# BRITISH VIEW

MULTIDISCIPLINARY JOURNAL

www.britishview.co.uk

Anthropologie, Applied Linguistics, Applied Physics, Architecture, Artificial Intelligence, Astronomy, Biological Sciences, Botany, Chemistry, Communication studies, Computer Sciences, Computing technology, Cultural studies, Design, Earth Sciences, Ecology, Education, Electronics, Energy, Engineering Sciences, Environmental Sciences, Ethics, Ethnicity and Racism Studies, Fisheries, Forestry, Gender Studies, Geography, Health Sciences, History, Interdisciplinary Social Sciences, Labour studies, Languages and Linguistics, Law, Library Studies, Life sciences, Literature, Logic, Marine Sciences, Materials Engineering, Mathematics, Media Studies, Medical Sciences, Museum Studies, Music, Nanotechnology, Nuclear Physics, Optics, Philosophy, Physics, Political Science, Psychology, Publishing and editing, Religious Studies, Social Work, Sociology, Space Sciences, Statistics, Transportation, Visual and Performing Arts, Zoology and all other subject areas.



Manuscripts typed on our article template can be submitted through our website here. Alternatively, authors can send papers as an email attachment to editor@britishview.co.uk
Editor Multidisciplinary Journals

British View ISSN 2041-3963 Volume 8 Issue 7 2023
Universal impact factor 8.528
SJIF 2022: 4.629
SJIF 2022: 4.629

# SIGNIFICANCE OF VDR GENE POLYMORPHISM AND THROMBIBILIA IN THE DEVELOPMENT OF ASESPTIC NECROSIS OF THE FEMORAL HEAD ASSOCIATED WITH COVID-19

**Mahmudov A.A**
**Doctor Traumatologist of the Scientific Research Institute of Traumatology and Orthopedics**

**Irismetov M.E**
**Doctor of Medical Sciences, Professor**

**Boboev K.T**
**Doctor of Medical Sciences, Professor**

**Abstract.** It is known that the incidence of aseptic necrosis of the femoral head increased significantly during the COVID-19 pandemic. In the development of the disease, the use of corticosteroid drugs in the acute phase of COVID-19, chronic hypercoagulopathy caused by COVID-19, lifestyle (negative habits) of patients, and genetic predisposition are of great importance. It is known that impaired blood microcirculation is an important pathogenetic factor in the development of aseptic necrosis. Therefore, in patients with Thrombophilic genes were calculated by aseptic necrosis, polymorphisms of the MTHFR A1298C gene (rs 1801131), C677T (rs 1801133) and the MTR A2756G gene (rs1805087), the MTRR A66G gene (rs1801394) in the Uzbek population and these genes, respectively, C (by determining the importance of minor alleles rs 1801131), T (rs 1801133), G (rs1805087) and G (rs1801394) in the development of SSBON associated with COVID-19, selecting those with a predisposition to developing the disease and studying the syntropic effects of additional exogenous factors (in particular, negative habits), through special preventive and therapeutic measures, it is possible to reduce the incidence of COVID-19-related SSBON disease and alleviate the severity of the disease.

**Key words:** *Aseptic necrosis of the femoral head, rs1544410, rs1799963, rs6025 polymorphism, hypercoagulopathy.*

**Introduction. Osteonecrosis of the femoral head (** also called avascular necrosis) is a pathological condition that causes the death of osteocytes, increased demineralization and a decrease in resorption of spongy bone tissue, a change in trabecular architecture over time as a result of a decrease in vascularization of the subchondral bone. femoral head (FGB) [1, 2]. Although understanding the pathophysiology and risk factors for SSBON is limited by the lack of long-term human studies and the lack of a model bipedal mammal [3], strong evidence points to impaired subchondral microcirculation as an important factor in the development of the disease. The study of the microcirculation of the SSS showed that the innervating vessels of the subchondral bone are sensitive to rupture, intravascular obstruction and external vascular compression [3]. Impaired perfusion in the reticular vessels leads to a decrease in the blood supply to the subchondral bone of the femoral head [4]. Other studies have shown that large areas of MN are accompanied by lesions of the superficial and inferior metaphyseal arteries [5].

The occurrence of necrosis of the femoral head (ANGBC) is mainly due to the development of bone cell death due to impaired blood microcirculation. Disorders of the microvasculature can occur by the following mechanisms:

1. Mechanical damage to blood vessels;

2. Obstruction of normal blood flow in the veins as a result of the action of intravascular factors;

3. Obstruction of normal blood flow in blood vessels as a result of extravascular factors [6,7].

*Decrease/stop blood flow due to extravascular factors.* Trauma is the most common cause of ANGBC [3], leading to disruption of normal blood flow and death of osteocytes as a result of mechanical trauma. Assessments of the occurrence and development of traumatic osteonecrosis of GBC may vary depending on the type of injury [8].

