriuretic peptide; Me [Q1; Q3], median and interquartile range.

Table 5. Results of factor analysis

Parameter	Factor loading	
	Factor 1	Factor 2
NGAL	0.730	0.177
GDF15	-0.653	0.469
NLR	0.592	-0.027
Fibrinogen	0.480	0.224
CRP	0.236	0.862

NGAL, neutrophil gelatinase-associated lipocalin; GDF15, growth/differentiation factor type 15; NLR, neutrophil-to-lymphocyte ratio.

constructed and the area under the curve (AUC) was 0.827 (95% CI 0.642–0.98; p = 0.031; Figure 2). The sensitivity of the model was 75% and the specificity was 76%.

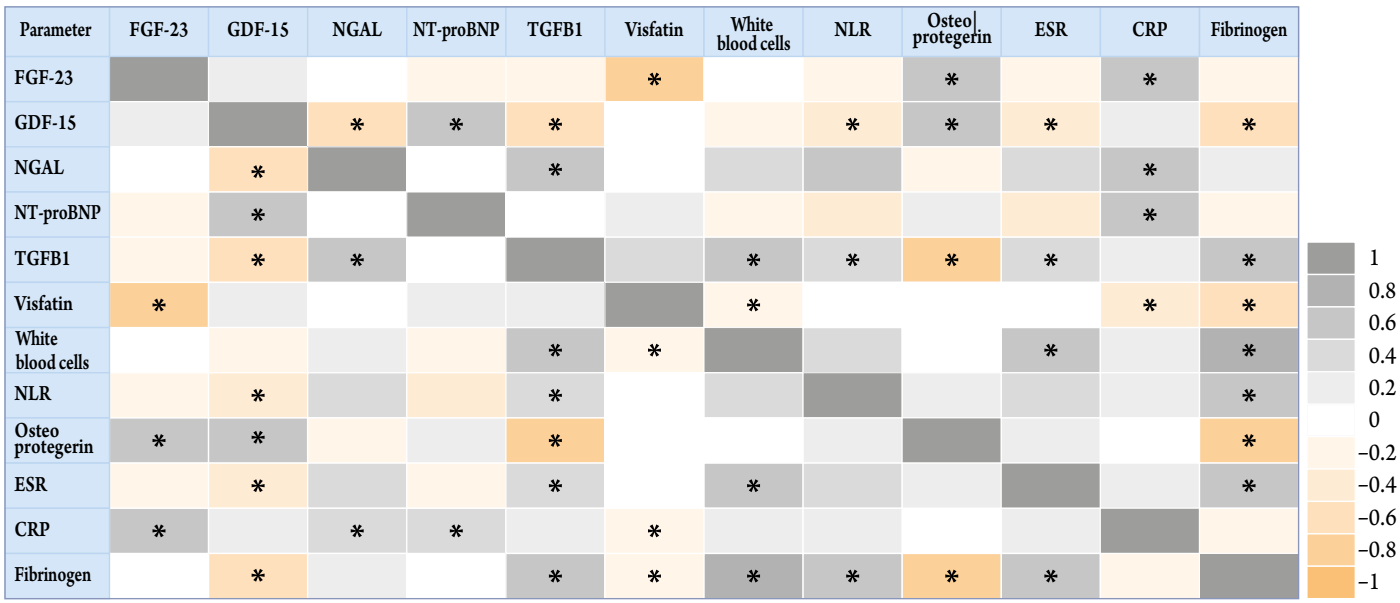
Discussion

Subclinical inflammation plays an important role in the development and progression of both CAD and heart failure [5, 9]. Some observational studies show the prognostic role of certain inflammatory markers in a cohort of patients with CHF and CAD, including after interventional or surgical myocardial revascularization.

Neutrophil gelatinase-associated lipocalin (NGAL) is primarily considered a marker of acute kidney injury, including acute cardiovascular complications. The literature suggests that postoperative elevation of NGAL levels after cardiac surgery is associated with acute kidney injury and is an unfavorable prognostic factor [10, 11].

Transforming growth factor beta-1 (TGFB1) is the prototype of the family of growth and differentiation factors [12]. There is evidence that this factor is activated in injured vessels after surgical myocardial revascularization, contributing to the development of intimal hyperplasia of transplanted vessels [13]. GDF15, a type 15 growth/differentiation factor, is a member of the TGFB protein family. Elevated levels of GDF15 in the blood serum

Figure 1. Heat map of correlations between analyzed biomarkers



* p<0.05; FGF23, fibroblast growth factor type 23; GDF15, growth/differentiation factor type 15; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal pro-brain natriuretic peptide; TGFB1, transforming growth factor beta-1; NLR, neutrophil-to-lymphocyte ratio.

