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PROGNOSTIC SIGNIFICANCE OF NON-SPECIFIC SYSTEMIC INFLAMMATION MARKERS IN PATIENTS WITH CORONARY HEART DISEASE

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To evaluate the prognostic significance of markers of nonspecific systemic inflammation as predictors of unfavorable prognosis in patients with coronary heart disease, data from 135 patients with uncomplicated disease and 27 with unfavorable outcomes were analyzed. A 2-year prospective study showed that unfavorable cardiovascular events were significantly more common in patients with coronary heart disease and elevated levels of biomarkers of nonspecific systemic inflammation compared with those with lower values. The presence of myocardial infarction at baseline, a decrease in left ventricular ejection fraction <50 %, and increased levels of markers of nonspecific systemic inflammation such as C-reactive protein, determined by a highly sensitive method, and tumor necrosis factor-α had significant predictive value for the likelihood of unfavorable events.

Key words: coronary heart disease, patient prognosis, nonspecific systemic inflammation, high-sensitivity C-reactive protein, tumor necrosis factor-α, fibrinogen, blood lipids, atherosclerosis.

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ПРОГНОСТИЧНА ЗНАЧИМІСТЬ МАРКЕРІВ НЕСПЕЦИФІЧНОГО СИСТЕМНОГО ЗАПАЛЕННЯ У ХВОРИХ НА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ

З метою оцінки прогностичної значимості маркерів неспецифічного системного запалення в якості предикторів несприятливого прогнозу у хворих на ішемічну хворобу серця були проаналізовані дані 135 пацієнтів з неускладненим перебігом захворювання і 27 – з несприятливим результатом. Проведене 2-річне проспективне дослідження показало, що несприятливі серцево-судинні події достовірно частіше виникали у хворих на ішемічну хворобу серця з вихідним підвищеним рівнем біомаркерів неспецифічного системного запалення у порівнянні з особами з нижчими їх значеннями. Значною передбачуваною цінністю в плані ймовірності настання несприятливих подій володіли наявність інфаркту міокарда на початку дослідження, зниження фракції викиду лівого шлуночка <50 % та підвищення рівнів маркерів неспецифічного системного запалення: С-реактивного протеїну, визначеного високочутливим методом, та фактору некрозу пухлин-α.

Ключові слова: ішемічна хвороба серця, прогноз пацієнтів, неспецифічне системне запалення, високочутливий С-реактивний протеїн, фактор некрозу пухлин-α, фібриноген, ліпіди крові, атеросклероз.

The study is a fragment of the research projects "Metabolic risk factors, cardiovascular remodeling and functional state of kidneys in patients with cardiovascular pathology. Possibilities of pharmacological correction", state registration No. 0119U101849 and "Cardiovascular remodeling, structural and functional state of the liver and kidneys and their relationship with cardiometabolic risk factors in patients with cardiac pathology and comorbidities. Possibilities of treatment optimization", state registration No. 0124U002036.

Despite the significant scientific advances in modern medicine, cardiovascular disease (CVD), and especially coronary heart disease (CHD), has not only remained the leading cause of death worldwide, including in Ukraine, for decades but has been steadily increasing [1, 12]. According to the WHO, in 2021, CVD caused 20.5 million deaths – a third of all deaths in the world, which is almost twice the cardiovascular mortality recorded in 1990 [1, 9, 12].

Mortality from CHD is most often associated with the occurrence of acute atherothrombotic complications caused by the formation of an occlusive or non-occlusive thrombus on the surface of an atherosclerotic plaque due to a violation of the integrity of its cover (erosion, rupture, hemorrhage, etc.). According to current recommendations, methods aimed at detecting foci of necrosis or transient myocardial dysfunction are used to diagnose such complications. However, an important and relevant area is also the search for markers that would allow predicting the development of such complications or diagnosing them before the onset of irreversible changes in the myocardium [4, 5].

The discrepancy between myocardial oxygen demand and oxygen supply is the main pathogenetic mechanism of coronary heart disease. The most common cause of insufficient myocardial blood supply is atherosclerosis of the epicardial coronary vessels, and less commonly, coronary spasm and microvascular dysfunction. Atherosclerosis is considered to be an elastic and muscular artery disease characterized by latent vascular inflammation, endothelial dysfunction, deposition of lipids, calcium, and cellular detritus in

the intima with subsequent plaque formation, vascular remodeling, acute and/or chronic obstruction, impaired laminar blood flow and reduced oxygen supply to the affected organs. Currently, atherosclerosis is viewed not only as a disease caused by disorders of lipid metabolism and transport but also as a long-term, sluggish chronic inflammation of the vascular wall with periods of stable course and exacerbation of the process [10, 14]. It is believed that activation of inflammation can play a significant role in the destabilization of atherosclerotic plaque [11, 14].

