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ФАКТОР ДИФФЕРЕНЦИРОВКИ РОСТА-15 (GDF-15) КАК БИОЛОГИЧЕСКИЙ МАРКЕР ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

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Growth Differentiation Factor-15 (GDF-15) is a Biological Marker in Heart Failure

Резюме

Сердечная недостаточность является важной медицинской, социальной и экономической проблемой во всем мире. В последние годы был изучен ряд диагностических и прогностических биологических маркеров крови при сердечно-сосудистых заболеваниях. Идентификация новых биологических маркеров, анализ их патофизиологических аспектов и изменения концентрации под действием различных вариантов лечения, позволяют понять многие патогенетические особенности развития и течения сердечной недостаточности. Последние десятилетия в клиническую практику внедрены натрийуретические пептиды, широко используемые в качестве надежных биомаркеров для диагностической и прогностической оценки. Фактор дифференцировки роста-15 — цитокин, принадлежащий к семейству трансформирующих факторов роста, активность которого значимо повышается стрессе и воспалении. У пациентов с хронической сердечной недостаточностью концентрация данного биомаркера связана с повышенным риском общей летальности и неблагоприятными сердечно-сосудистыми событиями; у пациентов с сердечной недостаточностью с сохранной фракцией выброса левого желудочка использование биомаркера показало прогностическую и диагностическую значимость. Данные Фрамингемского исследования сердца показали, что фактор дифференцировки роста-15 был единственным биомаркером в многофакторном анализе, который продемонстрировал статистически значимую связь со всеми неблагоприятными сердечно-сосудистыми событиями. В 8 исследованиях показано, что избыточная экспрессия фактора дифференцировки роста-15 была связана с повышенным риском смертности у пациентов с сердечной недостаточностью. ~~Показано, что~~ Фактор дифференцировки роста-15 как прогностический биомаркер у пациентов с острой сердечной недостаточностью не уступает предшественнику мозгового

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натрийуретического пептида. Для подтверждения ценности определения в крови данного биомаркера у пациентов с сердечной недостаточностью необходимо проведение обширных проспективных рандомизированных клинических исследований.

Ключевые слова: *хроническая сердечная недостаточность, фракция выброса левого желудочка, биомаркеры, фактор дифференцировки роста-15*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Heart failure is an important medical, social and economic problem around the world. In recent years, a number of diagnostic and prognostic biological markers of blood in cardiovascular diseases have been studied. Identification of new biological markers, analysis of their pathophysiological aspects and changes in concentration under the influence of various treatment options, allow us to understand many pathogenetic features of the development and course of heart failure. In recent decades, natriuretic peptides have been introduced into clinical practice, which are widely used as reliable markers for diagnostic and prognostic assessment. Growth differentiation factor-15 is a cytokine belonging to the family of transforming growth factors, the activity of which is significantly increased under stress and inflammation. In patients with chronic heart failure, the concentration of this marker is associated with an increased risk of overall mortality and adverse cardiovascular events; in patients with heart failure with preserved left ventricular ejection fraction, the use of the marker showed prognostic and diagnostic significance. Data from the Framingham Heart Study showed that growth differentiation factor-15 was the only marker in multivariate analysis that showed a statistically significant association with all adverse cardiovascular events. Eight studies showed that overexpression of growth differentiation factor-15 was associated with an increased risk of mortality in patients with heart failure. It was shown that growth differentiation factor-15 as a prognostic marker in patients with acute heart failure is not inferior to the brain natriuretic peptide precursor. To confirm the value of this marker in blood in patients with heart failure, it is necessary to conduct extensive prospective randomized clinical trials.

Key words: *chronic heart failure, left ventricular ejection fraction, biological markers, growth differentiation factor-15*

Conflict of interests

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CHF — chronic heart failure, CRP — C-reactive protein, DD — diastolic dysfunction, Gal-3 — galectin-3, GDF-15 — growth differentiation factor-15, HF — heart failure, IR, I/R — ischemia-reperfusion injury, LVEF — left ventricular ejection fraction, NT-proBNP — N-terminal pro-brain natriuretic peptide, ST2 — stimulating growth factor

Introduction

Heart failure (HF) is one of the world's pressurizing medical, social and economic problems [1]. The prevalence of HF in the adult population of developed countries is about 2–3 %. The risk of developing chronic heart failure (CHF) in patients over the age of 60 is more than 10 % [1]. According to EPOKHA-AG and EPOKHA-CHF studies, the prevalence of CHF in Russia approximates 7 % [2].

Identification of new biological markers, as well as the analysis of their pathophysiological role and changes in their levels under various treatment options allowed understanding many pathogenetic aspects of the development and course of HF [3]. Currently, the assessment of the level of brain natriuretic peptide (BNP) and its N-terminal precursor (NT-proBNP) is a kind of "gold standard" for diagnosing HF and predicting its course, however, limitations due to the impact of many factors, the ambiguity of threshold values, and sufficiently low information value in cases of CHF with preserved left ventricular ejection fraction (LVEF) contribute to the need for further search for highly sensitive and specific laboratory biomarkers [3, 4]. New biological markers such as fibrosis marker galectin-3 (Gal-3), peptide hormone

adrenomedullin, stimulating growth factor ST2, chemokine CX3CL1, vasopressin surrogate marker, and others are increasingly used in real clinical practice [3, 4]. A multibiomarker approach is also important for diagnosis of CHF, stratification of its risk, and evaluation of the effectiveness of the treatment prescribed [3, 4].

It is commonly known that inflammation is a common response of a living organism to various damaging factors and is aimed at restoring tissue integrity and minimizing cell death. An active role in inflammatory response is played by pro-inflammatory cytokines, particularly, interleukins (IL-1, IL-2, IL-6, IL-8), tumor necrosis factor-α (TNF-α), chemokines and their receptors, cell adhesion molecules, as well as the acute-phase proteins (C-reactive protein (CRP) and pentraxin 3 (PTX3)). Pro-inflammatory cytokines activate fibroblasts and cardiomyocytes in the area of inflammation. The activated cells then produce cytokines and growth factors that function as powerful chemotactic molecules that enhance inflammatory response. Neutrophils and monocytes secrete transforming growth factor-β (TGF beta), as well as growth differentiation factor15 (GDF-15) that inhibits macrophage response and the synthesis of proteolytic enzymes. Inflammatory reactions in CHF result in the damage to cardiomyocytes, their apoptosis, and activation of neurohumoral systems that trigger reactions of myocardial hibernation and its remodeling [5].

