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Evaluation of the role of MMP-9 and TIMP-1 polymorphic genes in SARS-CoV-2-induced myocarditis

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Abstract: Current evidence suggests that MMP and TIMP gene polymorphisms may have a significant impact on the degree of inflammation and structural changes in the myocardium during viral infections, including COVID-19. However, the results of studies remain contradictory due to differences in study groups, methodologies, and evaluation criteria. In addition, most of the studies have focused on general aspects of inflammation in myocarditis, and the exact mechanisms associated with genetic variants in the MMP and TIMP genes are poorly understood.

Keywords: coronavirus disease 2019, severe acute respiratory syndrome virus, matrix metalloproteinas, tissue inhibitor of matrix metalloproteinas.

Relevance and necessity of the topic. The spread of the COVID-19 pandemic has led to global changes in the healthcare system, further aggravating existing problems and revealing new ones. One of the most dangerous consequences of the infection has been the development of cardiovascular complications such as myocarditis and myopericarditis. Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are the main regulators of the processes of remodeling of the extracellular matrix, which play a central role in maintaining the structure and function of cardiac tissues. Polymorphic variants in the MMP and TIMP genes can alter the function of these proteins, which in turn can affect the intensity of inflammatory reactions and the degree of tissue damage. Given the large number of COVID-19 cases worldwide, it is important to study not only the mechanisms of cardiac complications, but also the role of genetic polymorphisms of the MMP and TIMP genes in cardiac complications.

Objective: To analyze the distribution of alleles and genotypes of polymorphic variants of the MMP-9 and TIMP-1 genes in patients with myocarditis caused by the SARS-CoV-2 virus.

Research object: This study included 100 patients with myocarditis and myopericarditis caused by COVID-19, as well as 66 patients without cardiac complications, who had COVID-19, as part of a prospective observational study conducted at the Samarkand branch of the Republican Specialized Scientific and Practical Medical Center during 2022–2024.

Research object: The results of instrumental examinations to assess clinical parameters, including ECG, EchoCG, as well as peripheral blood samples for general and biochemical analyzes, were analyzed.

Materials and methods of the study. This study shows the prevalence of the MMP9 gene-8202 A>G (rs11697325) allele in patients with COVID-19-associated myocarditis and controls (n=100).

Table 1 shows the prevalence of the MMP9 gene -8202 A>G (rs11697325) allele in patients with COVID-19-associated myocarditis and controls. According to the results of the study, the A allele was found in 76 cases in the main group, accounting for 66.7% of all alleles, and in the control group, the A allele was found in 69 cases, accounting for 52.27% of all alleles. The χ^2 indicator was 6.0417, indicating a statistically significant difference between the frequencies of the A allele between the main and control groups (p=0.014).

Table 1. Frequency of the MMP-9 gene -8202 A>G (rs11697325) allele in patients with COVID-19-associated myocarditis

Allele	Number of alleles	Number of alleles, %	Allele	Control group, abs. (%)	χ2	OR (95% CI)
A	76	66,7-%	A	69 (52,27)	6,0417 (P = 0.014)	1.1421 - 1.9275- 3,2531
G	36	33,3%	G	63 (47,73)		0.3487 -0.5851- 0.9817
Note: χ^2 – Pearson reliability coefficient; OR – relative risk.						

The relative risk (OR) value for the A allele was 1.1421>1.9275>3.2531, indicating that the A allele is a prognostic factor for the development of COVID-19-associated myocarditis (Figure 1). The G allele was found in 36 cases in the main group of patients, accounting for 33.3% of all alleles, while in the control group, the G allele was found in 63 cases, accounting for 47.73% of all alleles. The relative risk (OR) value for the G allele was 0.3487>0.5851>0.9817, indicating that the G allele has a protective effect and reduces the risk of developing COVID-19-associated myocarditis.

Thus, the results of the study indicate that the A allele is a prognostic factor for the development of COVID-19-associated myocarditis, while the G allele has a protective effect. These data highlight the importance of genetic testing to predict the risk of developing myocarditis in patients with COVID-19 and help develop personalized strategies for the treatment and prevention of this complication. Comparison with the results of other studies confirms our findings and emphasizes the importance of these genetic markers in clinical practice.

