**MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN**
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# ISCHEMIC HEART DISEASE AND PSYCHOEMOTIONAL DISORDER

Samarkand-2025

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**Ischemic Heart Disease and Psychoemotional Disorder [Text]: Monograph / I.R. Nasyrova Z.A. - Samarkand:....., 2024. – 224 p.**

*Recent studies highlight a high prevalence of depression among patients with cardiovascular diseases. Increasingly, stress, negative emotions, and depression are recognized as psychological risk factors for the development of somatic diseases. Depression, in particular, is most often considered a contributing factor to cardiovascular diseases. Both domestic and international researchers have proven that patients with ischemic heart disease exhibit high levels of trait anxiety, a tendency to somatize symptoms, chronic stress, difficulties in differentiating and verbalizing emotions, unresolved affective experiences, and emotional disturbances of anxious, hypochondriacal, and depressive types, which correlate with disease severity. In this regard, early psychological diagnosis of depression becomes especially relevant.*

*This monograph presents modern concepts of the psychoemotional state and its role in the development of ischemic heart disease. It includes contemporary literary sources from both CIS and foreign countries. The analyzed literature has enabled the authors to examine certain molecular-genetic aspects of predisposition to the destabilization of ischemic heart disease. Based on their own clinical, laboratory, and instrumental studies, the authors describe the characteristics of unstable angina variants depending on the psychoemotional state.*

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**Abbreviation full name**

| | |
|---|---|
| AHA | American Heart Association |
| ACC | American College of Cardiology |
| GWAS | Genome-Wide Association Study |
| HADS | Hospital Anxiety and Depression Scale |
| HADS-D | Depression Subscale of HADS |
| HADS-A | Anxiety Subscale of HADS |
| IL-10 | Interleukin-10 |
| IL-1β | Interleukin-1 Beta |
| IL-4 | Interleukin-4 |
| MPQ | McGill Pain Questionnaire |
| NO | Nitric Oxide |
| SNP | Single Nucleotide Polymorphism |
| TNF-α | Tumor Necrosis Factor Alpha |
| AP | Atherosclerotic Plaque |
| PP | Posterior Probability |
| HTN | Hypertension |
| ASH | Asymptomatic Hyperuricemia |
| OM | Obtuse Marginal Branch |
| HGP | Hypoxanthine-Guanine Phosphoribosyltransferase |
| GAD | Generalized Anxiety Disorder |
| HC | Hypercholesterolemia |
| DBP | Diastolic Blood Pressure |
| DB | Diagonal Branch |
| ED | Endothelial Dysfunction |
| eNOS | Endothelial NO System |
| PDA | Posterior Descending Artery |
| CAD | Coronary Artery Disease |
| NSTEMI | Non-ST Elevation Myocardial Infarction |
| STEMI ST | Elevation Myocardial Infarction |
| BMI | Body Mass Index |
| AI | Atherogenic Index |

| | |
|---|---|
| CA | Coronary Artery |
| CHD | Coronary Heart Disease |
| EDD | End-Diastolic Diameter |
| CBT | Cognitive Behavioral Therapy |
| ESD | End-Systolic Diameter |
| LCA | Left Coronary Artery |
| LA | Left Atrium |
| HDL | High-Density Lipoprotein |
| LDL | Low-Density Lipoprotein |
| PA | Personal Anxiety |
| IVS | Interventricular Septum |
| UA | Uric Acid |
| UA | Unstable Angina |
| CxA | Circumflex Artery |
| AMI | Acute Myocardial Infarction |
| ACS | Acute Coronary Syndrome |
| PICS | Post-Infarction Cardiosclerosis |
| RCA | Right Coronary Artery |
| LAD | Left Anterior Descending Artery |
| PED | Psychoemotional Disorder |
| ADS | Anxiety-Depressive Syndrome |
| RPI | Rank Pain Index |
| SBP | Systolic Blood Pressure |
| DM | Diabetes Mellitus |
| SSRI | Selective Serotonin Reuptake Inhibitor |
| SA | Stable Angina |
| CVD | Cardiovascular Diseases |
| CVS | Cardiovascular System |
| SA | Situational Anxiety |
| TG | Triglycerides |
| ADS | Anxiety-Depressive Syndrome |
| TT | Traditional Therapy |
| UA | Uric Acid Level |
| LVEF | Left Ventricular Ejection Fraction |

| | |
|---|---|
| TNF-α | Tumor Necrosis Factor Alpha |
| RF | Risk Factors |
| CHF | Chronic Heart Failure |
| PCI | Percutaneous Coronary Intervention |
| HR | Heart Rate |
| ET-1 | Endothelin-1 |

## PREFACE

Coronary artery disease (CAD) is a type of cardiovascular disease that occurs when plaques accumulate inside the arteries that supply blood to the heart muscle. This accumulation of plaques, known as atherosclerosis, can lead to narrowing or blockage of the arteries, reducing the blood flow to the heart. As a result, the heart may not receive the oxygen and nutrients it needs to function properly, which can lead to chest pain or discomfort (angina), a heart attack, or even death. CAD is a common and serious condition that affects millions of people worldwide and is a leading cause of death globally. Risk factors for CAD include high blood pressure, high cholesterol levels, smoking, diabetes, obesity, family history of the disease, and a sedentary lifestyle. Treatment for CAD typically includes lifestyle changes (such as a healthy diet and exercise), medications to control risk factors, and, in some cases, medical procedures or surgery. Recent research has highlighted the role of psychological factors in the development and progression of the disease. It has been shown that psychological factors such as depression, anxiety, stress, and personality traits have a significant impact on the risk of developing CAD and the outcomes after the disease diagnosis. Therefore, there is an increasing need for effective psychological interventions that can address the complex interaction between biological, psychological, and social factors influencing CAD. Such interventions can help individuals with CAD better cope with the disease, improve their quality of life, and reduce the risk of adverse health outcomes.

In recent years, scientific research dedicated to psychosomatic issues in cardiac pathology has been conducted in the Republic of Uzbekistan by leading specialists in this field, including Academician R.D. Kurbanov (2020), Professor N.M. Nurillaeva (2020), and Professor N.Kh. Khamidov (2013). These works focus on studying the role of anxiety-depressive disorders in the development and prognosis of cardiovascular diseases.

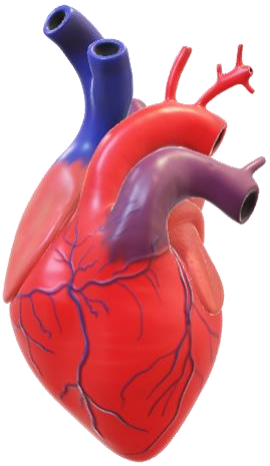
Unfortunately, the issue of the early manifestations of anxiety-depressive syndrome and the progression of unstable variants of angina, the selection of individualized treatment, and the prediction of adverse cardiovascular complications considering molecular-genetic predictors such as the polymorphism of genes TNF-α 308 G/A, IL-1β T/C 511, IL-4 C/T 589, and IL-10 C/T 819, along with pronounced anxiety-depressive conditions, hyperuricemia, and cytokine imbalance, remains insufficiently studied. This has determined the importance and relevance of this monograph.

Comprehensive studies conducted worldwide indicate a high prevalence of psychosomatic risk factors in general medical and cardiological practice. According to the EUROASPIRE IV study (2017), the prevalence of anxiety-depressive syndrome among patients with coronary heart disease (CHD) can range from 30 to 40% in different populations. A literature search reveals ongoing discussions about the prognostic significance of psychosomatic disorders (PES) in relation to the development and destabilization of CHD, as well as the risk of low patient adherence to long-term therapy.

Over the past two decades, research into the genetic basis of coronary artery disease has intensified, although clear data on the inheritance of complex diseases such as coronary artery disease (CAD) are lacking. Surprisingly, according to Libby and colleagues, almost 75% of single nucleotide polymorphisms (SNPs) in CAD occur in or near genes that have no direct connection to atherothrombotic mechanisms, complicating the understanding of the functions of these genes. More recently, research has focused on epigenetic variability (i.e., variations in gene expression without changes in the genome structure) and the importance of activation/inhibition of various epigenetic sites related to immune processes involved in the pathogenesis of CAD.

In this regard, the study by Bing-Jian Wang and his co-authors focused on the anti-inflammatory interleukin gene IL-10 C/T 819, which is more commonly found in patients with coronary heart disease (CHD), hypertension, hyperuricemia, diabetes, peptic ulcers, liver diseases, and other conditions. The researchers also noted that polymorphism cases were more frequent among patients over the age of 57. Researchers Mona Hussein Kandil and her co-authors observed that the IL-1 T/C 511 gene polymorphism is associated with atherosclerosis in the Egyptian population, particularly in individuals with pronounced kidney pathology. A study conducted by Ma L. et al. showed that the presence of the 511T allele in the promoter region of human IL-1 was linked to the development of an inflammatory process in blood vessels, exacerbating the clinical manifestation of coronary artery disease.

However, the lack of statistical power in recent meta-analyses prevents the identification of specific psychosocial factors that could be considered independent risk factors for serious cardiovascular events. Additionally, studying these genes collectively would help identify the interactions of gene polymorphisms, which would facilitate the timely detection and prediction of destabilization in coronary heart diseases, potentially leading to acute cardiovascular complications and fatal outcomes.



# CHAPTER 1. LITERATURE REVIEW

## §1.1. INNOVATIONS IN HEALTHCARE FOR CARDIOVASCULAR DISEASES

Innovations in healthcare refer to the deliberate introduction and application of new ideas, processes, products, or procedures within a role, group, or organization that are new to the respective unit of implementation and are intended to bring significant benefits to individuals, groups, or society as a whole [5]. Three main characteristics of innovations include novelty, an applied component, and the expected benefit. Despite ongoing efforts to stop cardiovascular diseases (CVD), their prevalence continues to rise in almost all countries. It is necessary to explore innovative solutions to this issue. Healthcare advancements that encompass new knowledge and technologies have the potential to modernize the treatment of cardiovascular diseases [133].

