ISSN 2304-3415, Russian Open Medical Journal
2025. Volume 14. Issue 1 (March). Article CID e0107
DOI: 10.15275/rusomj.2025.0107

Original article

Low-grade inflammation in prognosis in patients undergoing coronary artery bypass grafting: The importance of neutrophil-to-lymphocyte ratio and growth differentiation factor 15

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Received 25 July 2024, Revised 18 September 2024, Accepted 21 October 2024

Abstract: *Background* — Predicting major adverse cardiovascular events (MACE) after coronary interventions is an urgent and important mission. Subclinical inflammation markers are increasingly investigated for this purpose. *Objective:* To determine the role of neutrophil-to-lymphocyte ratio (NLR) and growth differentiation factor 15 (GDF-15) in predicting MACE in patients after coronary artery bypass grafting (CABG).
Methods — This prospective observational study included 80 patients with coronary artery disease who underwent CABG and were followed for at least a year. In prospective follow-up, the composite endpoint (MACE) constituted 27.5% (22 events).
Results — GDF-15 and NLR values were similar in the groups with and without MACE. ROC analysis showed low AUC for NLR (AUC=0.566, p=0.363) and GDF-15 (AUC=0.621, p=0.096). The value of the GDF-15×NLR product was calculated. The median was 3,108.05 (2,069; 4,145) for patients without MACE and 4,108.8 (2,779.4; 5,890.5) for patients with MACE (p=0.010). This association remained after adjustment for gender, age, diabetes mellitus, and left ventricular ejection fraction.
Conclusion — The product, NLR×GDF-15, is associated with adverse cardiovascular events in patients after CABG.

Keywords: CABG, inflammation, neutrophil-to-lymphocyte ratio, GDF15, MACE.

Cite as Garganeeva AA, Kuzheleva EA, Tukish OV, Repin AN. Low-grade inflammation in prognosis in patients undergoing coronary artery bypass grafting: The importance of neutrophil-to-lymphocyte ratio and growth differentiation factor 15. *Russian Open Medical Journal* 2025; 14: e0107.

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Introduction

Coronary artery disease (CAD) is among the main causes of chronic heart failure (CHF) and cardiovascular mortality [1]. The pathological effect of CAD on cardiac function is implemented in various ways. First of all, it is the development of myocardial infarction (MI) with rapid loss of a segment of viable myocardium and disruption of the structural function of the left ventricle (LV). However, even in the absence of MI, chronic coronary syndrome has a significant impact on the progression of cardiac dysfunction. Frequent episodes of transient ischemia result in the development of a myocardial stunning. Persistent reduction in coronary blood flow causes hibernating myocardium, which, with ongoing ischemia, inevitably ends in cardiomyocyte necrosis.

There are three strategic approaches to the treatment of patients with CAD including optimal drug therapy, alone or in combination with surgical myocardial revascularization. The latter presumes two options: coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). At the same time, the results of large randomized clinical trials comparing these treatment strategies are often contradictory and largely depend on the design of the study.

In the EXCEL study, which investigated the safety and efficacy of everolimus-eluting stents compared with CABG in patients with left main CAD, the incidence of major adverse cardiovascular events (MACE), such as death, ischemic stroke (IS), or MI, was approximately 15% in both groups over three years of follow-up (with only 5-7% of patients in the study cohort experiencing congestive CHF) [4].

In the recently reported REVIVED trial (REVIVED-BCIS2; NCT01920048), patients with LVEF ≤35%, extensive CAD amenable to PCI, and demonstrated myocardial viability were randomized to PCI followed by optimal medical therapy (PCI group) or optimal medical therapy alone. A total of 347 patients were included in the PCI group and 353 in the optimal medical therapy group. Over a median follow-up of 41 months, the mean rate of all-cause death or hospitalization for heart failure was 37.2% in the PCI group and 38.0% in the optimal medical therapy group (p=0.96) [5]. However, LVEF values were similar in both groups at 6 and 12 months. Thus, PCI revascularization, according to this study, had no advantage in the studied cohort compared with optimal medical therapy.

Prediction of MACE after high-tech interventions is an urgent and important task for the scientific and medical community. Subclinical markers of inflammation are increasingly studied for this purpose.

