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Features of Chd in Patients With Covid-19 And Metabolic Syndrome Depending On E Nos Gene Polymorphism

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Annotation: This analysis will not only more accurately determine the nature of the development of the metabolic syndrome, the progression of coronary artery disease, but will also help to identify the impact of 2019-nCoV infection on heart damage.

Objective: to study the pathogenetic significance of COVID-19 in the progression of the metabolic syndrome and destabilization of coronary artery disease.

The object of the study was 147 patients with coronary artery disease against the background of metabolic syndrome, who received treatment in a COVID specialized center.

The subject of the study is the blood and blood serum of patients with coronary artery disease for the quantitative determination of the main biochemical parameters (lipid spectrum) and the detection of the studied G/T polymorphism of the eNOS gene.

Conclusions: A feature of the clinical course of IHD with MS in patients with COVID-19 is frequent multiple anginal attacks, cases of tachycardia, impaired rhythm variability in the form of ventricular extrasystoles, complete blockade of the left bundle branch block, ST segment elevation on the ECG, increased T-wave inversion, progression unstable angina pectoris.

In patients with coronary artery disease against the background of MS with COVID-19, an increase in the atherogenic index, mean TG level, and a decrease in mean values of serum HDL concentration were found compared with the optimal parameters and values in the group of patients without MS.

Keywords: COVID-19, metabolic syndrome, coronary artery disease, comorbidity, cardiovascular complications.

Since January 2020, nearly 600 million people worldwide have been infected with the SARS-CoV-2 virus, the vast majority of whom have developed COVID-19 [1, 2, 5]. COVID-19 has also resulted in nearly 6 million deaths, mostly as a result of lung damage and its subsequent comorbidities. Despite the availability of several vaccines and boosters, the pandemic continues and the risks of complications continue to rise [3, 4] . The most recent viral variant in early 2022, omicron, has spread rapidly in virtually every country, with significant morbidity and mortality combined with a greater degree of contagiousness. Although most people infected with SARS-CoV-2 recover, there is a significant subpopulation of patients with persistent symptoms 4 weeks after infection, even among patients with mild to moderate COVID-19.

In addition, scientists are concerned whether patients with cardiovascular disease are at greater risk of 2019-nCoV and whether new coronavirus infections affect the cardiovascular system. Previous studies have shown an association between cardiovascular, metabolic diseases and SARS and MERS [9, 10]. A systematic analysis of 637 cases of MERS-CoV showed that diabetes and hypertension are common

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in about 50% of patients, and heart disease is present in 30% of cases. Diabetes has been considered as an independent predictor of mortality and morbidity in patients with SARS [11].

During acute COVID-19, CVD can occur as a direct consequence of viral infection or as an indirect result of inflammation and respiratory distress. The consequences of COVID-19 may differ in pathogenesis from acute SARS-CoV-2 infection, but it is appropriate to consider the underlying metabolic factors that contribute to the severity of the initial infection, in part if viral persistence and chronic inflammation in fat depots or elsewhere is the main risk for prolonged symptoms. The underlying metabolic dysfunction associated with obesity involves, in almost every case, a decrease in white adipose tissue functionality, characterized by inflammation and decreased neutral lipid accumulation in adipocytes. This, in turn, leads to the deposition of lipids in other tissues and provokes immune and vascular pathology [6-8].

Synthase (NOS) is one of the main candidate genes in the development of CAD. It synthesizes NO in a catabolic reaction in the presence of L-arginine. The gene is located on chromosome 7q36. The three isoforms of NOS are neuronal isoforms (nNOS), inducible isoform (iNOS), and endothelial NOS (eNOS). The ability of a blood vessel to expand largely depends on the activity of eNOS, so our work will focus on this isoform as one of the candidate genes. Endothelial NOS (eNOS), also known as nitric oxide synthase 3 (NOS3) or constitutive NOS (eNOS), is an enzyme in humans carrying the NOS3 gene, located in the 7q35-7q36 region of the chromosome. eNOS also acts as a powerful regulator of blood pressure and blood flow. Elevated iron levels can lead to the synthesis of free hydroxyl radicals, which leads to LDL oxidation, which is considered one of the main factors in the pathogenesis of atherosclerosis and cardiovascular diseases due to the accumulation of lipids in macrophages and foam cells, which gives toxicity to cells.

