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The role of growth differentiation factor-15 in assessing the prognosis of patients after uncomplicated myocardial infarction

Aim	To study the role of growth differentiation factor 15 (GDF-15) in the long-term prognosis for patients after uncomplicated myocardial infarction (MI).
Material and Methods	This study included 118 MI patients aged <70 years with and without ST-segment elevation on electrocardiogram (ECG). All patients underwent an examination that included ECG, echocardiography, Holter ECG monitoring, routine laboratory tests, and tests for plasma N-terminal pro-brain natriuretic peptide (NT-proBNT) and GDF-15. GDF-15 was measured by ELISA. The dynamics of patients was evaluated by interviews at 1, 3, 6, and 12 months. The endpoints were cardiovascular death and hospitalization for recurrent MI and/or unstable angina.
Results	Median concentration of GDF-15 in MI patients was 2.07 (1.55; 2.73) ng/ml. No significant dependence was found between GDF-15 concentration and age and gender, MI localization, smoking, body weight index, total cholesterol, and low-density lipoprotein cholesterol. During 12-month follow-up, 22.8% of patients were hospitalized for unstable angina or recurrent MI. In 89.6% of all cases of recurrent events, GDF-15 was ≥2.07 ng/ml. For patients with GDF-15 in the upper quartile, the time dependence of recurrent MI was logarithmic. High concentrations of NT-proBNP in MI patients were also associated with increased risk of cardiovascular death and recurrent cardiovascular events [RR, 3.3 (95% CI, 1.87–5.96), p=0.046].
Conclusion	A combination of GDF-15 and NT-proBNP at high concentrations significantly reflects an adverse prognosis for patients with uncomplicated MI within 12 months [RR, 5.4 (95% CI, 3.4–8.5), p=0.004].

Keywords	Myocardial infarction; prognosis; prognostic scales; growth differentiation factor 15; GDF-15; NT-proBNP
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Introduction

Myocardial infarction (MI) remains a significant clinical, social, and economic issue due to an unfavorable short-term and long-term prognosis [1]. Various examination data (e.g., left ventricular ejection fraction according to echocardiography) and laboratory (e.g., N-terminal pro-brain natriuretic peptide (NT-proBNP) indicators are used, which are combined into scores, to assess the prognosis of patients with a history of MI. The best-known scores TIMI [2] and GRACE [3] utilize various parameters, including markers of myocardial necrosis. None of these scores is ideal for predicting cardiovascular events in patients with a history of MI [4]. This may be due to the lack of information about changes occurring in MI. It seems promising from the point of view of a broader evaluation of pathophysiological processes in MI to study a relatively new biomarker growth differentiation factor-15 (GDF-15).

GDF-15 belongs to the transforming growth factors β superfamily. Proteins of this family are involved in the processes of development, differentiation, and regeneration of various tissues [5].

There is evidence that GDF-15 is associated with left ventricular remodeling [6–8]. Elevated levels of GDF-15 are associated with a higher risk of death and Recurrent MI within 1 year in patients with acute coronary syndrome, both with and without ST segment elevation on electrocardiogram (ECG) [9–11]. Only few studies investigate the prognosis of patients with a history of uncomplicated MI and without severe concomitant diseases.

Objectives and tasks

The objective of the study is to investigate the role of GDF-15 in long-term prognosis of patients with uncomplicated MI. The tasks are to determine the levels of GDF-15 in patients

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with uncomplicated MI, to estimate the prognostic value of the GDF-15 levels in patients with uncomplicated MI during long-term outpatient follow-up and the possibility of combined use of GDF-15 and NT-proBNP to determine the risk of recurrent cardiovascular events in patients with uncomplicated MI.

Material and methods

A prospective, non-randomized observational study was conducted, which included 118 patients with ST-elevation MI (STEMI) and non-ST-elevation MI (NSTEMI). MI was diagnosed based on clinical manifestations, elevated cardiac troponin I, and typical changes on the ECG. All patients were treated following the current guidelines. The study design with all inclusion and exclusion criteria is provided in Figure 1.

All patients included in the study signed the voluntary informed consent. The study was approved by the local ethics committee of the facility and conducted following the Good Clinical Practice and the Declaration of Helsinki.