Currently, inflammation is recognized as a universal way for the body to adapt to changing environmental conditions. The contemporary concept of the immunology of cardiovascular homeostasis is based on the so-called danger model proposed by P. Matzinger in 1994 [6]. According to this theory, there are danger signals called damage-associated molecular patterns (DAMPs),

which initiate an immune response in the absence of exogenous infectious pathogens [7,8]. Thus, acute or chronic damage to myocardial cells is associated with the release of cell degradation products, which are DAMPs [9]. In turn, the release of proinflammatory cytokines causes activation of tissue resident macrophages and leads to the recruitment of various populations of circulating immune cells to the heart under the influence of specific chemokine molecules [10]. Despite the active study of the pathogenesis of low-grade inflammation, it still remains incompletely understood.

It has been shown that low-grade inflammation plays a negative role in cardiovascular diseases (CVD) [11]. The development and progression of atherosclerosis and CHF is accompanied by activation of immune processes [12-14]. However, the lack of success in the development of new anti-inflammatory methods for the treatment of heart failure may be due to our poor understanding of the complex inflammatory systems in CVD [14].

Treatment of clinically pronounced CAD with obstructed arteries with myocardial revascularization via CABG is an effective contemporary method. However, the prognosis in patients after CABG may differ significantly from regression of coronary and heart failure symptoms to cardiovascular death [2]. During cardiopulmonary bypass (CPB), proinflammatory mediators trigger the activation of leukocytes, vascular endothelial cells, and platelets. This manifests as a systemic inflammatory response that leads to organ dysfunction affecting the heart, brain, lungs, and kidneys, and may affect the prognosis of patients.

According to the literature, the neutrophil-to-lymphocyte ratio (NLR) predicts the development of postpericardiotomy syndrome (PPS) [15], atrial fibrillation (AF) [16, 17], acute kidney injury (AKI) [18, 19], saphenous vein graft failure [20, 21], IS [22], and even early postoperative mortality [23-25] after CABG. Therefore, NLR is a promising marker of prognosis in patients after CABG.

Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor beta (TGF-β) superfamily of cytokines. Circulating GDF-15 concentrations are increased in a wide range of CVD, including acute and chronic CAD, congestive heart failure, and IS. GDF-15 is also increased by other cardiovascular events that induce oxidative stress, including pressure overload and atherosclerosis. Moreover, elevated circulating GDF-15 concentrations are associated with an increased risk of future MACE.

Elevated GDF-15 concentrations in CABG may help predict the development of postoperative AF [26] and AKI [27, 28].

In addition, some studies revealed that GDF-15 determination may help predict cardiovascular mortality in patients with CVD [29].

Hence, the goal of our study was to determine the role of NLR and GDF-15 in predicting MACE in CABG patients.

Material and Methods

Study population

Our prospective observational study included 80 patients with CAD who underwent CABG during the current hospitalization (inclusion years: 2019-2020). The study protocol complied with the principles of the Declaration of Helsinki and was approved by the local Ethics Committee (protocol No. 188 of September 18, 2019). Prior to the study, all patients signed a voluntary informed consent form.

Table 1. Clinical characteristics of patients before CABG in MACE-based groups

Parameter		*MACE– (n=58)*	*MACE+ (n=22)*	*p*
Gender: male/female, n (%)		51 (87.9) / 7 (12.1)	20 (90.9) / 2 (9.1)	1.000
Suffered MI/MI in anamnesis, n (%)		33 (56.9)	17 (77.3)	0.123
Type 2DM, n (%)		13 (22.4)	7 (31.8)	0.386
Obesity, n (%)		23 (39.7)	7 (31.8)	0.518
Stroke in anamnesis, n (%)		2 (3.4)	1 (4.5)	1.000
PCI in anamnesis, n (%)		10 (17.2)	5 (22.7)	0.749
PAD, n (%)		5 (8.6)	1 (4,5)	1.000
CAS (≥40%), n (%)		16 (27.6)	4 (18,2)	0.386
Classes of CHF sensu NYHA	I, n (%)	6 (10.3)	2 (9.1)	0,965
	II, n (%)	30 (51.7)	11 (50)	
	III, n (%)	22 (37.9)	9 (40.9)	
Smoking, n (%)		34 (58.6)	12 (54,5)	0.742
HFpEF, n (%)		32 (55.2)	9 (40,9)	0.287
HFmrEF, n (%)		8 (13.8)	2 (9.1)	
HFrEF, n (%)		18 (31)	11 (50)	
AF, n (%)		16 (27.6)	3 (13.6)	0.247
Grade II-III CKD, n (%)		16 (27.6)	10 (45.5)	0.128
Age, years: Me (Q25; Q75)		63.0 (58.7; 68.0)	61.0 (57.7; 65.0)	0.295
LVEF, %: Me (Q25; Q75)		54.5 (37; 64)	41 (27; 63)	0.156
eGFR, ml/min/1.73m^2, Me (Q25; Q75)		72.5 (59; 80)	68 (55.7; 77.0)	0.316
CPB, min, Me (Q25; Q75)		91.0 (75.8; 115.2)	101.5 (77.3; 128.9)	0.419
ACC, min, Me (Q25; Q75)		53.7 (43.9; 70.2)	55.4 (49.8; 83.5)	0.196