Materials and research methods. During the study, 147 people over 18 years of age were examined with a virus infection and all patients were distributed as follows: the main group, which included 59 patients with COVID-19 and CAD on the background of metabolic syndrome; the comparison group, which included 58 patients with COVID-19 and CAD without MS, the control group composed of 30 healthy individuals without clinical signs of coronary heart disease and metabolic syndrome.

Coronary artery disease (CAD) was diagnosed at the prehospital stage by collecting an anamnesis of clinical instrumental laboratory data.

The determination of the interdependence of the considered parameters of the samples using the Student's test and the Pearson chi test ($\chi 2$) was carried out using the test of its significance.

Results. We examined 147 patients hospitalized in the COVID Specialized Center and the Samarkand Regional Infectious Diseases Hospital with a verified diagnosis of COVID-19. Of these, patients with CAD and MS were 59 (30 men and 29 women) and 58 patients with CAD without MS (26 men and 32 women). Table 1 presents the complaints of hospitalized patients, anamnesis indicating the presence of bad habits (smoking), physical and ECG data.

The symptoms were analyzed , as well as the data obtained during the study (Table 1).

Table 1 Clinical characteristics patients with coronary artery disease in patients with COVID -19

	Women without MS	Women With MS	Men without MS	Men With MS
Pain in the region of the heart	27 (93.1 %)*	20 (66.67 %)*	25 (89.2 8%)	2 6 (8 6 . 67 %)**
Dyspnea	7 (2 4.1 %)	9 (30%)	7 (25%)	10 (3 3 , 33 %)
Nausea	4 (13 , 79 %)	7 (23.3%)	7 (2 5 %)	5 (17 , 24 %)
Oppression consciousness	2 (6.9 %)	3 (10%)	4 (14 , 28 %)	4 (13 , 79 %)
Weakness	2 5 (8 6 , 2 %)	2 7 (9 0 %)	25 (8 9 , 28 %)	2 8 (93,33%)
Smoking	2 (6.9 %)	2 (6.67%)	15 (53.57 %) _	4 (13 , 79 %)
Wheezing in the lungs	7 (2 4.1 %)	11 (36.67%)	7 (25%)	1 1 (3 9 , 28 %)

arrhythmias on auscultation	6 (20.68 %) _	9 (30%)	6 (2 1 , 4 3%)	8 (28.57 %)
ECG changes:				
ST segment elevation	17 (58 , 62 %)	22 (73.33%)	21 (7 5 %)	2 1 (7 5%)
Depression ST segment	1 2 (4 1 , 38 %)	8 (26.67%)	6 (2 1 , 4 3%)	9 (3 2 , 14 %)

* χ^2= 7.274 , p=0.0034 7 3 **χ^2=3.8, p=0.024 7 6

The results of the study showed that among women With COVID -19 against the background of MS Painless forms of coronary artery disease were more common 26.4% compared to women without coronary artery disease. Among men, more than 50% were smokers and also showed an earlier onset of coronary artery disease.

During hospitalization , in all patients , the pulse rate , oxygen saturation, and blood pressure were determined . blood pressure . _ In women without MS, the mean systolic pressure was 138.3±18.3 mm Hg. Art., diastolic - 81.7 ± 11.2 mm Hg. Art.; in women with MS - 140±40.7 and 83.1±22.4 mm Hg. Art. respectively. In men without MS, systolic pressure was 130.4 ± 21.9 mm Hg. Art., diastolic - 80 ± 12.8 mm Hg. Art.; in men with MS - 132.1±24.7 and 82.3±10.7 mm Hg. Art. respectively.

During hospitalization, the glucose level: in women with coronary artery disease without MS, on average, was 7.7±2.8 mmol/l; in women with MS - 9.8±5 mmol/l; while in men without MS this figure was 7.7±2.4 mmol/l; in men with MS - 12 ± 4.9 mmol/l, which indicates an increased glucose level in men with coronary artery disease and MS on the background of COVID-19. (Table 2) .