The objective of this review is to consider GDF-15 as a diagnostic and prognostic marker in HF.

Sourcing Methodology

This article presents the review of publications over the recent 10 years. The analysis of literature sources was carried out using PubMed, RSCI, MedLine, Google Scholar, Science Direct databases. The authors reviewed both foreign and Russian papers. The search was carried out using the following keywords: biomarkers, heart failure, growth factor of differentiation 15.

Structure and Functions of GDF-15

GDF-15 is a cytokine that belongs to the family of transforming growth factor beta (TGF-ß) [6]. Under physiological conditions, the concentration of this biomarker in blood plasma and most tissues of the body is minor. GDF-15 was discovered more than twenty years ago; it was previously called macrophage inhibitory cytokine-1 (MIC-1) due to its possible role of the antagonist of macrophage activation by inflammatory cytokines (interleukins and tumor necrosis factors). The detailed mechanism of functioning of this biomarker in human body has not been fully established. GDF-15 receptor, its signaling pathways and biological aspects are not actually understood. Cytokine expression is activated by stress or tissue damage and is associated with inflammatory conditions of different organs, including myocardium [7, 8].

In animal models, GDF-15 was originally described as a cardioprotective protein that prevents cell death. The elevated expression of this biomarker is observed in response to harmful stimuli such as pressure overload or tissue ischemia. Activation of the enzyme nitric oxide synthase (NOS-2) in stressful situations leads to the increased production of GDF-15 [6]. The results of experimental studies of genetically modified rats with GDF-15 deficiency established its protective role in myocardial damage [6]. Th elevated cytokine level in the cardiomyocytes of rats with decreased activity of growth hormone was also demonstrated; this fact indicates ~~its~~ the involvement of GDF-15 in signaling pathways activated by growth hormone [6].

The human GDF-15 locus was mapped by fluorescence in-situ hybridization (FISH) to chromosome 19p12.1-13.1; it was shown that the gene contained a single intron [6]. The human GDF-15 promoter has binding sites for several transcription factors, including the cell cycle regulatory transcription factor p53 protein, early growth response protein 1 (Egr1), cyclic adenosine monophosphate response element-binding protein (CREB), transcription factor Sp1, cyclic adenosine monophosphate-dependent transcription factor (ATF-3), C/EBP homologous protein (CHOP). GDF-15 expression is increased by peroxisome proliferator-activated receptor (PPAR) γ-ligands. Several polymorphisms in the GDF-15 gene were identified. GDF-15 is synthesized as a precursor protein (pro-GDF-15) with the weight of ≈40 kDa that subsequently undergoes disulfide dimerization. The unprocessed translated form of GDF-15 (pre-pro-GDF-15) has the length of 308 amino acid residues including a signal sequence (29 amino acids), a propeptide (167 amino acids), and a mature protein (112 amino acids) with a cystine knot that is typical for TGF-β. The mature protein is secreted as a homodimer bound by disulfide bonds and is released from the propeptide after intracellular cleavage [7].

Method for Determination of GDF-15 in Blood

The level of this biological marker is determined using the immunoradiometric assay to determine the amount of radioactively labeled antigen-antibody complex by enzymes or luminescence (chemiluminescence). The detection range is 400–20,000 ng/L; at good accuracy and reproducibility, the error is less than 10 % [8, 9].

GDF-15 and Heart Failure

The elevated cytokine concentration is associated with cancer, insulin resistance, type 2 diabetes mellitus, renal dysfunction, cardiac diseases, and overall mortality; moreover, the level of this biomarker increases with age [10–15]. Examination of children with congenital heart diseases and HF revealed significantly higher GDF-15 blood concentrations compared to healthy children [15].

In a number of studies, the levels of GDF-15 and BNP/NT-proBNP in different groups of patients with CHF were evaluated. The authors concluded that NT-proBNP levels were higher in HF patients with reduced LVEF (HFrEF) compared with patients with preserved LVEF (HFpEF); however, GDF-15 concentration was elevated in patients with both systolic and diastolic LV dysfunction. Moreover, GDF-15 was found to be an important biomarker of adverse cardiovascular events and mortality and independent on LV contractility and NT-proBNP concentration [17–21]. The evaluation of GDF-15 level at different CHF stages revealed that the cytokine is a biomarker indicating the progression of the disease; its concentration increases at an exponential rate with an increase in the functional class (FC) of CHF (according to New York Heart Association (NYHA) classification) and the severity of LV remodeling. An elevated level of the biomarker was observed at the preclinical stage of heart failure [22].

According to H. Du et al. (2020), the results of the examination of 300 patients with ischemic HF revealed the level of GDF-15 that amounted to (582.6 ± 104.4) pg/mL in patients with HF FC IV and (408.4 ± 94.8) pg/mL in patients with NYHA functional class I HF [23].

First major study on the predictive value of GDF-15 in CHFnEF was carried out on the basis of Valsartan Heart Failure Trial (Val-HeFT) protocol (a study of using valsartan in the patients with CHF). GDF-15 levels were assessed at baseline and after 12 months of follow-up; 85 % of patients had elevated levels of GDF-15 biomarker (> 1,200 ng/mL). The results of a multivariate statistical analysis that included clinical parameters, BNP, troponin, and CRP levels revealed that high concentrations of this biomarker were independently associated with the elevated risk of all-cause mortality (OR 1.007; 95 % CI: 1.001–1.014; p = 0.02), but not with subsequent adverse events (OR 1.003; 95 % CI: 0.997–1.008; p = 0.34) such as sudden death, acute HF, and the need for inotropic support. After 1 year of follow-up, a comparable increase in GDF-15 level was observed in the placebo group and in the group of patients treated with valsartan. The levels of this biological marker were independently associated with all-cause mortality and with first adverse cardiovascular event. There was no change in GDF-15 level due to HF treatment [15].

In the PARADIGM-HF study (sacubitril/valsartan compared with enalapril in patients with HFnEF), GDF-15 levels were determined in 1,935 patients. Its baseline values, as well as values after 1 month and 8 months of treatment were associated with the elevated risk of overall mortality, adverse cardiovascular events (CVS), and with cardiovascular mortality or hospitalization for decompensated CHF. There was no change in GDF-15 concentration associated with drug administration [24].