Table 6. Association of factor analysis results with the development of endpoints

Endpoint	Endpoint +	Endpoint –	p
Factor 1			
Cardiovascular death	-1.07 [-2.42; -0.16]	-0.014 [-0.46; 0.51]	0.011
Composite endpoint	-0.006 [-0.379; 0.51]	-0.15 [-0.9; 0.22]	0.552
Factor 2			
Cardiovascular death	0.295 [-0.68; 0.36]	-0.23 [-0.83; 0.51]	0.712
Composite endpoint	-0.19 [-0.9; 0.55]	-0.68 [-0.82; 0.36]	0.989

The data are presented as the medians and interquartile ranges (Me [Q1; Q3]) .

Table 7. Comparison of the groups with and without primary and secondary endpoints (statistical significance of differences in biomarker levels in the groups with and without primary and secondary endpoint development is given)

p	GDF15	NGAL	TGFB1	VF	WBCs	NLR	OPG	ESR	CRP	TF
Primary endpoint	0.413	0.133	0.122	0.228	0.822	0.074	0.845	0.822	0.256	0.428
Secondary endpoint	0.773	0.521	0.559	0.8	0.559	0.559	0.922	0.922	0.391	0.087

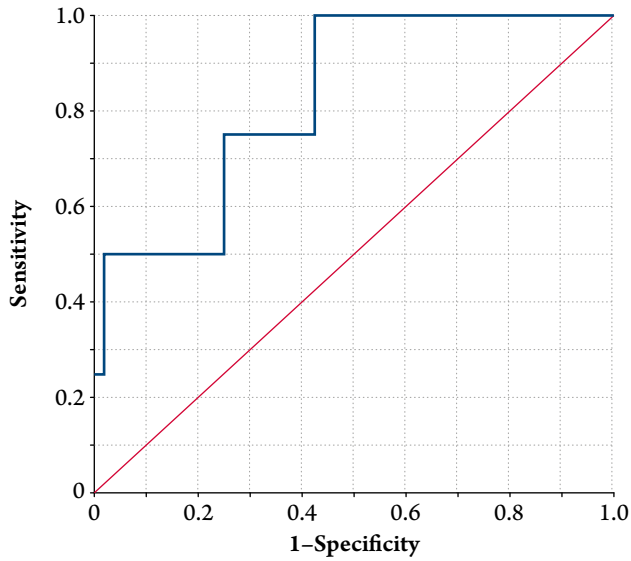
GDF15, growth/differentiation factor type 15; NGAL, neutrophil gelatinase-associated lipocalin; TGFB1, transforming growth factor beta-1; VF, visfatin; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; OPG, osteoprotegerin; TF, total fibrinogen.

Table 8. Results of the logistic regression analysis

Parameter	B	OR	95 % CI	p
Variables included in the equation				
Factor 1	-3.314	0.073	0.035–0.810	< 0.001
Variables not included in the equation				
Age				0.816
History of myocardial infarction				0.488
Diabetes mellitus type 2				0.901
CHF phenotype				0.747
CHF class (NYHA)				0.940
Cardiac arrhythmias				0.361
Glomerular filtration rate				0.546

B, regression equation coefficient;
OR, odds ratio; CI, confidence interval.

Figure 2. Logistic regression model ROC curve



may be indicative of ongoing cellular damage or a protective response to cellular stress. Several studies demonstrate a significant role of GDF15 in predicting lethal outcome in CHF patients with preserved LVEF [14, 15].

Visfatin/NAMPT (nicotinamide phosphoribosyltransferase) is an adipocytokine associated with metabolic disorders, endothelial dysfunction, and systemic inflammation [16]. Some studies reported that the level of visfatin is associated with the severity of coronary atherosclerosis in patients with coronary heart disease [17]. Osteoprotegerin, a regulator of bone remodeling, also has a negative effect on the development and progression of atherosclerosis. Osteoprotegerin is thought to promote inflammation within the vascular wall and to increase the adhesion of white blood cells to the vascular endothelium. Its contribution to the development of cardiovascular complications in patients with CAD is currently the subject of active research [18].

CRP is one of the best-known markers of inflammation. It induces the activation of the complement system in response to an infectious agent or the body's own cells undergoing necrosis and apoptosis and is also involved in the processes of autoimmune inflammation in the body [19, 20].

NLR is now being actively studied as a widely used marker of subclinical inflammation and as a predictor of the development of cardiovascular complications. According to the literature, high NLR values are associated with CHF decompensation and long-term mortality [8].

ISSN 0022-9040. Kardiologiia. 2024;64(2). DOI: 10.18087/cardio.2024.2.n2465

As an acute-phase protein fibrinogen reflects the degree of activation of the inflammatory process in the body, and its elevated levels may contribute to the progression of atherosclerosis. The negative effect of fibrinogen on the development and progression of CVDs was evident in the analysis of the Framingham study results and has been repeatedly confirmed in other studies [21].