Table 2The frequency of newly diagnosed sugar type 2 diabetes among patients with coronary artery disease and COVID -19

	Women with CAD without MS (n = 32)	Women with CAD and MS (n = 29)	Men with CAD without MS (n = 26)	Men with coronary artery disease and MS (n = 30)
Absolute number of patients with DM	3*	18**	1*	eleven**
% ratio of patients	12.5	60	1.7	37.5
Type 2 DM compensation phase :				
Compensated	1 (25%)	4 (22.2%)	0 (0%)	4 (33.3%)
Subcompensated	2 (75%)	12 (66.7%)	1 (100%)	3 (25%)
decompensated	0 (0%)	2 (11.1%) ***	0 (0%)	4 (33.3%) ***

* χ^2= 4.665 p=0.01539

** χ^2=3.139, p=0.03823

*** χ^2=3.577, p=0.02528

Among patients without MS, diabetes mellitus was detected in women in 12.5% of cases, while in women with MS, type 2 diabetes developed as a result of COVID -19 in 60%. Moreover, it should be noted that in patients with decompensated stage of DM among those with severe hyperglycemia, it was observed in patients with coronary artery disease with MS, which, seems to be due to the fact that severe forms of diabetes are combined with other components MS.

Thus, coronavirus infection was a pathogenetic impetus for the progression of MS and destabilization of coronary artery disease, resulting in the manifestation of decompensated type 2 diabetes.

atherogenic index, mean TG, VLDL levels was revealed compared with patients with IHD who do not have metabolic syndrome. The values of serum concentrations of TC and LDL in patients with coronary artery disease exceeded the optimal values, but the intergroup differences were not

significant. The mean HDL level was reduced in persons with metabolic syndrome compared to the optimal parameters and values in the IHD group (Table 3).

A significant increase in the prevalence of hyperlipidemia and dyslipidemia was found in the main study group. The most common variant of lipid metabolism disorders in the metabolic syndrome was a combination of hypertriglycerinemia , low HDL levels and an increase in the LDL fraction. (Table 4).

Table 3 Indicators lipid spectrum bloodat sick ischemic heart disease

Index (*M* ± *m*)	Group research	
	IHD+MS (*n* = 5 9)	ischemic heart disease (*n* = 5 8)
General cholesterol , mmol /l	7 ,4 8 ± 1, 87	6.3 7 ± 2.0 6
triglycerides , mmol /l	3, 92 ± 0.72 * _	1, 48 ± 0.51 _
LDL mmol /l	5, 64 ± 1, 6 2	4.5 2 ± 1.0 7
HDL, mmol /l	0.6 8 ± 0.0 8 •	2.2 4 ± 0.5 3
Index atherogenicity	5.3 3 ± 1, 13 *	2.6 7 ± 0.2 3

Note: * - the reliability of the difference in indicators when comparing with a group coronary artery disease $p < 0.05$, • – at $p < 0.01$

Table 4 Share persons With violation lipid exchange amongpatients having atherosclerotic defeat coronary arteries

Feature (*R* ± *m*)	Group IHD+MS (*n* = 5 9)		Group ischemic heart disease (*n* = 5 8)	
	absolute magnitude	%	absolute magnitude	%
TG > 1.7 mmol /l	38	64 *	25	43
LDL > 2.6 mmol /l	39	66	37	64
OH > 5.0 mmol /l	35	59	42	72
HDL < 1.0 mmol/l (husband.), < 1.3 mmol/l (female)	40	68 •	21	36

Note: * - the reliability of the difference in indicators for comparison With group ischemic heart disease at $R < 0.05$ • - at $R < 0.01$.

Thus, a significant increase in the prevalence of hyperlipidemia and dyslipidemia in patients with coronary artery disease with metabolic syndrome was revealed. In such patients, there was an increase in the atherogenic index, the average level of triglycerides, a decrease in the average values of HDL concentration in the blood serum compared to the optimal parameters and values in the COVID-19 and IHD group.

