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PROGNOSTIC VALUE OF CLINICAL, LABORATORY AND CARDIO IMAGING MARKERS OF PROGRESSION OF CORONARY ARTERY DISEASE

Feruza B. Abdumalikova [1], Nargiza M. Nurillaeva [2]

1 PhD, Doctoral student of the Department of Internal Medicine in Family Medicine No. 1 of the Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: abdumalikova.feruza@gmail.com

2 DSc, Head of the Doctoral student of the Department of Internal Medicine in Family Medicine No. 1 of the Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: nargizanur@yandex.ru

ABSTRACT

The purpose is evaluation of the prognostic value of clinical, laboratory and cardiographic markers of the progression of coronary heart disease.

Material and research methods. The objects of the clinical study were 152 patients with coronary artery disease (CAD), both genders, aged from 48 to 73 years. The main group included 73 patients with unstable angina pectoris (UAP). The comparison group consisted of 79 patients with stable angina pectoris (SAP) III FC. All patients with CAD underwent questionnaires (assessment of socio-anamnestic, behavioral, psychosocial indicators), clinical and functional status studies (ECG, EchoCG), biochemical (lipid spectrum, coagulogram), immunochemical (analysis of biomarkers of inflammatory response) indicators. In order to assess the cardio-visual aspects of the progression of coronary heart disease, an analysis of the value of the calcium index determined using multispiral computed tomography (MSCT) of the coronary arteries was carried out.

Results. Based on the regression analysis, the most significant independent predictors of the destabilization of the CAD course were identified, in descending order by degree of significance, they turned out to be: combination of a high level of the Coronary calcium index according to CCTA and an increased concentration of IL-6/TNF-α in the blood (p=0.003), significantly increased Agatstone index (p=0.001), increased levels of IL-6 and/or TNF-α in the blood (p=0.015), combined anxiety-depressive states (p=0.036), dyslipidemia (p=0.001), Systolic blood pressure per 20 mm Hg (p=0.026), obesity (p=0.05), smoking (p=0.05), male sex (p=0.05) and age>60 (p=0.036).

Conclusion. Thus, The results obtained prove the safety and high efficiency of the use of methods for predicting the risk of adverse cardiovascular events in patients with coronary heart disease, by quantifying a number of clinical and laboratory indicators, as well as cardioimaging markers according to Coronary computed tomography angiography (CCTA).

Key words: Coronary artery disease, unstable angina pectoris, coronary computed tomography angiography, coronary calcium score.

INTRODUCTION

According to the World Health Organization, "cardiovascular diseases (CVD) continue to occupy the first place in the world due to mortality, of which 41% is due to Coronary artery disease (CAD), which is more than 17 million people per year" [1]. To date, one of the most pressing issues in practical cardiology is the problem of early diagnosis and prediction of adverse complications of CVD, which remains a difficult task to identify reliable biomarkers of CVD. One of the promising options for studying and predicting the course of coronary heart disease is the modulation of risk factors.

In world practice, targeted scientific research, laboratory and clinical trials are continuing aimed at studying the multifaceted pathophysiology of coronary heart disease and such risk factors (RF) as obesity, dyslipidemia, hypertension, etc. The specificity and sensitivity of biological markers of damage, endothelial inflammation and myocardial ischemia are being investigated, which can potentially stratify the degree of ischemic damage with a higher expression in patients with multifactorial status [8].

The modern algorithm for the diagnosis of coronary heart disease includes both simple and well-known instrumental research methods and relatively new variants of instrumental [3], biochemical [9] and molecular genetic diagnostic techniques. Currently, various imaging methods of the cardiovascular system, including CT coronary angiography with the study of quantitative indicators of significant clinical and laboratory data that affect not only the severity of the pathological process, but also the degree of transformation of the coronary bed, are the cornerstone in the diagnosis of myocardial ischemia in medium and high risk groups [2,4].