All patients underwent a laboratory examination: complete blood count with white blood cell differential, blood biochemistry test including creatinine, urea, potassium, sodium, alanine aminotransferase and aspartate aminotransferase, total bilirubin, glucose, lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), high-sensitivity cardiac troponin T, NT-proBNP, glomerular filtration rate (MDRD), blood clotting indicators, thyroid-stimulating hormone.

The levels of GDF-15 were estimated by enzyme immunoassay in blood plasma in the first 48 hours from the onset of MI clinical picture. Within 30 minutes after the collection, samples were centrifuged for 15 minutes and frozen at –70°C. The assay was performed using ELISA Kit for Growth Differentiation factor 15 (Cloud-Clone Corp., USA). The GDF-15 detection range was 0.156–10 ng/mL.

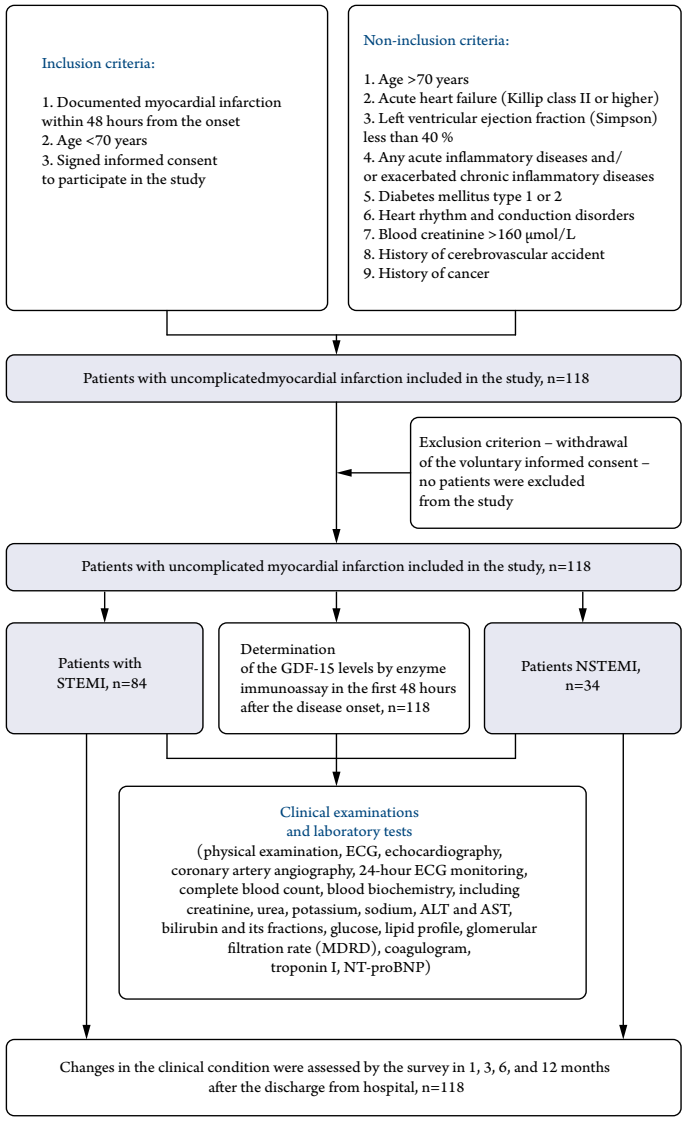
Further, repeated hospitalizations and deaths reported during the follow-up were analyzed. Changes in the patients' condition were assessed by the survey in 1, 3, 6, and 12 months after the discharge from hospital.

The included patients were divided into two subgroups based the ECG data analysis: patients with STEMI (MI with persistent ST-segment elevations in the early stages of the disease in at least two adjacent leads or acute left bundle branch block) and patients with NSTEMI (MI without persistent ST-segment elevation in the early stages in at least two adjacent leads and acute left bundle branch block).

Cardiovascular death, hospitalization for recurrent MI, and/or unstable angina were the endpoints of the study.