In Malaysia, the prevalence of coronary heart disease has tripled over the last 40 years. In 2006, the prevalence of hypertension reached a staggering 42.6%, and the prevalence of diabetes increased from 14.9% in 2006 to 20.6% in 2011. This trend of rising cardiovascular diseases and major risk factors raises concern and emphasizes the need for new interventions to combat this problem.

Modern medicine initially focused on treating the symptoms of cardiovascular diseases. After identifying the multifaceted basis of the disease, the cornerstone Framingham study gradually shifted the focus toward prevention. Initially, efforts were aimed at individual risk factors such as hypertension, hyperlipidemia, and diabetes. Over time, medicine adopted a global risk factor approach. Currently, research supports new approaches such as combination pills and lifetime risk calculators. Technological advancements in monitoring have entered the market with home monitoring devices, such as glucose meters and blood pressure measurement devices. These devices immediately changed how doctors approach working with patients. Innovations have also occurred in diagnostic testing, including on-site tests, such as the Troponin T/I test for assessing acute chest pain. Many technological advancements in medicine have taken place in cardiology to reduce mortality and morbidity from coronary heart disease [144,161].

There are several potential areas for developing innovations in healthcare related to cardiovascular diseases.

Genetic family history of cardiovascular diseases is one of the main risk factors for disease development and illustrates the interaction between genes and the environment in the pathophysiology of the disease. In the field of pharmacogenetics in oncology, doctors are already able to distinguish individuals with a likely response to a specific drug from patients who do not respond to treatment. The potential of pharmacogenetics remains immense in terms of selecting medications based on genetic profiles to control risk factors in patients with cardiovascular diseases [132].

Modern technologies allow extrapolation of individual risk prediction based only on population studies. New biomarkers and diagnostic tools (such as heart scanning) help only minimally in risk prediction and early diagnosis. The translation of current risk assessment means that out of 100 patients with a similar risk profile, 20 will experience a serious cardiovascular event within ten years, while 80 out of 100 will not. However, all of them fall into the high-risk category and receive management. Healthcare innovations capable of identifying those at risk will allow resources to be directed toward people who truly face a high risk, and reduce overtreatment of false positive results [158].

Changing patient behavior remains a complex and daunting task. One study showed that 62% of smokers resumed smoking within a year after a myocardial infarction. Individuals who continue smoking are three times more likely to die compared to those who quit. Evidence supports the effectiveness of lifestyle interventions, but professionals need new strategies and methods to successfully intervene in dysfunctional lifestyles.

More than one in five patients discontinued aspirin, beta-blockers, or statins, and one in eight stopped all three medications within a month after a myocardial infarction. Despite healthcare workers trying various methods to improve adherence, the review showed that improvements were modest even with the most effective methods. Healthcare workers need effective medical innovations in patient self-care [178].

Evidence and epidemiological data in the field of cardiovascular diseases have primarily been obtained from studies conducted in high-income developed countries. However, low- and middle-income countries are increasingly bearing the overwhelming burden of cardiovascular diseases. The disease is more common among the poor and also contributes to poverty, creating a vicious cycle that hinders development. Developing countries urgently need cost-effective healthcare innovations. When transferring low-cost, evidence-based interventions to resource-poor countries, research should demonstrate the feasibility of successfully implementing cost-effective innovations in these countries [211].

There are gaps in knowledge and approaches to treating cardiovascular diseases in specific populations, such as women, indigenous peoples, and youth. The notion that cardiovascular diseases are a disease of older men persists, despite data showing increased prevalence among women and certain ethnic groups. Healthcare

innovations should include a plan for the inclusion of these vulnerable populations to ensure that those at risk are not marginalized [198].

Inertia toward change remains a common obstacle to healthcare innovations, especially regarding the existing healthcare system and policies. These factors, along with financial issues, hinder the implementation of healthcare innovations. For example, an unhealthy lifestyle continues to be a primary risk factor for cardiovascular diseases, yet both doctors and patients recognize the need for changing unhealthy behaviors. Despite this awareness, doctors often cite healthcare system barriers, such as lack of time or resources, as the main reasons for not promoting lifestyle change measures. Future healthcare innovations will require the use of complex intervention strategies to overcome numerous barriers in order to achieve success [178].

Due to their nature, healthcare innovations require practical evaluation before they are implemented. Economic efficiency, acceptability, and accessibility remain unknown until trials are conducted. Likewise, negative aspects or adverse consequences of healthcare innovations may not become apparent in the initial stages for months or years after implementation, as evidenced by drugs like thalidomide, used for morning sickness during pregnancy in the 1960s, which led to children being born without limbs. New methods require ongoing post-marketing surveillance to detect any rise in morbidity and mortality. Technological innovations in healthcare could also depersonalize patient care. Unintended consequences may arise, such as patients using incorrect self-care methods by finding inaccurate information on the internet through search engines. Clinical practice may become overly reliant on technology, leading to the loss of essential skills, such as surgical experience. Healthcare providers must always ensure adherence to ethical principles such as patient confidentiality, autonomy, beneficence, and non-maleficence when implementing technological inventions in healthcare. Above all, professionals must preserve patient-centered care and decision-making [165,201].

The 21st century represents an exciting era for the development of healthcare innovations. Healthcare innovators are ready to tackle the epidemic of cardiovascular diseases. Gaps in existing knowledge and practice of cardiovascular diseases should be seen as opportunities to improve ideas, practices, and technologies. However, healthcare professionals must be aware of the limitations of new inventions and prioritize patient well-being.

## § 1.2. IMMUNO-MEDIATED INFLAMMATION IN THE PROGRESSION OF CORONARY HEART DISEASE

The molecular mechanisms of atherosclerosis involve cholesterol deposition and immune cell aggregation in the arterial wall. Both innate and adaptive immune cells, with pro-inflammatory and anti-inflammatory actions, regulate the subsequent progression of atherosclerosis. The transition of stable plaques to unstable plaques with subsequent rupture or erosion and thrombosis formation contributes to acute coronary syndrome (ACS) [2, 22, 27]. The relationship between immune-mediated

inflammation and the progression of ischemic heart disease (IHD) is complex, and the main mechanisms of IHD are not yet fully understood. The pathogenesis of IHD can be divided into plaque rupture with systemic inflammation and red thrombus, plaque rupture with low systemic inflammation, plaque erosion with white thrombus, and IHD without thrombus or epicardial coronary artery stenosis [57, 72, 98].

Typically, at sites of plaque rupture, activated macrophages and T-cells secrete cytokines that trigger a self-perpetuating vicious cycle, ultimately leading to the fragility and thinning of the fibrous cap, as well as the accumulation of a central lipid core [6, 8]. Therefore, both systemic and local inflammatory responses are important causes of IHD. Plaque rupture with mild systemic inflammation is characterized by a lack of macrophage accumulation in ruptured plaques and sluggish systemic inflammation. This type of plaque rupture is caused by psychological stress or local vessel wall tension. Similarly, the erosion of coronary plaques with white thrombi is not associated with macrophage-mediated inflammation but with platelet aggregation. Although coronary plaque erosion is considered not to have a direct connection with systemic inflammation, it has been shown that immune cells and inflammatory factors play a role in this process [30, 32]. IHD without thrombus or epicardial coronary artery stenosis may be the result of coronary vasospasm or microvascular diseases.

Immuno-mediated inflammatory diseases, including rheumatic diseases, inflammatory bowel diseases (IBD), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), are also closely associated with acute cardiovascular events, independent of traditional cardiovascular risk factors. Coronary heart disease (CHD) is very common in young women with IBD, who often exhibit high levels of C-reactive protein (CRP) [9, 20]. Therefore, the primary cause of these acute cardiovascular events is immune-mediated inflammation rather than traditional risk factors. However, a retrospective cohort study of 300 patients with IBD, without traditional risk factors, at the North Shore University Hospital did not find an association between IBD and acute cardiovascular events [108, 120, 135]. It is possible that the level of inflammation is insufficient to cause plaque rupture. However, the activity of inflammation is more important than the duration of inflammatory disorders. This cause-and-effect relationship is not limited to rheumatic diseases and CHD. Any conditions associated with systemic inflammation can damage the coronary arteries and subsequently lead to acute coronary syndrome (ACS) [145, 162]. This immunological pathogenesis may provide a theoretical foundation for potential clinical applications and interventions.

Accumulating data suggest that vascular inflammation plays a key role in the pathogenesis of coronary heart disease (CHD), and thus CHD is considered an inflammation-related disease. After systemic or local inflammatory activation, endothelial cells enhance the adhesion and migration of T-lymphocytes and macrophages into the arterial wall through activated adhesion molecules. During this process, both pro-atherogenic and anti-atherogenic immune networks are activated.

Once the balance is disrupted by various traditional cardiovascular risk factors, CHD develops and progresses to acute coronary events [181, 210, 212].

The innate immune system is the first barrier to self-protection, activating nonspecific immune cells to respond to pathogens [120, 143], and immune cells are normally restricted from penetrating the endothelial layer under physiological conditions [191, 197]. Platelets are not only important for thrombosis but also contribute to atherosclerotic inflammation. Platelets can induce the migration and recruitment of monocytes, leading to plaque formation.

A thin fibrous cap is characteristic of unstable plaques [27, 71] and is associated with impaired interstitial collagen metabolism [43, 110]. Typically, stretched interstitial collagen is resistant to degradation by most proteases, except for matrix metalloproteinases (MMPs) [203, 108]. Macrophages are a primary source of synthetic MMPs [37]. Increased activity or abundance of MMPs promotes the destruction of the arterial extracellular matrix and plaque rupture [39]. Recent research showed that inhibition of MMP-13 derived from macrophages in mice increased the amount of interstitial collagen and subsequently stabilized the plaques [96, 99].

The nucleotide-binding leucine-rich repeat-containing inflammasome of pyrin receptor 3 (NLRP3) is a critical component of the innate immune system and triggers the release of inflammatory cytokines by immune cells [24, 37, 184]. In acute coronary syndrome (ACS), the activated NLRP3 inflammasome produces bioactive IL-1β and IL-18 through activated caspase-1 in patients with atherosclerosis [18]. Both IL-1β and IL-18 destabilize plaques by activating VCAM, thereby inducing T-cell differentiation and stimulating subsequent pro-inflammatory responses [160, 171].