MI, myocardial infarction; DM, diabetes mellitus; PCI, percutaneous coronary intervention; PAD, lower extremity peripheral artery disease; CAS, carotid atherosclerosis; NYHA, New York Heart Association; CHF, chronic heart failure; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; AF, atrial fibrillation; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; CPB, duration of cardiopulmonary bypass; ACC, aortic cross-clamping time; Me (Q25; Q75), median and interquartile range; p, statistical significance according to the Wald test.

Table 2. The significance of the main laboratory parameters

Parameter, Me (Q25; Q75)	*MACE– (n=58)*	*MACE+ (n=22)*	*p*
WBC, 10^9/l	6.9 (6.1; 8.3)	7.1 (6.1; 8.7)	0.575
Platelets, 10^9/l	208 (175; 248)	208 (166; 244)	0.901
ESR, mm/h	9 (5; 14)	10 (3; 15)	0.927
Fibrinogen, g/l	3.44 (3.1; 4.0)	3.14 (2.90; 3.69)	0.080
Lymphocytes, 10^9/l	2.6 (2.2; 3.1)	2.5 (1.9;3.1)	0.670
Neutrophils, 10^9/l	3.34 (2.6; 4.4)	3.8 (2.7;5.2)	0.431
NLR, pg/ml	1.33 (1.03; 1.67)	1.38 (1.09; 1.97)	0.362
GDF-15, pg/ml	2235 (1633; 2907)	2328 (2145; 3172)	0.096
CRP, mg/l	4.45 (2.17; 8.90)	4.8 (2.52; 9.03)	0.419

WBC, white blood cells; ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte ratio; GDF-15, growth differentiation factor 15; CRP, C-reactive protein; Me (Q25; Q75), median and interquartile range; p, statistical significance according to the Wald test.

Table 3. Logistic regression results confirming the independent prognostic value of GDF-15×NLR for MACE

Indicator	*B (regression coefficient)*	*Wald test of significance*	*p*
Gender (1 – male)	-0.082	0.008	0.928
Age, years	-0.038	0.929	0.335
Type 2DM, (1 – yes)	-0.474	0.582	0.446
LVEF (%)	-0.022	1.417	0.234
GDF15*NLR	0,000	4,328	0,037
Constant	1,553	0.335	0.563

p, statistical significance according to the Wald test; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; GDF15×NLR, the value of the NLR×GDF-15 product.

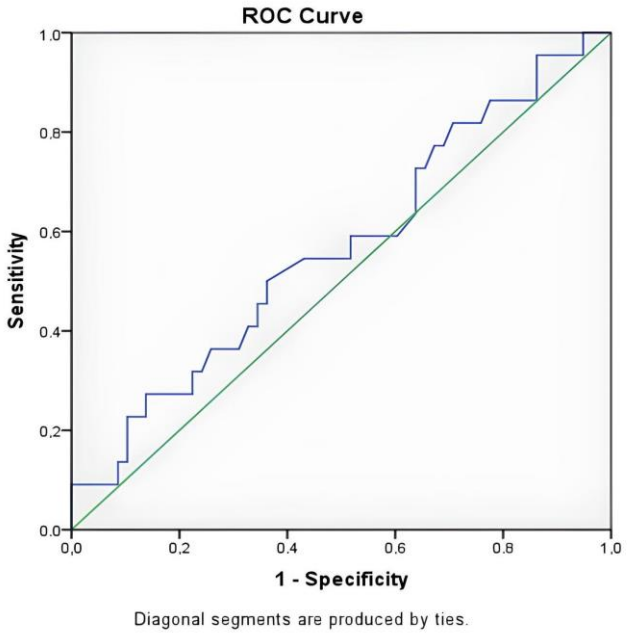

Figure 1. ROC analysis of NLR and MACE development: AUC=0.566 (p=0.363).