*Obstruction of blood flow due to intravascular factors.* This obstruction can be caused by various etiological factors, thrombosis or lipid thrombi as a result of hypercoagulability, the development of intravascular obstruction as a result of increased erythrocyte aggregation in diseases associated with hemoglobinopathies [9].

Genetic defects leading to hypofibrinolysis or thrombophilia can lead to increased thrombosis and impaired blood flow in the bone circulation [10, 11, 12]. A high level of plasminogen activator inhibitor (PAI) in addition to hypofibrinolysis was found in 31% of patients with OH of the femoral head [10]. Another study showed that the factor V mutation was statistically significantly higher in patients with OH than in the control [13]. Jones et al. found that 82.2% of patients with OH had at least one abnormal clotting factor (genetic defect) compared to 30% in the control group without OH. It was reported that 50% of the patients of interest had genetic defects in two or more clotting factors [14]. Similarly, high levels of lipoprotein A, von Willebrand factor, and low levels of proteins C and S have been reported to be statistically higher in patients with idiopathic ON and secondary ON compared to healthy controls [16]. A decrease in the level of protein C and S and resistance to activated protein C due to mutations cause hypercoagulation as a result of a decrease in the physiological regulation of prothrombotic factors, such as V and VIII, which contributes to the development of intravascular ischemia and necrosis in the femoral head [15].

*Slowing/stopping blood flow due to intraosseous extravascular compression. The concept of the Starling resistor can* be used to conceptualize this subset of etiologies that lead to ANGBC. This resistor consists of a solid-walled chamber through which compressed tubes pass. The flow of fluid through these pipes is due to the action of pressure caused by external factors of the chamber. Increased pressure within the intraosseous extravascular space, even if it is not recorded continuously, can reduce blood flow, adversely affecting the blood flow in the small vessels passing through it [2]

Lipid accumulation (fat deposition) and adipocyte hypertrophy in the chest cavity are the two main clinical conditions that can reduce blood circulation, causing an increase in intraosseous extravascular pressure [15]. Often, these conditions are associated with the abuse of corticosteroids or alcohol, and an increase in extravascular pressure leads to ischemia of bone marrow elements and GBA osteocytes, causing hypoperfusion by reducing arterial blood flow or damping by reducing venous outflow [17]. Alcohol and corticosteroid consumption have been shown to increase the size of adipocytes, cause obesity by causing lipid metabolism disorders, and change cell type from osteocytes to adipocytes [17, 18].

The development of aseptic necrosis of the femoral head in patients infected with COVID-19 is associated with the interaction of several factors and is of great theoretical and practical importance in their understanding, primarily in understanding the mechanism of ischemia in the pathogenesis of COVID-19 and the development of SSBON disease, as well as in understanding the origin of avascular osteonecrosis.

The type of coronaviruses (Coronaviruses - CoVs) belongs to the "Coronaviridae" family, and the capsid of these viruses is held outside by crown-like appendages (Latin Corona = means corona), hence the name coronaviruses. As a result of the research, scientists came to the conclusion that SARS-CoV-2 belongs to the family Coronaviridae, the subfamily Coronavirinae and the genus Betacoronavirus [21, 22]. The SARS-CoV-2 virus contains one RNA (+) strand (a genome 30 kb long) enclosed in a nucleocapsid and expresses 16 non-structural, 4 structural, and 9 auxiliary proteins [23, 24].

The SARS-CoV-2 virus differs from other coronaviruses in its very rapid spread and wide adaptability, high rate of formation of new strains, exhibits tropism to many organs using several receptors (in particular, type II alveolar cells, enterocytes, neurons, damages cardiomyocytes, liver cholangiocytes, proximal tubules of the kidneys, cells of the genitourinary system through the ACE2 receptor, macrophages, monocytes and T-lymphocytes through CD147 and the S-type lectin receptor), In severe cases, SARS, acute respiratory distress syndrome, pulmonary fibrosis, "cytokine storm", it has been established that it causes vasculitic autoimmune diseases, thrombosis and thromboembolism, cardiovascular diseases, mental and neurological disorders [19, 20].

Due to its cytopathic effect on the host cell, SARS-CoV-2 causes its lysis (especially in the acute period of the disease), massive apoptosis and necrosis of epithelial and endothelial cells, thereby causing their overexpression and hypersecretion of many cytokines. studies, the SARS-CoV-2 virus itself increases the secretion of pro-inflammatory cytokines and inhibits the secretion of anti-inflammatory cytokines [21, 22].

**Material and methods.** For clinical trials, conducted during 2021-2023, 98 patients with aseptic necrosis of the femoral head after the acute period of COVID-19 disease, who were treated in the Department of Adult Orthopedics "Republican Specialized Traumatology and Orthopedic Scientific and Practical Medical Center", were taken.

