

Original article

Reprint

Polymorphisms of hemostasis and folate cycle genes as predictors of COVID-19 severity

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Abstract:

Objective: to identify the frequency of single nucleotide polymorphisms (SNPs) of hemostasis and folate cycle genes in patients with stable coronary artery disease (CAD) depending on the severity of COVID-19 in the acute period.

Materials and methods. Our study included 416 patients with CAD who had COVID-19 more than 12 weeks ago with documented severity course. All patients were distributed among two groups. Group 1 included patients with mild severity (n=203), while Group 2 comprised patients with moderate severity (n=213) of COVID-19. All study subjects were examined for polymorphisms of hemostasis and folate cycle genes. We performed an assessment of the following genetic variants: 20210 G>A of the F2 gene, 1691 G>A of the F5 gene, 807 C>T of the ITGA2 gene, 10976 G>A of the F7 gene, 1298A>C of the MTHFR gene, 66 A>G of the MTRR gene, 2756 A>G of the MTR gene, 677 C>T of the MTHFR gene, 455 G>A of the FGB gene, 103 G>T of the F13A1 gene, 675 5G>4G of the SERPINE1 (PAI-1) gene, and 1565 T>C of the ITGB3 gene. These polymorphisms are likely to contribute to a more severe course of COVID-19 in patients with CAD.

Results. Predisposing factors for the development of a more severe course of COVID-19 among patients with CAD may be the presence of heterozygous polymorphism (455 G>A) of the FGB gene and 1565 T>C polymorphism (CC genotype) of the ITGB3 gene. Contrariwise, the 807 C>T polymorphism (CC genotype) of the ITGA2 gene in the analyzed sample was associated with a mild course of COVID-19.

Conclusion. SNPs 455 G>A of the FGB gene and 1565 T>C (rs5918) of the ITGB3 gene are potential markers for identifying and predicting a more severe course of COVID-19 in patients with CAD.

Keywords: coronary artery disease, post-COVID-19 period, COVID-19, polymorphisms, hemostasis genes, folate cycle genes

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Introduction

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) significantly affected global healthcare [1]. The clinical manifestations of COVID-19 range from asymptomatic infection to severe or extreme conditions. Severe forms of COVID-19 with aggravation of the patient's condition resulting in hospitalization in the intensive care unit during the first wave of the pandemic accounted, on average, for 15% of all cases of the disease, which, in turn, was accompanied by a high risk of death [2].

Despite the favorable prognosis for the disease in most patients, statistics reveals vulnerable demographic groups including the elderly, obese individuals, and patients with comorbid chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular conditions and cardiovascular disorders. All these categories of patients may have less favorable prognoses for the disease course [3].

In Russia, cardiovascular diseases play a key role among top noncommunicable chronic diseases causing the highest mortality [4]. Previous studies demonstrated that patients with coronary artery disease (CAD) are more susceptible to COVID-19, since SARS-CoV-2 infection further increases the likelihood of acute cardiovascular events, thereby contributing to an aggravated severity of the disease. At the same time, patients with CAD experience worse outcomes, including respiratory diseases and an adverse prognosis of vitality [5]. Arrhythmias, heart failure, and cardiomyopathy are determinants of poor prognosis in patients with COVID-19. Preexisting CAD is also associated with adverse outcomes in patients with COVID-19 [6]. However, the prognosis of COVID-19 for patients with stable CAD remain largely uncertain and limited.

Also, CAD is accompanied by clinically important manifestations of chronic pathomorphological process in the intima of coronary arteries as a result of interaction between

genetic and environmental factors. At the cellular level, atherosclerosis involves a complex process that mainly manifests itself via vascular endothelial dysfunction, lipid accumulation, migration and replacement of circulating blood cells, smooth muscle cell proliferation, calcification, inflammation, and ultimately thrombus formation [7]. Prothrombotic and cardiovascular complications are the most common adverse events in patients suffering from COVID-19. These complications are associated with poor prognosis and higher mortality rates [8]. However, adverse outcomes were observed not only in elderly patients with comorbidities but also in younger people. This finding suggests that susceptibility to developing serious complications of the infection varies on a person-to-person basis and is probably the result of a complex interaction between multiple factors, including genetic predisposition [4, 5].