The development of a method for assessing calcium in the coronary arteries (CA), and then the Coronary computed tomography angiography (CCTA), became a potential additional tool for imaging coronary plaques and creating the basis for direct individual treatment [4,5]. Given the low level of radiation when using new scanners (up to 1 mSv when using some scanners and safety protocols), the possibility of performing CCTA instead of CAC has become widespread in patients with coronary heart disease.

In addition to stenosis and clinical variables, recent data show that the total number of coronary plaques according to CCTA is a leading predictor of the occurrence of CHD cases [5,10]. Indeed, the ability to detect calcified and non-

calcified plaques is a unique property of CCTA. The standard assessment of plaque load in CCTA is based on a visual or semi-quantitative assessment of coronary segments using the segment involvement scale (SIS), the segment stenosis scale (SSS) and the CT-adapted Liman scale (CT-Leaman) [7]. SIS provides independent prognostic information in addition to the presence of obstructive coronary artery disease [7,11]. In the MiHeart study conducted in asymptomatic individuals with independent predictors: old age, male gender, tobacco use, diabetes, overweight and obesity, 49% of participants had coronary plaques detected using CCTA [6].

Although the presence of signs of high-risk plaques is widely recognized in predicting clinical events, its positive predictive value for ACC events is still limited. Further randomized CCTA trials are needed to investigate the pathophysiology of the rapid progression of high-risk coronary plaques leading to ACCC events, which will have clinical value in the treatment of asymptomatic patients.

THE AIM OF OUR WORK

Evaluation of the prognostic value of clinical, laboratory and cardiographic markers of the progression of coronary heart disease.

MATERIAL AND RESEARCH METHODS

The objects of the clinical study were 152 patients with coronary heart disease, both genders, aged from 48 to 73 years. The main group included 73 patients with unstable angina pectoris (UAP). The comparison group consisted of 79 patients with stable angina pectoris (SAP) III FC. At the time of inclusion in the study, there were no statistically significant differences in age, gender, duration of coronary heart disease and the frequency of concomitant diseases between the formed groups.

At the initial stage of the study, all patients underwent a questionnaire (assessment of socio-anamnestic, behavioral, psychosocial RF and the degree of adherence to treatment), a comprehensive examination, including studies of clinical and functional status (ECG, EchoCG), biochemical (lipid spectrum, coagulogram), hemobiological (thromboprofile), immunochemical (analysis of biomarkers of inflammatory response) indicators of patients with coronary heart disease.

In order to assess the cardiovisual aspects of the progression of coronary heart disease, the analysis of the value of the calcium index determined using multispiral computed tomography (MSCT) of the coronary arteries, a non-invasive method for diagnosing the degree of damage to the coronary arteries and destabilization of coronary sclerosis, was carried out.

To assess the X-ray morphological type of coronary artery lesion, a classification proposed by the American College of Cardiology/ American Heart Association (ACC/AHA) (stenosis morphology classification) was used, taking into account the degree of narrowing, extent and shape of stenosis, its oral, eccentric or bifurcation location, the presence of calcifications and blood clots, involvement of lateral branches in stenosis and some other signs [12].

The degree of coronary artery stenosis was assessed according to the following gradations:

- absence of stenosis
- stenosis < 50% (hemodynamically insignificant)
- stenosis > 50%, but < 90% (hemodynamically significant)
- stenosis > 90% (critical stenosis)
- occlusion of the coronary artery.

Statistical processing of the obtained results was carried out using Microsoft Excel spreadsheets and a package of statistical programs STATISTICA 6.0, SAS 6.3. An electronic database was created using Excel Microsoft Office 2012. On the basis of logistic regression models, odds ratios (OR) corresponding to 95% confidence interval (CI) and p-value (Wald criterion) were calculated. The level of statistical significance was considered to be $p<0.05$.