P. Foley et al. (2009) in their study evaluated GDF-15 level during cardiac resynchronization therapy. 72 % of 158 patients had a good response to treatment; however, the patients with serum GDF-15 level above 2,720 ng/L demonstrated a significantly higher risk of cardiovascular mortality and rehospitalization due to HF decompensation in 30 months [25].

The study of D. Lok et al. (2013) included the analysis of the levels of NT-proBNP, GDF-15, Gal-3 and troponin in patients with FC III CHF (NYHA). The authors summarized that the GDF-15 biomarker is an indicator with better predictive value compared to NT-proBNP and other analyzed biomarkers [26].

In 2012, Dutch researchers analyzed GDF-15 concentration in the myocardial tissue of patients with non-ischemic dilated cardiomyopathy (DCM). Tissue samples were obtained during implantation of devices that support the left ventricle function or during heart transplantation. A strong statistically significant correlation was found between GDF-15 level and the severity of myocardial fibrosis [27]. One month after implantation of the device, GDF-15 levels were significantly reduced compared to the pre-implantation period; this fact indicates a relationship between the level of the analyzed biomarker and the severity of myocardial dysfunction [27].

O. M. Drapkina (2013) in her study with the participation of 55 patients with HF established a relationship between the GDF-15 biomarker and LV diastolic dysfunction (DD) parameters — peak E/A ratio (according to echocardiography (ECHO-CG)) (r = –0.26); this may represent an additional rationale for the use of GDF-15 as a laboratory diagnostic instrument for HFnEF. The data on a lower concentration of the GDF-15 biomarker in the patients treated with angiotensin II receptor blockers [28] can serve as indirect evidence of the involvement of this biological marker in HFpEF pathogenesis.

According to Ye. V. Bazaeva (2017), the levels of NT-proBNP, GDF-15, Gal-3 and PTX3 have statistically significant diagnostic value only in patients with NYHA FC I–II CHF with reduced LV contractility [29].

We should mention the work performed by Russian researchers that included the analysis of the relationship

of GDF-15 level in blood with ECHO-CG parameters in 34 CHF patients of comparable age with intermediate EF of LV (HFpEF) depending on the presence of myocardial infarction (MI) in their history. In patients without MI, there was a moderate negative correlation between LVEF and GDF-15 concentration ($r = -0.51$, $p = 0.050$), as well as a strong inverse relationship with LV stroke volume ($r = -0.722$, $p = 0.002$). Post-MI patients demonstrated no association between GDF-15 levels and the degree of systolic dysfunction [30].

According to V. D. Sivolap and Ya. V. Zemlyany (2014), the most significant prognostic potential in patients with HFpEF who developed adverse cardiovascular events belonged to the levels of GDF-15 and NT-proBNP, as well as to E/E' value according to ECHO-CG results. In patients with asymptomatic LV diastolic dysfunction, only GDF-15 had the highest prognostic value. In both groups, the combination of these two biological markers increased the predictive value of each of them [31].

In 2018, J. Li et al. (2018) examined 219 HF patients admitted to the Cardiology Department of Tianjin Medical Center and 32 healthy volunteers. Levels of circulating GDF-15, NT-proBNP, pro-collagen type I C-terminal propeptide (PICP) and pro-collagen type III N-terminal propeptide (PIIINP) were determined. All patients were followed up during 12 months. Plasma GDF-15 levels in HF patients were higher than in the control group ($p < 0.05$) and elevated with the progression of the disease ($p < 0.05$). Patients with HFnEF had higher GDF-15 levels compared to patients with HFpEF ($p < 0.05$). GDF-15 level demonstrated positive correlation with LV mass index (LVMI) ($r = 0.433$, $p < 0.05$), PICP ($r = 0.378$, $p < 0.001$), and PIIINP ($r = 0.382$, $p < 0.001$). When plotting ROC curves, the combination of GDF-15 and NT-proBNP (AUC = 0.905, 95% CI: 0.868–0.942, $p < 0.001$) was superior to NT-proBNP (AUC = 0.869, 95% CI: 0.825–0.913, $p < 0.001$) in the diagnosis of HF. Thus, GDF-15 in combination with NT-proBNP significantly improves the accuracy of diagnosing HF [32].

The research performed by American scientists N. Nair and E. B. Gongora is also of interest (2018): they examined 24 patients with DCM and 8 healthy volunteers. Coronary angiography revealed intact coronary arteries in all patients with DCM. Plasma levels of GDF-15, matrix metalloproteinase-2 (MMP2), MMP3, MMP9, tissue inhibitor of MMP 1 (TIMP1), ST2, and BNP were determined. The results of statistical analysis revealed a strong correlation of GDF-15 with TIMP1 ($r = 0.83$, $p < 0.0001$), a weaker one with MMP3 ($r = 0.41$, $p = 0.011$) and MMP2 ($r = 0.47$, $p = 0.003$). MMP9 also demonstrated a weak correlation with GDF-15 ($r = 0.3036$, $p = 0.046$). GDF-15 had negative correlation with the MMP2/TIMP1 ratio ($r = -0.47$, $p = 0.006$); strong correlation of ST2 with GDF-15 was observed ($r = 0.7$, $p < 0.0001$). GDF-15 level correlated negatively with LVEF ($r = -0.49$, $p = 0.004$) and positively with LV end-diastolic size ($r = 0.58$, $p = 0.0006$). GDF-15 demonstrated a significant direct relationship with HF FC (NYHA) ($r = 0.71$, $p < 0.00001$) and BNP concentration ($r = 0.86$, $p < 0.00001$) [33].

A year later, the employees of the Department of Cardiology of the Institute of Clinical and Experimental Medicine-IKEM (Czech Republic) evaluated the role of GDF-15 in patients with heart failure and chronic kidney disease who had estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. As a part of the study, 358 patients with stable systolic HF were followed up for 1,121 days. The authors concluded that GDF-15 in this category of patients had stronger association with adverse outcomes than BNP [34]. Similar evidence was obtained by C. Tuegel et al. (2018) (University of Washington School of Medicine) [35].

A number of studies revealed increased GDF-15 levels in patients with decompensated heart failure (NT-proBNP above 1,200 ng/L); patients with higher levels of the GDF-15 biomarker on admission to the hospital and with its high increase during hospitalization had a high risk of readmissions and mortality after discharge [36, 37].