To assess the type of LV remodeling, echocardiographic parameters were determined in accordance with the ASE/EACVI recommendations, such as the thickness of the interatrial septum, the posterior wall of the left ventricle, the mass of the left ventricular myocardium, end-diastolic size, LV end-systolic size (ESD), relative LV wall thickness, LV myocardial mass index.

The average values of the ejection fraction and stroke volume calculated by the disk method in the main group were 50.93 ± 3.63 and 26.56 ± 2.48 ml/m ^{2,} in the comparison group -56.52 ± 2.29 and 30, 18 ± 1.34 ml / m ^{2} , respectively. The mean LVMI in patients with COVID-19 and coronary artery disease against the background of MS was significantly higher than in the comparison group. The left ventricular SIVR in diastole in both groups corresponded to normal values (<0.45), however, in patients with CAD without MS, it was significantly higher than in the CAD+MS group (tab. 5 and 6).

According to echocardiography in patients with coronary heart disease against the background of MS, dilatation of the pulmonary artery (PA) trunk up to 3.3 cm and its branches up to 2.0 cm was revealed, as well as a decrease in ejection fraction (47.3 -54.56%) and an increase in pressure in the pulmonary artery (SPPA>36 mm Hg).

Table 5 M-modal echocardiographic indicators at sick COVID-19 with ischemic sickness hearts

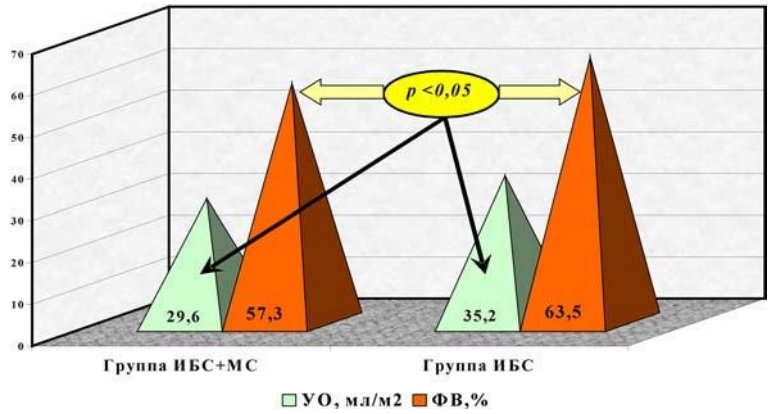
Index (*M* ± *m*)	ischemic heart disease + MS (*n* = 59)	ischemic heart disease (*n* = 58)	control (*n* = thirty)
ao , cm	3.10 ± 0.17	3.05 ± 0.19	3.17 ± 0.23
ak, cm	2.15 ± 0.04	2.18 ± 0.02	2.28 ± 0.06
PSJ, cm	0.57 _ _ ± 0.12	0.5 3 ± 0.04	0.48 ± 0.07
PZRPZH, cm	3.19 ± 0.01	3.16 ± 0.03	3.08 ± 0.12
DLA, cm	3.3 ± 0.0 6	2.7 ± 0.02	2.01 ± 0.15
SDLA mm Hg st	46.42 ± 0.52	39.15 ± 0.05	31.02 ± 0.12
LP, cm	4.07 ± 0.16**●	3.54 ± 0.07	3.49 ± 0.14
MZHP, cm	1.27 ± 0.05*●	1.05 ± 0.09	0.96± 0.04
ZSLZh, cm	1.04 ± 0.02	1.06 ± 0.04	0.98 ± 0.03
KSD, cm	4 , 2 2 ± 0.62	4.01 ± 0.94 _	3.64 ± 0.16
KDD, cm	5.87 ± 0.24***●	5.43 ± 0.18	5.03 ± 0.12
F V, %	50 .93 ± 3.63	56 .52 ± 2.29	64.84 ± 4.23

Note. * - significance of differences in indicators when compared with the CHD group at p < 0.05, ** - at p < 0.01, *** - at p < 0.001, ● - significance of differences in indicators when compared with the control group at p < 0.001 .