The markers of inflammatory response activity recommended by the European Society of Cardiology for cardiovascular risk assessment are fibrinogen and high-sensitivity C-reactive protein (hs-CRP) [2].

The purpose of the study was to evaluate the prognostic significance of the presence and severity of nonspecific systemic inflammation as predictors of unfavorable prognosis in patients with coronary heart disease.

Materials and methods. The study included 173 patients with CHD (mean age 57.24±5.12 years) who were initially treated in the cardiology department of the Vinnytsia Regional Clinical Hospital named after M.I. Pirogov and the myocardial infarction department of the Vinnytsia Regional Clinical Diagnostic and Treatment Center for Cardiovascular Pathology and subsequently followed up on an outpatient basis for 24 months.

Stable CHD was diagnosed in 92 patients (45 II and 47 III functional classes, respectively) and 81 patients were hospitalized with acute coronary syndromes (43 of them were subsequently diagnosed with unstable, namely progressive angina, and 38 with acute myocardial infarction (MI)). The diagnosis of stable CHD and acute coronary syndrome variants was established following the 2012, 2013, and 2015 European Society of Cardiology Guidelines and Orders of the Ministry of Health of Ukraine No. 455 of July 02, 2014, No. 164 of March 03, 2016 and No. 152 of March 02, 2016 (Fig. 1).

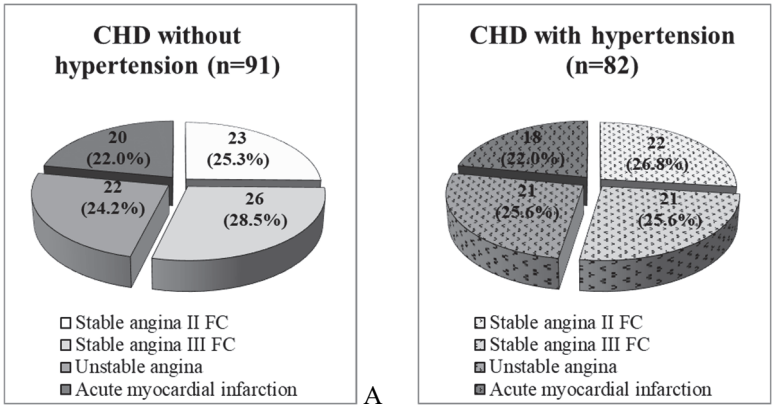

Fig. 1. Distribution of examined patients by diagnosis and presence of concomitant arterial hypertension. A – CHD without hypertension, B – CHD with hypertension.

The study did not include persons over 75 years of age with chronic heart failure of NYHA functional classes III-IV, malignant neoplasms, secondary arterial hypertension, acute inflammatory diseases or exacerbation of chronic diseases at the time of the examination, obesity of II-III degrees, liver and kidney diseases with impaired function, diseases causing secondary dyslipidemia (diabetes mellitus, hypothyroidism, nephrotic syndrome, cholestasis).

Blood sampling from the cubital vein for clinical and biochemical examination was performed on the first day of hospital admission (in ACS – in the first 2 hours). At the beginning of the follow-up, all patients underwent a complete blood count and urinalysis, blood lipid profile, glucose level, blood electrolytes (K+, Na+), urea and creatinine levels, total protein, fibrinogen, prothrombin index or INR, total bilirubin and its fractions, alanine and aspartate aminotransferase activity. Markers of nonspecific systemic inflammation in the blood serum of patients with coronary heart disease were determined by enzyme-linked immunosorbent assay using special reagent kits (ELISA kits "hs-CRP ELISA" manufactured by DRG, USA and "TNF-α ELISA test kit" manufactured by Diaclone, France).

The average duration of follow-up was 23.1±1.2 months. Contact with 5 patients (2.9 %) was lost and their data were excluded from further analysis. During the observation period, 30 unfavorable cardiovascular events were noted in 27 of 168 patients (16.1 %), which determined their unfavorable prognosis.

Since the long-term prognosis of a patient is largely determined by the adequacy of therapy, the data of 6 patients (3.57 %) with low compliance were excluded when analyzing the prognosis criteria. Thus, at the final stage of the study, the data of 135 patients with uncomplicated disease and 27 patients with unfavorable outcomes were analyzed.

Excel-2010 spreadsheets and StatSoft “Statistica” v.6.0 and 10.0 software were used to create the database and analyze the results. The reliability of differences was determined using the Student's and Mann-Whitney's t-test. To determine the independent predictors of the course of atherosclerosis and

coronary heart disease, a multivariate analysis was performed using multiple stepwise regression (Multiple Regression module of StatSoft "Statistica" v. 6.0), and the odds ratio was estimated.