Predicting the COVID-19 severity is complicated and requires integrating risk factors with protective factors, none of which are entirely reliable predictors. In addition, COVID-19 can rapidly worsen, necessitating frequent reassessment and continuous improvement of predictive models in clinical practice. Despite ongoing efforts, predicting severe COVID-19 cases remains challenging due to the multifactorial nature of the disease [9].

It is well known that genetic polymorphism plays a major role in both susceptibility and immunity to various viral infections. By now, many studies have been conducted on the associations between single nucleotide polymorphisms (SNPs) of CAD and COVID-19 [10]. Some studies revealed that the C677T SNP of methylenetetrahydrofolate reductase (MTHFR) is involved in the incidence and severity of COVID-19 [11, 12]. A study by G. Ponti et al. demonstrated that the 5G/5G genotype of the SERPINE1 gene (-675 5G/4G) is a marker of a milder course of COVID-19, while the 4G/4G genotype is a marker of its more severe course [13]. Differences were found between fibrinolytic factors and interleukin-1 β in the 4G/5G (but not 43 G>A) SNP of the PAI-1 gene [14]. Inflammatory-induced endothelial dysfunction in combination with excessive activation of the fibrinolytic system is a risk factor for patients with the 5G5G genotype [15]. Despite the scarce scientific evidence on this issue, some studies established a link between CAD and SARS-CoV-2 infection. Currently, several hypotheses are proposed to elucidate the relationship between this infection and an elevated risk of ischemic events [16]. Exacerbation of inflammation, immobility, hypoxemia and, in some cases, disseminated intravascular coagulation syndrome (especially in combination with each other) can trigger a prothrombotic state, which plays an important role in the occurrence and development of CAD [17, 18]. Determining the genetic risk of thrombotic events is of high scientific and practical value, since immunothrombosis/thromboinflammation syndrome is crucial for the pathogenesis of severe COVID-19. However, the role of prothrombotic polymorphism carriage in COVID-19 remains uncertain.

Identification of gene polymorphisms associated with CAD and the severity of COVID-19 will allow the development of more effective treatment strategies and will help identify subjects at risk, thereby facilitating an introduction of early safeguards. Hence, many studies are

aimed at identifying acquired and inherited risk factors for this complex disease.

Objective: to identify the frequency of single nucleotide polymorphisms (SNPs) of hemostasis and folate cycle genes in patients with stable CAD depending on the severity of COVID-19 in the acute period.

Materials and methods

In order to identify candidate genes of varying COVID-19 severity, the frequency of occurrence of SNPs of the hemostasis and folate cycle genes was measured in 416 patients with CAD who experienced COVID-19 more than 12 weeks ago and received treatment at the Novosibirsk Regional Clinical Cardiology Dispensary from 2020 to 2022. Our study was prospective in its nature; it was approved by the Ethics Committee of the Novosibirsk State Medical University of the Russian Federation Ministry of Healthcare (protocol No. 149 of December 20, 2022). The study was conducted in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki (2024 edition). All patients signed consent to participate in the study.

The severity of COVID-19 in the acute period was measured in accordance with the Temporary Guidelines for the Prevention, Diagnosis and Treatment of a New Coronavirus Infection (version 15 of February 22, 2022). Based on the severity of the infectious disease, all patients were allocated to two groups. Group 1 included patients with mild severity (n=203), while Group 2 comprised patients with moderate severity (n=213) of COVID-19, of which 132 (65.3%) and 132 (62.0%), respectively, were male and 71 (34.7%) and 81 (38.0%), respectively, were female. The median and interquartile age of patients was 61.00 [55.00; 66.00] years and 62.00 [57.00; 66.00] years in Group 1 and Group 2, correspondingly (p=0.54). The values of the main anamnestic and clinical characteristics in groups were similar, which allowed for their further comparisons.

For diagnostic purposes, we used venous blood DNA. Gene SNPs were determined using the real-time polymerase chain reaction method on the Vector-Best equipment (Novosibirsk, Russia).

Statistical analyses. The distribution of genotypes across the studied polymorphic loci was tested for compliance with the Hardy–Weinberg equilibrium (HWE) using the χ^2 criterion. The normality of continuous distributions was tested using the Shapiro–Wilk criterion. The parameters were described by median [first quartile; third quartile] (Me [Q1; Q3]), mean $\pm$ standard deviation (mean $\pm$ SD), maximum and minimum values (min–max). For binary parameters, the number of events and frequency with a 95% confidence interval were calculated using the Wilson formula (n, % [95% CI]). For categorical parameters, the number of patients and frequency in each category were computed.