Statistical processing of the study results was carried out using parametric and non-parametric analysis in STATISTICA v10.0 and SPSS v23.1.1. The compliance of quantitative indicators with the normal distribution was estimated using the Kolmogorov–Smirnov test. Normally distributed quantitative indicators are presented as the means and standard deviations (M±σ). Non-normally distributed quantitative indicators were described using the medians and the lower and upper quartiles (Me [Q1; Q3]). The statistical significance of the differences between quantitative variables was assessed using the Student's t-test for normal distribution and the non-parametric Mann–Whitney U test, and the Pearson's χ^2 test was used for the qualitative indicators. The independent effects of GDF-15 and other potential risk factors on the likelihood of recurrent cardiovascular events within 12 months of follow-up were evaluated in a regression analysis using a Cox proportional hazards model. Results were statistically significant at $p \leq 0.05$.

Figure 1. Study design



ALT, alanine aminotransferase; AST, aspartate aminotransferase; MI, myocardial infarction; ECG, electrocardiography; GDF-15, growth differentiation factor 15; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 1. Main patient characteristics

Parameter	Patients (n = 118) M ± σ/Me (Q1; Q3)
Age, years	57.3±8.7
Sex: male, n (%) / female, n (%)	97 (82.2)/21 (17.8)
History of essential hypertension, %	65.3
Smoking, %	35.6
History of myocardial infarction, %	12.7
History of coronary artery stenting, %	5.9
History of coronary artery bypass grafting, %	2.5
Systolic BP at admission, mm Hg	129.6±19.2
Diastolic BP at admission, mm Hg	78.2±11.2
Heart rate at admission, bpm	74.9 ±11.2
Body mass index, kg/m^2	28.0±4.6
Myoglobin, ng/mL	116 (49.2; 264.2)
Troponin I, ng/mL	21.1 (5.9; 100.0)
NT-proBNP, pg/mL	294.5 (123.7; 1157)
Total cholesterol, mmol/L	5.0±1.3
Creatinine, μmol/L	93.1±15.6
Sodium, mmol/L	141.3±3.8
Potassium, mmol/L	4.1±0.6
Alanine aminotransferase, U/L	28.2 (20.1; 44.4)
Aspartate aminotransferase, U/L	31.9 (23.0; 50.2)
Total bilirubin, μmol/L	9.7 (7.4; 14.6)
Hemoglobin, g/L	141.8±14.2
Erythrocytes, ×10^{12}/L	4.5±0.5
Leukocytes, ×10^9/L	9.8±3.5
Platelets, ×10^9/L	260.5 (222.8; 296.8)
Prothrombin time, sec	11.8 (10.7; 13.2)
Fibrinogen, g/L	2.7 (2.2; 3.4)
GDF-15, ng/mL	2.07 (1.55; 2.73)
LVEF, %	50.8±7.4
LV mass index, kg/m^2	106.1±28.1

BP, blood pressure; LVEF, left ventricular ejection fraction; GDF-15, growth differentiation factor 15; NT-proBNP, N-terminal pro-brain natriuretic peptide

Table 2. Comparative characteristics of patients with STEMI and NSTEMI

Parameter	STEMI (n = 84) M ± σ/%/Me (Q1; Q3)	NSTEMI (n = 34) M ± σ/%/Me (Q1; Q3)	p
Sex, %	85.7 муж.	73.5 муж.	0.11
Age, years	56.88±9.57	58.38±6.16	0.78
Body mass index, kg/m^2	28.01±4.74	28.06±4.52	0.92
Total cholesterol, mmol/L	5.14±1.41	4.95±1.36	0.51
Low-density lipoprotein cholesterol, mmol/L	3.35±1.21	3.19±1.20	0.51
High-density lipoprotein cholesterol, mmol/L	0.95±0.23	0.94±0.19	0.86
Triglycerides, mmol/L	1.87±1.05	1.81±1.06	0.78
Creatinine, μmol/L	94.7±17.0	89.3±11.3	0.08
Ejection fraction (Simpson), %	49.69±7.23	53.73±7.13	0.007
Smoking, %	36.9	32.4	0.64
History of essential hypertension, %	58.3	82.4	0.01
History of post-infarction cardiosclerosis, %	9.5	20.6	0.10
History of coronary artery stenting, %	4.8	8.8	0.39
History of coronary artery bypass grafting, %	1.2	5.9	0.14
GDF-15, ng/mL	2.2 (1.7; 2.9)	1.9 (1.3; 2.5)	0.04

MI, myocardial infarction; GDF-15, growth differentiation factor 15.