Results of the study and their discussion. A prospective 2-year study analyzing clinical and laboratory parameters in two groups of patients: without and with unfavorable cardiovascular events, showed that such events were significantly more common in the group of patients with coronary heart disease with initially elevated levels of biomarkers of nonspecific systemic inflammation (18.75 %) compared with those with levels of these biomarkers within the reference range (5.0 %). When comparing clinical data in the groups with complicated and uncomplicated CHD, it was found that the prognosis of patients with CHD did not significantly depend on the patient's age, gender, smoking, BMI, and the presence of concomitant hypertension (Table 1, $p>0.05$). At the same time, the prognosis was significantly influenced by a decrease in left ventricular ejection fraction ($p<0.01$) and the course of coronary heart disease at the beginning of the study, with the highest reliability in the group of patients with acute MI ($p<0.05$). When assessing the impact of MI that had occurred long before the start of the study on the two-year prognosis, only a tendency to reliability was found ($0.05<p<0.1$).

Table 1

Clinical and laboratory parameters in patients with complicated and uncomplicated coronary heart disease

Index	Complicated course (n=27)	Uncomplicated course (n=135)	P
Age, years	59.64±2.62	56. 17±3. 18	ns
Male gender, n (%)	20 (74.07 %)	98 (72.59 %)	ns
Frequency of hypertension, n (%)	13 (48.15 %)	68 (50.37 %)	ns
Smoking, n (%)	18 (66.67 %)	70 (51.85 %)	ns
BMI, kg/m^2	29.90±0.76	29.71±0.38	ns
Myocardial infarction before the study, n (%)	17 (62.96 %)	60 (44.44 %)	<0. 1
Revascularization before the study, n (%)	19 (70.37 %)	70 (51.85 %)	ns
Stable course, n (%)	9 (33.33 %)	77 (57.04 %)	<0.05
Unstable course, n (%)	18 (66.67 %)	58 (42.96 %)	<0.05
Acute MI, n (%)	11 (40.74 %)	26 (19.26 %)	<0.05
Unstable angina, n (%)	7 (25.93 %)	32 (23.70 %)	ns
Left ventricular hypertrophy, n (%)	15 (55.56 %)	72 (53.33 %)	ns
Output EF, %	48.67±1.88	55.69±0.97	<0.01
Blood fibrinogen, g/l	3.98±0. 11	3.74±0.05	<0.05
hs-CRP, mg/l	7.65±0.55	4.88±0.21	<0.0001
TNF-α, pg/ml	5.57±0.39	3.59±0.19	<0.0001
Total cholesterol, mmol/l	6.02±0.31	5.96±0.06	ns
LDL cholesterol, mmol/l	4.05±0.19	3.97±0.08	ns
HDL cholesterol, mmol/l	1.11±0.03	1.17±0.02	<0. 1
TG, mmol/l	1.91±0.04	1.83±0.03	ns
Atherogenicity index, units	4.42±0.48	4.09±0.10	ns

Notes: P is the significance of the difference between the groups with complicated and uncomplicated courses; ns – no significant difference ($p>0.05$)

According to Table 1, the baseline levels of hs-CRP and TNF-α were significantly higher in patients with an unfavorable prognosis ($p<0.001$), and the degree of increase in the mean fibrinogen level in the compared groups was less, but also significant ($p<0.05$).

The baseline levels of lipid profile indices did not differ significantly in patients with complicated and uncomplicated disease, only for HDL cholesterol levels there was a tendency to reliability ($0.05<p<0.1$).

Estimation of the odds ratio of clinical and instrumental factors showed that an unstable course of coronary heart disease (OR – 2.655, 95 % CI 1.113-6.556) and, first of all, acute myocardial infarction at the beginning of the study (OR – 2.882, 95 % CI 1.197-6.941) and a decrease in left ventricular EF of less than 50 % (OR – 2.473, 95 % CI 1.052-5.812). Thus, an unfavorable prognosis, characterized by the development of cardiovascular events, was observed almost three times more often in patients who were hospitalized with a diagnosis of acute coronary syndrome and almost 2.5 times in patients with insufficient myocardial contractility, which was probably due to the greater severity of the disease in such patients.

When assessing the significance of previous myocardial infarction and coronary revascularization on the prognosis of the disease, only a tendency to a significant effect was found (OR – 2.12, 95 % CI 0.907-4.980 and OR – 2.205, 95 % CI 0.903-5.382, respectively).

A significantly higher probability of developing unfavorable cardiovascular events was found in patients with high levels of hs-CRP and TNF-α. When evaluating the lipid spectrum parameters, only a tendency to a significant association of HDL-C <1.1 mmol/L with the prognosis of the disease was found (0.05<p<0.1). The effect of other lipid spectrum parameters and blood fibrinogen levels on the two-year prognosis of the disease was not significant (p>0.05) (Table 2).