AUC	*SE*	*Asymptotic significance*	*Asymptotic 95%CI*	
			Lower boundary	Upper boundary
0.566	0.073	0.363	0.423	0.709

Test result variable: neutrophil-to-lymphocyte ratio (NLR); ROC, receiver operating characteristic; MACE, major adverse cardiovascular events; AUC, area under the curve; SE, standard error; CI, confidence interval.

Exclusion criteria were refusal to participate in the study, MI, IS within the last 6 months, implanted heart rhythm control devices, the need for additional cardiac surgeries other than CABG, the presence of advanced kidney disease (eGFR<30 ml/min/1.73 m^2) and severe comorbidities (active cancer, infiltrative CVD, autoimmune diseases, acute infections, and exacerbation of chronic somatic diseases). Also, patients were excluded from the study if they died during hospitalization.

Research methods

The diagnosis of CHF was established based on current clinical guidelines. Multivessel CAD was diagnosed using invasive coronary angiography on the angiographic complex, Cardio-scop-V and ACOM.PC by Siemens (Germany), according to clinical indications. Echocardiography was performed on the ultrasound system, Philips HD15.

In addition to clinical and laboratory examination (complete blood count with leukocyte formula, biochemical blood test with calculation of estimated glomerular filtration rate (eGFR) based the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation), the concentration of GDF-15 was studied by the enzyme immunoassay using the Human GDF-15/MIC1 ELISA kit (BioVendor, Czech Republic). The result is presented in pg/ml. The study was conducted using the equipment of the Medical Genomics Center for Collective Use at the Research Institute of Cardiology, National Medical Research Center of Tomsk of the Russian Academy of Sciences, Tomsk, Russia.

Blood was collected from the cubital vein in the morning on an empty stomach one day before CABG. Further preparation of blood samples for analysis included centrifugation, separation of serum and freezing at -80 °C. The analysis was performed after a single defrosting of the blood serum.

Patients were monitored for 12 months. The drug therapy prescribed after surgery was fully consistent with current clinical guidelines and did not differ significantly among patients with and without adverse cardiovascular events (MACE+ and MACE–, respectively).

In our study, MACE served as a composite endpoint, which was recorded during prospective follow-up, including CVD death, decompensated heart failure, need for intravenous diuretic therapy or doubling of the diuretic dose, acute ischemic event requiring unplanned revascularization, IS, unplanned hospitalization for CAD and/or CHF (a total of 22 events [27.5%]).

Statistical data processing

Data processing was performed using IBM SPSS version 21 and MS Excel software. Continuous variables are presented as median and interquartile range (Me [Q25; Q75]) taking into account the non-normal distribution of investigated parameters. Categorical data are presented in counts and relative values: n (%). Continuous variables in independent samples were analyzed using the Mann-Whitney U test. Spearman's rank correlation coefficient was employed to assess correlation relationships. Statistical significance of differences for categorical variables was determined using the Pearson's χ^2 test and two-tailed Fisher's exact test. The effects of the studied factors on the development of MACE were analyzed using logistic regression analysis and receiver operating characteristic (ROC) analysis. The latter involved

calculating area under the curve (AUC). A value of p<0.05 was considered statistically significant.

Results

The main characteristics of the study cohort are presented in *Table* 1.

The patient groups, both with and without MACE during the year, did not differ in the main clinical and anamnestic parameters: 90% of patients were male, and their mean age was 63 years. More than half of the patients had heart failure with preserved ejection fraction (HFpEF) or heart failure with moderately reduced ejection fraction (HFmrEF) of the LV and class II CHF sensu the New York Heart Association (NYHA) classification. The duration of CPB during CABG, as well as the time of aortic cross-clamping during CABG, were similar in the study groups.

We detected no significant differences between the groups in terms of the content of the main laboratory inflammation markers in the blood (*Table 2*).