Due to the lack of normal distribution for the majority (98%) of the studied parameters, the Mann–Whitney U test was employed for statistical testing of hypotheses about the equality of the numerical characteristics of the sample distributions in the compared groups. Binary and categorical parameters were compared using Fisher's exact test. Relationships between the severity of COVID-19 and gene

SNPs were assessed by calculating the biserial correlation coefficient.

All comparison criteria were two-sided. Statistical hypotheses were tested at a critical significance level of $p=0.05$, that is, the difference was considered statistically significant at $p \leq 0.05$. Statistical data processing was performed in the Rstudio IDE (version 2023.09.1 Build 494) in the R language (version 4.1.3, additional packages: dplyr 1.0.8, binom 1.1-1.1, ggplot2 3.3.6).

Results

For a more complete description of the characteristics in the compared patient groups, we analyzed demographic, clinical, and treatment and diagnostic parameters of patients (Table 1).

The groups of patients with mild and moderate severity of the disease statistically significantly differed in body mass index: 29.06 [25.97; 32.08] kg/m² in Group 1 vs. 31.56 [27.36; 35.00] kg/m² in Group 2 ($p=0.01$). These groups also differed in the treatment regimen: in Group 1, a larger proportion (98.5%) of patients received outpatient care, while

in Group 2 patients received mostly inpatient treatment (82.2%) ($p=0.001$). Functional class I angina pectoris was observed significantly more frequently in Group 1, while functional class III was more common in patients with moderate course of COVID-19 ($p=0.006$). The onset of CAD was detected after COVID-19 in 105 (55.3%) patients of Group 1 and in 89 (41.8%) patients of Group 2 ($p=0.007$). Hypertension (HTN) was present in the overwhelming majority of patients of Groups 1 and 2 (97.5 and 98.1%, respectively), but a longer history of HTN was characteristic for patients in Group 2 (8.1 ± 6.9 vs. 13.8 ± 10.8 years; $p=0.024$). Uncontrolled HTN upon admission to hospital was present in 131 (64.5%) patients of Group 1 and in 104 (48.8%) individuals of Group 2. It should be clarified that metabolic disorders such as obesity, diabetes mellitus and dyslipidemia have a negative impact on the course of COVID-19 and the prognosis of patients [19]. In the group of patients with moderate COVID-19, type 2 diabetes mellitus was significantly more often detected (38.9%) than in patients of Group 1 (28.1%; $p=0.031$). As part of this study, we determined polymorphism of hemostasis and folate cycle genes (Table 2).

Table 1. General characteristics of patients in the analyzed groups

Parameter	Group		<i>p</i>
	1 <i>n</i> =203	2 <i>n</i> =213	
Men	132. 65.3% [58.6%; 71.6%]	132. 62.0% [55.3%; 68.2%]	>0.999
Age, years	61.00 [55.00; 66.00]	62.00 [57.00; 66.00]	0.540
Body mass index, kg/m ²	29.06 [25.97; 32.08]	31.56 [27.36; 35.00]	0.010*
Obesity, count (%):			
Class I	62 (30.5)	74 (35.1)	0.347
Class II	26 (12.8)	50 (23.7)	0.005*
Treatment in the acute period of COVID-19, count (%): inpatient	3 (1.5)	175 (82.2)	0.001*
outpatient	200 (98.5)	38 (17.8)	
Functional class of coronary artery disease, count (%): I	54 (26.6)	40 (18.7)	0.044*
II	100 (49.3)	93 (43.7)	0.280
III	48 (23.6)	77 (36.2)	0.006*
Duration of angina pectoris, years	2.00 [1.00; 6.00]	3.00 [1.00; 8.00]	0.133
Newly diagnosed coronary artery disease in the post-COVID-19 period, count (%)	105 (55.3)	89 (41.8)	0.007*
Coronary artery disease progression in the post-COVID-19 period, count (%)	96 (49.7)	125 (58.7)	0.073
Uncontrolled hypertension, count (%)	131 (64.5)	104 (48.8)	0.147

* $p < 0.05$, the difference is statistically significant.