In a study conducted by M. Boulogne et al. (2017) with the participation of 55 patients with HFnEF, serial measurements of several biomarkers were carried out at the beginning of hospitalization for disease decompensation and after 1 month. Similar trends in the changes of GDF-15 and BNP levels were observed. In this study, a rapid drop in GDF-15 levels was accompanied by apparent clinical improvement in patients. Moreover, the models with the combination of GDF-15 with known and well-studied biological markers such as troponin and BNP have demonstrated that the addition of this parameter increased the predictive value of laboratory biomarkers [38].

In 2020, Tomsk researchers examined 87 patients with nonvalvular atrial fibrillation (AF). All patients underwent general clinical examination, echocardiography, and laboratory tests including fasting blood glucose, creatinine, eGFR, NT-proBNP, highly sensitive CRP, and GDF-15. According to the results of the study, elevated GDF-15 concentrations were associated with age, HF severity and arterial hypertension, increased risk of thromboembolic complications according to the CHA2DS2-VASc scale, impaired carbohydrate metabolism, increased CRP and NT-proBNP levels, increased size of both atria, signs of diastolic LV dysfunction and its remodeling in the form of eccentric hypertrophy [39].

The same year, Austrian physicians conducted a study to investigate the correlation of serum levels of soluble urokinase-type plasminogen activator receptor (suPAR), GDF-15, heart-type fatty acid-binding protein (H-FABP), and ST2 with LVEF in 361 patients with ischemic HF. There was a statistically significant negative correlation between suPAR, GDF-15, H-FABP, and ST2 levels with LVEF. A multiple logistic regression model demonstrated independent relationship between GDF-15 ($p = 0.009$) and NT-proBNP ($p = 0.003$) and LVEF. The authors concluded that in addition to NT-proBNP that is a well-known marker for risk predicting, GDF-15 may be an additional laboratory instrument for the diagnosis and clinical follow-up of patients with HF [40].

Researchers at the University of Bergen conducted a study of a panel of 37 biomarkers to predict adverse cardiovascular events in post-MI patients. The protocol included the analysis of GDF-15, proadrenomedullin (MR-proADM), soluble tumor necrosis factor receptor (sTNFR), C-terminal proendothelin-1 (CT-pro-ET-1), C-terminal telopeptide of type 1 collagen (ICTP), C-terminal provasopressin (CT-proAVP), uric acid, chromogranin A (CGA), and procollagen type III N-terminal propeptide (PIIINP). This group of biomarkers proved to have the strongest predictive value of all-cause mortality and mortality from cardiovascular diseases including that from HF. In multivariate statistical analysis, incremental capacity of laboratory biomarkers was observed even after adjusting for several clinical covariates [41].

In 2021, P. Lourenço et al. examined patients with acute HF and concluded that patients with GDF-15 levels ≥ 3,500 ng/mL on admission to the hospital and ≥ 3,000 ng/mL on discharge were at high risk of death within 1 year [42].

The results obtained by German researchers (K. Nolte et al., 2015) demonstrated that in patients with asymptomatic LV diastolic dysfunction, plasma concentrations of GDF-15, MR-proADM and CT-proAVP were significantly higher compared to the control group. In contrast, the levels of NT-proBNP, MR-proANP, and CT-proET1 showed no statistically significant difference [43].

Ischemic/reperfusion (I/R) injury that inevitably develops during heart transplantation is a major factor leading to organ failure and transplant rejection. To develop novel treatment to prevent I/R injury, both a murine heart transplantation model with 24-hour cold I/R and an in vitro cell culture system were used to determine whether GDF-15 is a protective factor in preventing I/R injury during heart transplantation. Cold I/R was found to cause severe damage to endocardium, epicardium, and myocardium in heart transplants from wild-type C57BL/6 mice, while transplants from GDF-15 transgenic mice showed less damage, as demonstrated by decreased cell apoptosis/death, decreased neutrophil infiltration, and preservation of the normal structure of heart. Overexpression of GDF-15 reduced the expression of the phosphorylated transcription factor RelA p65 and pro-apoptotic genes, while it enhanced the phosphorylation of the Foxo3a gene in vitro and in vivo. Overexpression of GDF-15 inhibited cell apoptosis and reduced neutrophil infiltration. This study first demonstrated that GDF-15 was a promising target for preventing cold I/R injury in heart transplantation. It also demonstrated that the resulting protective effects were mediated by Foxo3 and NF-κB signaling pathways [44].

Conclusion

According to the Framingham study, five-year survival after the onset of clinical HF symptoms is only 25 % and 38 % in male and female patients, respectively [1]. CHF clinical manifestations are not specific enough, and ECHO-CG does not always reveal diagnostically significant changes, so, if CHF is suspected, biological markers in blood can be used as an alternative non-invasive diagnostic instrument. New markers, such as fibroblast growth factor 23, adrenomedullin, fibrosis marker Gal-3, stimulating growth factor ST2, chemokine CX3CL1, vasopressin surrogate marker, and others, are increasingly being used in real clinical practice. Currently, we have advanced technologies for identifying new biomarkers. The next step will be the development of a multi-biomarker model that will require the improvement of bioinformational technologies used for a large database analysis. The potential of this field is enormous not only for the discovery of new diagnostic biological markers, however, also for the improvement of HF treatment.

GDF-15 is a serum biological marker that is expressed due to stress, tissue damage, and inflammation [45]. Unlike other markers of necrosis that have cycles of rise and fall, GDF-15 is relatively stable and causes no particular difficulties in its implementation in clinical practice [46]. GDF-15 concentration in patients with CHF is associated with an increased risk of overall mortality and adverse cardiovascular events; GDF-15 demonstrated prognostic and diagnostic value in patients with HFpEF (Figure 1).

Data from the Framingham Heart Study that included evaluation of 85 biomarkers in 3,523 participants over 14-year follow-up, demonstrated that GDF-15 was the only biomarker in multivariate analysis that was statistically significantly associated with

all adverse cardiovascular events [7]. Pooled data from eight studies including 4,126 patients demonstrated that overexpression of GDF-15 was associated with an increased risk of mortality in patients with HF [47]. In 2019, Chinese researchers reported that GDF-15 was not inferior to NT-proBNP as a prognostic biomarker in patients with acute HF [48].