In patients with ANGBC, ANGBC was determined by radiography, MRI, densitometry and ultrasound. According to him, 5.1% (n=5) of the total number of patients (n=98) had bilateral ANGBC stages 1-2, 14.3% (n=14) had bilateral ANGBC stages 2-3, 7, 14% (n= 7) had unilateral ANGBC stage 3-4, 69.4% (n=68) had bilateral ANGBC stage 3-4 and 4.1% (n=4) bilateral ANGBC stage 4-5. Taking into account that negative habits, in particular alcohol abuse and smoking, are recognized as risk factors for the development of aseptic bone necrosis, the main group of patients (98 people) was regrouped, of which 48 chronic smokers, alcohol and tobacco products - the first group and 50 patients who do not drink alcohol and do not smoke - in the second group. As a control group, 96 conditionally healthy patients who had a history of COVID-19, but who did not develop ANGBC, were selected. Polymorphisms F2 genes G20210A (rs1799963), F5 genes G1691A (rs6025) va VDR genes BSML (rs1544410) identified single nucleotide polymorphism by polymerase chain reaction in the DT-Lite 48 amplifier using reagents. DNA technology (Russia). In addition, taking into account that the abuse of corticosteroid drugs is an important risk factor for the development of ANGBC associated with COVID-19, the total number of dexamethasone taken in the acute period of COVID-19 disease in general patients.

**Statistical processing of research results. The χ2 test was used to assess genotypes and compare the distribution of genotypes and alleles,** taking into account the Hardy-Weinberg equilibrium. If the χ2 criterion was used to confirm the presence of a predisposition to the studied pathology through the association of alleles and genotypes, then the pathogenetic significance of alleles and genotypes in the studied disease was confirmed by a relative risk ratio (RR) and a odds ratio (O R) with a 95% confidence interval (95% CI:). A p level < 0.05 was considered statistically significant. Statistical data processing was carried out using Statistica 6.1 (StatSoft, USA).

**Results and discussion.** In the study, there were 98 COVID-19-related ANGBC core group and 96 healthy individuals who had COVID-19 but did not have an A-control group with rs1799963, rs6025 and rs1544410 single-point polymorphisms (SNPs), such as molecular genetic testing, showed the distribution of alleles and genotypes, as shown in Table 1.

**Table 1.**

**Distribution of different gene polymorphisms (SNPs) by alleles and genotypes in the main and control groups.**

| Polymor-Physes | Main group | | | | | Control group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Alleles | | Genotypes | | | Alleles | | Genotypes | | |
| | Wild allele (%) | Minor allele (%) | Homozy-goth wild type (%) | Hetero-zygote (%) | Homozygotic non-wild type (%) | Wild allele (%) | Minor allele (%) | Homozy-goth wild type (%) | Hetero-zygote (%) | Homozygotic non-wild type (%) |
| F2 rs1799963 | 99,0 | 1,0 | 97,9 | 2.0 | 0,0 | 99,5 | 0,5 | 99,0 | 1,0 | 0,0 |
| F5 6025 | 96,4 | 3,6 | 92,8 | 7.1 | 0,0 | 99,0 | 1,0 | 97,9 | 2.1 | 0,0 |
| VDR rs1544410 | 79,0 | 21,0 | 62,2 | 33,6 | 4.0 | 76,6 | 23,4 | 59,4 | 34,4 | 6.2 |

When analyzing the data presented in Table. 1, the results of polymorphisms identified in the main and control groups were checked according to the Hardy-Weinberg law in order to verify the correspondence of the distribution of alleles at the population level. And according to the results obtained in the main and control groups, there was no significant deviation from the expected or observed empirical or theoretical results for all identified polymorphisms ($\chi2<3.85$, $p>0.05$) (see Tables 2 and 3). This shows that the results obtained in the course of the study violate the Hardy-Weinberg law.

**Table 2.**

**Results of testing of various gene polymorphisms in the main group according to the Hardy-Weinberg law.**

| Type of polymorphism | Main group | | | | | | ч2 | p-value |
|---|---|---|---|---|---|---|---|---|
| | Observed | | | Expected | | | | |
| | Homozy-goth wild type | Hetero-zygote | Homozygotic non-wild type | Homozy-goth wild type | Hetero-zygote | Homozygotic non-wild type | | |

| | (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| F2 rs1799963 | 0,98 | 0,02 | 0,0 | 0,98 | 0,019 | 0,01 | 0,01 | 0,99 |
| F5 6025 | 0,93 | 0,07 | 0,0 | 0,93 | 0,07 | 0,0 | 0,13 | 0,681 |
| VDR rs1544410 | 0,62 | 0,34 | 0,04 | 0,63 | 0,33 | 0,04 | 0,03 | 0,825 |