In addition to interleukin-like pro-atherogenic cytokines, TNF-α, released by macrophages, induces vascular endothelial dysfunction, promoting thrombosis and continuously activating CD47 [25, 108]. Excessive necrotic phagocytic debris stimulates Toll-like receptors (TLRs) via damage-associated molecular patterns (DAMPs), further amplifying the inflammatory response [84]. Thus, a positive feedback loop develops, in which all pro-atherogenic cytokines exacerbate endothelial damage through various pathways, and as a result, more immune cells are recruited to the atheromatous focus [98].

## § 1.3. SIGNS OF DEVELOPMENT OF CAD FROM THE PERSPECTIVE OF GENETIC ARCHITECTURE

The genetic architecture of a phenotypic trait (a biological characteristic that can be quantitatively assessed) refers to the genes and their variants that determine the trait of interest or its association with it.
Before delving into the study of the genetic architecture of a trait, it is important to first determine whether the genetic component is significant. Several cohort studies have shown that a family history of coronary artery disease (CAD) is associated with an increased risk of the disease, suggesting that genetic factors are important;

however, it is also crucial to consider that family background not only transmits genetic information but also attitude and lifestyle. Heritability of a trait is an indicator of the proportion of its variability linked to genetic variability in the population [161]. Published estimates of the heritability of CAD range from 35% to 55% [150, 161].
Once the importance of the genetic component is established, research can be designed to identify genes and genetic variants associated with CAD. Regarding genetic transmission, two broad groups of phenotypes or diseases can be distinguished [199]:

- **Monogenic (or oligogenic)**, where the risk of disease is linked to the presence of variants in a single gene or a small number of genes. A good example is familial hypercholesterolemia, the onset of which is determined by sequence variants in a discrete group of genes (LDLR, APOB, PCSK9, and LDLRAP1).
- **Polygenic or complex**, where the risk of disease is determined by a multitude of genes, multiple variants of these genes, and their interaction with environmental factors. CAD is a prime example of a polygenic or complex trait [199].

The genetic architecture of a phenotypic trait can be studied using four approaches:

1. ***Linkage Analysis***: This type of analysis has proven useful in studying monogenic and oligogenic diseases. Linkage studies are conducted in families where the disease is initially diagnosed in at least one member (the proband), and other family members with the disease are found across multiple generations. Family members are analyzed for several hundred genetic markers distributed across the genome, and the transmission of these markers from generation to generation is analyzed to identify any association with the onset of the disease (segregation). The goal is to locate the genomic region containing the gene and identify the disease-causing genetic variant. Once the genomic region is identified, further studies, including genotyping and usually sequencing, are carried out to precisely identify the gene and variant causing the disease. This type of analysis has been very useful in studying monogenic and oligogenic diseases. For example, in familial hypercholesterolemia, linkage analysis identified a region on chromosome 1 containing the PCSK9 gene, and subsequent sequencing analysis identified sequence variants in PCSK9 that cause the disease. Although linkage analysis is less useful in studying complex diseases, sequence variants associated with CAD have been identified in the ALOX5AP and MEF2A genes [199, 187].
2. ***Candidate Gene Association Studies****:* This type of analysis typically uses a "case-control" design to determine whether one or more variants of a specific gene occur more or less frequently in patients with the disease compared to healthy individuals in the control group. In this hypothesis-testing approach, a candidate gene is chosen based on the understanding of the disease's

pathophysiology, and the genetic variants being analyzed are usually common (allele frequency > 5%). Candidate gene association studies have contributed little to the understanding of the genetic architecture of CAD or other complex phenotypes [175, 189]. The main problem with this approach is poor reproducibility, often due to small sample sizes in these studies, which leads to insufficient statistical power to identify weakly associated variants.

3. ***Genome-Wide Association Studies (GWAS)****:* Over the past 20 years, new genome sequencing technologies and genotyping of multiple sequence variants in a single sample have expanded our understanding of the genetic basis of complex diseases. Moreover, the publication of the HapMap study revealed that many common sequence variants are population-associated (they are in linkage disequilibrium) [137, 199]. Along with technological advancements, the knowledge of the linkage disequilibrium pattern in the human genome led to the development of laboratory kits capable of detecting between 100,000 and 500,000 sequence variants. This type of analysis covers much of the common genetic variation in the human genome and has enabled the development of GWAS approaches, which are used to study hundreds of thousands of genetic features and their relationships to phenotypic traits without hypotheses. The lack of a guiding hypothesis has two main consequences for the design and interpretation of GWAS:

a) In the sample, a number of sequence variants are identified that show a potential connection with the trait of interest, and the results of this initial sample are validated through replication in an independent sample.
b) Simultaneous analysis of hundreds of thousands of sequence variants generates a massive number of multiple comparisons, and the P-value required to assign statistical significance tends to be $<1 \times 10^{-8}$.

Early work with GWAS showed that common genetic variants demonstrate only weak associations with complex traits of interest, with odds ratios (OR) ranging from 1.1 to 1.4. The need to identify weakly associated variants with such small P-values and replicate the results in independent samples led to international collaboration, resulting in the collection of samples that included thousands of people [199].

The first two GWAS for coronary artery disease (CAD) yielded consistent results, identifying sequence variants in chromosome 9 associated with an increased risk of the disease. Since then, several GWAS studies have been published, and a meta-analysis of accumulated results in 2015 revealed 55 loci associated with CAD, each containing one or more sequence variants (Table 1) [199]. These variants explain about 15% of the heritability of CAD; furthermore, some of them are also associated with lipid metabolism, blood pressure, and inflammation, which confirms the importance of these risk factors in the etiology and pathogenesis of CAD. Later approaches in systems biology revealed an overrepresentation of genes associated with CAD in several processes and metabolic pathways, including lipid metabolism,

sulfur-containing amino acid metabolism, polyamine metabolism, innate immunity, extracellular matrix degradation, and the family of mediator proteins involved in the collapse response [174]. Moreover, most of these variants are located in intergenic regions near gene promoters, suggesting a potential impact on gene expression and highlighting the importance of gene expression and epigenetics in determining the risk of CAD. All GWAS results related to CAD, its risk factors, and other complex traits have been cataloged to provide easy access for researchers and clinicians [175, 199].

**Table 1.**

**Summary of Key Results from Recent Meta-analysis of Genome-Wide Association Studies Investigating DNA Sequence Variants Associated with Coronary Artery Disease**

| SNP | Nearest gene | Chromosome | Risk/Non-risk Allele | Risk Allele Frequency | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| rs11206510 | PCSK9 | 1 | T / C | 0,848 | 2.34 E-08 | 1,08 (1,05–1,11) |
| rs9970807 | PPAP2B | 1 | C / T | 0,915 | 5.00 E-14 | 1,13 (1,10–1,17) |
| rs7528419 | *SORT1* | 1 | A / G | 0,786 | 1,97 E-23 | 1,12 (1,10–1,15) |
| rs6689306 | *IL6R* | 1 | A / G | 0,448 | 2.60 E-09 | 1,06 (1,04–1,08) |
| rs67180937 | *MIA3* | 1 | G / T | 0,663 | 1.01 E-12 | 1,08 (1,06–1,11) |
| rs16986953 | *AK097927* | 2 | A / G | 0,105 | 1,45 E-08 | 1,09 (1,06–1,12) |
| chr2: 21378433: D | *APOB* | 2 | D / I | 0,746 | 2,89 E-08 | 1,07 (1,04–1,10) |
| chr2: 44074126: D | *ABCG5-ABCG8* | 2 | I / D | 0,745 | 2.60 E-08 | 1,06 (1,04–1,09) |
| rs7568458 | *VAMP5-VAMP8-GGCX* | 2 | B | 0,449 | 3.62 E-10 | 1,06 (1,04–1,08) |
| rs17678683 | *ZEB2-ACO74093.1* | 2 | G / T | 0,088 | 3.00 E-09 | 1,10 (1,07–1,14) |

| SNP | Nearest gene | Chromosome | Risk/Non-risk Allele | Risk Allele Frequency | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| chr2: 203828796: I | *WDR12* | 2 | I / D | 0,108 | 2.15 E-18 | 1,15 (1,11–1,18) |
| chr3: 138099161: I | *MRAS* | 3 | I / D | 0,163 | 2,89 E-09 | 1,08 (1,05–1,10) |
| rs4593108 | *EDNRA* | 4 | C / G | 0,795 | 8,82 E-10 | 1,07 (1,05–1,10) |
| rs72689147 | *GUCY1A3* | 4 | G / T | 0,817 | 6.07 E-09 | 1,07 (1,05–1,10) |
| rs17087335 | *ОТДЫХ-NOA1* | 4 | T / C | 0,210 | 4.60 E-08 | 1,06 (1,04–1,09) |
| rs273909 | *SLC22A4-SLC22A5* | 5 | G / A | 0,117 | 1,24 E-04 | 1,06 (1,03–1,09) |
| rs6903956 | *ADTRP-C6orf105* | 6 | A / G | 0,354 | 0,96 | 1,00 (0,98–1,02) |
| rs9349379 | *PHACTR1* | 6 | G / A | 0,432 | 1.81 E-42 | 1,14 (1,12–1,16) |
| rs17609940 | *ANKS1A* | 6 | G / C | 0,824 | 0,03 | 1,03 (1,00–1,05) |
| rs56336142 | *KCNK5* | 6 | T / C | 0,807 | 1.85 E-08 | 1,07 (1,04–1,09) |
| rs12202017 | *TCF21* | 6 | A / G | 0,700 | 1.98 E-11 | 1,07 (1,05–1,09) |
| rs55730499 | *SLC22A3-LPAL2-LPA* | 6 | T / C | 0,056 | 5,39 E-39 | 1,37 (1,31–1,44) |
| rs4252185 | *PLG* | 6 | C / T | 0,060 | 1,64 E-32 | 1,34 (1,28–1,41) |
| rs2107595 | *HDAC9* | 7 | A / G | 0.200 | 8.05 E-11 | 1,08 (1,05–1,10) |