Thus, the values of both parameters analyzed in this study (GDF-15 and NLR) were similar in the groups with and without MACE. ROC analysis was performed to identify statistical associations of GDF-15 and NLR with MACE development. Both parameters demonstrated a low AUC: for NLR, AUC=0.566 (p=0.363); and GDF-15, AUC=0.621 (p=0.096). These findings confirm the absence of association of these markers with MACE in the studied cohort (*Figures* 1 and 2).

It is interesting to note the visual approximation of the scatterplot to a hyperbolic curve, mathematically described by the function y=k/x.

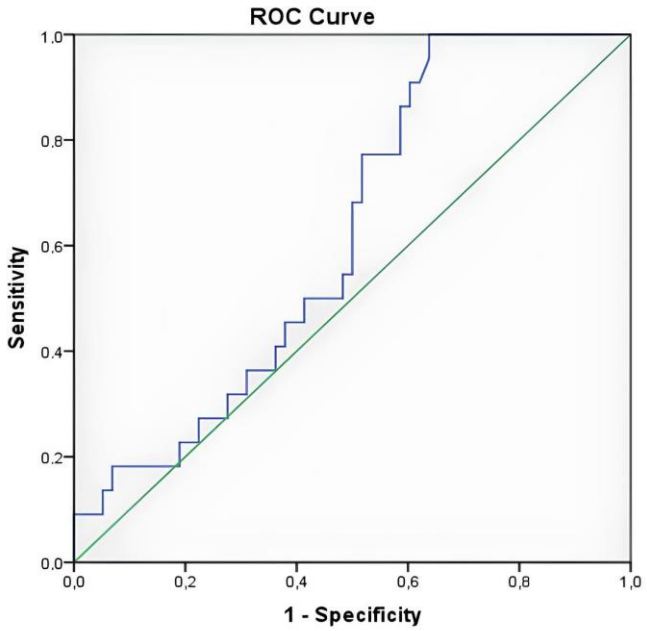

Figure 2. ROC analysis of GDF-15 and MACE development: AUC=0.621 (p=0.096).

AUC	*SE*	*Asymptotic significance*	*Asymptotic 95%CI*	
			Lower boundary	Upper boundary
0.621	0.064	0.096	0.496	0.746

Test result variable: GDF-15, pg/ml; ROC, receiver operating characteristic; MACE, major adverse cardiovascular events; AUC, area under the curve; SE, standard error; CI, confidence interval.

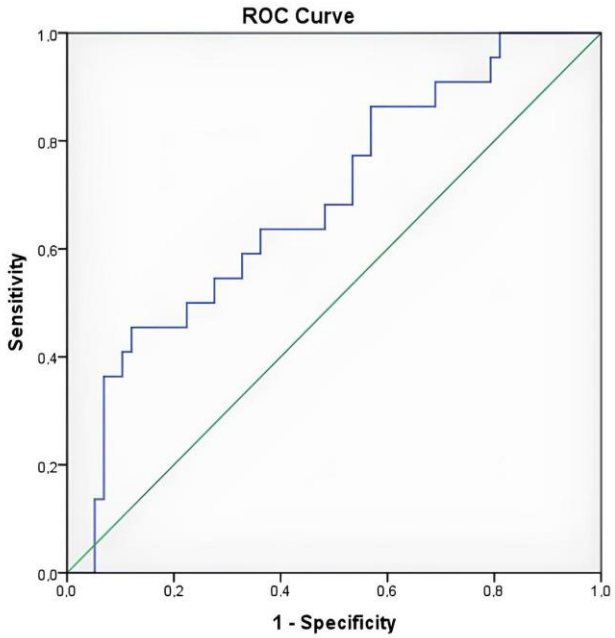

Figure 3. ROC analysis of the NLR×GDF-15 product and MACE development: AUC=06.87; p=0.010.

AUC	*SE*	*Asymptotic significance*	*Asymptotic 95%CI*	
			Lower boundary	Upper boundary
0.687	0.066	0.010	0.557	0.816

Test result variable: NLR×GDF-15; ROC, receiver operating characteristic; MACE, major adverse cardiovascular events; AUC, area under the curve; SE, standard error; CI, confidence interval.

We assumed that with increasing k, equal to the product of the concentrations of GDF-15 and NLR, the probability of MACE increases. To test this hypothesis, the value of the product, GDF-15×NLR, was calculated. The median was 3,108.05 (2,069; 4,145) for patients without MACE and 4,108.8 (2,779.4; 5,890.5) for patients with MACE. The differences were statistically significant: p=0.010.