*Hint: df=1*

**Table 3.**

**Results of testing of various gene polymorphisms in the control group according to the Hardy-Weinberg law.**

| Type of polymorphism | Контрольная группа | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Observed | | | Expected | | | ч2 | p-value |
| | Homozy-goth wild type | Hetero-zygote | Homozygotic non-wild type | Homozy-goth wild type | Hetero - zygote | Homozygotic non-wild type | | |
| F2 rs1799963 | 0,99 | 0,01 | 0,0 | 0,99 | 0,01 | 0,0 | 0,00 | 0,99 |
| F5 6025 | 0,98 | 0,02 | 0,0 | 0,98 | 0,02 | 0,0 | 0,01 | 0,876 |
| VDR rs1544410 | 0,59 | 0,34 | 0,06 | 0,59 | 0,36 | 0,05 | 0,17 | 0,648 |

*Hint: df=1*

*Pathogenetic significance of genetic markers.* In addition, when studying the results of the G1691A polymorphism of the F5 gene, the frequency of the wild allele and minor allele did not differ statistically significantly in the main and control groups (respectively, G - allele 96.4% and 9.9%; A - allele 3.6% and 1.0%, $\chi 2 = 2.7$, $p = 0.1$). Similar to the results of genotype distribution, the homozygous homozygous genotype of the wild type reduced the risk of developing the disease by 70% in terms of the odds ratio (O R = 0.3; 95% CI: 0.06 - 1.24), and the heterozygous genotype reduced the risk of developing the disease by 70% (OR = 0.3; 95% CI: 0.06–1.24). do not show a significant relationship between the non-wild genotype and the disease ($\chi 2>3.85$, $p<0.05$) (Table 4).

| Alleles and genotypes | Number of alleles and genotypes | | χ2 | p | RR | | 95% CI | OR |
|---|---|---|---|---|---|---|---|---|
| | Main group | Control group | | | | | | |

| | n | % | n | % | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| G | 189 | 96,4 | 190 | 99,0 | 2,7 | p = 0,10 | 1,0 | 0,48 - 1,99 | | 0,3 | |
| A | 7 | 3,6 | 2 | 1,0 | 2,7 | p = 0,10 | 1,0 | 0,09 - 11,35 | | 3,5 | 0 |
| G/G | 91 | 92,9 | 94 | 97,9 | 2,8 | p = 0,10 | 0,9 | 0,45 - 1,99 | | 0,3 | |
| G/A | 7 | 7.1 | 2 | 2.1 | 2,8 | p = 0,10 | 3.4 | 1,63 - 7,2 | | 3,6 | |

**Table 4.**

**Distribution and pathogenetic significance of the G1691A polymorphism of the F5 gene in the main and control groups.**

Similarly, in the group of patients with negative habits, the frequency of wild and minor alleles did not differ statistically significantly in the main and control groups (respectively, allele G - 97.9% and 99.0%, 2.1% and allele A - 1.0). %, $\chi 2=0.05$, p=0.5), respectively, there was no statistically significant association in the development of COVID-19-associated ANGBC disease in patients with wild homozygous and heterozygous genotypes ($\chi 2<3.85$, $p>0.05$).

**Table 5.**

**Patients with negative habits in the main group and in the control groupF5 G1691A gene spread and pathogenetic significance of polymorphism.**

| Alleles and genotypes | Number of alleles and genotypes | | | | χ2 | p | RR | 95% CI | OR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | Drinker and smoker | | Control group | | | | | | | |
| | n | % | n | % | | | | | | |
| G | 94 | 97,9 | 190 | 99,0 | 0,5 | p = 0,50 | 1,0 | 0,14 - 6,94 | 0,5 | 0,07 - 3,43 |
| A | 2 | 2.1 | 2 | 1,0 | 0,5 | p = 0,50 | 1,0 | 0,15 - 6,94 | 2.0 | 0,29 - 14,02 |
| G/G | 46 | 95,8 | 94 | 97,9 | 0,5 | p = 0,50 | 1,0 | 0,14 - 7,06 | 0,5 | 0,07 - 3,45 |
| G/A | 2 | 4.2 | 2 | 2.1 | 0,5 | p = 0,50 | 2.0 | 0,28 - 14,42 | 2.0 | 0,29 - 14,41 |