Thus, each of the studied markers serves as a predictor of cardiovascular complications in different cohorts of cardiac patients, characterizing separate links of the inflammatory process in the body. At the same time, studying several parameters at the same time presents significant difficulties and is impossible without the use of modern methods of information processing.

We presented a factor analysis of 10 inflammatory biomarkers in patients undergoing elective CABG. One of the factors derived from the analysis was statistically significantly associated with the development of fatal outcomes during prospective follow-up. After adjustment for age, CRP, severity of heart failure and coronary artery disease, and the presence of DM, this association remained significant. Thus, factor analysis was shown to identify related subgroups of factors that together have a significant impact on long-term prognosis in patients with CHF and CAD undergoing surgical myocardial revascularization. Moreover, the results of factor analysis can be implemented in real clinical practice in the future to distinguish a group of patients at high risk of cardiovascular death in the long-term postoperative period, because the analysis of blood markers was performed before cardiac surgery, which emphasizes the significance of the findings.

Obviously, the present study has some limitations. The first is the small size of the cohort and, as a consequence, the small number of cardiovascular complications. The second is that the quality of factor and regression models, while formally acceptable, can be improved by adding additional parameters, increasing the sample size, and increasing the follow-up period. These are limitations that can be overcome with further research in this area.

Conclusion

A number of inflammatory markers, including neutrophil gelatinase-associated lipocalin, type 15 growth/differentiation factor, neutrophil-to-lymphocyte ratio, and blood fibrinogen levels in patients with chronic heart failure and atherosclerotic coronary artery stenosis, may be combined into a single factor reflecting subclinical inflammatory processes. The value of the factor can be a predictor of cardiovascular death in the long-term after myocardial revascularization surgery.

Funding

This study was a part of the State Assignment, FNI # 122020300045–5.

No conflict of interest is reported.

The article was received on 20/03/2023

REFERENCES

1. Tereshchenko S.N., Galyavich A.S., Uskach T.M., Ageev F.T., Arutyunov G.P., Begrambekova Yu.L. et al. 2020 Clinical practice guidelines for Chronic heart failure. Russian Journal of Cardiology. 2020;25(11):311–74. [Russian: Терещенко С.Н., Галявич А.С., Ускач Т.М., Агеев Ф.Т., Арутюнов Г.П., Беграмбекова Ю.Л. и др. Хроническая сердечная недостаточность. Клинические рекомендации 2020. Российский кардиологический журнал. 2020;25(11):311-74]. DOI: 10.15829/1560-4071-2020-4083
2. Garganeeva A.A., Kuzheleva E.A., Kuzmichkina M.A., Ryabov V.V., Mareev Yu.V., Mareev V.Yu. Characteristics and treatment of patients with heart failure admitted to a cardiology department in 2002 and 2016. Kardiologiia. 2018;58(12S):18–26. [Russian: Гарганеева А.А., Кужелева Е.А., Кузьмичкина М.А., Рябов В.В., Мареев Ю.В., Мареев В.Ю. Изменения характеристик и лечения больных с хронической сердечной недостаточностью, поступивших в кардиологический стационар в 2002 и 2016 годах. Кардиология. 2018;58(12S):18-26]. DOI: 10.18087/cardio.2605
3. Ageev F.T., Skvortsov A.A., Mareev V.Yu., Belenkov Yu.N. Heart failure on the background of coronary heart disease: some issues of epidemiology, pathogenesis and treatment. Russian Medical Journal. 2000;8(15):622–6. [Russian: Агеев Ф.Т., Скворцов А.А., Мареев В.Ю., Беленков Ю.Н. Сердечная недостаточность на фоне ишемической болезни сердца: некоторые вопросы эпидемиологии, патогенеза и лечения. РМЖ. 2000;8(15):622-6]
4. Shirazi LF, Bissett J, Romeo F, Mehta JL. Role of Inflammation in Heart Failure. Current Atherosclerosis Reports. 2017;19(6):27. DOI: 10.1007/s11883-017-0660-3
5. Kuzheleva E.A., Fedyunina V.A., Garganeeva A.A. Patterns of immunological reactions in the pathogenesis of chronic heart failure: review. Kardiologiia. 2021;61(12):94–104. [Russian: Кужелева Е.А., Федюнина В.А., Гарганеева А.А. Паттерны иммунологических реакций в патогенезе хронической сердечной недостаточности: обзор литературы. Кардиология. 2021;61(12):94-104]. DOI: 10.18087/cardio.2021.12.n1598
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021;42(36):3599–726. DOI: 10.1093/eurheartj/ehab368
7. Vasyuk Yu.A., Kopeleva M.V., Korneeva O.N., Krikunov P.V., Ryabov V.V., Surkova E.A. et al. Recommendations for quantifying the structure and function of heart chambers. Russian Journal of Cardiology. 2012;17(4s4):1–28. [Russian: Васюк Ю.А., Копелева М.В., Корнеева О.Н., Крикунов П.В., Рябов В.В., Суркова Е.А. и др. Рекомендации по количественной оценке структуры и функции камер сердца. Российский кардиологический журнал. 2012;17(4s4):1-28]
8. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. Expert Review of Cardiovascular Therapy. 2016;14(5):573–7. DOI: 10.1586/14779072.2016.1154788
9. Kalogeropoulos AP, Georgiopoulou VV, Butler J. From Risk Factors to Structural Heart Disease: The Role of Inflammation. Heart Failure Clinics. 2012;8(1):113–23. DOI: 10.1016/j.hfc.2011.08.002
10. Perry TE, Muehlschlegel JD, Liu K-Y, Fox AA, Collard CD, Shernan SK et al. Plasma Neutrophil Gelatinase-Associated Lipocalin and Acute Postoperative Kidney Injury in Adult Cardiac Surgical Pa-