RESEARCH RESULTS AND DISCUSSION

During the study, we conducted a comparative assessment of the basic characteristics, the prevalence of risk factors (RF), and the clinical and laboratory parameters of patients with coronary heart disease in both groups. The results of a comparative assessment of the occurrence of cardiovascular risk factors showed that smokers were 2 times more common among Unstable angina pectoris (UAP) patients in 31.5% of cases versus 15.2% in the comparison group ($p<0.01$). Physical activity in patients with stable angina pectoris (SAP) was higher by 10.8%, relative to the main group, but was not statistically different. The average body mass index (BMI) values did not differ in the main and compared groups, which amounted to 32.8±1.14 and 30.1±1.00 kg/m2, respectively, but the degree of obesity in UAP patients tended to increase with a predominance of grade 3 by 2.6 times ($p<0.01$) relative to the comparison group. When using psychometric research methods in patients with coronary heart disease, we revealed a frequent occurrence of psychosocial RF, in particular anxiety-depressive syndrome (ADS) in 41 (56.1%) of UAP patients, compared with 34 (43%) of SAP patients.

Table 1

Comparative analysis of the occurrence of cardiovascular risk factors depending on the progression of coronary artery disease

Main RF	UAP patients, n=73	SAP patients, n=79
Smoking, n (%)	23 (31,5%)**	12 (15,2)%
Physical inactivity, n (%)	43 (58,9%)	38 (48,1)%
BMI, (kg/m^2)	32,8±1,14	30,1±1,00
Obesity, n (%) **Grade 1, n (%)** **Grade 2, n (%)** **Grade 3, n (%)**	43 (58,9%) 23 (31,5%) 9 (12,3%)* 11 (15,1%)**	40 (50,6%) 29 (36,7)% 6 (7,6%) 5 (6,3%
AG (grade) **Grade 1, n (%)** **Grade 2, n (%)** **Grade 3, n (%)**	 17 (23,3%) 21 (28,8%) 35 (47,9%)**	 28 (35,4%)** 30 (38%)* 21 (26,6%)
ADS, n (%)	41 (56.1%)**	34 (43%)

Note: *P<0.05, **P<0.01 - significance of differences between groups of patients with IHD

A comparative analysis of clinical, functional, and biochemical parameters revealed that UAP patients experienced a more severe clinical course. This was characterized by a 20% increase in hypertension ($p<0.01$) primarily due to elevated systolic blood pressure (SAD) by 8% ($p>0.05$), a higher level of pain intensity by 12% ($p<0.05$) according to a Visual analog scale (VAS), a longer duration of anginal pain ($p<0.01$), and a higher frequency of angina attacks ($p<0.05$), and destabilization of blood pressure ($p<0.05$), as well as lower exercise tolerance (ET) ($p<0.05$) and increased sizes of interventricular septal thickness (IST) and left ventricular posterior wall thickness (LVPWT) ($p<0.01$). Also, UAP patients had significantly higher indices of total cholesterol (TC) ($p<0.01$), LDL-C and atherogenic coefficient (AC) ($p<0.001$), elevated values of fibrinogen ($p<0.001$), prothrombin index (PTI) ($p<0.01$) and low indicators of prothrombin time (PT), thrombin time (TT) and activated partial thromboplastin time (APTT) ($p<0.01$), which indicates a more severe clinical course of CAD caused by anxiety-depressive syndrome. According to the hemobiological indicators in UAP patients, the risk of developing shifts in the morphological picture of platelets increased by 2.3 and 2.5 times, which indicates a high thrombogenic risk of blood due to destabilization of coronary sclerosis.

Table 2

Comparative clinical characteristics of patients with coronary artery disease

Clinical and hemodynamic parameters	UAP patients (n=73)	SAP patients (n=79)
The level of pain syndrome, VAS (M±m)	68,6±1,44*	56,6±1,38
Number of anginal attacks per week, (M±m)	3,56±0,72**	1,36±0,58
Frequency of blood pressure destabilization per week, (M±m)	3,82±0,32*	2,16±0,28
Heart beats rate, min (M±m)	78,6±1,68*	74,8±1,74
Blood pressure, mm Hg. **SAD, mmHg (M±m)** **DAD, mmHg (M±m)**	 156,0±3,34* 89,5±1,72	 147,3±2,05 85,5±1,54

Note: *P<0.05, **P<0.01 - significance of differences between groups of patients with IHD.