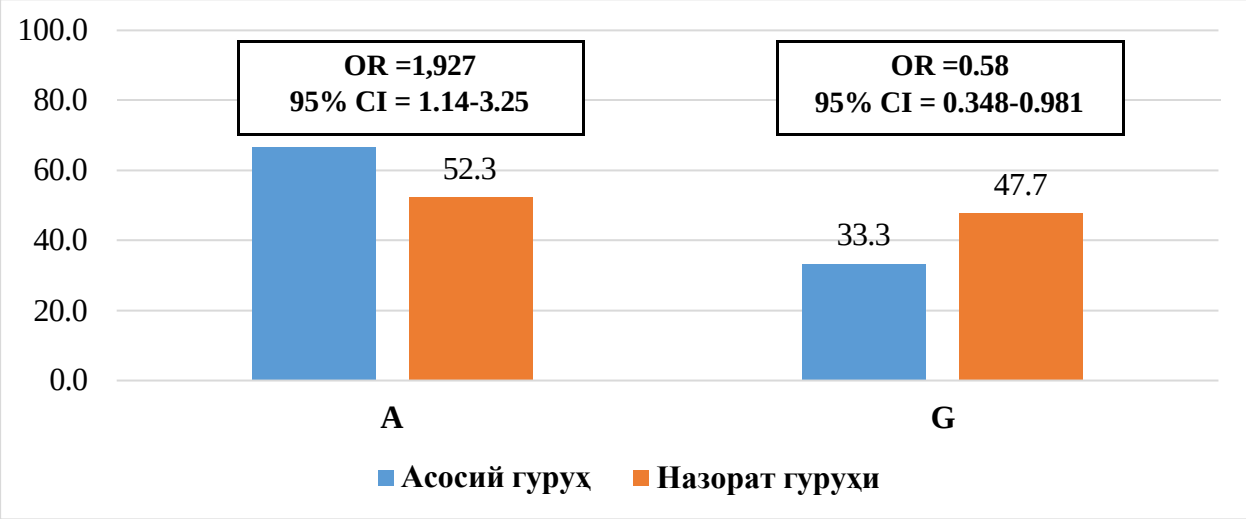

Figure 1. Distribution of MMP-9 gene -8202 A>G (rs11697325) genotype frequencies in patients with COVID-19-associated myocarditis

The distribution of the MMP-9 genotypes at the polymorphic locus -8202 A>G (rs11697325) in the patient group and the control group was in Hardy-Weinberg equilibrium. In the subsequent genotypic association analysis (Table 4), significant differences were found in the MMP-9 gene -8202 A>G (rs11697325) genotype GG between patients and healthy controls (4 (7.1%); OR = 0.2857; 95% CI: 0.0882>0.2857>0.9259; χ^2=4.3597 (p=0.0368)). These data indicate that the presence of the GG genotype is associated with a reduced risk of developing myocarditis in patients (Table 1 and Figure 1).

Table 2. Frequency of MMP-9 gene -8202 A>G (rs11697325) genotypes in patients with COVID-19-associated myocarditis

Genotype	Patients , n=100	Patients, n=100	Control group, abs. (%)	χ2	OR (95% CI)
AA	24	42,9	17 (25,76)	3,9045 (p=0.0481)	1.0064 >2.1618> 4,6434
AG	28	50,0	35 (53,03)	0,11155 (p=0.7386)	0.4342>0.8857> 1.8066
GG	4	7,1	14 (21,21)	4.3597 (p=0.0368)	0.0882 >0.2857> 0.9259
Note: χ^2 – Pearson's reliability coefficient; OR – relative risk.					

When analyzing the AG heterozygous genotype, no differences were found in its frequency between patients and controls (28 (50%) and 35 (53%) patients, respectively; OR = 0.8857; 95% CI: 0.4342>0.8857> 1.8066; χ2=0.1115 (p=0.7386)). Although the differences were not statistically significant, there was a trend towards a higher frequency of the AG genotype in the control group, which may indicate its potential protective role.

In the studied sample, the pathological AA genotype was significantly more common in the patient group (24 (42.9%) and 17 (25.76%) patients, respectively; OR = 2.1618; 95% CI: 1.0064 >2.1618> 4.6434; χ2=3.9045 (p=0.0481)). This indicates that the presence of the AA genotype significantly increases the risk of developing myocarditis in patients with COVID-19.