ROC analysis was performed to determine the statistical relationship of GDF15×NLR with the development of MACE. The area under the curve was AUC=0.687, and the relationship was statistically significant (p=0.010) (*Figure* 3).

We carried out the logistic regression to identify the independent predictive value of the NLR×GDF-15 product. We made adjustments for gender, age, diabetes mellitus (DM) and LVEF. The results of the logistic regression analysis are presented in *Table* 3.

According to the analysis, NLR×GDF-15 was an independent predictor of MACE within 12 months after CABG (p=0.037). According to the ROC analysis, the cutoff point for this parameter was 3,216, which allowed predicting the development of MACE with a sensitivity of 68% and a specificity of 52%.

Discussion

Low-grade inflammation plays an important role in the development and progression of CAD and CHF [11]. Experimental and clinical studies confirmed that atherosclerosis is an inflammatory disease [30-32].

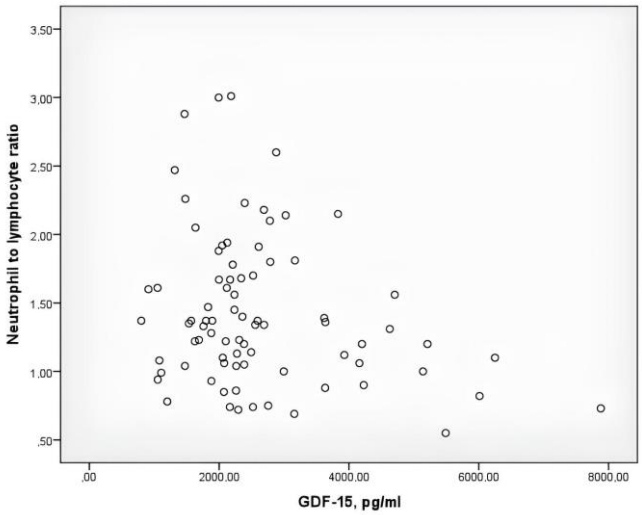

Figure 4. Scatterplot for NLR and GDF-15: no significant linear correlation between the indicators (r=-0,185, p=0.101).

Exposure to cardiovascular risk factors leads to the loss of protective endothelium and accumulation of low-density lipoproteins in the subendothelial space of the vascular wall, which causes a weak inflammatory response [33]. At the same time, an increase in the concentration of some inflammatory biomarkers, including immune cell populations and inflammasomes, allows predicting the progression of CAD independently of conventional risk factors [34-36]. In our study, the content of high-sensitivity C-reactive protein (hs-CRP), as well as traditional inflammatory parameters of the complete blood count (leukocytes, erythrocyte sedimentation rate) were not associated with the development of MACE. This is probably due to the fact that the study included patients with elective cardiac surgery, which excluded patients with inflammation. Recently, the publications focused on the inflammatory index reflecting low-grade systemic inflammation such as NLR, platelet-to-lymphocyte ratio (PLR), and (neutrophils)×PLR. The latter is a systemic immune inflammation index (SII) [37, 38].

To analyze the relationship between GDF-15 and NLR, we constructed a scatter plot (*Figure 4*). Spearman's rank correlation coefficient, r=-0.185, p=0.101; hence, we revealed no significant linear correlation between the two.

The NLR is among the most frequently considered and widely available indices reflecting systemic inflammatory processes. It is currently widely used in virtually all areas of medicine as an easily accessible and informative marker of the immune response to infectious and noninfectious agents. The pathogenetic significance of this marker is explained by the fact that NLR reflects the dynamic relationship between innate (neutrophils) and adaptive (lymphocytes) cellular immune responses during disease development and progression. The normal range of NLR values is between 1 and 2, while values above 3.0 and below 0.7 in adults are interpreted as pathological. A small increase in NLR between 2.3 and 3.0 may be an early sign of the disease, including those of atherosclerotic genesis [39].

According to the literature, markers that demonstrate associations with the most accurate prognosis in patients after CABG are widely available. For example, an increase in NLR above 8.34 in patients after CABG is associated with PPS [15], while an increase in NLR above 2.13 at any time (before or after CABG) is associated with a high risk of the development or recurrence of AF [17].

In addition, an NLR value above 2.675 before CABG is associated with saphenous vein graft failure, but the study [21] failed to achieve the required level of statistical significance (p=0.075). In another study [23], an increase in NLR> 6.4 and 31.8 in the first hour and day after surgery, respectively, was closely associated with mortality.