In patients with UAP, there was a significant predominance of the average values of key cytokines, such as interleukin-6 (IL-6) by 2.1 times and TNF-α by 2.6 times in relation to these indicators of patients in the comparison group, respectively (p<0.05). This fact indicates the predisposition of patients with coronary heart disease to the progression of the disease with increased production of inflammatory markers, through cardiac depression.

Diagnostic data on the condition of the coronary arteries according to CCTA were obtained in 93% of cases – in 141 patients out of 152; in 11 cases, it was impossible to determine the degree of stenosis due to artifacts or high calcium content. According to CCTA data in patients of the main group, with a verified diagnosis of UAP, the absence of stenoses was revealed in 4 patients (5.5% of cases), hemodynamically insignificant stenoses in 12 patients (16.4% of cases), hemodynamically significant stenoses in 52 patients (71.2% of cases) and in 5 (6.9%) – critical stenosis. Whereas, in patients of the SAP comparison group, unchanged CA was detected in 13 patients (16.5% of cases), hemodynamically insignificant stenoses in 17 patients (21.5% of cases), hemodynamically significant stenoses in 46 patients (58.2% of cases) and critical stenosis in 3 (3.8%).

Based on the analysis of CCTA indicators of the studied groups, statistically significant differences between cardiovisualizing criteria for the progression of atherosclerotic process in coronary arteries (CA) were revealed (Table 3). Thus, in the group of patients with UAP, the number of atherosclerotic plaques (AP) significantly prevailed in Left anterior descending artery (LAD) (p<0.05), whereas in Trunk of the Left coronary artery (LCA) (p>0.05), Left circumflex artery (LCx) (p>0.05) and Right coronary artery (RCA) (p>0.05) did not have a statistically

significant predominance over the group with SAP patients. The volume of AP had a significant tendency to increase in patients of the main group compared with the comparison group in Trunk of the LCA ($p<0.05$), LAD ($p<0.01$) and LCx ($p<0.05$), which amounted to 73.8±12.3 mm3, 248.9±16.3 mm3 and 85.2±11.7 mm3, accordingly. The mass of AP (mg), as well as the number of AP, was statistically significantly higher in LAD ($p<0.05$) in patients with coronary heart disease manifestation compared with patients with stable course, however, there were no significant differences in other CA.

A calcium score (sometimes called an Agatston score) is calculated based on the amount of plaque observed in the CCTA. Conceptually, the Agatston score is a summed score of all coronary calcified lesions, accounting for both the total area and the maximal density of coronary calcification [11]. Thus, according to the results of quantitative assessment of the Agaston index index according to CCTA data, the studied groups revealed a statistically significant predominance of the sum of the coronary calcium index in patients of the main group with UAP compared with the comparison group of SAP patients, on average 462.9±98.3 versus 321.9±57.8, respectively.

Table 3

Indicators of Coronary computed tomography angiography in patients with coronary artery disease, depending on the progression of the atherosclerotic process

Artery	The number of AP		The volume of AP (mm^3)		The mass of AP (mg)		CA-score (Agatston)	
	UAP	***SAP***	***UAP***	***SAP***	***UAP***	***SAP***	***UAP***	***SAP***
Trunk of the LCA	1,2 ±0,04	0,9 ±0,04	73,8 ±12,3*	48,8 ±8,25	48,9 ±8,3	31,2 ±6,81	27,6 ±6,24	19.5 ±5,85
LAD	2,8 ±0,05*	1,5 ±0,04	248,9 ±46,3**	133,4 ±14,3	68,81 ±10,2*	43,6 ±8,06	314,7 ±53,25*	212.5 ±38,11
LCx	1,2 ±0,04	0,7 ±0,04	85,2 ±11,7*	35,2 ±7,1	36,7 ±8,0	28,1 ±6,25	72,5 ±10,25	47,5 ±8,73
RCA	0,3 ±0,04	0,2 ±0,03	17,5 ±8,81	15,9 ±7,9	12.9 ±5,25	8.6 ±2,25	48.1 ±8,95	42.4 ±8,27
Total	5,5 ±0,05*	3,3 ±0,04	425,4 ±82,1**	233,3 ±22,3	167,3 ±20,2*	111.5 ±11,7	462.9 ±98,3 *	321,9 ±51,8