GDF-15 meets the criteria defined by R. S. Vasan (2006) as a biological marker of increased cardiovascular risk [49]. Table 1 presents the results of the most significant studies of the effect of GDF-15 on CVDs and their outcomes. To confirm the value of determination of blood GDF-15 in patients with HF, additional studies are required.

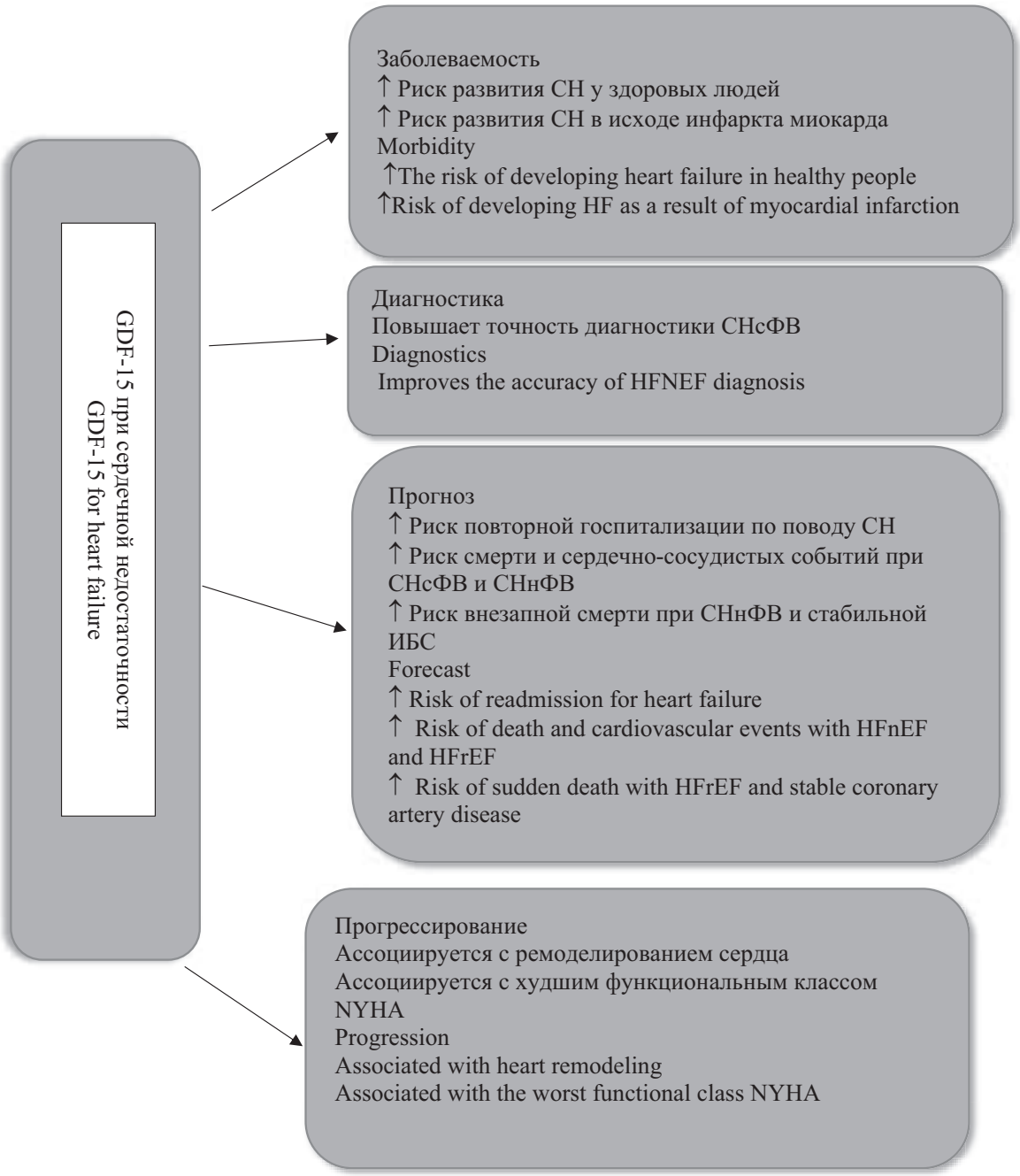

Figure 1. *Relation of GDF-15 to clinical aspects in heart failure*

Legend: HF — heart failure; IHD- ischemic heart disease; HFrEF — heart failure with reduced LV EF; HFnEF — heart failure with normal LV EF; NYHA — New York Heart Association Functional Classification

Table 1. *The most significant studies on the impact of GDF-15 on CVD and their outcomes*

Researchers	Markers	Members	Results
Khan S.Q. et al. [13]	GDF-15, NT-proBNP	• 1142 patients with acute myocardial infarction: 509 with ST elevation myocardial infarction; 633 with non-ST elevation myocardial infarction). • Age 67 (IQR: 24-97) years.	• GDF-15 increased with increasing Killip class (p <0,001) and correlated with NT-proBNP (r=0,47, p < 0,001). • AUROC for predicting death and HF: GDF-15 — 0,73, NT-proBNP — 0.76, combination of biomarkers — 0,81.
Anand I.S. et al. [14]	GDF-15	• 1734 patients from the Val-HeFT study (the efficacy of Valsartan in patients with heart failure) • Age 67 (IQR: 24-97) years • NYHA III and IV FC — 43 %	An increase in GDF-15 of 100 ng/L over 12 months has been associated with an increased risk of: • death by 1.7 % (HR: 1,017; 95 % CI 1,014 — 1,019; p <0.001) • the first pathological event (CPR, hospitalization for heart failure, inotropic support) by 2,0 % (HR: 1,020; 95 % CI 1,017 — 1,023; p <0,001)
Xie S. et al. [16]	GDF-15	Metaanalysis: • 31 studies (53706 subjects with 7020 adverse outcomes (MI, HF, death). • Follow-up for at least 3 months. • Average age ranged from 42 to 79 years	As GDF-15 increased, the risk of adverse events increased: • CVD mortality (HR: 2,11; 95 % CI, 1,57–2,66), • all-cause mortality (HR: 2,70; 95 % CI, 2,29-3,12), • adverse outcome (RR: 1.96; 95 % CI 1.64–2.29).
Sinning C. et al. [18]	sST2, GDF-15, NT-proBNP СРБ	5,000 people from the Grutenberg Population Health Study (randomly selected): • 2460 women (mean age 55 years • 2540 men (mean age 56)	• AUROC for the diagnosis of CHF -GDF-15 — 0,79, NT-proBNP — 0,77, CRP — 0,66, sST2 — 0,62 • in addition to NT-proBNP improved detection of HF (OR: 1,4, 95 % CI: 1,1-1,7) • The best biomarkers for predicting all-cause mortality were NT-proBNP (HR: 1,9, 95 % CI: 1,6–2,2; p <0.001) and GDF-15 (HR: 1.7, 95 % CI: 1,6–1,9, p <0,001)
Bouabdallaoui N. et al. [24]	GDF-15	• 1935 patients with NYHA II–IV HF, elevated BNP or NT-proBNP, SDLV (EF≤40 %) from the PARADIGM-HF study (RCT on the effect of ARNI on CVD death and hospitalization for HF). • Mean age 67 ± 10 years	An increase in GDF-15 at each point (baseline, 1 and 8 months later) of 20 % was associated with a higher risk of: • mortality (HR: 1,13, 95 % CI 1,08-1,18, p <0.001), • hospitalizations for heart failure and cardiovascular events (HR: 1,09, 95 % CI 1,05-1,14, p <0,001), • death from heart failure (HR: 1,16, 95 % CI 1,05-1,28, p <0,001)
Bonaca M. et al. [46]	GDF-15	• 3501 post-ACS patients (~day 7) from the PROVE IT-TIMI 22 trial to investigate the efficacy of standard or intensive statin therapy. • Follow-up period 2 years. • Mean age 58,1 ± 11.1 years	• At established thresholds, GDF-15 (<1200, 1200-1800, and >1800 ng/L) were associated with a 2-year risk of death or MI (5,7 %, 8,1 %, and 15,1 %, respectively; p <0,001) • GDF-15 was associated with risk of death or MI (adjusted RR per unit increase in GDF-15: 2,1, 95 % CI, 1,6–2,9; p <0,001)