Interestingly, the G1691A polymorphism of the F5 gene was analyzed when studying the results of a group of patients without bad habits. Accordingly, in patients with bad habits, there was a statistically significant association between the wild-type G allele and wild-type G/G genotypes and the development of COVID-19-related ANGBC (OR = 0.2, 95% CI: 0.04 - 0.9 and O R = 0.2, 95% CI: 0.04 - 0.88, $\chi 2 = 4.4$, p = 0.05,) has a protective effect, on the other hand, in carriers of the minor A allele and the G / A genotype, the probability of developing the disease statistically significantly increases (respectively, O R = 5.0, 95% CI: 1.11-22.48 and OR = 5.2, 95% CI: 1.14-23.99, $\chi 2 = 6.1$, p = 0.03). This means that the correlation between the minor allele of the G1691A polymorphism of the F5-G gene and the heterozygous genotype - A/G and the COVID-19-related ANGBC disease was statistically significant only in the group of patients without negative habits ($\chi 2>3.85?p<0.05$), indicating that the G1691A polymorphism of the F5 gene can independently (compared to negative habits) statistically significantly increase the risk of developing ANGBC, related to COVID-19 (see Table 6).

**Table 6.**

**Patients without bad habits in the main group and in the control groupF5 gene G1691Adistribution and pathogenetic significance of polymorphism.**

| Alleles and genotypes | Number of alleles and genotypes | | | | χ2 | p | RR | 95% CI | OR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | Non-drinker and non-smoker | | Control group | | | | | | | |
| | n | % | n | % | | | | | | |
| G | 95 | 95,0 | 190 | 99,0 | 4.4 | p = 0,05 | 1,0 | 0,36 - 2,54 | 0,2 | 0,04 - 0,9 |
| A | 5 | 5,0 | 2 | 1,0 | 4.4 | p = 0,05 | 1,0 | 0,1 - 10,4 | 5,0 | 1.11 - 22.48 |
| G/G | 45 | 90,0 | 94 | 97,9 | 4,5 | p = 0,05 | 0,9 | 0,33 - 2,58 | 0,2 | 0,04 - 0,88 |
| G/A | 5 | 10,0 | 2 | 2.1 | 4,5 | p = 0,05 | 4,8 | 1,71 - 13,47 | 5.2 | 1.14 - 23.99 |

In the G20210A polymorphism type (rs1799963) of the F2 gene, the minor allele excluded a small percentage in the main and control groups, and no subjects with a homozygous wild genotype (A/A) were detected. Although the minor allele-A was detected to a greater extent in the main group than in the control group, its association with ANGBC associated with COVID-19 was not statistically significant ($\chi 2<3.85$, $P>0.05$). Similarly, in terms of the odds ratio (O R) of the homozygous genotype G/G and the heterozygous genotype G/A of the wild type showed a protective and inducing role in the development of the disease, respectively (O R = 0.5; 95% CI : 0.045-5.66 and O R = 1, 98; 95% CI: 0.176-22.19), the pathogenetic significance of these genotypes was not statistically significant ($\chi 2<3.85$, $p>0.05$) (see Table 7).

**Table 7.**

**Distribution and pathogenetic significance of the G20210A polymorphism of the F2 gene in the main and control groups.**

| Alleles and genotypes | Number of alleles and genotypes | | | | χ2 | p | RR | 95% CI | OR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | Main group | | Control group | | | | | | | |
| | n | % | n | % | | | | | | |
| G | 194 | 99 | 191 | 99,5 | 0,32 | 0,575 | 0,76 | 0,337-1,693 | 0,51 | 0,046-5,65 |
| A | 2 | 1 | 1 | 0,5 | 0,32 | 0,575 | 1,32 | 0,591-2,96 | 1,97 | 0,177-21,89 |
| G/G | 96 | 98 | 95 | 99,0 | 0,31 | 0,573 | 0,75 | 0,335-1,69 | 0,50 | 0,045-5,66 |
| G/A | 2 | 2.0 | 1 | 1,0 | 0,31 | 0,573 | 1,33 | 0,589-2,99 | 1,98 | 0,176-22,19 |

Similarly, in the group of patients with negative habits, the frequency of wild and minor alleles did not differ between the main and control groups (x2=0.05, p=0.48), according to which there was no statistically significant association in the development of COVID-19-related ANGBC disease in patients with wild-type homozygous and heterozygous genotypes (x2=0.5, p=0.48) (Table 8).

