ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 11| Issue: 9| September 2025|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2025: 8.691 || ISI Value: 1.188

EVALUATION OF THE SIGNIFICANCE OF THE ARG506GLN POLYMORPHISM OF THE F5 GENE IN THE RISK OF MYOCARDIAL INFARCTION

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ABSTRACT

In this study, we evaluated the association of Arg506Gln polymorphism of the F5 gene in the development of myocardial infarction (MI) in patients with COVID-19 coronavirus infection. A comparative analysis of the genotypes of the Arg506Gln polymorphism of the F5 gene in each subgroup of patients with MI yielded the following results. Compared with controls, a subgroup of patients with COVID-19 associated MI showed a significant increase in the content of the unfavorable Arg/Gln genotype (11.3% vs. 1.1% at $\chi 2=7.5$; $p=0.01$; OR=11, 4; 95% CI: 1.99-64.92), which represents a high risk of developing myocardial infarction, by 11.4 times.

KEYWORDS: *Myocardial infarction, COVID-19, Arg506Gln genetic polymorphism in the F5 gene*

INTRODUCTION

Over the past two years, the results of cohort studies, a number of reviews and descriptions of clinical observations on complications caused by the SARS-CoV-2 virus, in particular in the cardiovascular system, have been published. The development of cardiovascular disorders exacerbated the severity of the patients' condition and increased the risk of mortality. For example, doctors in Italy reported a case of a 53-year-old patient whose clinical manifestations of COVID-19 were severe pericarditis with fever rather than pneumonia [6, p. 364-374; 3, p. 268-271]. In patients who died from COVID-19, biomarker levels before death were 12 times higher in the presence of morphological signs of myocardial damage than in their absence [5, p. 1511-1513]. An increase in biomarker values is a sign of an unfavorable outcome of an existing disease. Undoubtedly, further research is needed on the diagnostic and prognostic role of biomarkers of myocardial stress in COVID-19. To this end, we studied the role of the Arg506Gln polymorphism in the F5 gene in the risk of myocardial infarction (MI) in patients with a history of COVID-19 viral infection and in patients who did not have a history of transferred COVID-19. This marker is associated with resistance to the action of activated protein C of the blood coagulation system (Leiden mutation). The F5 gene encodes clotting factor V (factor Leiden), the main plasma protein that regulates blood clotting (coagulation), acting as a cofactor in the conversion of prothrombin to thrombin by factor F10. Arg506Gln is the substitution of the amino acid arginine for glutamine in the amino acid sequence of the F5 protein. Hemostasis disorders in COVID-19 play an important role in the pathogenesis and clinical manifestations of the disease. The ability to identify factors and risk groups for the development of thrombotic complications, interpret peripheral blood parameters and coagulograms in dynamics, knowledge of diagnostic criteria for possible hemostasis disorders (DIC, sepsis-induced coagulopathy, antiphospholipid, hemophagocytic, hypercoagulable syndromes, etc.) are necessary to determine the scope of the examination , differentiated prescription of adequate therapy (including anticoagulants, blood components, plasmapheresis), which determines the greater effectiveness of complex treatment and the prognosis of patients with COVID-19 [1, p. 5-6; 2, p. 645-657]. The introduction of coronavirus into the body and its interaction with toll-like receptors induces an excessive, uncontrolled response of innate immunity with the release of an unbalanced amount of pro-inflammatory cytokines (IL-1β, IL-18, TNF-α, IL-6, IL-8 and IL-10) which is called the cytokine storm. Released cytokines provoke interstitial inflammation, endothelial damage, and activation of coagulation, in the pathogenesis of which the tissue factor plays a key role. It is secreted by monocytes, as well as endothelial cells damaged or activated due to the action of cytokines. As a result, thrombin is formed, which leads to thrombosis of the alveolar capillaries [4, p. 235; 5, p. 1511-1513]. Regardless of the underlying cardiovascular disease, abnormally elevated markers of myocardial injury, and they are closely associated with the progression and prognosis of the disease. Among 41 patients diagnosed with COVID-19, according to Huang et al., 5 (12%) were diagnosed with acute myocardial injury, mainly manifested by an increase in troponin I [7, p. 247-250]. In a retrospective study, 99 patients with the diagnosis of COVID-19 published by Chen et al., most patients had elevated markers of myocardial injury. In another single center retrospective study of 138 patients diagnosed with COVID-19, 10 patients (7.2%) an acute injury was diagnosed myocardium, of which 2 were mild diseases, which accounted for 2% of the total number, 8 patients had a severe course, which was equal to 22% of the total number of patients. Except in addition, the level of creatine kinase isoenzymes (CKMV), LDH and TnI in severe patients admitted in the intensive care unit, was higher than that indicates that myocardial damage in patients with COVID-19 is associated with disease progression. Among the earliest published deaths, one patient was hospitalized with myocarditis associated with COVID-19. The diagnosis was confirmed by an increase biomarkers of myocardial damage and corresponding abnormal electrocardiographic manifestations [8].