Legend: ACS — acute coronary syndrome ARNI — angiotensin receptor and neprilysin inhibitor; AUROC — area under the ROC curve; BNP — brain natriuretic peptide; CI — confidence interval; CPR — cardiopulmonary resuscitation; CRP, C-reactive protein; CVD — cardiovascular diseases; CVE — cardiovascular events; EF — ejection fraction; GDF-15, growth differentiation factor 15; HF — heart failure; HR — Hazard ratio; MI STEMI — myocardial infarction with ST segment elevation; ; SDLV — systolic dysfunction of the left ventricle; NT-proBNP — N-terminal pro-brain natriuretic peptide; STEMI — myocardial infarction without ST segment elevation; sST2 — soluble tumorigenicity suppression receptor type II

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Список литературы / References:

1. Braunwald E. Heart failure. JACC Heart Fail. US National Institutes of Health. 2013; 1(1): 1-20. DOI: 10.1016/j.jchf.2012.10.002.
2. Фомин И.В. Хроническая сердечная недостаточность в Российской Федерации: что сегодня мы знаем и что должны делать. Российский кардиологический журнал. 2016; (8):7-13. DOI:10.15829/1560-4071-2016-8-7-13
   Fomin I.V. Chronic heart failure in the Russian Federation: what we know today and what we must do. Russian journal of cardiology. 2016; (8): 7-13. DOI: 10.15829/1560-4071-2016-8-7-13. [in Russian].
3. Алиева А.М., Резник Е.В., Гасанова Э.Т. и др. Клиническое значение определения биомаркеров крови у пациентов с хронической сердечной недостаточностью. Архивъ внутренней медицины. 2018; 8(5): 333-345. DOI: 10.20514 / 2226-6704-2018-8-5-333-345.
   Alieva A.M., Reznik E.V., Hasanova E.T. Clinical significance of the determination of blood biomarkers in patients with chronic heart failure. Archive of Internal Medicine. 2018; 8 (5): 333-345. DOI: 10.20514 / 2226-6704-2018-8-5-333-345. [in Russian].
4. Gasparyan A.Zh., Shlevkov N.B., Skvortsov A.A. Possibilities of modern biomarkers for assessing the risk of developing ventricular tachyarrhythmias and sudden cardiac death in patients with chronic heart failure. Kardiologiia. 2020;60(4):101–108. DOI: 10.18087/cardio.2020.4.n487. [in Russian].
   Гаспарян А.Ж., Шлевков Н.Б., Скворцов А.А. Возможности современных биомаркеров для оценки риска развития желудочковых тахиаритмий и внезапной сердечной смерти у пациентов хронической сердечной недостаточностью. Кардиология. 2020;60(4):101–108. DOI: 10.18087/cardio.2020.4. n487.
5. Emmerson P.J., Duffin K.L., Chintharlapalli S. et al. GDF15 and Growth Control. Front Physiol. 2018; 9:1–7. DOI: 10.3389/fphys.2018.01712
6. Kempf T., Eden M., Strelau J. et al. The transforming growth factor-superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. Circ Res. 2006;98(3):351–60. DOI: 10.1161/01.RES.0000202805.73038.48
7. Ho J., Mahajan A., Chen M. et al. Clinical and genetic correlates of growth differentiation factor 15 in the community. Clin Chem. 2012;58(11):1582-1591. DOI:10.1373/clinchem.2012.190322.
8. May B.M., Pimentel M., Zimerman L.I. et al. GDF-15 as a Biomarker in Cardiovascular Disease. Arquivos Brasileiros de Cardiologia. 2021;116(3):494-500. DOI: 10.36660/abc.20200426
9. Wang T., Liu J., McDonald C. et al. GDF 15 is a heart-derived hormone that regulates body growth. EMBO molecular medicine. 2017;9(8):1150-1164. DOI: 10.15252/emmm.201707604
10. Wollert K.C., Guba-Quint A., Torgerson J. et al. An automated assay for growth differentiation factor 15. The Journal of Applied Laboratory Medicine. 2017;1(5):510–21. DOI: 10.1530/EJE-12-0466
11. Kempf T., Horn-Wichmann R., Brabant G. et al. Circulating concentrations of growth-differentiation factor 15 in apparently healthy elderly individuals and patients with chronic heart failure as assessed by a new immunoradiometric sandwich assay. Clinical chemistry. 2007;53(2):284–91. DOI: 10.1373/clinchem.2006.076828
12. Wollert K.C., Kempf T., Wallentin L. et al. Growth differentiation factor 15 as a biomarker in cardiovascular disease. Clinical chemistry. 2017; 63:140–51. DOI: 10.1373/clinchem.2016.255174