Result

The mean age of patients included in the study was 57.3±8.7 years. Table 1 provides some key characteristics of patients and Table 2 presents a comparative description of patients with STEMI and NSTEMI.

The median GDF-15 value was 2.07 (1.55; 2.73). The analysis showed no dependence of the GDF-15 levels on age and sex of patients. The subgroup analysis of GDF-15 levels did not show a statistically significant dependence on the presence of risk factors such as smoking, high body mass index, and essential hypertension. There was also no association of GDF-15 levels with the concentrations of total cholesterol and low-density lipoprotein cholesterol.

No relation was shown between the elevated levels of GDF-15 and localization of MI. The levels of GDF-15 were higher in the STEMI group than in the NSTEMI group [2.2 (1.7; 2.9) versus 1.9 (1.3; 2.5), p=0.04].

During the 12-month follow-up, the following outcomes were reported in patients with a history of uncomplicated MI: hospitalization for unstable angina pectoris (n=19), hospitalization for recurrent MI (n=8), and death (n=2; due to recurrent transmural MI).

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Table 3. Results of the univariate and multivariate Cox regression analysis to assess risk factors for recurrent cardiovascular events in patients with uncomplicated myocardial infarction

Parameter	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
GDF-15, ng/mL	4.3	2.4–7.9	0.004	1.46	1.13–1.89	0.004
NT-proBNP, pg/mL	3.3	1.87–5.96	0.046	3.9	1.01–12.4	0.004
Age, years	1.17	1.47–5.54	0.014	1.05	0.98–1.12	0.172
LDL cholesterol, mmol/L	3.87	2.22–6.67	0.043	1.19	0.81–1.76	0.381
GFR, mL/min	0.97	0.94–0.99	0.027	0.97	0.88–1.10	0.51

GDF-15, growth differentiation factor 15; NT-proBNP, N-terminal pro-brain natriuretic peptide; LDL, low density lipoprotein; GFR, glomerular filtration rate

To further analyze the results obtained, GDF-15 levels were divided into quartiles: 1st quartile (<1.55 ng/mL); 2nd quartile (1.55–2.07 ng/mL); 3rd quartile (2.07–2.73 ng/mL); 4th quartile (>2.73 ng/mL). Within 12 months of follow-up, 22.8% of patients were hospitalized for unstable angina or recurrent MI. GDF-15 fell in the third and fourth quartiles (≥2.07 ng/mL) in 89.6% of all recurrent events.

The levels of GDF-15 were in the upper quartile, which corresponds to values >2.73 ng/mL, in all patients with recurrent MI and cases of death.

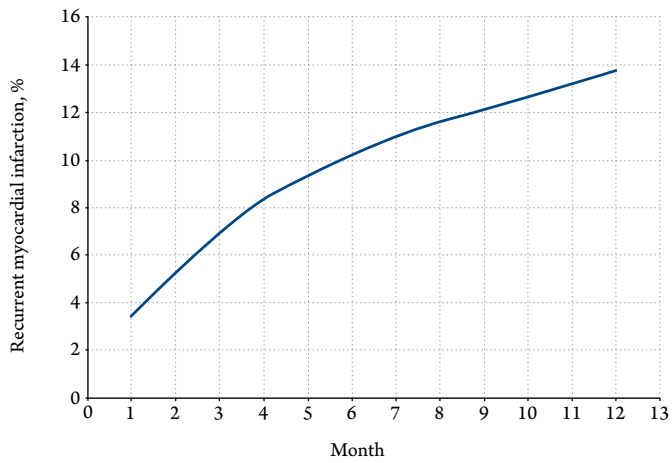
Within 12 months of follow-up, the time dependence of recurrent MI was logarithmic in patients with GDF-15 levels in the upper quartile, which is shown in Figure 2.

A regression analysis was performed to assess the risk factors of recurrent cardiovascular events in patients with uncomplicated MI. The results for the main risk factors are presented in Table 3. Regression analysis included 110 parameters including clinical indicators (such as blood pressure, heart rate, body mass index, medical history (hypertensive heart disease, postinfarction cardiosclerosis, stenting, and/or coronary artery bypass grafting), laboratory indicators (such as complete blood count with white blood cell differential, blood biochemistry test, troponin T, NT-proBNP, GDF-15, indicators of blood clotting, thyroid-stimulating hormone), and examination data (such as echocardiogram, coronary artery angiography, and Holter monitoring). The multivariate analysis included the factors with statistically significant results of the univariate analysis.