In patients with chronic coronary total occlusion, NLR and its dynamics after PCI are associated with the development of MACE during 9-12 months of follow-up [40]. However, we could not find similar data in the literature for patients who underwent CABG with CPB. Hence, its role in predicting long-term outcomes in patients after CABG is currently unclear. In our cohort, NLR is not associated with the development of MACE during prospective follow-up for one year (AUC=0.565; p=0.368). This may be partly due to the fact that NLR is influenced by many conditions such as age and the presence of chronic diseases (including DM, obesity, psychiatric diagnosis, cancer, anemia and stress) [41].

GDF-15, or macrophage inhibitory cytokine-1, acts as an inflammatory marker and plays a role in the pathogenesis of CVD, metabolic disorders, and neurodegenerative processes. Serum GDF-15 levels also increase with age and in response to cellular stress and mitochondrial dysfunction [41]. Recently, the role of GDF-15 in aging and metabolic disorders was actively discussed by the scientific community. In particular, the GDF-15 receptor, its main signaling pathways, and biological effects are poorly understood [42].

Some studies have demonstrated a role for GDF-15 in predicting adverse outcomes in CHF, both with reduced LVEF [43] and with preserved LVEF [44]. At the same time, the dynamics of GDF-15 concentrations in patients with decompensated heart failure reflected an increased risk of rehospitalization and death in the RELAX-AHF study [45].

However, GDF-15 remains a relatively poorly studied marker in patients with CABG. There are conflicting data in the literature regarding the association of GDF-15 with the development of MACE in patients with CABG. O. Bouchot et al. [26] showed that low GDF-15 values are associated with the development of postoperative AF. However, other studies demonstrated that high GDF-15 values are unfavorable, being associated with the development of AKI [41].

In addition, the study by M. Heringlake et al. [29] showed that the plasma GDF-15 level before CABG is an independent predictor of postoperative mortality and morbidity in patients with CVD. This is an important addition to the known scales for risk stratification in these patients.

In our cohort, we observed no statistically significant association with the development of MACE during the one-year follow-up period (AUC=0.621; p=0.096).

However, given the wide diversity of immune processes and the lack of evidence for a correlation between GDF-15 and NLR, we performed a correlation analysis between GDF-15 and NLR. No significant linear correlation was found (r=-0.184, p=0.102). At the same time, visual inspection of the scatterplot (*Figure* 3) led us to the conclusion about the presence of a nonlinear relationship between these parameters. This relationship, according to the distribution of points on the scatterplot, could be a hyperbola. In this case, the product of NLR and GDF-15 would have a separate

prognostic value. Such data are not described in the literature, so we propose a scientific hypothesis. According to the ROC analysis, the AUC for predicting MACE is 0.648 (p=0.011). The cutoff point for the NLR*GDF-15 product is 3,216. It predicts the development of MACE with a sensitivity of 68% and a specificity of 52%.

It is fundamentally important to note that the statistically significant association of the NLR×GDF-15 product with the development of MACE in patients who underwent CABG still remained after adjustments for gender, age, the presence of DM, and LVEF. Hence, this indicator is an independent predictor of MACE. These new findings have not yet been confirmed by other studies. They may form the basis for new scientific hypotheses and new large-scale studies.

Conclusion

The value of the NLR×GDF-15 product indicators is associated with the development of MACE in patients after CABG.

Limitations

The main limitation of our study is its small sample size, which is partially offset by the high homogeneity of the group (excluding any additional cardiac surgery and severe associated pathology of inflammatory etiology. Further research is needed to support our results.

Author contributions

Conceptualization, G.A. and R.A.; methodology, K.E.; formal analysis, K.E. and T.O.; investigation, K.E. and T.O.; data curation, G.A.; writing (original draft preparation), K.E. and T.O.; writing (review and editing), K.E. and T.O.; supervision, R.A. and G.A.; funding acquisition, G.A. All authors have read and agreed to the published version of the manuscript.

Funding

This research was funded by the Government Procurement, FSR #122020300045-5 (February 03, 2022).

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Ethics Committee at Cardiology Research Institute, National Medical Research Center of Tomsk, Russia (Protocol #188 of September 18, 2019).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Conflict of interest

The authors declare no conflicts of interest.

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