**Table 8.**

**Distribution and pathogenetic significance of the G20210A polymorphism of the F2 gene in patients with negative habits in the main and control groups**

| Alleles and genotypes | Number of alleles and genotypes | | | | χ2 | p | RR | 95% CI | OR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | Drinker and smoker | | Control group | | | | | | | |
| | n | % | n | % | | | | | | |
| G | 96 | 100 | 191 | 99,5 | 0,50 | 0,48 | - | - | - | - |
| A | 0 | 0,0 | 1 | 0,5 | 0,50 | 0,48 | - | - | - | - |
| G/G | 48 | 100 | 95 | 99,0 | 0,50 | 0,48 | - | - | - | - |
| G/A | 0 | 0,0 | 1 | 1,0 | 0,50 | 0,48 | - | - | - | - |

When comparing the results of the G20210A polymorphism type (rs1799963) of the F2 gene between the group of patients without bad habits and the control group, although the minor allele-A was detected more often in the main group than in the control group, its association with ANGBC disease associated with COVID-19 was not statistically significant ($\chi2<3.85$, $p>0.05$). Similarly, in the odds ratio (OR) homozygous G/G and heterozygous genotype G/A of wild type showed a protective and inducing role in the development of the disease, respectively (O R = 0.25; 95% CI: 0.023-2.86 and O R = 3.95; 95% CI: 0.022-2.85), the pathogenic significance of these genotypes was not statistically significant ($\chi2<3.85$, $p>0.05$) (see Table 9).

**Table 9.**

**Distribution and pathogenetic significance of the G20210A polymorphism of the F2 gene in patients without bad habits in the main and control groups.**

| Alleles and genotypes | Number of alleles and genotypes | | | | χ2 | p | RR | 95% CI | OR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | Non-drinker and non-smoker | | Control group | | | | | | | |
| | н | % | н | % | | | | | | |
| G | 98 | 98,0 | 191 | 99,5 | 1,4 | 0,23 | 0,51 | 0,225-1,15 | 0,25 | 0,023-2,86 |
| A | 2 | 2.0 | 1 | 0,5 | 1,4 | 0,23 | 1,96 | 0,87-4,44 | 3,89 | 0,349-43,5 |
| G/G | 48 | 96,0 | 95 | 99,0 | 1,43 | 0,23 | 0,50 | 0,219-1,16 | 0,25 | 0,022-2,85 |
| G/A | 2 | 4.0 | 1 | 1,0 | 1,43 | 0,23 | 1,98 | 0,86-4,56 | 3,95 | 0,35-44,76 |

Factor V (F5) of the coagulation cascade promotes the activation of prothrombin catalyzed by factor X. The A2 domain of factor V is inactivated by proteolytic cleavage of the active protein C complex (APC)/protein S. The mutation of factor V Leiden causes a single-point polymorphism in the F5 gene, replacing glutamine with arginine at position 506 of the protein. As a result, this mutation changes the conformation of the A2 domain, which leads to a decrease in APC inhibition and thrombophilia phenotype [40].

Similarly, prothrombin (encoded by the factor II-F2 gene) is a precursor to thrombin and plays a crucial role in fibrin formation. Prothrombin also ensures the normal functioning of the

hemostasis system by regulating the blood clotting process by activating blood clotting factors, in particular, by activating factors V, VIII and XIII, and platelets, as well as by activating natural anticoagulants such as protein S and protein C.

According to the studies, it has been suggested that a single-point polymorphism of G20210A in the prothrombin gene (F2) can increase the level of prothrombin and, therefore, increase the risk of arterial and venous thrombosis. Mutation of the F2 gene can alter the transcription of the prothrombin gene, leading to an increase in the production of thrombin, a key clotting factor [43]. In representatives of the Caucasian race, prothrombin G20210A is one of the most common hereditary thrombophilic diseases with a population distribution of the minor allele of 2-3% [44]. In the presence of the G20210A prothrombin mutation, the risk of venous thrombosis increases by 2-3 times [45]. W a hlander K et al also reported that mutations in the G20210A prothrombin gene may be potential risk factors for venous thrombosis after hip or knee replacement surgery [46]. Thus, prothrombin G20210A may increase the risk of thrombosis as a result of excessive clotting factors. This risk may be particularly increased when exposed to environmental factors, in particular, hyperergic inflammation caused by COVID-19.

**Findings.** Among the polymorphisms studied in the course of the study, the G1691A polymorphism of the F5 gene with a statistically significant positive association with the development of ANGBC disease associated with COVID-19 is statistically significant, since the minor allele is the A allele and the heterozygous is the genotype G / A, regardless of negative habits, it was found that they increase the likelihood of the disease, respectively, 5.0 times (OR = 5.0;95% CI: 1.11 - 22.48, $\chi 2 = 4.4$, $p = 0.05$) and 5.2 times (OR = 5.2;95% CI: 1.14 - 23.99, $\chi 2=4.5$, $p=0.05$). Other types of polymorphisms (F2 G20210A – rs1799963 and VDR BsmI – rs1544410) did not find a statistically significant positive association between the development of COVID-19-related ANGBC ($\chi 2<3.85$, $p>0.05$). Thus, individuals with the minor allele of the G1691A polymorphism of the F5 gene are more likely to develop ANGBC than those who do not have such an allele, which requires special additional preventive measures to prevent them from developing ANGBC disease.