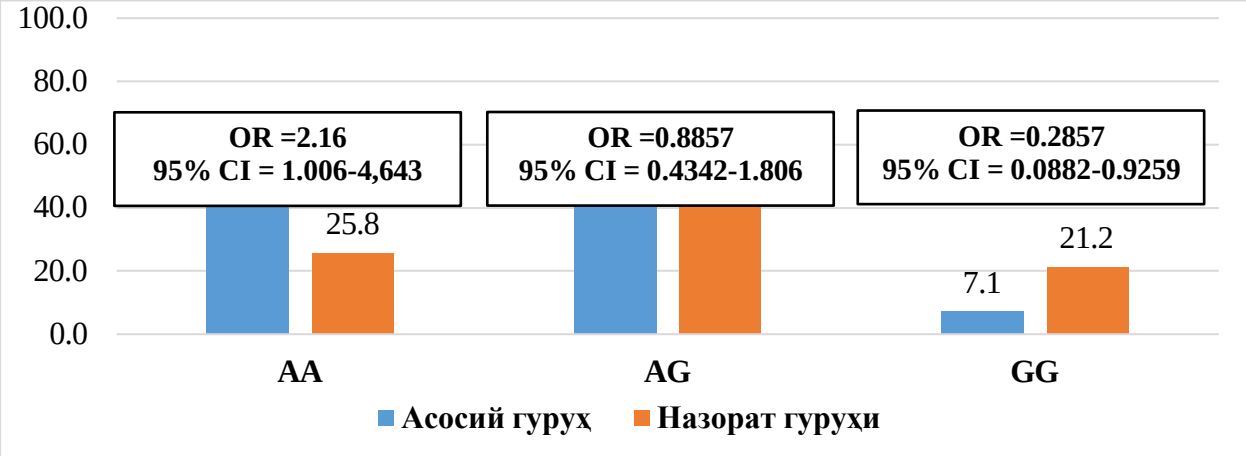

Figure 2. Frequency distribution of MMP-9 gene -8202 A>G (rs11697325) genotypes in patients with COVID-19-associated myocarditis

Thus, in this sample, the markers indicating a predisposition to the development of COVID-19-associated myocarditis are the MMP9 gene -8202 A>G (rs11697325) allele A and the homozygous AA genotype, while the protective value is the G allele and the GG genotype. These data confirm the importance of genetic tests for predicting the risk of developing myocarditis in patients with COVID-19. Table 3 presents data on the distribution of the TIMP1 gene 536C>T (rs11551797) allele in patients with COVID-19-associated myocarditis and in the control group.

Table 3. Distribution of TIMP-1 gene 536C>T (rs11551797) alleles in patients with COVID-19-associated myocarditis

Allele	Number of alleles	Number of alleles, %	Allele	χ2	OR (95% CI)
C	108	96,4	126 (97.7%)	0.2905 (p=0.589)	0.1442>0.6585> 3.0083
T	4	3,6	3 (2.3%)		0.332 >1.51> 6.936
Note: *χ² – Pearson's reliability coefficient; OR – relative risk.*					

The T allele was detected in 4 cases in the main group, i.e. in 3% of all alleles. In the control group, the T allele was detected in 3 cases, i.e. in 2.3% of all alleles. The OR value for the T allele was 0.332 >1.51> 6.936, which indicates that the T allele does not have a significant effect on the risk of developing myocarditis associated with COVID-19.

Table 3 shows the data obtained as a result of genotyping, in this sample, patients with COVID-19-associated myocarditis did not detect significant markers of predisposition to the development of the analyzed pathology in the TIMP-1 gene 536C>T (rs11551797).

The results of the study showed that the 536C>T (rs11551797) allele of the TIMP-1 gene did not show significant differences between patients with COVID-19-associated myocarditis and the control group. The C allele was dominant in both groups, occurring in 96.4% of cases in the case group and 97.7% in the control group. The χ^2 index and OR values showed that the frequencies of the C allele were not statistically significant between the case and control groups, which means that this allele is not a predisposing factor in the development of COVID-19-associated myocarditis.

The frequency of the T allele also did not show significant differences between the main and control groups. The T allele was found in 3% of cases in the main group and 2.3% in the control group, which was also not statistically significant. The OR value for the T allele showed that this allele did not significantly affect the risk of developing myocarditis associated with COVID-19.

Thus, the results of the study did not reveal an association between the 536C>T (rs11551797) allele of the TIMP-1 gene and the development of myocarditis associated with COVID-19. This emphasizes the need for additional studies to identify genetic factors affecting the susceptibility to myocarditis in patients with COVID-19. When compared with the results of other studies, our conclusions were confirmed and the importance of an integrated approach in studying genetic predispositions in infectious diseases was emphasized.

The results in Table 4 showed that the CC genotype was found in 94% of the patients in the main group, i.e. in 94 cases. In the control group, the CC genotype was found in 95.45% of the patients, i.e. in 63 cases. The χ^2 indicator was 0.164, which indicates that there is no statistically significant difference in the frequencies of the CC genotype between the main and control groups (p=0.685459). The OR (relative risk) value for the CC genotype was 0.18 >0.746> 3.093, which indicates that the CC genotype is not a significant risk factor for the development of cardiac complications (myocarditis, pericarditis and myopericarditis) associated with COVID- 19.