13. Khan S.Q., Kelvin Ng., Dhillon O. et al. Growth differentiation factor-15 as a prognostic marker in patients with acute myocardial infarction. European heart journal. 2009;30(9):1057–65. DOI: 10.1093/eurheartj/ehn600
14. Anand I.S., Kempf T., Rector T.S. et al. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. Circulation. 2010;122(14):1387–95. DOI: 10.1161/CIRCULATIONAHA.109.928846
15. Ho J.E., Lyass A., Courchesne P. et al. Protein biomarkers of cardiovascular disease and mortality in the community. Journal of the American Heart Association. 2018;7(14): e008108. DOI: 10.1161/JAHA.117.008108
16. Xie S., Lu L., Liu L. et al. Growth differentiation factor-15 and the risk of cardiovascular diseases and all-cause mortality: A meta-analysis of prospective studies. Clinical cardiology. 2019;42(5):513–23. DOI: 10.1002/clc.23159
17. Sinning C. Zengin E., Zeller T. et al. Candidate biomarkers in heart failure with reduced and preserved ejection fraction. Biomarkers. 2015;20(4):258–65. DOI: 10.3109/1354750X.2015.1068856
18. Sinning C., Kempf T., Schwarzl M. et al. Biomarkers for characterization of heart failure–distinction of heart failure with preserved and reduced ejection fraction. International journal of cardiology. 2017;227: 272–7. DOI: 10.1016/j.ijcard.2016.11.110.
19. Chan M.M.Y., Santhanakrishnan R., Chong J.P.C. et al. Growth differentiation factor 15 in heart failure with preserved vs. reduced ejection fraction. European journal of heart failure. 2016;18(1):81–8. DOI: 10.1002/ejhf.431.
20. Santhanakrishnan R., Chong J.P.C., Tze P.Ng. et al. Growth differentiation factor 15, ST2, high-sensitivity troponin T, and N-terminal pro brain natriuretic peptide in heart failure with preserved vs. reduced ejection fraction. European journal of heart failure. 2012;14(12):1338–47. DOI: 10.1093/eurjhf/hfs130.
21. Sharma A., Stevens S.R., Lucas J. et al. Utility of growth differentiation factor-15, a marker of oxidative stress and inflammation, in chronic heart failure: insights from the HF-ACTION study. JACC: Heart Failure. 2017;5(10):724–34. DOI: 10.1016/j.jchf.2017.07.013.
22. Li J., Cui Y., Huang A. et al. Additional diagnostic value of growth differentiation factor-15 (GDF-15) to N-terminal B-type natriuretic peptide (NT-proBNP) in patients with different stages of heart failure. Medical science monitor: international medical journal of experimental and clinical research. 2018; 24:4992–9. DOI: 10.12659/MSM.910671.
23. Du H., Yang L., Zhang H., et al. Correlation between growth differentiation factor-15 and the severity of chronic heart failure in patients with coronary atherosclerosis. Eur Rev Med Pharmacol Sci. 2020 Dec;24(24):12844-12848. DOI: 10.26355/eurrev_202012_24186.
24. Bouabdallaoui N., Claggett B., Zile M.R. et al. Growth differentiation factor-15 is not modified by sacubitril/valsartan and is an independent marker of risk in patients with heart failure and reduced ejection fraction: the PARADIGM-HF trial. European journal of heart failure. 2018;20(12):1701–9. DOI: 10.1002/ejhf.1301.
25. Foley P.W. X., Stegemann B., Kelvin Ng. et al. Growth differentiation factor-15 predicts mortality and morbidity after cardiac resynchronization therapy. European heart journal. 2009;30(22):2749–57. DOI: 10.1093/eurheartj/ehp300.
26. Lok D.J., Klip I.T., Lok S.I. et al. Incremental prognostic power of novel biomarkers (growth-differentiation factor-15, high-sensitivity C-reactive protein, galectin-3, and high-sensitivity troponin-T) in patients with advanced chronic heart failure. The American journal of cardiology. 2013;112(6):831–7. DOI: 10.1016/j.amjcard.2013.05.013.
27. Lok S.I., Winkens B., Goldschmeding R. et al. Circulating growth differentiation factor-15 correlates with myocardial fibrosis in patients with non-ischaemic dilated cardiomyopathy and decreases rapidly after left ventricular assist device support. European journal of heart failure. 2012;14(11):1249–56. DOI: 10.1093/eurjhf/hfs120.