Table 6 Indicators geometric models left ventriclein patients I в C

Index (*M* ± *m*)	Group observations	
	IHD+MS (*n* = 59)	ischemic heart disease (*n* = 58)
LVMI, g/m ^{2}	116.23 ± 3.85*	104.63 ± 4.31
IOTS LV	0.39 ± 0.017*	0.43 ± 0.013

Note : LVMI - index masses myocardium left ventricle, IOTS - index relative thickness myocardium V diastole; * *p* < 0.05.



Rice. 1 Indicators of contractility of the myocardium of the left ventricle in the studied groups

When determining the type of geometric model of the left ventricle in the main study group, a significant increase in the number of IHD patients with LVMI ≥ 118 g/m ^{2} and pathological LV remodeling was revealed.

Table 7 Prevalence hypertrophy And pathological deviations geometric models LV V groups research

Feature (*R* ±*m*)	Group research			
	IHD+MS (*n* = 59)		ischemic heart disease (*n* = 58)	
	absolute magnitude	%	absolute magnitude	%
LVMI > 118 g/ ^{m2}	29	49**	10	17

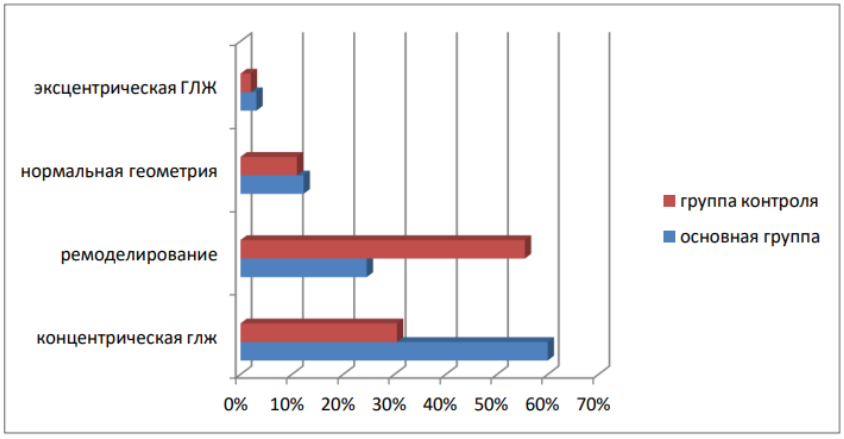
remodeling LV (without accounting type)	37	6 3 *	25	43

Note: * - the reliability of the difference in indicators for comparison with the IHD group at $p < 0.05$, ** - at $p < 0.01$.

In the structure of left ventricular remodeling in patients with coronary artery disease in combination with metabolic syndrome, eccentric LV hypertrophy prevailed ($p < 0.05$), in the comparison group, concentric LV myocardial hypertrophy was more common, but intergroup differences were not significant.

The proportion of persons with mitral insufficiency among patients of the main study group leads to an excess of their number in the comparison and control groups ($\chi 2 = 6.48$, $p < 0.05$). When analyzing Doppler indicators echocardiography revealed an increase in the flow rate of the late left ventricular expansion and a decrease in the average ratio of E/A of the transmitral blood flow in patients with COVID-19 and CAD against the background of MS.

Patients with COVID-19 and coronary artery disease against the background of MS included in the study also showed signs of right ventricular diastolic dysfunction (Fig. 2).



Rice. 2 The presence and severity of cardiac remodeling in groups of patients with coronary artery disease in

According to the criteria of the components, the following variants of MS can be distinguished: complete (combination of hypertension, dyslipidemia, obesity, DM) and incomplete (does not include one of the listed components).

When analyzing the dependence of the type of LV remodeling in patients with COVID-19 and MS variant (complete or incomplete), the following results were obtained (Table 3.14).

As follows from the data presented in Fig. 3 in the group of patients with coronary artery disease and MS were more often diagnosed with unfavorable types of LV remodeling (eccentric and concentric LVH). When assessing the significance of differences according to Pearson's χ^2 criterion, statistically significant results were obtained in the frequency of detection of LV concentric remodeling (less often in the group with CAD and incomplete MS $\chi^2 1 = 10.97$, $p<0.005$), the frequency of concentric LVH (more often in the group with CAD and incomplete MS $\chi^2 2=11.6$, $p<0.005$) and frequency of eccentric LVH (more often in the group with CAD and complete MS $\chi^2 1=34.19$ $p<0.005$).