| SNP | Nearest gene | Chromosome | Risk/Non-risk Allele | Risk Allele Frequency | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| rs10953541 | *7q22* | 7 | C / T | 0,783 | 1.02 E-05 | 1,05 (1,03–1,08) |
| rs11556924 | *ZC3HC1* | 7 | C / T | 0,687 | 5.34 E-11 | 1,08 (1,05–1,10) |
| rs17087335 | *NOS3* | 7 | T / C | 0,060 | 1,70 E-09 | 1,14 (1,09–1,19) |
| rs264 | *LPL* | 8 | G / A | 0,853 | 1.06 E-05 | 1,06 (1,03–1,09) |
| rs2954029 | *TRIB1* | 8 | A / T | 0,551 | 2.61E-06 | 1,04 (1,03–1,06) |
| rs2891168 | *9n21* | 9 | G / A | 0,489 | 2.29 E-98 | 1,21 (1,19–1,24) |
| rs2891168 | *9n21* | 9 | G / A | 0,489 | 2.29 E-98 | 1,21 (1,19–1,24) |
| rs2519093 | *ABO* | 9 | T / C | 0,191 | 1.19 E-11 | 1,08 (1,06–1,11) |
| rs2487928 | *KIAA1462* | 10 | A / G | 0,418 | 4.41 E-11 | 1,06 (1,04–1,08) |
| rs1870634 | *CXCL12* | 10 | G / T | 0,637 | 5.55 E-15 | 1,08 (1,06–1,10) |
| rs1412444 | *LIPA* | 10 | T / C | 0,369 | 5.15 E-12 | 1,07 (1,05–1,09) |
| rs11191416 | *CYP17A1-CNNM2-NT5C2* | 10 | T / G | 0,873 | 4.65 E-09 | 1,08 (1,05–1,11) |
| rs2128739 | *PDGFD* | 11 | A / C | 0,324 | 7.05 E-11 | 1,07 (1,05–1,09) |
| rs964184 | *ZNF259-APOA5-APOA1* | 11 | G / C | 0,185 | 5.60 E-05 | 1,05 (1,03–1,08) |

| SNP | Nearest gene | Chromosome | Risk/Non-risk Allele | Risk Allele Frequency | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| rs10840293 | *SWAP70* | 11 | A / G | 0,550 | 1.38 E-08 | 1,06 (1,04–1,08) |
| rs2681472 | *ATP2B1* | 12 | G / A | 0,201 | 6.17 E-11 | 1,08 (1,05–1,10) |
| rs3184504 | *SH2B3* | 12 | T / C | 0,422 | 1.03 E-09 | 1,07 (1,04–1,09) |
| rs1180803 | *KSR2* | 12 | G / T | 0,360 | 3.12 E-09 | 1,12 (1,08–1,16) |
| rs9319428 | *FLT1* | 13 | A / G | 0,314 | 7.13 E-05 | 1,04 (1,02–1,06) |
| rs11838776 | *COL4A1 / A2* | 13 | A / G | 0,263 | 1.83 E-10 | 1,07 (1,05–1,09) |
| rs10139550 | *HHIPL1* | 14 | G / C | 0,423 | 1.38 E-08 | 1,06 (1,04–1,08) |
| rs4468572 | *ADAMTS7* | 15 | C / T | 0,586 | 4.44 E-16 | 1,08 (1,06–1,10) |
| rs17514846 | *FURIN-FES* | 15 | Conditioner | 0,440 | 3.10 E-07 | 1,05 (1,03–1,07) |
| rs56062135 | *SMAD3* | 15 | C / T | 0,790 | 4.50 E-09 | 1,07 (1,05–1,10) |
| rs8042271 | *MFGE8-ABHD2* | 15 | G / A | 0,900 | 3.70 E-08 | 1,10 (1,06–1,14) |
| rs216172 | *SMG6* | 17 | C / G | 0,350 | 5.07 E-07 | 1,05 (1,03–1,07) |
| rs12936587 | *RAI1-PEMT-RASD1* | 17 | G / A | 0,611 | 8.24 E-04 | 1,03 (1,01–1,05) |
| rs46522 | *UBE2Z* | 17 | T / C | 0,513 | 1.84 E-05 | 1,04 (1,02–1,06) |

| SNP | Nearest gene | Chromosome | Risk/Non-risk Allele | Risk Allele Frequency | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| rs7212798 | *BCAS3* | 17 | C / T | 0,150 | 1.90 E-08 | 1,08 (1,05–1,11) |
| rs663129 | *PMAIP1-MC4R* | 18 | A / G | 0,260 | 3.20 E-08 | 1,06 (1,04–1,08) |
| rs56289821 | *LDLR* | 19 | G / A | 0,900 | 4.44 E-15 | 1,14 (1,11–1,18) |
| rs4420638 | *APOE-APOC1* | 19 | G / A | 0,166 | 7.07 E-11 | 1,10 (1,07–1,13) |
| rs12976411 * | *ZNF507-LOC400684* | 19 | T / A | 0,090 | 1.18 E-14 | 1,49 (1,35–1,67) |
| rs28451064 | *KCNE2* | 21 | A / G | 0,121 | 1.33 E-15 | 1,14 (1,10–1,17) |
| rs180803 | *POM121L9P-ADORA2A* | 22 | G / T | 0,970 | 1.60 E-10 | 1,20 (1,13–1,27) |

A, adenine; C, cytosine; D, deletion; G, guanine; I, insertion; OR - odds ratio; SNP - single nucleotide polymorphism; T, thymine; 95% CI, 95% confidence interval.

**Table 1** shows the most informative SNPs in each identified locus, the nearest gene, the chromosome on which it is located, the risk allele and its frequency, the P value, and the association magnitude [199].

The main advantages of GWAS include the consistency of the results obtained, the creation of intergroup collaborations, and the provision of data for the scientific community. Available GWAS databases include the European Genome-phenome Archive, the American Genotype-phenotype Database (dbGaP), and the combined database of genetic variants associated with coronary artery disease (CARDIoGRAMplusC4D consortium), which includes data from more than 60,000 patients and over 123,000 control participants [199].

The main limitations of GWAS are that the identified sequence variants are not necessarily causally related to the phenotype under study (they may be in linkage disequilibrium with the causal variant) and that they do not provide information about the associated pathophysiological mechanism, which must therefore be determined through specific functional studies. Moreover, these studies are mainly aimed at identifying common sequence variants with small effects and are less suitable for detecting rare variants with large effects [175].

Characterizing the yet undiscovered heritable component is one of the main challenges in the genetics of complex diseases. This heritability may be related to yet unidentified gene sequence variants associated with the disease. On the other hand, it may be related to changes elsewhere that do not affect the base sequence of the gene of interest but instead modulate its DNA structure, influencing its expression through epigenetic changes [187].

4. ***Genome sequencing studies.*** Sequencing methodology has traditionally been used to study monogenic and oligogenic diseases that exhibit clear familial segregation. Sequencing studies can focus on an individual gene, a group of genes, the exome (the part of the genome that encodes proteins), or the entire genome. The human genome contains approximately 3.1 billion nucleotides, while the exome consists of only 30 million nucleotides and around 23,000 genes. Large-scale sequencing studies of coronary artery disease (CAD) may uncover rare genetic variants that theoretically have a greater effect than more common variants. In a recent study, exome sequencing was followed by targeted sequencing of exons in approximately 6,700 patients and 6,700 control subjects; the analysis revealed rare sequence variants in LDLR and APOA5 associated with a higher risk of acute myocardial infarction (OR from 1.5 to 4.5), further confirming the significant impact of lipid metabolites (low-density lipoprotein cholesterol and triglycerides) on cardiovascular risk. Other studies focused on specific genes and also identified rare CAD-associated variants in genes involved in lipid metabolism: APOC3, NPC1L1, SCARB1, ANGPTL4, LPL, and SVEP1 [175, 182, 193].

To date, GWAS approaches have identified 55 gene loci associated with coronary artery disease (CAD). Of these, only one-third are related to classical risk factors, suggesting the potential to uncover new mechanisms and therapeutic targets. In an earlier meta-analysis of 361 GWAS studies published before February 2001, 991 genes linked to traits were identified as potential drug targets. In the same study, it was found that for 63 patients, the identified gene was a target for a drug already used for the treatment or prevention of the condition in question. Moreover, for another 92 patients, the gene associated with the trait was a target for a drug or drugs used to treat another condition, indicating the possibility of drug repositioning.

Despite these promising results, the identification of a sequence variant associated with a disease does not confirm that the gene is a therapeutic target. An example of an identified gene that became a target for a drug is PCSK9. Linkage analysis showed that this gene is associated with familial hypercholesterolemia, and subsequent studies revealed that the enzyme encoded by PCSK9 increases HDL levels by promoting the degradation of the LDL receptor. It has been shown that specifically developed antibodies against PCSK9 reduce LDL levels, and these PCSK9 inhibitors are currently undergoing phase III clinical trials to assess their efficacy in preventing clinical events.

However, more frequently, the association with a disease does not lead to new treatments, highlighting the need to define the mechanism linking the sequence variant to the disease trait. An example of this is the 9p21 region, which was shown to be associated with CAD in the first GWAS reports published in 2007. The sequence variants associated with CAD are located in an intergenic region near a gene cluster encoding cell cycle regulators (CDKN2A and CDKN2B) and the non-coding RNA CDKN2BAS (also called ANRIL). Several explanations for the association with CAD have been proposed, but the primary mechanism remains unclear, impeding the development of new drugs for cardiovascular disease prevention.

## § 1.4. CORONARY ANGIOGRAPHY – THE GOLD STANDARD FOR DIAGNOSING CORONARY ARTERY DISEASE

Coronary artery disease (CAD) is known as the "leading killer of human health." According to data published by the WHO in 2019, cardiovascular diseases account for 31% of all global deaths annually, surpassing any other cause of mortality. However, the diagnosis of cardiovascular diseases remains costly, limiting the widespread adoption of modern technologies worldwide, especially in some developing regions. Therefore, there is an urgent need for a method that allows for rapid and effective diagnosis of CAD at a lower cost [8,9,40].