Table 2. Distribution of genotype and alleles of hemostasis and folate cycle genes in patients with coronary artery disease after COVID-19

Group (<i>n</i>)	Genotype, count (%)			Allele, count (%)		HWE $\chi^2_{critical}=3.841$
20210 G>A (rs1799963) of the <i>F2</i> gene						
	GA	GG	–	G	A	
1 (<i>n</i> =112)	1 (0.9)	111 (99.1)	–	223 (99.55)	1 (0.45)	0.0023 <i>p</i> ≥0.05
2 (<i>n</i> =116)	2 (1.7)	114 (98.3)	–	230 (99.14)	2 (0.86)	0.0088 <i>p</i> ≥0.05
1691 G>A (Leiden mutation, rs6025) of the <i>F5</i> gene						
	GA	GG	–	G	A	
1 (<i>n</i> =112)	5 (4.5)	107 (95.5)	–	219 (97.77)	5 (2.23)	0.0584 <i>p</i> ≥0.05
2 (<i>n</i> =116)	3 (2.6)	113 (97.4)	–	229 (98.71)	3 (1.29)	0.0199 <i>p</i> ≥0.05
807 C>T (rs1126643) of the <i>ITGA2</i> gene						
	CC*	CT	TT*	C	T*	
1 (<i>n</i> =136)	71 (52.2)	50 (36.8)	15 (11.0)	192 (70.59)	80 (29.41)	1.899 <i>p</i> ≥0.05
2 (<i>n</i> =138)	39 (28.3)	62 (44.9)	37 (26.8)	140 (50.72)	136 (49.28)	1.415 <i>p</i> ≥0.05
10976 G>A (rs6046) of the <i>F7</i> gene						
	GG	GA	AA	G	A	
1 (<i>n</i> =112)	85 (75.9)	26 (23.2)	1 (0.9)	196 (87.5)	28 (12.5)	0.4198 <i>p</i> ≥0.05
2 (<i>n</i> =116)	86 (74.1)	27 (23.3)	3 (2.6)	199 (85.78)	33 (14.22)	0.247 <i>p</i> ≥0.05
1298A>C (rs1801131) of the <i>MTHFR</i> gene						
	AA	AC	CC	C	A	
1 (<i>n</i> =112)	53 (47.3)	45 (40.2)	14 (12.5)	73 (32.59)	151 (67.41)	0.8197 <i>p</i> ≥0.05
2 (<i>n</i> =116)	58 (50.0)	49 (42.2)	9 (7.8)	67 (28.88)	165 (71.12)	0.093 <i>p</i> ≥0.05
66 A>G (rs1801394) of the <i>MTRR</i> gene						
	AA	AG	GG	G	A	
1 (<i>n</i> =112)	60 (53.6)	34 (30.4)	18 (16.1)	70 (31.25)	154 (68.75)	9.648 <i>p</i><0.05
2 (<i>n</i> =116)	59 (50.9)	33 (28.4)	24 (20.7)	81 (34.91)	151 (65.09)	16.229 <i>p</i><0.05
2756 A>G (rs1805087) of the <i>MTR</i> gene						
	AA	AG	GG	G	A	
1 (<i>n</i> =112)	58 (51.8)	49 (43.8)	5 (4.5)	59 (26.34)	165 (73.66)	1.8201 <i>p</i> ≥0.05
2 (<i>n</i> =116)	74 (63.8)	36 (31.0)	6 (5.2)	46 (20)	184 (80)	0.3426 <i>p</i> ≥0.05
677 C>T (rs1801133) of the <i>MTHFR</i> gene						
	CC	CT	TT	C	T	
1 (<i>n</i> =112)	59 (52.7)	48 (42.9)	5 (4.5)	166 (74.11)	58 (25.89)	1.5264 <i>p</i> ≥0.05
2 (<i>n</i> =116)	57 (49.1)	47 (40.5)	12 (10.3)	161 (69.4)	71 (30.6)	0.2466 <i>p</i> ≥0.05
455 G>A (rs1800790) of the <i>FGB</i> gene						
	AA	GA*	GG*	G	A*	
1 (<i>n</i> =112)	1 (0.9)	34 (30.4)	77 (68.8)	188 (83.93)	36 (16.07)	1.758 <i>p</i> ≥0.05
2 (<i>n</i> =116)	4 (3.4)	52 (44.8)	60 (51.7)	172 (74.14)	60 (25.86)	3.3128 <i>p</i> ≥0.05
103 G>T (rs5985) of the <i>FI3A1</i> gene						
	GG	GT	TT	G	T	
1 (<i>n</i> =112)	59 (52.7)	46 (41.1)	7 (6.2)	164 (73.21)	60 (26.79)	0.249 <i>p</i> ≥0.05
2 (<i>n</i> =116)	59 (50.9)	52 (44.8)	5 (4.3)	170 (73.28)	62 (26.72)	2.425 <i>p</i> ≥0.05
675 5G>4G (rs1799768) of the <i>SERPINE1</i> (<i>PAI-1</i>) gene						
	4G/4G	5G/4G	5G/5G	5G	4G	
1 (<i>n</i> =112)	27 (24.1)	56 (50.0)	29 (25.9)	114 (50.89)	110 (49.11)	0.00 <i>p</i> ≥0.05
2 (<i>n</i> =116)	25 (21.6)	64 (55.2)	27 (23.3)	118 (50.86)	114 (49.14)	1.2493 <i>p</i> ≥0.05
1565 T>C (rs5918) of the <i>ITGB3</i> gene						
	CC*	TC	TT	C	T	
1 (<i>n</i> =112)	1 (0.7)	43 (31.6)	92 (67.6)	45 (16.54)	227 (83.46)	2.8587 <i>p</i> ≥0.05
2 (<i>n</i> =116)	15 (10.9)	37 (26.8)	86 (62.3)	67 (24.28)	209 (75.72)	10.1145 <i>p</i><0.05