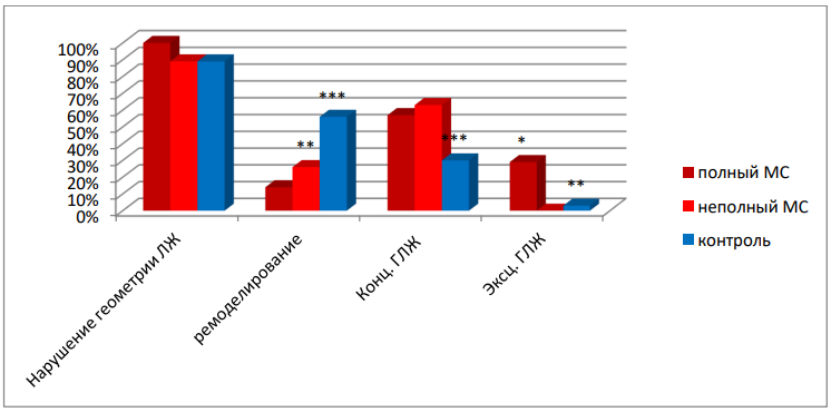


Fig 3. Percentage ratio patients With ischemic heart disease And changegeometry hearts V dependencies from availability and expressiveness MS

Note:

*-comparison patient groups With complete MS With group with incomplete MS

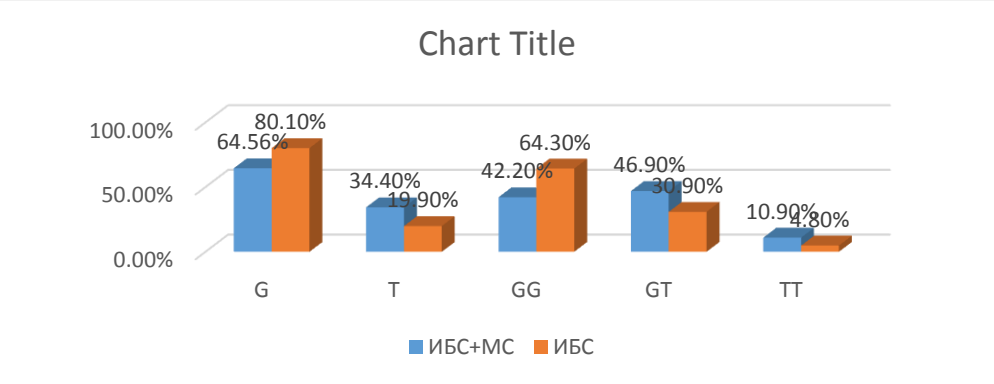
**-comparison groups patients With complete MS With group of patients With ischemic heart disease without MS

***-comparison groups patients With incomplete MS With group patients With ischemic heart disease without MS ,Criterion χ2 pearson, p<0.005

According to the set goal, we studied the distribution of allele and genotype frequencies of the polymorphic variant of the e NOS3 gene in patients with coronary artery disease and healthy individuals of Uzbek nationality.

The table shows the allele and genotype frequencies of NOS3 variants in all cases and controls. In all samples, the genotype frequencies did not differ (all $P > 0.05$). We found that the T allele ($P = 0.009$) and TT genotype ($P = 0.008$) of the T-786C SNP were significantly less prevalent among MS-related CAD patients with COVID -19 than in normal weight CAD subjects. The prevalence of the T allele C774T ($P = 0.003$) was higher in patients with MS compared with healthy controls. The heterozygous C774T genotype ($P = 0.035$) were more common in MS patients compared to healthy controls. In addition, the frequencies of the GG genotype ($P = 0.002$), in turn, were lower in patients with MS compared with healthy controls.