Currently, the most common diagnostic method for CAD is coronary angiography, an invasive procedure considered the "gold standard" for diagnosing coronary artery disease. However, coronary angiography presents the following disadvantages for patients:

1. **Induces Arrhythmia**: Ventricular fibrillation is the most serious complication, which can be triggered by several contributing factors. The primary factors include the dose of the contrast agent administered, the duration of the procedure, and the depth of catheter insertion into the coronary artery ostium. If coronary blood flow is blocked for too long, the procedure may lead to myocardial ischemia, electrical instability of the heart, pericardial tamponade, coronary artery dissection, and even acute myocardial infarction.
2. **Adverse Reactions to Contrast Agents**: These are primarily allergic reactions and nephrotoxicity.
3. **Vasovagal Reflex**: This occurs more frequently during coronary angiography, particularly after the procedure or during the removal of the arterial sheath. Various stimuli affect the cortical center and hypothalamus, suddenly increasing the tension of autonomic cholinergic nerves, which causes strong reflex dilation of small vessels in internal organs and muscles. Patients may experience pallor, a drop in blood pressure, bradycardia, yawning, cold sweat, nausea, vomiting, visual disturbances, and even cardiac arrest.

4. **The Procedure is Invasive**: At the puncture site, complications such as bleeding, hematoma, pseudoaneurysm, and arteriovenous fistula can occur. Additionally, a prolonged period is required to achieve hemostasis after the procedure.
5. **Patients undergoing femoral artery puncture require short-term hospitalization for approximately three days.**
6. **Radiation exposure during coronary angiography has a certain impact on the human body.**
7. **The cost of coronary angiography is high, posing a significant financial burden for low-income patients.**

Biochemical blood test indicators can illustrate the degree of coronary artery obstruction [47,51,169]. After myocardial injury, cardiac troponin complexes are released into the bloodstream, with their concentration gradually increasing and remaining elevated for a prolonged period. Therefore, when a patient presents with symptoms of cardiovascular disease, blood tests to monitor troponin levels are often necessary. Physicians can determine whether the patient has heart disease and assess its severity based on the test results. Thus, blood tests can be used to predict the risk of cardiovascular diseases.

On the other hand, color Doppler echocardiography reports are also highly valuable for diagnosing coronary artery disease. This technique utilizes the Doppler principle and a range of electronic technologies to display a real-time spectrogram of blood flow in a specific volume (SV) at a particular point in the heart or major blood vessels, all within the two-dimensional positioning of an echocardiogram. Coronary atherosclerotic heart disease is a type of atherosclerotic lesion of the coronary arteries, leading to vascular lumen stenosis or occlusion, which results in myocardial ischemia, hypoxia, or necrosis [30,44,50].

**Ischemic heart disease (IHD) has garnered significant attention within the scientific community.** Researchers have conducted in-depth studies on risk prediction models for IHD from various perspectives and have achieved notable results. The Framingham study was the first to apply traditional cardiovascular risk factors to create a predictive model based on multiple regression equations to forecast heart disease. Subsequently, it published a series of risk prediction models for various types of cardiovascular diseases. In addition to the Framingham model, researchers have developed other risk assessment models such as SCORE, PROCAM, Reynolds, and QRISK to predict heart disease in different countries and regions.

The Tianjin Laboratory of Information Sensing and Intelligent Control utilized the correlation between cardiac motion signals and electrocardiogram (ECG) signals to develop a regression prediction model for forecasting heart disease. However, these cardiovascular risk prediction models are based on statistical regression techniques and exhibit limitations in predicting heart disease [135, 162].

In the aforementioned studies, most experiments relied on a limited set of indicators to assess the risk of IHD, often neglecting the overall health status of

patients. The predictive accuracy of IHD in most literature sources is below 90%, which fails to meet clinical practice requirements. In literature utilizing deep learning algorithms, most focus on analyzing coronary angiography images. However, due to the numerous disadvantages of coronary angiography mentioned earlier, many physicians and patients are reluctant to use this method. Therefore, there is an urgent need to find a method that enables the rapid, efficient, and accurate diagnosis of ischemic heart disease at a lower cost.

## 1.5. ASSESSMENT OF THE PREVALENCE, SEVERITY, AND RISK FACTORS OF DEPRESSIVE SYMPTOMS AMONG PATIENTS WITH CORONARY ARTERY DISEASE

Depressive disorders are a leading and growing cause of disability, estimated to affect over 264 million people worldwide. The position statements from the American Heart Association and the European Society of Cardiology recognize that depression may be a modifiable prognostic factor in ischemic heart disease (IHD), contributing to improved recognition and treatment of the condition [103, 188].

However, there are uncertainties in the epidemiological data underlying this potential connection. First, several studies have used broad psychological distress indicators, leaving doubts about whether depressive symptoms themselves are directly linked to cardiovascular disease risk. Second, most studies have had limited statistical power, preventing reliable characterization of the relationships across the full spectrum of depressive symptom severity. Third, studies have used varying approaches to adjust for potential confounding factors, making it difficult to draw firm conclusions about whether the associations are independent of established cardiovascular risk factors. Fourth, inconsistent disease definitions across studies hinder standardized analysis of cardiovascular disease subtypes or direct comparisons of depressive symptom associations across multiple conditions [94,95].

Depression is a common condition globally, estimated to affect 3.8% of the population, including 5.0% of adults and 5.7% of adults over the age of 60. Approximately 280 million people worldwide suffer from depression. Despite the availability of effective treatments for mental health disorders, more than 75% of people in low- and middle-income countries receive no treatment at all [39].

During a depressive episode, an individual experiences a depressed mood (feeling sad, irritable, or empty) or a loss of pleasure or interest in activities for most of the day, nearly every day, for at least two weeks. Additional symptoms may include poor concentration, feelings of excessive guilt or low self-esteem, hopelessness about the future, thoughts of death or suicide, sleep disturbances, changes in appetite or weight, and feelings of marked fatigue or low energy [29, 45].

In certain cultural contexts, some individuals may be more inclined to express mood changes through physical symptoms (e.g., pain, fatigue, weakness). However, these physical symptoms are not linked to any other medical condition [79, 81].

During a depressive episode, a person experiences significant difficulties in personal, family, social, educational, professional, and other important areas of

functioning. A depressive episode can be classified as mild, moderate, or severe, depending on the number and severity of symptoms and the degree of functional impairment [100, 107].

There are various mood disorder patterns, including:

- **Depressive disorder with a single episode**, meaning the first and only episode in an individual;
- **Recurrent depressive disorder**, indicating that the individual has had at least two depressive episodes;
- **Bipolar disorder**, characterized by alternating depressive episodes and periods of manic symptoms.

The World Health Organization (WHO) has developed brief psychological intervention guidelines for depression that non-specialists can deliver to individuals and groups [183].

Patients with ischemic heart disease (IHD) often have multiple chronic conditions that can be managed to improve overall outcomes. These include hypertension, hyperlipidemia, diabetes mellitus, obesity, nicotine dependence, and physical inactivity. The goal of each clinical visit is to integrate pharmacological and non-pharmacological interventions to manage these conditions and reduce cardiovascular risk. Additionally, depression is another condition that needs to be identified and treated in patients with IHD. Research indicates that 20% to 40% of IHD patients suffer from clinically significant depression. The prevalence of depression among IHD patients is higher than in the general population.

More than 25 years ago, the seminal study by Frasure-Smith et al. identified depression as a significant predictor of mortality in patients with IHD following myocardial infarction (MI) [121]. Since this initial study, numerous investigations have shown that patients with coexisting IHD and depression experience worse health outcomes. In 2014, the American Heart Association issued a scientific statement recommending that depression following acute coronary syndrome should be considered a risk factor for cardiac morbidity and mortality.

The **TRIUMPH study** (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status) was the first to evaluate the relationship between acute myocardial infarction (AMI) patients and depression, comparing those receiving depression treatment with those who were not. A total of 4,062 patients were enrolled across 24 hospitals in the United States. The results showed that AMI patients with untreated depression had a **70–90% higher risk of death** within one year compared to those without depression or with treated depression. Based on these findings, the TRIUMPH research team recommends **including depression screening as part of the care protocol** for AMI patients to allow for early intervention and reduce mortality risk [194].

The **ENRICHD trial** (Enhancing Recovery in Coronary Heart Disease Patients) identified patients with recent MI who met criteria for minor or major

depression [87]. Patients were randomized to receive either usual medical care or **cognitive-behavioral therapy (CBT)**, supplemented with **selective serotonin reuptake inhibitors (SSRIs)** when indicated. A total of 2,481 patients were enrolled across 8 clinical centers. The results indicated that patients receiving CBT experienced **reduced depression and social isolation**. However, when comparing usual medical care to CBT, there was **no reduction in mortality or recurrent MI rates**. Based on these findings, ENRICHD researchers recommend **screening MI patients for depression** and ensuring **appropriate follow-up and treatment** when depression is identified [87].

The **CREATE study** (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy) aimed to determine whether treatment with **citalopram (an SSRI)** and **interpersonal psychotherapy** could reduce depressive symptoms in patients with IHD and major depression. A total of **284 patients** from 9 Canadian academic centers participated. The results showed that **citalopram outperformed placebo** in reducing depressive symptoms, while interpersonal psychotherapy provided **no additional benefits** compared to standard clinical care. Based on these results, the CREATE research team recommends considering **citalopram or sertraline** in combination with clinical care as the **first-line treatment** for patients with IHD and major depression [87, 194].

A **recent study** conducted by the **Intermountain Heart Institute** revealed that patients diagnosed with depression at any point after an ischemic heart disease (IHD) diagnosis have **twice the risk of death** compared to IHD patients without a depression diagnosis. This study included **24,137 patients** with **angiographically confirmed IHD** (stenosis ≥70%). Furthermore, it was found that **depression is a stronger predictor of mortality** than any other risk factor or comorbidity, independent of baseline characteristics and the severity of IHD. Based on these findings, researchers from the **Intermountain Heart Institute** recommend that **regular depression screening** be included in the **follow-up care** of IHD patients [160].