HWE, Hardy–Weinberg equilibrium; * $p < 0.05$, the difference is statistically significant

The distribution of polymorphic loci in most of the studied patients' genes corresponded to theoretically expected distribution under Hardy-Weinberg equilibrium.

Patients in the groups had similar frequencies of the 20210 G/A SNP of the F2 gene, 1691 G/A SNP of the F5 gene, 10976 G/A SNP of the F7 gene, 1298 A/C SNP and 677 C/T SNP of the MTHFR gene, 2756 A/G SNP of the MTR gene, c. 103 G/T SNP of the F13A1 gene, and -675 5G/4G polymorphism of the PAI-1 gene.

Genetic risk factors associated with a preexisting prothrombotic state seem to play a major role in determining individual susceptibility to both SARS-CoV-2 infection and the clinical course of the disease. Furthermore, in our case, patients of Group 1 had a higher frequency of carriage of the CC genotypes in the ITGA2 gene encoding the integrin α -2 protein: 807 C/T in 71 (52.2%) patients vs. 39 (28.3%) patients Group 2 ($p < 0.001$). Same was true for the GG polymorphism of fibrinogen FGB: -455 G/A in 77 (68.8%) patients vs. 60 (51.7%) subjects in Group 2 ($p = 0.01$). Moreover, among patients of Group 2, carriage of the TT genotype of the ITGA2 gene was significantly more common: 807 C/T in 37 (26.8%) examined patients vs. 15 (11.0%) patients in the Group 1 ($p = 0.001$). Same was true for the GA genotype of the FGB gene polymorphism: -455 G/A in 52 (44.8%) patients vs. 34 (30.4%) patients in Group 1 ($p = 0.029$); and for the CC genotype of the ITGB3 gene: 1565 T/C in 15 (10.9%) patients vs. 1 (0.7%) patient in Group 1 ($p < 0.001$).

In addition, we established correlations between the severity of COVID-19 and the 807C>T polymorphism of the ITGA2 gene ($r = 0.37$; $p = 0.04$), as well as the 1565 T/C polymorphism of the ITGB3 gene ($r = 0.31$; $p = 0.03$).

Discussion

According to the collected data, gene SNPs of hemostasis and folate cycle (20210 G/A of the F2 gene, 1691 G/A of the F5 gene, 10976 G/A of the F7, 1298 A/C and 677 C/T of the MTHFR gene, 2756 A/G of the MTR gene, c. 103 G/T of the F13A1 gene, and -675 5G/4G of the PAI-1 gene) in patients with stable CAD who experienced mild and moderate COVID-19 did not affect the disease severity in its acute phase.

Genetic analysis allowed identifying patients with genotypes predisposing to a more severe and complicated course of COVID-19. E.g., the ITGB3 (platelet glycoprotein receptor for fibrinogen gene) and ITGA2 (platelet collagen receptor gene) encode subunits of the platelet glycoprotein IIb/IIIa belonging to the integrin complex (GPIIb/IIIa) responsible for platelet adhesion and activation, thereby indicating its involvement in the pathogenesis of prothrombotic complications. The C allele of the ITGB3 gene causes elevated platelet adhesion and increases the risk of developing acute coronary syndrome (ACS). Our data on the higher frequency of the 807 C/T TT genotype of the ITGA2 gene and the 1565 T/C CC genotype of the ITGB3 gene in a cohort of patients with moderate COVID-19 course may imply a connection between SNP in these genes and a higher severity of the disease in the acute phase.