Patients with GDF-15 in the upper quartile were at a higher risk of recurrent cardiovascular events, such as cardiovascular death and hospitalizations for unstable angina and recurrent MI (hazard ratio (HR) 4.3 [95% confidence interval (CI) 2.4–7.9], p=0.004).

NT-proBNP was also correlated with recurrent cardiovascular events in our study. For the purpose of the analysis, NT-proBNP levels were divided into quartiles: 1st quartile (< 151,0 pg/mL); 2nd quartile (151.0–424.0 pg/mL); 3rd quartile (424.0–1418.0 pg/mL); 4th quartile (> 1418.0 pg/mL).

Figure 2. Time-dependence curve of recurrent myocardial infarction in patients with GDF-15 in the upper quartile (> 2.73 ng/mL) within 12 months of follow-up



Elevated levels of NT-proBNP (> 1418.0 pg/mL) were associated with an increased risk of cardiovascular death and repeated hospitalizations for unstable angina and recurrent MI [HR 3.3 (95% CI 1.87–5.96), p=0.046] and also showed a separate statistically significant association with the risk of recurrent MI [HR 4.7 (95% CI 1.43–15.29), p=0.004].

The combined use of two biomarkers (GDF-15 and NT-proBNP) was even more significant: patients who had both GDF-15 and NT-proBNP levels in the upper quartiles (GDF-15>2.73 ng/mL, NT-proBNP>1418.0 pg/mL) face a 5.4-fold risk of recurrent cardiovascular events, including cardiovascular death and repeated hospitalizations for unstable angina pectoris and recurrent MI, compared to patients with both biomarkers within the lower quartiles [HR 5.4 (95% CI 3.4–8.5), p=0.004].

Discussion

The GDF-15 levels were estimated in patients with STEMI and NSTEMI. Only a few studies to date have focused on the role of GDF-15 in MI. The results of available prospective studies suggest that GDF-15 is positively correlated with smoking, essential hypertension and diabetes mellitus, a his-

tory of MI, renal dysfunction [12–18]; there is a negative correlation of GDF-15 with the levels of total cholesterol and high-density lipoprotein cholesterol and a positive correlation between GDF-15 and NT-proBNP and CRP [19–21]. GDF-15 was positively correlated with troponin T in most researches [11–22]. We did not identify a statistically significant difference and any significant correlation between GDF-15 and such risk factors as smoking, high body mass index, arterial hypertension, and the levels of total cholesterol and low-density lipoprotein cholesterol. However, a moderate correlation was found between GDF-15 and NT-proBNP (r=0.36, p=0.0001) and between GDF-15 and troponin I (r=0.21, p=0.02) [23].

Our previous 6-month summary [23] showed a close-to-linear «time of recurrent MI onset/GDF-15» dependence curve, but the subsequent 12-month follow-up data were expressed by a logarithmic curve, which can be explained by longer follow-up period and seems more logical from a statistical point of view.

It was suggested that the levels of GDF-15 reflect integral information on cell oxygenation, inflammatory response, and heart dysfunction [24]. Moreover, there is evidence that GDF-15 and NT-proBNP are associated with the levels of soluble angiotensin-converting enzyme 2 and cause higher risk of death [25]. Several studies have concluded that GDF-15 is independently associated with mortality in patients with NSTEMI [9, 10, 26].

Thus, GDF-15 was included in the GRACE score to increase its prognostic value in patients with NSTEMI [3]. Our study showed that the combined use of two biomarkers, GDF-15 and NT-proBNP, is promising for the evaluation of the long-term prognosis in patients with a history uncomplicated MI.

Limitations

The small number of recurrent cardiovascular events in our study, including deaths, within the 12-month follow-up period may restrict the interpretation of the study findings.

Conclusion

Our study confirms the prognostic value of GDF-15 in patients with MI. The combination of two biomarkers, GDF-15>2.73 ng/mL and NT-proBNP>1418 pg/mL, reflects significantly the unfavorable 12-month prognosis of patients with uncomplicated MI, which allows these indicators to be used in evaluating the long-term prognosis.

No conflict of interest is reported.

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