Significant advancements in the treatment of IHD patients have contributed to an overall reduction in mortality. **Interventions** such as **surgical revascularization**, **pharmaceutical developments**, and **risk factor management** have played crucial roles in improving outcomes. However, despite these improvements, there is still a critical need to focus on the **diagnosis and treatment of depression** in IHD patients to further enhance health outcomes. As previously discussed, **evidence-based recommendations** from clinical trials and studies include the following:

- **Regular depression screening** as part of standard care for IHD patients;
- **Consideration of cognitive-behavioral therapy (CBT)**, with the addition of **SSRIs** (*citalopram* or *sertraline*) as necessary for treating patients with major depression and IHD [210].

**Effective depression screening tools** suitable for clinical use include the **Beck Depression Inventory**, the **Hamilton Depression Rating Scale**, the **Patient Health Questionnaire (PHQ-9)**, and the **Primary Care Evaluation of Mental Disorders (PRIME-MD)** Level I screener. In addition to routine assessments such as **blood pressure**, **lipid profiles**, **body mass index (BMI)**, and **A1C levels**, **depression screening** should be integrated into IHD patient care. Identifying and treating depression can significantly contribute to **reducing morbidity and mortality** in this population [210].

## 1.6. PSYCHOSOCIAL RISK FACTORS IN CORONARY ARTERY DISEASE: SCREENING BEYOND ANXIETY AND DEPRESSION

**Psychosocial risk factors** (PSRF) are widely used to describe both the presence of distress and the lack of positive psychological resources. These factors significantly impact the prognosis of coronary artery disease (CAD) and substantially worsen health-related quality of life (HRQoL) for patients [12,16]. Recent studies indicate that several PSRFs—such as **depression**, **anxiety**, **burnout**, **anger**, **hostility**, **work-related stress**, **Type D personality**, **social isolation**, and **low socioeconomic status**—increase the risk of recurrent cardiovascular events, as well as **cardiac mortality** and **mortality from all causes** in CAD patients. Conversely, positive psychological resources, such as **strong social support**, have been identified as protective factors against CAD.

PSRFs have an adverse effect on cardiac outcomes by promoting **unhealthy lifestyles** and reducing the likelihood of successful modification of cardiovascular risk factors. They also contribute to lower adherence to treatment regimens and weaken the effects of **cardiac rehabilitation**. Furthermore, recent research has shown that **loneliness** is associated with the onset of **cardiovascular diseases** and related hospitalizations. This association has been recognized as independent of other risk factors, suggesting that loneliness influences cardiovascular disease through its own mechanisms, which include the **immune system**, the **sympathetic nervous system**, and the **hypothalamic-pituitary-adrenal axis**. Specifically, it is believed that there is **vegetative co-activation**, an **increase in pro-inflammatory cytokines**, **high reactivity**, and **increased daily secretion**.

Additionally, **Type D personality** has been described as a contributing factor to **cardiac rehabilitation dropout** and the emergence of symptoms of **anxiety and depression** [114,126]. It is possible that **inflammation** could also be one of the mechanisms linking **Type D personality** with cardiovascular disease risk.

Based on these and other findings, European guidelines for the prevention of cardiovascular diseases in clinical practice recommend assessing **psychosocial risk factors** (PSRFs) and considering individualized clinical management to improve **quality of life** and **prognosis** in coronary artery disease (CAD) [123,134]. Assessment methods include **clinical interviews**, **questionnaires**, and **standardized structured interviews** [144,147]. Recommendations from both the

European and American **Cardiological Societies** and **Associations** suggest the use of validated scales such as:

- **Patient Health Questionnaire (PHQ)**
- **Beck Depression Inventory (BDI)**
- **Hospital Anxiety and Depression Scale (HADS)**
- **State Anxiety Inventory (SSAI)** for assessing depression and anxiety;
- **ENRIIHD Social Support Tool (ESSI)** for assessing social support;
- **State-Trait Anger Expression Inventory (STAXI)** and **Cook-Medley Hostility Scale (Ho)** for measuring anger and hostility;
- **Type D Scale 14**;
- **HeartQoL** for assessing quality of life [124].

Other recommended types of tools include structured interviews, such as the **WHO Composite International Diagnostic Interview (CIDI)** for diagnosing depression and anxiety [25].

Comprehensive screening for PSRFs during cardiac rehabilitation is not yet routine and at best includes only a few PSRFs, such as depression, anxiety, or health-related quality of life (HRQoL). Although screening tools for PSRFs are widely used, they are typically applied by specialized mental health professionals, and their use is not common among other healthcare providers treating CAD patients. Moreover, assessing and interpreting these scales can be complex and may require substantial time and resources, which busy healthcare professionals in overcrowded medical settings may not have. An important limitation in clinical application is the variety of response formats across different PSRF questionnaires, which can make their use cumbersome in everyday practice. Currently, the focus of PSRF screening is on anxiety and depression [137,179]. While many other well-known PSRFs exist, the interactions between these factors and their significance for short- and long-term success in cardiac rehabilitation, as well as their impact on morbidity and mortality, are less understood.

## CHAPTER 2. THE ROLE OF RISK FACTORS IN PREDICTING CORONARY HEART DISEASE

### 2.1. ASSESSMENT OF PSYCHOEMOTIONAL STATE IN PATIENTS WITH DESTABILIZATION OF CHRONIC CORONARY HEART DISEASE AMONG THE UZBEK POPULATION

One of the objectives of this study was to determine the prevalence of psychoemotional distress in patients with destabilization of coronary artery disease (CAD). To achieve this, the study included 429 patients with CAD, including 309 patients with unstable angina (Group 1), 120 patients with stable angina (Group 2), and 80 practically healthy individuals as a control group.

Several methods were chosen to identify psychoemotional distress. One of the key methods for assessing the psychoemotional state was the Hospital Anxiety and Depression Scale (HADS), which was used to evaluate the level of anxiety and depression in patients with destabilization of chronic coronary heart disease.

A detailed analysis of the psychoemotional status of 429 patients at the time of inclusion in the study using the HADS questionnaire revealed that the prevalence of psychoemotional distress (PED) among CAD patients was 58.5% (n=251), indicating a high occurrence of affective disorders in cardiac pathology.

Based on these findings, CAD patients were categorized according to the presence of psychoemotional conditions, as determined by the HADS-A/D scale. PED was verified in patients scoring ≥7 points on both subscales of the questionnaire. Accordingly, each group was divided into two subgroups: patients with unstable angina and PED – 183 (59.2%) and patients with unstable angina without PED – 126 (40.8%). Among patients with stable angina, 31 (25.8%) had PED, while 89 (74.2%) did not.

According to the questionnaire results, the main group scored an average of 11.47±2.93 points on the HADS-A subscale and 10.8±3.42 points on the HADS-D subscale, which was significantly higher than the mean values in the comparison group ($p<0.001$), where scores were 8.0±2.31 and 8.25±0.44, respectively. In the control group, the average scores were 4.5±1.73 on HADS-A and 4.26±1.98 on HADS-D, which also excluded the presence of PED in healthy individuals (Figure 3.1).

**Table 2.1.1**

**Anxiety and Depression Scores According to the HADS-D/A Scale**

| HADS Indicators | Unstable Angina Patients (n=309) | | Stable Angina Patients (n=120) | | P-value |
|---|---|---|---|---|---|
| Patients with PED (n=183) | Patients without PED (n=126) | Patients with PED (n=31) | | Patients with PED (n=183) | Patients without |

| | | | | | PED (n=126) |
|---|---|---|---|---|---|
| Anxiety | 11.47 ± 2.93 | 4.57 ± 1.73 | 8.0 ± 2.31 | Anxiety | 11.47 ± 2.93 |
| Depression | 10.80 ± 3.42 | 4.26 ± 1.98 | 8.25 ± 0.44 | Depression | 10.80 ± 3.42 |

**Note**: PED – Psychoemotional distress, HADS – Hospital Anxiety and Depression Scale.

In the study of PED severity, we identified 44.2% (n=81) cases of subclinical depression and 55.7% (n=102) cases of clinical depression among patients with unstable angina (UA) and PED. In contrast, among patients with stable angina (SA) and PED, 25.8% (n=31) had subclinical depression, while no cases of clinically significant depression were found. Additionally, 35.5% (n=65) of patients with UA and PED had subclinical anxiety, and 59.0% (n=108) had clinical anxiety. Among patients with SA, 17.5% (n=21) had subclinical anxiety, and 2.5% (n=3) had clinically significant anxiety (Tables 3.2, 3.3). It is worth noting that the mean anxiety and depression scores were insignificantly higher in patients with UA and PED: subclinical depression was 8.9±0.44 points, clinical depression was 13.7±0.56 points, subclinical anxiety was 8.9±0.42 points, and clinical anxiety was 13.8±0.45 points. Meanwhile, in patients with SA, subclinical anxiety was 8.68±0.32 points, clinical anxiety was 12.4±0.44 points, subclinical depression was 8.4±0.33 points, and clinical depression was 12.4±0.48 points.

**Table 2.1.2**

**Severity of PED According to the HADS-D Scale**

| Severity Level (HADS-D) | Patients with UA and PED (n=183) | Patients with SA and PED (n=31) | P-value |
|---|---|---|---|
| **Subclinical Depression** | 44.2% (n=81) | 25.8% (n=31) | 0.018 |
| **Clinical Depression** | 55.7% (n=102) | 0% (n=0) | ∞ |

**Note**: UA – Unstable angina, SA – Stable angina, PED – Psychoemotional distress, HADS-D – Hospital Anxiety and Depression Scale (Depression subscale).

**Table 2.1.3**

**Severity of PED According to the HADS-A Scale**

| Severity Level (HADS-A) | Patients with UA and PED (n=173) | Patients with SA and PED (n=24) | P-value |
|---|---|---|---|
| **Subclinical Anxiety** | 35.5% (n=65) | 17.5% (n=21) | 0.001 |
| **Clinical Anxiety** | 59.0% (n=108) | 2.5% (n=3) | 0.001 |

**Note**: UA – Unstable angina, SA – Stable angina, PED – Psychoemotional distress, HADS-A – Hospital Anxiety and Depression Scale (Anxiety subscale).