The -455GA polymorphism of the G-455A gene is localized in the promoter region of the β -fibrinogen gene, which is associated with higher plasma fibrinogen levels, and systemic arterial and venous thromboembolism. The frequencies of homo- and heterozygous mutations in the general population in our study are 2.7% and 24.7%, respectively. The -455 G/A SNP of the AA genotype of the

FGB gene acts as an individual risk factor for ACS and peripheral artery disease. The presence of the AA genotype of the FGB gene (rs1800790) in patients with COVID-19 is associated with a more severe course of the disease, while in patients with moderate COVID-19, we revealed a higher frequency of the -455 G/A polymorphism of the GA genotype of the FGB gene. Since this polymorphism is associated with elevated plasma levels of the acute phase fibrinogen protein, it is considered an independent predictor of CAD, playing a role in increasing susceptibility to the development of a hyperinflammatory state, which is one of the hallmarks of a more severe course of COVID-19 [19, 20]. The integrin β -3 (ITGB3) polymorphism of the PIA1/A2 gene and an SNP in the β -fibrinogen gene are important for increasing the risk of severe course in patients after COVID-19. Thus, we have identified specific genetic factors that can serve as biomarkers for assessing the risk of complications in terms of the interaction between CAD and previous COVID-19. These data open new perspectives for the development of individualized therapeutic and prevention strategies.

Conclusion

Among the wide range of examined genetic polymorphisms in patients with stable CAD, we revealed associations of the ITGA2 807 C>T (rs1126643) gene, the FGB 455 G>A (rs1800790) gene, and the ITGB3 1565 T>C (rs5918) gene with COVID-19 suffered more than 12 weeks ago. Contrariwise, other polymorphisms of the hemostasis and folate cycle genes (F2: 20210 G/A; F5: 1691 G/A; F7: 10976 G/A; MTHFR: 1298 A/C; MTHFR: 677 C/T; MTR: 2756 A/G; F13A1: c. 103 G/T; and PAI-1: -675 5G/4G) in patients with stable CAD and COVID-19 in anamnesis did not affect the severity of infection course in the acute period.

Genetic risk factors associated with a preexisting prothrombotic state seem to play a key role in determining individual susceptibility to both SARS-CoV-2 infection and the clinical course of the disease. Genotype and allele analysis revealed that the CC genotype of the ITGA2 gene 807 C>T and the GA genotype of the FGB gene 455 G>A were associated with a higher risk of a more severe COVID-19 course, while the TT genotype of the ITGA2 gene 807 C>T was detected in patients with a milder COVID-19 course.

Since the GG genotype of the ITGB3 gene 1565 T>C was associated with elevated plasma levels of the acute-phase fibrinogen protein, we consider it an independent predictor of CAD, playing a role in increasing susceptibility to the development of a proinflammatory state, which is one of the signs of a more severe COVID-19 course. Our results suggest a higher risk of severe COVID-19 in patients with CAD who are carriers of the CC genotype of the ITGB3 1565 T>C gene.

Study limitations. Among limitations, we should mention the lack of a control group of patients with stable CAD but without COVID-19 in anamnesis. Another limitation is that our sample is limited in terms of geographic location, which may not reflect the full spectrum of genetic diversity in the broader population. Further studies will contribute to the development of targeted therapeutic strategies based on a more comprehensive understanding of the role of genetic factors regulating hemostasis and folate cycle in the development and progression of CAD in patients after COVID-19.