tients. Anesthesia & Analgesia. 2010;110(6):1541–7. DOI: 10.1213/ANE.0b013e3181da938e
11. Ghonemy T, Amro G. Plasma neutrophil gelatinase-associated lipocalin (NGAL) and plasma cystatin C (CysC) as biomarker of acute kidney injury after cardiac surgery. Saudi Journal of Kidney Diseases and Transplantation. 2014;25(3):582–8. DOI: 10.4103/1319-2442.132194
12. Morikawa M, Derynck R, Miyazono K. TGF-β and the TGF-β Family: Context-Dependent Roles in Cell and Tissue Physiology. Cold Spring Harbor Perspectives in Biology. 2016;8(5):a021873. DOI: 10.1101/cshperspect.a021873
13. Ungogo MA. Targeting Smad-Mediated TGFß Pathway in Coronary Artery Bypass Graft. Journal of Cardiovascular Pharmacology and Therapeutics. 2021;26(2):119–30. DOI: 10.1177/1074248420951037
14. Stahrenberg R, Edelmann F, Mende M, Kockskämper A, Düngen H-D, Lüers C et al. The novel biomarker growth differentiation factor 15 in heart failure with normal ejection fraction. European Journal of Heart Failure. 2010;12(12):1309–16. DOI: 10.1093/eurjhf/hfq151
15. Mendez Fernandez AB, Ferrero-Gregori A, Garcia-Osuna A, Mirabet-Perez S, Pirla-Buxo MJ, Cinca-Cuscullola J et al. Growth differentiation factor 15 as mortality predictor in heart failure patients with non-reduced ejection fraction. ESC Heart Failure. 2020;7(5):2223–9. DOI: 10.1002/ehf2.12621
16. Dakroub A, A. Nasser S, Younis N, Bhagani H, Al-Dhaheri Y, Pintus G et al. Visfatin: A Possible Role in Cardiovasculo-Metabolic Disorders. Cells. 2020;9(11):2444. DOI: 10.3390/cells9112444
17. Duman H, Özyıldız AG, Bahçeci İ, Duman H, Uslu A, Ergül E. Serum visfatin level is associated with complexity of coronary artery disease in patients with stable angina pectoris. Therapeutic Advances in Cardiovascular Disease. 2019;13:1753944719880448. DOI: 10.1177/1753944719880448
18. Dutka M, Bobiński R, Wojakowski W, Francuz T, Pająk C, Zimmer K. Osteoprotegerin and RANKL-RANK-OPG-TRAIL signalling axis in heart failure and other cardiovascular diseases. Heart Failure Reviews. 2022;27(4):1395–411. DOI: 10.1007/s10741-021-10153-2
19. Melnikov IS, Kozlov SG, Saburova OS, Avtaeva YN, Prokofieva LV, Gabbasov ZA. Current Position on the Role of Monomeric C-reactive Protein in Vascular Pathology and Atherothrombosis. Current Pharmaceutical Design. 2020;26(1):37–43. DOI: 10.2174/1381612825666191216144055
20. Zhou R, Xu J, Luan J, Wang W, Tang X, Huang Y et al. Predictive role of C-reactive protein in sudden death: a meta-analysis of prospective studies. Journal of International Medical Research. 2022;50(2):3000605221079547. DOI: 10.1177/03000605221079547
21. Surma S, Banach M. Fibrinogen and Atherosclerotic Cardiovascular Diseases – Review of the Literature and Clinical Studies. International Journal of Molecular Sciences. 2021;23(1):193. DOI: 10.3390/ijms23010193

ISSN 0022-9040. Kardiologiia. 2024;64(2). DOI: 10.18087/cardio.2024.2.n2465