**Table 2.1.4**

**HADS Scores in Patients with UA and PED by Gender**

| Indicators | Women with UA (n=137) | Men with SA (n=172) | P-value |
|---|---|---|---|
| **HADS-D (points)** | 9.5 ± 1.71 | 9.5 ± 2.11 | 0.982 |
| **HADS-A (points)** | 8.8 ± 1.11 | 8.9 ± 1.08 | 0.993 |
| **Indicators** | **Women with UA (n=57)** | **Men with SA (n=63)** | **P-value** |
| **HADS-D (points)** | 5.3 ± 0.58 | 5.7 ± 0.64 | 0.372 |
| **HADS-A (points)** | 5.1 ± 0.39 | 5.3 ± 0.58 | 0.532 |

**Note**: UA – Unstable angina, SA – Stable angina, PED – Psychoemotional distress, HADS-D – Hospital Anxiety and Depression Scale (Depression subscale), HADS-A – Hospital Anxiety and Depression Scale (Anxiety subscale).

To determine the type of anxiety, the Spielberger-Khanin scale was used. This scale allowed for the identification of situational anxiety (SA) and trait anxiety (TA), as well as their severity levels. The questionnaire revealed that situational anxiety was significantly common among patients with CAD during both destabilization and stability periods (n=251). However, in terms of severity, moderate and severe anxiety were significantly more frequent in patients with unstable CAD compared to those with stable angina (Table 3.5).

**Table 2.1.5**

**Severity of Situational and Trait Anxiety According to the Spielberger-Khanin Questionnaire**

Situational Anxiety

| Severity Level | Patients with UA (n=309) | Patients with SA (n=120) | P-value |
|---|---|---|---|
| **Mild** | 58 (18.7%) | 57 (47.4%) | 0.211 |
| **Moderate** | 163 (52.7%) | 53 (44.1%) | 0.001 |
| **Severe** | 88 (28.4%) | 10 (8.3%) | 0.001 |

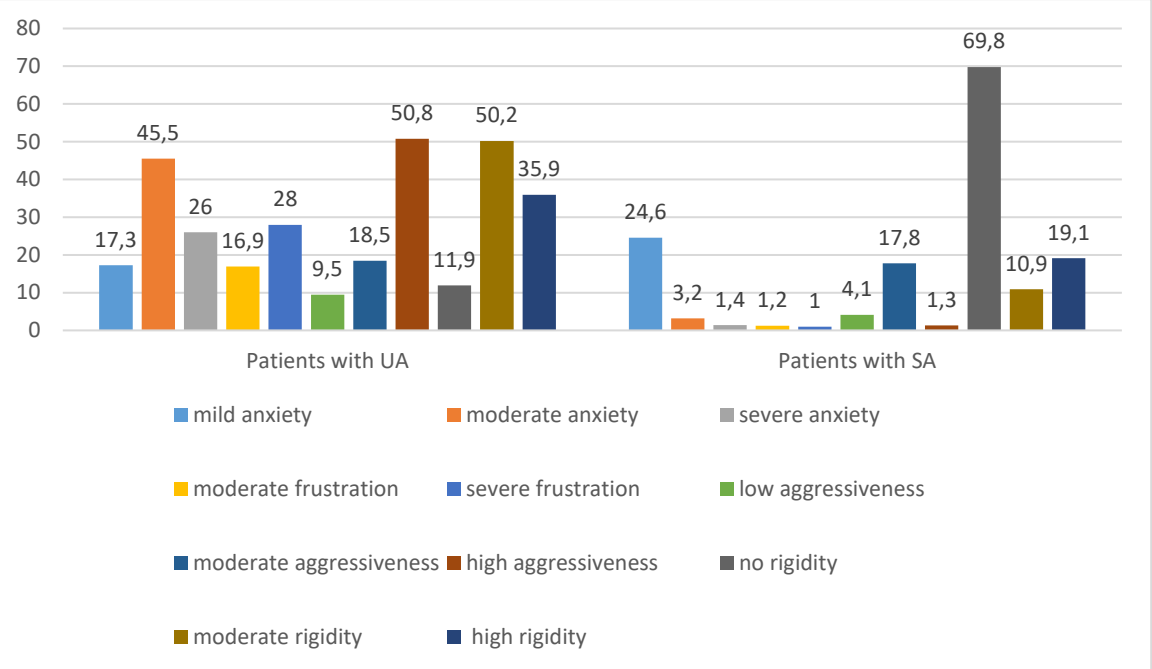
Trait Anxiety

| Severity Level | Patients with UA (n=309) | Patients with SA (n=120) | P-value |
|---|---|---|---|
| **Mild** | 75 (23.1%) | 70 (58.3%) | 0.001 |
| **Moderate** | 162 (52.4%) | 41 (34.1%) | 0.001 |
| **Severe** | 72 (23.3%) | 9 (7.5%) | 0.001 |

**Note**: UA – Unstable angina, SA – Stable angina.

In addition, the Eysenck questionnaire was used, which is a self-assessment tool for diagnosing psychological states such as anxiety, frustration, aggressiveness, rigidity, and their severity. It is noteworthy that among patients with unstable forms of angina, moderate anxiety (45.5%) and severe anxiety (26.0%) were frequently observed, along with high levels of aggressiveness (50.8%) and pronounced rigidity (35.9%). In contrast, among patients with stable angina, mild anxiety (24.6%) and aggressiveness (23.2%) were more prevalent.

**Figure 2.1.1. Distribution of Psychoemotional States in Patients with UA and SA According to the Eysenck Scale**




A comparative analysis of the socio-demographic characteristics of CAD patients based on their psychoemotional status revealed a diverse pattern. Patients with CAD and PED had a significantly lower level of education: 100 patients (39.8%) had higher education, while 151 (60.2%) had secondary education ($p<0.07$). In contrast, among patients without PED, higher education was more common—122 (68.5%) had higher education, and 56 (31.4%) had secondary education ($p<0.01$).

According to the Eysenck scale, 34 (10.8%) patients with PED and no formal education exhibited pronounced frustration, whereas among patients with higher education, only 9 (2.8%) had mild frustration.

**Table 2.1.6**

**Characteristics of CAD Patients with and without Psychoemotional Disorders (PED)**

| Parameters | CAD with PED (n=251) | CAD without PED (n=178) | P-value |
|---|---|---|---|
| **Age (years) (M±m)** | 63.4±4.2 | 60.1±3.8 | 0.871 |
| **Male gender, n (%)** | 172 (68.5%)* | 85 (47.7%) | 0.028 |
| **Education:** | | | |
| Higher, n (%) | 100 (39.8%) | 122 (68.5%) | 0.07 |
| Secondary specialized, n (%) | 151 (60.2%)** | 56 (31.4%) | 0.01 |
| **Social status:** | | | |
| Employed, n (%) | 56 (22.3%) | 116 (65.1%) | 0.075 |
| Unemployed, n (%) | 69 (27.4%) | 62 (34.8%) | 0.974 |

| Parameters | CAD with PED (n=251) | CAD without PED (n=178) | P-value |
|---|---|---|---|
| Retired, n (%) | 183 (72.9%) | 113 (63.5%) | 0.875 |
| Disabled, n (%) | 24 (9.6%) | 32 (17.9%) | 0.352 |
| **Family history of cardiovascular diseases, n (%)** | 132 (52.5%) | 106 (59.6%) | 0.095 |
| **Duration of CAD (years) (M±m)** | 5.3±0.8 | 5.5±0.61 | 0.863 |

* **Statistically significant differences** ($p<0.05$).
** **Highly significant differences** ($p<0.01$).

**Note:** *p<0.05, **p<0.01 – statistical significance of differences between groups of CAD patients.*

During the clinical collection of anamnesis data, it was determined that among CAD patients without PED, a significantly higher prevalence of a family history of cardiovascular diseases (CVD) was observed in more than 59.6% of cases, compared to 52.5% in the main group (p<0.095).

A comparative assessment was conducted on the prevalence of modifiable CVD risk factors such as smoking, obesity, sedentary lifestyle, hypertension, asymptomatic hyperuricemia, and stress among CAD patients with PED (Table 3.7).

**Table 2.1.7.**

**Comparative analysis of the prevalence of modifiable cardiovascular risk factors depending on the presence of psychoemotional disorders (PED)**

| Main Risk Factors | CAD with PED, n=251 | CAD without PED, n=178 | P-value |
|---|---|---|---|
| **Smoking, n (%)** | 69 (27.4%) *** | 21 (11.8%) | <0.001 |
| **Sedentary lifestyle, n (%)** | 92 (36.7%) *** | 63 (35.4%) | <0.001 |
| **BMI (kg/m²)** | 32.8±3.2 ** | 30.1±3.17 | 0.022 |
| **Serum uric acid (µmol/L)** | 462.2±7.42 * | 348.5±5.38 | 0.03 |
| **Excess body weight, n (%)** | 164 (65.3%) *** | 82 (46.1%) | <0.001 |
| 1st degree obesity, n (%) | 44 (17.5%) * | 26 (14.6%) | 0.041 |
| 2nd degree obesity, n (%) | 68 (27.1%) ** | 25 (14.0%) | 0.039 |
| 3rd degree obesity, n (%) | 52 (20.7%) | 72 (40.4%) | 0.004 |

| Main Risk Factors | CAD with PED, n=251 | CAD without PED, n=178 | P-value |
|---|---|---|---|
| **Hypertension (HTN) stages** | | | |
| HTN stage 1, n (%) | 172 (68.5%) *** | 89 (50.0%) | <0.001 |
| HTN stage 2, n (%) | 106 (42.2%) *** | 66 (37.0%) | <0.001 |
| HTN stage 3, n (%) | 42 (16.7%) *** | 11 (6.2%) | <0.001 |
| **Stress level (points, M±m)** | 12.06±2.17 *** | 4.68±1.92 | <0.001 |

**Note:** *p<0.05, **p<0.01, ***p<0.001 – statistical significance of differences between groups.*

Thus, smokers were twice as common among patients with CAD and PEP, accounting for 27.4% of cases compared to 11.8% in the comparison group (p<0.001). Physical activity was significantly higher (p<0.001) in patients without PEP compared to the main group. Additionally, the mean BMI values differed between the main and comparison groups, amounting to 32.8±1.14 and 30.1±1.00 kg/m², respectively (p<0.022). The degree of obesity in patients with CAD and anxiety-depressive syndrome tended to increase, with a predominance of grade 3 obesity, which was 1.9 times more frequent (p<0.004) compared to the comparison group.