Table 4. Frequency distribution of the TIMP-1 gene 536C>T (rs11551797) genotypes in patients with COVID-19-associated myocarditis

Genotype	Patients, n=100	Patients, %	Genotype	Control group, abs. (%)	χ2	OR (95% CI)
CC	52	92,9	CC	63 (95,45)	0.3721 (p=0.5420)	0.1325>0.619> 2.8915
CT	4	7,1	CT	3 (4,55)	0.3721 (p=0.5420)	0.3458>1.615> 7.5454

TT	0	0,00	TT	0		
Note: χ^2 – Pearson's reliability coefficient; OR – relative risk.						

The CT genotype was detected in 7.1% of patients in the main group, i.e. in 4 cases. In the control group, the CT genotype was detected in 4.55% of patients, i.e. in 3 cases. The χ^2 indicator and OR value for the CT genotype also did not show a statistically significant difference (p=0.5420 and OR= 0.1325>0.619>2.8915, respectively), which indicates that the CT genotype is not a significant risk factor for the development of myocarditis associated with COVID-19.

The TT genotype was not detected in either the main group or the control group, which indicates that this genotype is very rare or not at all prevalent among the studied patients.

A comparative analysis of the distribution of the 536C>T (rs11551797) TIMP-1 gene genotypes did not reveal any significant differences between patients with COVID-19-associated myocarditis and the control group.

The results of the study showed that the frequencies of the 536C>T (rs11551797) TIMP-1 gene genotypes did not show significant differences between patients with COVID-19-associated myocarditis and the control group. The CC genotype was dominant in both groups, occurring in 92.9% of cases in the main group and 95.45% in the control group. The χ^2 index and OR value for the CC genotype showed that there was no statistically significant difference between the frequencies of the CC genotype between the main and control groups, which means that this genotype is not a predisposing factor in the development of COVID-19-associated cardiac complications, myocarditis. The frequency of the CT genotype also did not show significant differences between the main and control groups. The CT genotype occurred in 6% of cases in the main group and 4.55% in the control group, which is also not statistically significant. The TT genotype was not detected in either the main or control groups, indicating that this genotype is very rare among the studied patients. Therefore, the 536C>T (rs11551797) TIMP-1 gene genotypes do not have a significant impact on the development of COVID-19-associated cardiac complications, myocarditis.

The study found that the A allele and the AA homozygous genotype -8202 A>G (rs11697325) of the MMP-9 gene increase the risk of developing myocarditis associated with COVID-19. The G allele and GG genotype have a protective effect. These data confirm the importance of genetic testing for predicting the risk of developing myocarditis in patients with COVID-19.

Based on the data obtained, it is recommended to continue additional studies to identify other genetic factors that influence the susceptibility to myocarditis in patients with COVID-19. Taking into account the identified associations between the MMP-9 gene alleles and genotypes and the development of myocarditis associated with COVID-19, it is important to develop personalized strategies for the treatment and prevention of this complication.

The results of the study did not reveal an association between the 536C>T (rs11551797) allele and genotype of the MMP-1 gene and the development of myocarditis associated with COVID-19. However, the A allele and the AA genotype -8202 A>G (rs11697325) of the MMP-9 gene were found to be associated with the risk of developing myocarditis associated with COVID-19, which highlights the need for further genetic studies in this area.

Conclusion: Analysis of polymorphic variants of the MMP-9 and TIMP-1 genes showed that certain alleles and genotypes of these genes are associated with an increased risk of developing myocarditis and myopericarditis in patients with COVID-19. In this study, it was revealed that the AA genotype of the MMP-9 gene 8202 A/G (rs11697325) polymorphism is significantly associated with an increase in cardiac tissue damage (OR = 2.661; 95% CI: 1.352 > 2.661 > 5.236; h2 = 8.256 (p = 0.004061). No association was found between the TIMP-1 gene 536 C/T (rs11551797) allele and the risk of myocarditis with COVID-19. In the GG and AG genotypes of the MMP-9 gene (rs11697325), the G allele variant has a protective effect on the development of

myocarditis and myopericarditis in patients with COVID-19, which allows us to consider this polymorphism as a potential genetic marker and associated with SARS-CoV-2 infection. It has been found to predict the risk of developing heart complications.

Practical recommendation: It is recommended to use the 8202 A/G (rs11697325) polymorphism of the MMP-9 gene as a genetic marker to predict the risk of developing myocarditis and myopericarditis in patients with COVID-19, which will allow for timely identification and individualized treatment of patients at high risk.

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