To explore how polymorphisms in the *NOS3 gene* may have pathophysiological implications when considering the risk of MS in COVID -19 and CHD subjects, we assessed NOS3 polymorphisms for associations with biochemical features of MS in these groups. Patients with COVID -19 CAD in MS with the TT T-786C SNP genotype showed lower levels of total cholesterol compared with carriers of the GG genotype ($P = 0.016$). No significant effect of genotype on serum nitrite levels was found in these groups.



Rice. 4 Distribution of frequencies of alleles and genotypes of E *NOS gene polymorphism*

It was found that in the group of patients with MS, the allele frequency *C* was lower than that in the group of healthy donors (p=0.0004), and the allele frequency *T* at the same time turned out to be higher (p=0.0004) (Fig. 4). The frequency distribution of the genotypes of the *C774T polymorphism of the NOS3* gene in the group of patients with MS was as follows: *CC* - 42.2%, *CT* - 46.9%, *TT* - 10.9%, which corresponded to the Hardy- Weinberg equilibrium (c2=0.19, p=0.66). In the control group, the frequency of genotypes for this polymorphic variant was: *CC* - 64.3%, *CT* - 30.9%, *TT* - 4.8%, which is also corresponded to the Hardy- Weinberg equilibrium (c2=0.21, p=0.64). Significant differences were found between the groups of patients with MS and healthy donors in terms of the distribution of genotype frequencies: among patients with MS, homozygotes for the allele were less common *C (* p=0.001), and the frequency of the *CT genotype* in patients with MS was higher than in the group of healthy donors (p=0.014) (Fig. 1). Thus, the *T allele* (OR=2.06; CI: 1.38-3.08) and the *CT genotype* (OR=1.97; CI:1.14-3.40) *C774T polymorphisms of the NOS3* gene are associated with an increased risk of developing MS. At the same time, allele *C* (OR=0.48; CI: 0.32-0.72) and homozygous *CC* genotype (OR=0.41; CI: 0.24-0.69) are associated with a reduced risk of developing MS. .

Table 8 Polymorphism E NOS 3 for associations with biochemical signs of MS

	GG	G T	TT	P
Patients with IHD+MS Glucose _	5.7 ± 0.93	4.95 ± 0.41	5.10 ± 0.57	0.123
OH	5.39 ± 1.23	5.03 ± 1.3	5.09 ± 1.32	0.854
HDL	1 ± 0.41	0.78 ± 0.28	1.17 ± 0.52	0.367
LDL	3.83 ± 0.97	3.12 ± 0.75	3.24 ± 1.1	0.338
TG	1.4 ± 0.57	.37 ± 0.57	1.43 ± 0.43	0.986
Patients with MS Glucose _	6.27 ± 0.99	6.13 ± 0.7	5.96 ± 1.17	0.766
OH	4.71 ± 1.16	4.03 ± 0.82	4.65 ± 1.56	0.12
HDL	1.22 ± 0.27	1.08 ± 0.29	1.15 ± 0.22	0.292
LDL	2.94 ± 1.05	2.37 ± 0.59	2.95 ± 1.1	0.094
TG	1.45 ± 0.59	1.44 ± 0.77	1.38 ± 0.8	0.981

When assessing the eNOS3 polymorphism for associations with the biochemical signs of MS, it was found that patients with CAD and MS with the TT eNOS genotype showed lower levels of total cholesterol compared with carriers of the GG genotype (P = 0.016).

Thus, the clinical course of IHD with MS in patients with COVID-19 is characterized by frequent multiple attacks of angina pectoris, cases of tachycardia, disturbances in rhythm variability in the form of ventricular extrasystoles, complete blockade of the left bundle branch block, ST segment elevation on the ECG, an increase in T wave inversion , progression unstable angina.

Carriers of the T/T genotype of the polymorphic marker of the eNOS3 gene (rs1799983) had a lower BMI, and carriers of the risk alleles of the combination of both genes had a higher level of fasting glycemia. When assessing the eNOS3 polymorphism for associations with the biochemical signs of MS, it was found that patients with CAD and MS with the T/T eNOS3 genotype showed lower levels of total cholesterol compared with carriers of the GG genotype (P = 0.016).

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