## References.

1. Gou WL, Lu Q, Wang X, Wang Y, Peng J, Lu SB. Key pathway to prevent the collapse of femoral head in osteonecrosis. Eur Rev Med Pharmacol Sci. 2015;19(15):2766–2774.
2. Petek D, Hannouche D, Suva D. Osteonecrosis of the femoral head: pathophysiology and current concepts of treatment. EFORT Open Rev. 2019;4(3):85–97.
3. Aaron RK, Gray R. Osteonecrosis: etiology, natural history, pathophysiology, and diagnosis. In: Callaghan JJ, Rosenberg AG, Rubash HE, editors. The adult hip. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 465–76
4. Atsumi T. Bone arteriography of the femoral head of humans in normal and pathological conditions. In: Schoutens A et al., editors. Bone circulation and vascularization in normal and pathological conditions. US: Springer; 1993. p. 293–9.
5. Kenzora JE GM, et al. Osteonecrosis. In: Kelly WN HE, Ruddy S, et al., editors. Textbook of rheumatology. Philadelphia: WB Saunders; 1981. pp. 1755–82.
6. Shah K, Racine J, Jones L, et al. Pathophysiology and risk factors for osteonecrosis. Curr Rev Musculoskelet Med 2015;8:201–9. 4

7. Cui Q, Botchwey E. Treatment of precollapse osteonecrosis using stem cells and growth factors. Clin Orthop Relat Res 2011;469:2665–9.
8. James J, Steijn-Myagkaya GL. Death of osteocytes. Electron microscopy after in vitro ischaemia. J Bone Joint Surg (Br) 1986;68(4):620–4.
9. Jiang Y, Rubin L, Peng T, et al. Cytokine storm in COVID-19: from viral infection to immune responses, diagnosis and therapy. Int J Biol Sci. 2022;18(2):459-472. Published 2022 Jan 1. doi:10.7150/ijbs.59272
10. Zhang Q, L V J, Jin L. Role of coagulopathy in glucocorticoid-induced osteonecrosis of the femoral head. J Int Med Res. 2018 Jun;46(6):2141-2148. doi: 10.1177/0300060517700299. Epub 2017 May 1. PMID: 28459353; PMCID: PMC6023042.
11. Matsuo K et al. Influence of alcohol intake, cigarette smoking, and occupational status on idiopathic osteonecrosis of the femoral head. Clin Orthop Relat Res. 1988;234:115–23
12. Guerado E, Caso E: The physiopathology of avascular necrosis of the femoral head: An update. Injury 2016;47:S16-S26.
13. Choi HR, Steinberg ME, E YC: Osteonecrosis of the femoral head: Diagnosis and classification systems. Curr Rev Musculoskelet Med 2015;8:210-220.
14. Mont MA, Pivec R, Banerjee S, Issa K, Elmallah RK, Jones LC: High-dose corticosteroid use and risk of hip osteonecrosis: Meta-analysis and systematic literature review. J Arthroplast 2015;30:1506-1512.e5
15. Jiang Y, Rubin L, Peng T, et al. Cytokine storm in COVID-19: from viral infection to immune responses, diagnosis and therapy. Int J Biol Sci. 2022;18(2):459-472. Published 2022 Jan 1. doi:10.7150/ijbs.59272
16. Herrmann M, et al. Increased osteoclast activity in the presence of increased homocysteine concentrations. Clin. Chem. 2005;51:2348–2353. doi: 10.1373/clinchem.2005.053363.
17. Stühlinger MC, et al. Homocysteine impairs the nitric oxide synthase pathway: role of asymmetric dimethylarginine. Circulation. 2001;104:2569–2575. doi: 10.1161/hc4601.098514.
18. Lentz SR. Mechanisms of homocysteine-induced atherothrombosis. J. Thromb. Haemost. 2005;3:1646–1654. doi: 10.1111/j.1538-7836.2005.01364.x.
19. Ganesh B, Rajakumar T, Malathi M, et al. Epidemiology and pathobiology of SARS-CoV-2 (COVID-19) in comparison with SARS, MERS: An updated overview of current knowledge and future perspectives. Clin Epidemiol Glob Health. 2021;10:100694. doi:10.1016/j.cegh.2020.100694.
20. Orooji Y, Sohrabi H, Hemmat N, et al. An Overview on SARS-CoV-2 (COVID-19) and Other Human Coronaviruses and Their Detection Capability via Amplification Assay, Chemical Sensing, Biosensing, Immunosensing, and Clinical Assays. Nanomicro Lett. 2021;13(1):18. doi:10.1007/s40820-020-00533-y
21. Mir, T., Almas, T., Kaur, J., Faisaluddin, M., Song, D., Ullah, W., Mamtani, S., Rauf, H., Yadav, S., Latchana, S., Michaelson, N. M., Connerney, M., & Sattar, Y. (2021). Coronavirus disease 2019 (COVID-19): Multisystem review of pathophysiology. Annals of medicine and surgery (2012), 69, 102745. https://doi.org/10.1016/j.amsu.2021.102745
22. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. Virol Sin. 2020;35(3):266-271. doi:10.1007/s12250-020-00207-4