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References

- George PM, Barratt SL, Condliffe R, et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax* 2020; 75(11): 1009-16. <https://www.doi.org/10.1136/thoraxjnl-2020-215314>
- Lippi G, Sanchis-Gomar F, Henry BM. Coronavirus disease 2019 (COVID-19): The portrait of a perfect storm. *Ann Transl Med.* 2020; 8(7): 497. <https://www.doi.org/10.21037/atm.2020.03.157>
- Parasher A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. *Postgrad Med J.* 2021; 97(1147): 312-20. <https://www.doi.org/10.1136/postgradmedj-2020-138577>
- Liu H, Wang Z, Sun H, et al. Thrombosis and coagulopathy in COVID-19: Current understanding and implications for antithrombotic treatment in patients treated with percutaneous coronary intervention. *Front Cardiovasc Med.* 2021; 7: 599334. <https://www.doi.org/10.3389/fcvm.2020.599334>
- Attaway AH, Scheraga RG, Bhimraj A, et al. Severe COVID-19 pneumonia: Pathogenesis and clinical management. *BMJ* 2021; 372: n436. <https://www.doi.org/10.1136/bmj.n436>
- Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med.* 2021; 27: 601-15. <https://www.doi.org/10.1038/s41591-021-01283-z>
- Ilaria BL, Prosperi S, Sara M, et al. Follow-up of hospitalized COVID-19 survivors: Assessment OF short and long-term cardiovascular sequelae after SARS-COV-2 infection. *J Am Coll Cardiol.* 2022; 79(9): 2157. [https://www.doi.org/10.1016/S0735-1097\(22\)03148-5](https://www.doi.org/10.1016/S0735-1097(22)03148-5)
- Farshidfar F, Koleini N, Ardehali H. Cardiovascular complications of COVID-19. *JCI Insight* 2021; 6(13): e148980. <https://www.doi.org/10.1172/jci.insight.148980>
- Delanghe JR, Speeckaert MM, De Buyzere ML. COVID-19 infections are also affected by human ACE1 D/I polymorphism. *Clin Chem Lab Med.* 2020; 58(7): 1125-6. <https://www.doi.org/10.1515/ccbm-2020-0425>
- Gómez J, Albaiceta GM, García-Clemente M, et al. Angiotensin-converting enzymes (ACE, ACE2) gene variants and COVID-19 outcome. *Gene* 2020; 762: 145102. <https://www.doi.org/10.1016/j.gene.2020.145102>
- Deng H, Yan X, Yuan L. Human genetic basis of coronavirus disease 2019. *Signal Transduct Target Ther.* 2021; 6(1): 344. <https://www.doi.org/10.1038/s41392-021-00736-8>
- Wang W, Zhang W, Zhang J, et al. Distribution of HLA allele frequencies in 82 Chinese individuals with coronavirus disease-2019 (COVID-19). *HLA* 2020; 96(2): 194-6. <https://www.doi.org/10.1111/tan.13941>
- Ponti G, Pastorino L, Manfredini M, et al. COVID-19 spreading across world correlates with C677T allele of the methylenetetrahydrofolate reductase (MTHFR) gene prevalence. *J Clin Lab Anal.* 2021; 35(7): e23798. <https://www.doi.org/10.1002/jcla.23798>
- Zhang Q, Jin Y, Li X, et al. Plasminogen activator inhibitor-1 (PAI-1) 4G/5G promoter polymorphisms and risk of venous thromboembolism – A meta-analysis and systematic review. *Vasa* 2020; 49(2): 141-6. <https://www.doi.org/10.1024/0301-1526/a000839>
- Yatsenko T, Rios R, Nogueira T, et al. The influence of 4G/5G polymorphism in the plasminogen-activator-inhibitor-1 promoter on COVID-19 severity and endothelial dysfunction. *Front Immunol.* 2024; 15: 1445294. <https://www.doi.org/10.3389/fimmu.2024.1445294>
- Nikolaeva LI, Stuchinskaya MD, Dedova AV, et al. Association of polymorphic variants of hemostasis system genes with the course of COVID-19. *Issues in Virology* 2023; 68(5): 445-53. (In Russ.) <https://www.doi.org/10.36233/0507-4088-197>
- Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect.* 2020; 80(6): 607-13. <https://www.doi.org/10.1016/j.jinf.2020.03.037>
- Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181(2): 271-80.e8. <https://www.doi.org/10.1016/j.cell.2020.02.052>
- Martiskainen M, Oksala N, Pohjasvaara T, et al. Beta-fibrinogen gene promoter A -455 allele associated with poor longterm survival among 55–71 years old Caucasian women in Finnish stroke cohort. *BMC Neurol.* 2014; 14: 137. <https://www.doi.org/10.1186/1471-2377-14-137>
- Sypniewski M, Król ZJ, Szyda J, et al. Gene variants related to cardiovascular and pulmonary diseases may correlate with severe outcome of COVID-19. *Int J Mol Sci.* 2022; 23(15): 8696. <https://www.doi.org/10.3390/ijms23158696>

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