Table 2

Comparative analysis of the probability of unfavorable prognosis patients with coronary heart disease during 2 years of follow-up depending on the level of markers of nonspecific systemic inflammation and blood lipids

Parameter	Cutoff point	OR	95 % CI	χ2	P
hs-CRP, mg/l	>3.5	10.00	2.27–43.02	13.065	<0.001
TNF-α, pg/ml	>3.0	12.68	2.80–55.69	16.924	<0.001
Fibrinogen, g/l	>3.5	1.45	0.63–3.41	0.635	>0.05
Cholesterol, mmol/l	>5.0	1.22	0.51–3.87	0.005	>0.05
TG, mmol/l	>3.5	1.28	0.51–2.97	0.212	>0.05
LDL cholesterol, mmol/l	>3.8	1.35	0.57–3.22	0.079	>0.05
HDL mmol/l cholesterol,	<1.1	2.66	1.08–6.51	3.117	<0.1
AI, units	>4.0	1.16	0.51–2.66	0.178	>0.05

Our findings on the prognostic significance of markers of nonspecific systemic inflammation in patients with coronary heart disease are in line with the results of studies by other authors. A meta-analysis of 31 studies involving more than 150,000 people conducted by the Fibrinogen Studies Collaboration group of experts demonstrated a 3.1-fold increase in the risk of cardiovascular death, a 1.8-fold increase in the risk of myocardial infarction and unstable angina, and 1.8-fold increase in stroke with a 1.0 g/l increase in plasma fibrinogen [6]. However, an increase in plasma fibrinogen cannot be a specific indicator of vascular inflammation, as it is also a reflection of the activation of the blood coagulation system [8].

According to the summarized data of several clinical trials conducted by *Braunwald E.* [2], the baseline level of C-reactive protein has an independent prognostic value in patients with ACS. An increase in its level above 3 mg/l was accompanied by a more frequent development of unfavorable events, such as progressive angina, myocardial infarction, or death; and a level above 10 mg/l in patients with unstable angina determined an increased risk of complications (death and MI) during 6 months of follow-up, regardless of the baseline troponin level [2].

The JUPITER study (Members of the Justification of the Use of Statins in Preventions: an Intervention Trial Evaluating Rosuvastatin) confirmed the role of hs-CRP as an independent risk factor for CHD and an object for intervention associated with an increased risk of atherosclerotic cardiovascular events in people with low or normal LDL cholesterol levels but elevated hs-CRP (more than 2 mg/L) [7, 10].

Vascular inflammation is accompanied by the expression of genes that induce the synthesis of proinflammatory cytokines, among which TNF-α has the most pronounced proatherogenic effect, the concentration of which in atherosclerotic plaques exceeds that in the unchanged vascular wall, especially in plaques with high inflammatory activity [7, 13].

The data were confirmed by stepwise linear regression analysis. There was an association between the development of unfavorable cardiovascular events and the presence of MI at the beginning of the study (R2=0.49; p<0.0001), baseline left ventricular ejection fraction <50.0 % (R2=0.50; p<0.0001) and inflammatory biomarkers – hs-CRP (R2=0.59, p<0.0001), TNF-α (R2 =0.57; p<0.0001).

In a comprehensive analysis of forecasting, considering the identification of unfavorable prognosis factors using correlation and regression analyses, the sensitivity was 86 %, the specificity was 80 %, the estimated value of a positive outcome was 75 %, and the estimated value of a negative outcome was 96 %.

The study found no significant association between baseline levels of hs-CRP and TNF-α in patients with coronary heart disease and markers of myocardial necrosis – troponin I and T concentrations determined in the first hours of MI, which allows us to consider these indicators as markers of damage and instability of atherosclerotic plaque and predictors of acute coronary syndrome, as noted by other authors [4, 7, 11].

Thus, the levels of hs-CRP and TNF-α can be regarded as independent predictors of unfavorable cardiovascular events in the long-term prognosis in patients with coronary heart disease, which are superior to traditional risk factors for cardiovascular complications in terms of prognostic significance.

Conclusion

The results suggest that biomarkers of nonspecific systemic inflammation can be considered independent risk factors for the development of unfavorable cardiovascular events in patients with different clinical variants of coronary heart disease.

The presence of myocardial infarction at the beginning of the study, reduced myocardial contractility (left ventricular ejection fraction <50 %), and activation of a nonspecific systemic inflammatory response, as evidenced by increased levels of such markers as hs-CRP and TNF-α, have significant predictive value in terms of the likelihood of unfavorable events.

Further research in this area will improve risk stratification and prognosis of the disease course in patients with coronary heart disease depending on the type of initiating event, the presence of comorbidities and complications, and the presence and activity of a nonspecific inflammatory response.

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