23. Gorkhali R, Koirala P, Rijal S, Mainali A, Baral A, Bhattarai HK. Structure and Function of Major SARS-CoV-2 and SARS-CoV Proteins. Bioinform Biol Insights. 2021;15:11779322211025876. Published 2021 Jun 22. doi:10.1177/11779322211025876
24. Bai C, Zhong Q, Gao GF. Overview of SARS-CoV-2 genome-encoded proteins. Sci China Life Sci. 2022;65(2):280-294. doi:10.1007/s11427-021-1964-4
25. Niedźwiedzka-Rystwej P, Majchrzak A, Kurkowska S, et al. Immune Signature of COVID-19: In-Depth Reasons and Consequences of the Cytokine Storm. Int J Mol Sci. 2022;23(9):4545. Published 2022 Apr 20. doi:10.3390/ijms23094545
26. C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China Lancet, 395 (10223) (2020), pp. 497-506, 10.1016/S0140-6736(20)30183-5
27. Zanza C, Romenskaya T, Manetti AC, et al. Cytokine Storm in COVID-19: Immunopathogenesis and Therapy. Medicina (Kaunas). 2022;58(2):144. Published 2022 Jan 18. doi:10.3390/medicina58020144
28. Jiang Y, Rubin L, Peng T, et al. Cytokine storm in COVID-19: from viral infection to immune responses, diagnosis and therapy. Int J Biol Sci. 2022;18(2):459-472. Published 2022 Jan 1. doi:10.7150/ijbs.59272
29. Young R.E., Thompson R.D., Larbi K.Y., La M., Roberts C.E., Shapiro S.D., Perretti M., Nourshargh S. Neutrophil elastase (NE)-deficient mice demonstrate a nonredundant role for NE in neutrophil migration, generation of proinflammatory mediators, and phagocytosis in response to zymosan particles in vivo. Journal. 2004;172:4493–4502
30. Chen IY, Moriyama M, Chang MF, Ichinohe T. Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. Front Microbiol. 2019;10:50.
31. Kayagaki N., Stowe I. B., Lee B. L., O'rourke K., Anderson K., Warming S., et al. (2015). Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. Nature 526 666–671. 10.1038/nature15541
32. Zhang Q., VJ L., Jin L. Role of coagulopathy in glucocorticoid-induced osteonecrosis of the femoral head. J Int Med Res. 2018;46(6):2141.
33. Zhang Q, L V J, Jin L. Role of coagulopathy in glucocorticoid-induced osteonecrosis of the femoral head. J Int Med Res. 2018 Jun;46(6):2141-2148. doi: 10.1177/0300060517700299. Epub 2017 May 1. PMID: 28459353; PMCID: PMC6023042.
34. Glueck CJ, McMahon RE, Bouquot JE, Stroop D, Tracy T, Wang P, Rabinovich B. Thrombophilia, hyperfibrinolysis, and alveolar osteonecrosis of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;81:557–566.
35. Zalavras CG, Vartholmatos G, Dokou E, Malizos KN. Genetic background of osteonecrosis: associated with thrombophilic mutations? Clin Orthop Relat Res. 2004;422:251–255.
36. Zalavras CG, Vartholomatos G, Dokou E, Malizos KN. Genetic background of osteonecrosis: associated with thrombophilic mutations? Clin Orthop Relat Res. 2004 May;(422):251-5. PMID: 15187864.
37. Peng KT, Huang KC, Huang TW, Lee YS, Hsu WH, Hsu RW, Ueng SW, Lee MS. Single nucleotide polymorphisms other than factor V Leiden are associated with coagulopathy and osteonecrosis of the femoral head in Chinese patients. PLoS One. 2014 Aug 13;9(8):e104461. doi: 10.1371/journal.pone.0104461. PMID: 25119470; PMCID: PMC4131902.

38. Zalavras CG, Vartholomatos G, Dokou E, Malizos KN (2004) Genetic background of osteonecrosis: associated with thrombophilic mutations? Clin Orthop 422: 251–255.
39. Bjorkeman A, Burtscher IM, Svensson PJ, Hillarp A, Besjakov J, Benoni G. Factor V Leiden and the prothrombin 20210A gene mutation and osteonecrosis of the knee. Arch Orthop Trauma Surg. 2005;125:51–5.
40. Segers K, Dahlbäck B, Nicolaes GA (2007) Coagulation factor V and thrombophilia: background and mechanisms. Thromb Haemost 98: 530–542.