Note: *P<0.05, **P<0.01 - significance of differences between groups of patients with IHD

In order to assess the predictor value of the dominant factors having independent pathogenetic significance in the processes of atherogenesis, as well as key indicators of cardiovisualization of CCTA, we carried out research about the

interrelated influence of which leads to the progression of coronary heart disease and, a multifactorial logistic regression analysis.

Based on the regression analysis, the most significant independent predictors of the destabilization of the CAD course were identified, in descending order by degree of significance, they turned out to be: combination of a high level of the Coronary calcium index according to CCTA and an increased concentration of IL-6/TNF-α in the blood - OR 8.72, CI 2.05-37.39 (p=0.003), significantly increased Agatstone index - OR 3.22, CI 1.41-2.80 (p=0.001), increased levels of IL-6 and/or TNF-α in the blood OR 1.75, CI 1.19-2.91 (p=0.015), combined anxiety-depressive states - OR 2.31, CI 1.09-4.87 (p=0.036), dyslipidemia - OR 2.34, CI 1.58-3.51 (p=0.001), Systolic blood pressure per 20 mm Hg - OR 1.78, CI 1.07-2.77 (p=0.026), obesity - OR 1.51, CI 0.92-2.32 (p=0.05), smoking - OR 1.59, CI 0.89-2.67 (p=0.05), male sex - OR 2.08, CI 0.95-4.37 (p=0.05) and age>60 - OR 3.67, CI 1.17-13.29 (p=0.036).

Multivariate regression analysis showed that all significant predictors of the progression of coronary heart disease have almost the same weight in determining the risk of adverse angina. Optimally, the doctor at the reception, when determining the chance of developing unstable angina in a patient with CAD, needs to calculate the contribution of each significant factor, since each factor has its own weight. However, with the tight time frame in which the doctor is assigned on an outpatient appointment, it is quite difficult to calculate the contribution of each factor to identifying the risk of progression of coronary heart disease. During the study, the numbers of predictor factors contributing to the manifestation of the clinical condition of CHD patients were summarized, namely: in the presence of 1 of any factor, the chance of CHD progression increases 2.9 times, in the presence of 2 of any factors, the chance of CHD progression increases 3.2 times, any three factors increase the chance of CHD progression times, 4 factors – they increase the chance of CHD progression by 9 times, the presence of 5 factors increases the chance of CHD progression by 16.5 times (the frequency of UAP development exceeds 80%).

CONCLUSION

The results obtained prove the safety and high efficiency of the use of methods for predicting the risk of adverse cardiovascular events in patients with coronary heart disease, by quantifying a number of clinical and laboratory indicators, as well as cardioimaging markers according to CCTA. The prognostic role of clinical and laboratory markers and cardiovascular risk factors, and also, in particular, the analysis of the calcium component of vulnerable coronary plaques

using CCAT with the obtained evidence of the predictive significance of the state of coronary sclerosis allows not only to improve the stratification of the risk of an unfavorable course of coronary artery disease, but also to identify a high-risk group of UAP for dispensary observation, assessing the personal risk of progression of coronary artery disease at an early stage of the manifestation of the disease, which leads to timely correction of treatment tactics and reduction of the risk of exceptionally high premature mortality in this severe cohort of patients. Ultimately, this makes it possible to reduce the economic costs of prevention and treatment of socially significant cardiovascular pathology.

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