PURPOSE OF THE STUDY

To study and evaluate the contribution of the Arg506Gln polymorphism in the F5 gene to the risk of myocardial

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infarction (MI) in patients with a history of COVID-19 viral infection and in patients who did not have a history of COVID-19.

MATERIAL AND METHODS OF RESEARCH

In a specialized center for the treatment of patients infected with COVID-19 in the Andijan branch of the Republican Specialized Scientific and Practical Medical Center for Cardiology, in the cardiology department of the Andijan Regional Multidisciplinary Center and in the Andijan branch of the Republican Scientific Center for Emergency Medical Care, clinical and laboratory materials were collected from patients being treated for cardiovascular disease. In particular, patients with myocardial infarction were involved in the study. These patients were divided into two groups: patients with myocardial infarction with a history of COVID-19 viral infection and patients with myocardial infarction without a history of viral infection with COVID-19. In total, 94 patients with myocardial infarction aged over 18 years were involved in the study. Of them:

- The First Group - 53 patients with myocardial infarction who had a history of viral infection with COVID-19;
- The Second Group - 41 patients with myocardial infarction who did not have a history of viral infection COVID-19
- The Third Group - a control group of 90 conditionally healthy donors.

Statistical processing of the results was performed using the standard software package OpenEpi V.9.2. Analysis of the deviation of empirical genotype frequencies from the theoretically expected Hardy–Weinberg distribution was carried out using the Statistica software package.

THE RESULTS OBTAINED AND THEIR DISCUSSION

In the main group of patients and controls, the proportion of Arg and Gln alleles is estimated at 96.3% and 99.4% versus 3.7% and 0.6%, respectively. Statistical evaluation revealed an increase in the frequency of the wild Arg allele and the Arg/Arg genotype (92.6% vs.) in patients with MI compared with conditionally healthy donors. The risk of developing MI in the presence of a functional unfavorable Gln allele increased significantly - 6.9 times ($\chi2$=4.3; P=0.05; OR=6.9; 95% CI: 1.12-42.75), and when an unfavorable Arg/Gln genotype was detected, 7.2 times ($\chi2$=4.4; p=0.05; OR=7.2; 95% CI: 1.15-44.71) compared with the exclusion of the control group. This OR value is considered as a sign of an increased risk of MI. The presence of the wild Arg allele and the expected Arg/Arg genotype on the presence of a protective effect against the risk of developing MI ($\chi2$=4.3; p=0.05; OR=0.1; 95% CI: 0.02-0.89 and $\chi2$ =4.4; p=0.05; OR=0.1; 95% CI: 0.02-0.87) (Table 1).

Table 1. Carriage of alleles and genotypes of the Arg506Gln polymorphism in the F5 gene in the study and control groups.

Study groups	Alleles and Genotypes	Statistical difference in relation to the control group			
		Odds Ratio		$\chi2$	p-value
		OR	95% CI:		
Main group (n=94)	Arg	0,1	0,02 - 0,89	4,3	p = 0,05
	Gln	6,9	1,12 - 42,75	4,3	p = 0,05
	Arg/Arg	0,1	0,02 - 0,87	4,4	p = 0,05
	Arg/Gln	7,2	1,15 - 44,71	4,4	p = 0,05

In the studied group of patients with MI and in the control group, the non-noble Gln/Gln genotype was not detected. A comparative analysis of the genotypes of the Arg506Gln polymorphism in the F5 gene in each subgroup of patients with MI yielded the following results. The proportion of Arg and Gln alleles in patients with COVID-19 associated MI and controls was 94.3% and 5.7% versus 99.4% and 0.6%, respectively. Statistical processing of the results revealed a significant decrease in the frequency of the favorable Arg allele and a significant increase in the unfavorable Gln allele in patients with COVID-19 associated MI compared with conditionally healthy donors. The calculated odds ratio showed that the chance of detecting a functional unfavorable Gln allele in respondents with COVID-19 associated MI increased 10.7 times compared to the control group ($\chi2$=7.3; p=0.01; OR=10, 7, 95% CI: 1.91-60.24). This value indicates an increased risk factor for the development of myocardial infarction in patients with a history of COVID-19 viral infection (Table 2).