28. Драпкина О.М., Палаткина Л.О. Маркеры цитокиновой активации и оксидативного стресса у пациентов хронической сердечной недостаточностью. Сердечная Недостаточность. 2013; 14(6): 341-6.
Drapkina O.M., Palatkina L.O. Markers of cytokine activation and oxidative stress in patients with chronic heart failure. Heart Failure 2013; 14 (6): 341-6. [in Russian].
29. Базаева Е.В. Клиническая картина, параметры систолической и диастолической функций миокарда левого желудочка и уровней биохимических маркеров у пациентов с хронической сердечной недостаточностью с различной величиной фракции выброса левого желудочка: автореферат, дис. ... кандидата медицинских наук. Москва, 2017. 25 с.
Bazaeva E.V. Clinical picture, systolic and diastolic parameters of left ventricular myocardial function and biochemical marker levels in patients with chronic heart failure with different values of left ventricular ejection fraction: dissertation. Moscow, 2017. p. 25. [in Russian].
30. Кужелева Е.А., Гарганеева А.А., Александренко В.А. и др. Ассоциации ростового фактора дифференцировки 15 с клиническими особенностями хронической сердечной недостаточности с промежуточной и сохраненной фракцией выброса в зависимости от анамнеза инфаркта миокарда. Кардиология. 2021;61(5):59-64. DOI: 10.18087/cardio.2021.5.n1449.
Kuzheleva E.A., Garganeeva A.A., Aleksandrenko V.A. et al. Associations of growth factor differentiation 15 with clinical features of chronic heart failure with intermediate and preserved ejection fraction depending on the history of myocardial infarction. Cardiology. 2021;61(5): 59-64. DOI: 10.18087/cardio.2021.5.n1449. [in Russian].
31. Сиволап В.Д., Земляний Я.В. Прогностическое значение уровней GDF 15 и NTproBNP и эхокардиографических показателей у пациентов сердечной недостаточностью с сохраненной фракцией выброса и бессимптомной диастолической дисфункцией, перенесших инфаркт миокарда на фоне артериальной гипертензии. Запорожский медицинский журнал. 2014;3(84):13–17.
Sivolap V.D., Zemlyaniy Ya.V. Prognostic value of GDF 15 and NTproBNP levels and echocardiographic parameters in patients with heart failure with preserved ejection fraction and asymptomatic diastolic dysfunction who suffered myocardial infarction on the background of arterial hypertension. Zaporozhye Medical Journal. 2014;3(84):13–17. [in Russian].
32. Li J., Cui Y., Huang A. et al. Additional Diagnostic Value of Growth Differentiation Factor-15 (GDF-15) to N-Terminal B-Type Natriuretic Peptide (NT-proBNP) in Patients with Different Stages of Heart Failure. Med Sci Monit. 2018; 24:4992-4999. DOI: 10.12659/MSM.910671.
33. Nair N., Gongora E. Correlations of GDF-15 with sST2, MMPs, and worsening functional capacity in idiopathic dilated cardiomyopathy: Can we gain new insights into the pathophysiology? J Circ Biomark. 2018; 7:1849454417751735. DOI: 10.1177/1849454417751735.
34. Benes J., Kotrc M., Wohlfahrt P. et al. The Role of GDF-15 in Heart Failure Patients with Chronic Kidney Disease. Can J Cardiol. 2019;35(4):462-470. doi: 10.1016/j.cjca.2018.12.027.
35. Tuegel C., Katz R., Alam M. et al. GDF-15, Galectin 3, Soluble ST2, and Risk of Mortality and Cardiovascular Events in CKD. Am J Kidney Dis. 2018 Oct;72(4):519-528. DOI: 10.1053/j.ajkd.2018.03.025.
36. Cotter G., Voors A.A., Prescott M.F. et al. Growth differentiation factor 15 (GDF-15) in patients admitted for acute heart failure: results from the RELAX-AHF study. European journal of heart failure. 2015;17(11):1133–43. DOI: 10.1002/ejhf.331.
37. Jankovic-Tomasevic R., Pavlovic S.U., Jevtovic-Stoimenov T. et al. Prognostic utility of biomarker growth differentiation factor-15 in patients with acute decompensated heart failure. Acta cardiologica. 2016;71(5):587–95. DOI: 10.2143/AC.71.5.3167503.
38. Boulogne M., Sadoune M., Launay J.M. et al. Inflammation versus mechanical stretch biomarkers over time in acutely decompensated heart failure with reduced ejection fraction. International journal of cardiology. 2017; 226:53–9. DOI: 10.1016/j.ijcard.2016.10.038.
39. Гизатулина Т.П., Мартьянова Л.У., Петелина Т.И. и др. Ростовой фактор дифференцировки 15 как интегральный маркер клинико-функционального статуса пациента с неклапанной фибрилляцией предсердий. Вестник аритмологии. 2020;27(3):25-33. DOI:10.35336/VA-2020-3-25-33.
Gizatulina T.P., Martyanova L.U., Petelina T.I. Growth differentiation factor 15 as an integral marker of the clinical and functional status of a patient with non-valvular atrial fibrillation. Bulletin of Arrhythmology. 2020;27(3):25-33. DOI: 10.35336/VA-2020-3-25-33.
40. Dalos D., Spinka G., Schneider M. et al. New Cardiovascular Biomarkers in Ischemic Heart Disease-GDF-15, A Probable Predictor for Ejection Fraction. J Clin Med. 2019;8(7):924. DOI: 10.3390/jcm8070924.
41. Manhenke C., Orn S., Haehling S. et al. Clustering of 37 circulating biomarkers by exploratory factor analysis in patients following complicated acute myocardial infarction. Int J Cardiol. 2013;166(3):729-35. DOI: 10.1016/j.ijcard.2011.11.089.
42. Lourenço P., Cunha F.M., Ferreira-Coimbra J. et al. Dynamics of growth differentiation factor 15 in acute heart failure. ESC Heart Fail. 2021;8(4):2527-2534. DOI: 10.1002/ehf2.13377.
43. Nolte K., Gabriel F., Stahrenberg R. et al. GDF-15, MRproADM, CTproET1 und CTproAVP bei Patienten mit asymptomatischer diastolischer Dysfunktion [GDF-15, MRproADM, CTproET1, and CTproAVP in patients with asymptomatic diastolic dysfunction]. Dtsch Med Wochenschr. 2015;140(13): e120-8. German. DOI: 10.1055/s-0041-102543.
44. Zhang Y., Moszczynski L.A., Liu Q. et al. Over-expression of growth differentiation factor 15 (GDF15) preventing cold ischemia reperfusion (I/R) injury in heart transplantation through Foxo3a signaling. Oncotarget. 2017;8(22):36531-36544. DOI: 10.18632/oncotarget.16607.
45. Lodi R., Yu B., Xia L. et al. Roles and Regulation of Growth differentiation factor-15 in the Immune and tumor microenvironment. Hum Immunol. 2021: S0198-8859(21)00170-1. DOI: 10.1016/j.humimm.2021.06.007.
46. Bonaca M., Morrow D.A., Braunwald E.et al. Growth differentiation factor-15 and risk of recurrent events in patients stabilized after acute coronary syndrome: observations from PROVE IT-TIMI 22. Arterioscler Thromb Vasc Biol. 2011;31(1):203-10. DOI: 10.1161/ATVBAHA.110.213512.
47. Zeng X., Li L., Wen H., Bi Q. Growth-differentiation factor 15 as a predictor of mortality in patients with heart failure: a meta-analysis. J Cardiovasc Med (Hagerstown). 2017;18(2):53-59. DOI: 10.2459/JCM.0000000000000412.
48. Hao J., Cheang I., Zhang L. et al. Growth differentiation factor-15 combined with N-terminal prohormone of brain natriuretic peptide increase 1-year prognosis prediction value for patients with acute heart failure: a prospective cohort study. Chin Med J (Engl). 2019;132(19):2278-2285. DOI: 10.1097/CM9.0000000000000449.
49. Vasan R.S. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation. 2006;113(19):2335-62. DOI: 10.1161/CIRCULATIONAHA.104.482570.