Table 2. Association between the Arg506Gln polymorphism in the F5 gene in patient and control groups.

Study groups	Alleles and Genotypes	Statistical difference in relation to the control group			
		Odds Ratio		$\chi2$	p-value
		OR	95% CI:		
COVID-19 associated MI (n=53)	Arg	0,1	0,02 - 0,52	7,3	p = 0,01
	Gln	10,7	1,91 - 60,24	7,3	p = 0,01
	Arg/Arg	0,1	0,02 - 0,5	7,5	p = 0,01
	Arg/Gln	11,4	1,99 - 64,92	7,5	p = 0,01

The wild homozygous Arg/Arg genotype was detected in 88.7% of patients with COVID-19 associated MI, and in the control group in 98.9% of individuals. As can be seen, the frequency of the ancestral Arg/Arg genotype among patients with COVID-19 associated MI was significantly lower than in the control group ($\chi2$=7.5; p=0.01; OR=0.1; 95% CI: 0, 02-0.5), which indicates a protective effect of this genotype on the development of myocardial infarction in patients with a history

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of COVID-19. Compared with controls, a subgroup of patients with COVID-19 associated MI showed a significant increase in the content of the unfavorable Arg/Gln genotype (11.3% vs. 1.1% at $\chi2$=7.5; p=0.01; OR=11, 4; 95% CI: 1.99-64.92), which represents a high risk of developing myocardial infarction, by 11.4 times.

Table 3. Association between the Arg506Gln polymorphism in the F5 gene in groups of patients with myocardial infarction without a history of COVID-19 and controls.

Study groups	Alleles and genotypes	Statistical difference in relation to the control group			
		Odds Ratio		$\chi2$	p-value
		OR	95% CI:		
MI without COVID-19 (n=41)	Arg	0,5	0,03 - 6,83	0,3	p = 0,6
	Gln	2,2	0,15 – 33,36	0,3	p = 0,6
	Arg/Arg	0,4	0,03 - 6,87	0,3	p = 0,6
	Arg/Gln	2,2	0,15 - 34,02	0,3	p = 0,6

In patients with MI without a history of COVID-19 and controls, the proportion of Arg and Gln alleles was 98.8% and 1.2% versus 99.4% and 0.6%, respectively. The calculated odds ratio showed that the chance of detecting a functional unfavorable Gln allele in respondents with a history of myocardial infarction without COVID-19 significantly increased, while the wild Arg allele was slightly lower compared to the control group ($\chi2$=0.3; p =0.6, OR=2.2, 95%CI: 0.15-33.36 and $\chi2$=0.3, p=0.6, OR=0.5, 95%CI: 0.03-6 .83) (Table 3). The same pattern was observed in the results of studies of the Arg506Gln genotypes in the F5 gene. The wild Arg/Arg genotype in patients with MI without a history of COVID-19 and controls was detected in 97.6% and 98.9% of cases. As can be seen, the frequency of the ancestral Arg/Arg genotype among patients with MI without a history of COVID-19 was slightly lower than in the control group ($\chi2$=0.3; p=0.6; OR=0.4; 95% CI: 0.03-6.87). The heterozygous Arg/Gln genotype was detected in 2.4% of cases ($\chi2$=0.3; p=0.6; OR=2.2; 95% CI: 0.15–34.02).

CONCLUSION

In the group of patients with COVID-19 associated MI, the frequency of occurrence of the favorable Arg allele (94.3% versus 98.8% with $\chi2$=2.5; p=0.2; OR=0.2; 95% CI: 0.03 –1.44) and wild genotype Arg/Arg (88.7% versus 97.6% at $\chi2$=2.6; p=0.2; OR=0.2; 95% CI: 0.03–1, 4) were insignificant in relation to patients with MI without a history of COVID-19. But in the presence of an unfavorable Gln allele (5.7% versus 1.2% at $\chi2$=2.5; p=0.2; OR=4.9; 95% CI: 0.7–33.92) and an unfavorable genotype Arg/Gln (11.3% vs. 2.4% at $\chi2$=2.6; p=0.2; OR=5.1; 95% CI: 0.72–36.42) there is a tendency to the risk of MI in patients with a history of COVID-19 by 4.9 and 5.1 times than in patients with MI without a history of COVID-19. Thus, the obtained results of isolation of the Arg506Gln locus in the F5 gene in the main group of patients indicate a significant contribution of the unfavorable Gln allele and the associated Arg/Gln genotype to the development of MI. The study was conducted on a small number of subjects as a limitation and that further research.

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