When studying the clinical condition of patients depending on the degree of hypertension at the time of examination, it was found that in patients with CAD and PEP, grade 1 hypertension was recorded in 42.2%, grade 2 in 16.7%, and grade 3 in 9.6%. In contrast, among patients with CAD without PEP, grade 1 hypertension was recorded in 37.0%, grade 2 in 6.2%, and grade 3 in 6.7%, respectively.

The study of the mean serum uric acid (UA) level among patients with CAD and PEP showed an average of 462.2±7.42 μmol/L, whereas in patients with CAD without PEP, this indicator was 348.5±5.38 μmol/L, and these differences were statistically significant (p=0.03). This suggests that the development of PEP is associated not only with the above-mentioned factors but also with asymptomatic hyperuricemia.

To identify the destabilization of coronary artery disease among patients with and without PEP, we conducted a comparative assessment of cardiac parameters based on ECG and echocardiography data.

The results of hemodynamic parameters showed that LVEF was statistically lower in patients with UA compared to those with SA (p=0.042). In patients with UA and PEP, LVEF was slightly lower than in those with UA without PEP. Additionally, cases of ST-segment depression were 28.2% more frequent in patients with UA and PEP compared to those without PEP (p=0.032).

The data above indicate that the comorbidity of psycho-emotional disorders leads to the destabilization of CAD, which, in turn, worsens the condition and quality of life of these patients.

To assess pain intensity among patients with UA, we used the McGill Pain Questionnaire (MPQ).

The McGill Pain Questionnaire (MPQ) consists of a list of 73 words divided into three domains (sensory, affective, and evaluative) and six words to indicate current pain intensity. In total, the three domains include up to 20 subcategories, each containing between 3 and 6 descriptive words. The first domain (sensory), which includes subcategories 1 to 13, contains 52 descriptors. The second domain (affective) consists of six sections with 16 descriptors. The third domain (evaluative) consists of one section and includes 5 descriptors. Each subcategory is assigned a numerical score corresponding to the ranking order of the highest selected descriptor.

Although the validity of the MPQ domains has been questioned by some authors, our study demonstrates the opposite, highlighting its practical value, which aligns with the opinions of most researchers.

During the patient survey aimed at determining pain intensity during angina attacks, it was found that 197 (63.7%) patients with UA described their pain as intense across all scales of the McGill Pain Questionnaire. Notably, among these 197 patients, 176 (89.3%) had psycho-emotional disorders of varying severity, indicating a direct correlation between pain syndrome occurrence and psycho-emotional disturbances.

The Pain Rank Index (PRI) for patients with PED was 18.9±2.78, indicating moderate pain intensity. The results for this parameter were significantly lower ($p<0.001$) in patients with angina without PED, suggesting a lower pain intensity in this group.

Patients with PED subjectively rated their pain higher on all three scales of the McGill Pain Questionnaire and used higher-ranking descriptive terms than those without PEP. The Number of Words Chosen Index (NWCI) of the McGill Pain Inventory Scale was also significantly higher ($p<0.001$) in patients with PED (7.4±0.7 vs. 3.5±0.4). Patients with PED selected significantly more descriptive words when characterizing their pain compared to those without PED.

Thus, the study of the frequency and severity of clinical manifestations of PED in patients with coronary artery disease during destabilization showed that almost every second patient had PED, with one-third exhibiting clinically significant levels of anxiety and depression. CAD patients with PED had significant differences in certain socio-demographic parameters: they were more likely to have a secondary education (151 cases, 60.2%) and were unemployed in 69 cases (27.4%) compared to patients without psycho-emotional disorders.

The analysis of cardiovascular risk factors showed that independent psycho-emotional risk factors such as anxiety and depression in CAD patients were often associated with smoking (69 cases, 27.4%), hyperuricemia (66.1%), severe arterial hypertension (172 cases, 68.5%), and excess body weight (164 cases, 65.3%).

However, these factors were not directly related to age, sex, genetic predisposition, or low physical activity, raising interest in studying the condition of the coronary arteries in patients with unstable CAD.

## 2.2. THE ROLE OF CORONARY ANGIOGRAPHY IN PREDICTING CORONARY ARTERY DISEASE

Coronary artery disease (CAD) is known as the "number one killer of human health." According to data published by the WHO in 2019, cardiovascular diseases account for 31% of all deaths worldwide annually, surpassing any other cause of mortality. However, the diagnosis of cardiovascular diseases remains expensive, limiting the widespread adoption of modern technologies globally, particularly in some developing regions. Therefore, it is urgently necessary to find a method that allows for the rapid and effective diagnosis of coronary artery disease at a lower cost [8,9,40].

Currently, a common method for diagnosing coronary artery disease is coronary angiography—an invasive procedure considered the "gold standard" for CAD diagnosis. However, for patients, coronary angiography has the following disadvantages:

8. **Causes Arrhythmia.** Ventricular fibrillation is the most severe complication, which can be triggered by multiple contributing factors, primarily the dose of the contrast agent, the duration of the procedure, and the depth of catheter insertion into the coronary artery ostium. If coronary blood flow is blocked for too long, the procedure can lead to myocardial ischemia, electrical instability of the heart, pericardial tamponade, coronary artery dissection, and even acute myocardial infarction.
9. **Adverse Reactions to Contrast Agents,** mainly allergic reactions and nephrotoxicity.
10. **Vasovagal Reflex.** This occurs more frequently during coronary angiography, either post-procedure or when removing the arterial sheath. Various stimulating factors affect the cortical center and hypothalamus, suddenly increasing the tension of autonomic cholinergic nerves, leading to intense reflexive vasodilation of small vessels in the internal organs and muscles. Patients may become pale, experience a drop in blood pressure, bradycardia, yawning, cold sweats, nausea, vomiting, vision disturbances, and even cardiac arrest.
11. **The Procedure is Invasive.** Puncture site complications include bleeding, hematoma, pseudoaneurysm, and arteriovenous fistula formation. Additionally, it takes a significant amount of time to stop bleeding post-procedure.
12. **Patients Undergoing Femoral Artery Puncture Require Short-Term Hospitalization** for approximately three days.
13. **Radiation Exposure During Coronary Angiography** has certain effects on the human body.

14. **High Cost of Coronary Angiography** poses a significant financial burden, especially for economically disadvantaged patients.

Biochemical blood test indicators can illustrate the degree of coronary artery obstruction [47,51,169]. After myocardial injury, cardiac troponin complexes are released into the bloodstream, with their concentration gradually increasing and remaining elevated for a prolonged period. Therefore, when a patient presents with symptoms of cardiovascular disease, blood tests are often necessary to monitor troponin levels. Physicians can determine whether the patient has heart disease and assess its severity based on test results. Thus, blood tests can be used to predict cardiovascular disease risk.

On the other hand, **color Doppler echocardiography reports** are also highly valuable for diagnosing coronary artery disease. This method uses the Doppler principle along with advanced electronic technologies to visualize the blood flow spectrum of a specific volume (SV) in a particular location of the heart or major blood vessels in real-time, under two-dimensional echocardiographic positioning.

**Coronary atherosclerotic heart disease** is a type of atherosclerotic lesion affecting the coronary arteries, leading to vascular lumen stenosis or occlusion, which causes myocardial ischemia, hypoxia, or necrosis [30,44,50].

Coronary artery disease (CAD) has garnered significant attention within the scientific community. Researchers have conducted in-depth studies on risk prediction models for CAD from various perspectives and have achieved notable results. The Framingham study was the first to apply traditional cardiovascular risk factors to develop a predictive model based on multiple regression equations for forecasting heart disease. Subsequently, a series of risk prediction models for different types of heart disease were published.

In addition to the Framingham model, researchers have also developed other risk assessment models such as **SCORE, PROCAM, Reynolds, and QRISK** to predict heart disease across different countries and regions. The **Tianjin Laboratory of Information Perception and Intelligent Control** utilized the correlation between heart motion signals and electrocardiogram (ECG) signals to develop a regression-based predictive model for heart disease. However, these prediction models rely on statistical regression techniques, which have limitations in accurately forecasting cardiovascular diseases [135, 162].

Most of the aforementioned studies assessed CAD risk using only a few indicators without considering the overall condition of patients. The predictive accuracy of CAD models in the majority of existing literature is below 90%, which does not meet the requirements for clinical practice. In studies using deep learning algorithms, most analyses focus on **coronary angiography images**. However, due to the various limitations of coronary angiography mentioned earlier, many physicians and patients are reluctant to rely on it.

Therefore, there is an urgent need to develop a **fast, efficient, and cost-effective method for accurately diagnosing coronary artery disease** while minimizing expenses.

## 2.3. CORONARY ARTERY STATUS IN PATIENTS WITH UNSTABLE ANGINA BASED ON CORONARY ANGIOGRAPHY RESULTS

One of the objectives of our study was to assess the extent of coronary artery involvement in patients with coronary artery disease (CAD), depending on the presence of psychoemotional conditions. Upon hospital admission, patients with unstable angina underwent diagnostic coronary angiography. To determine the localization and severity of coronary artery (CA) lesions, angiography was performed via femoral artery catheterization in 25.2% of cases and via radial artery in 74.8% of cases.

A total of 269 patients with unstable angina were examined. Hemodynamically significant coronary artery lesions were not detected in 96 patients (35.7%). Single-vessel disease was identified in 47 patients (17.5%), two-vessel disease in 39 patients (14.4%), three-vessel disease in 21 patients (7.8%), and multivessel disease involving more than three coronary arteries was found in 66 patients (24.5%) (Fig. 2.2.1).

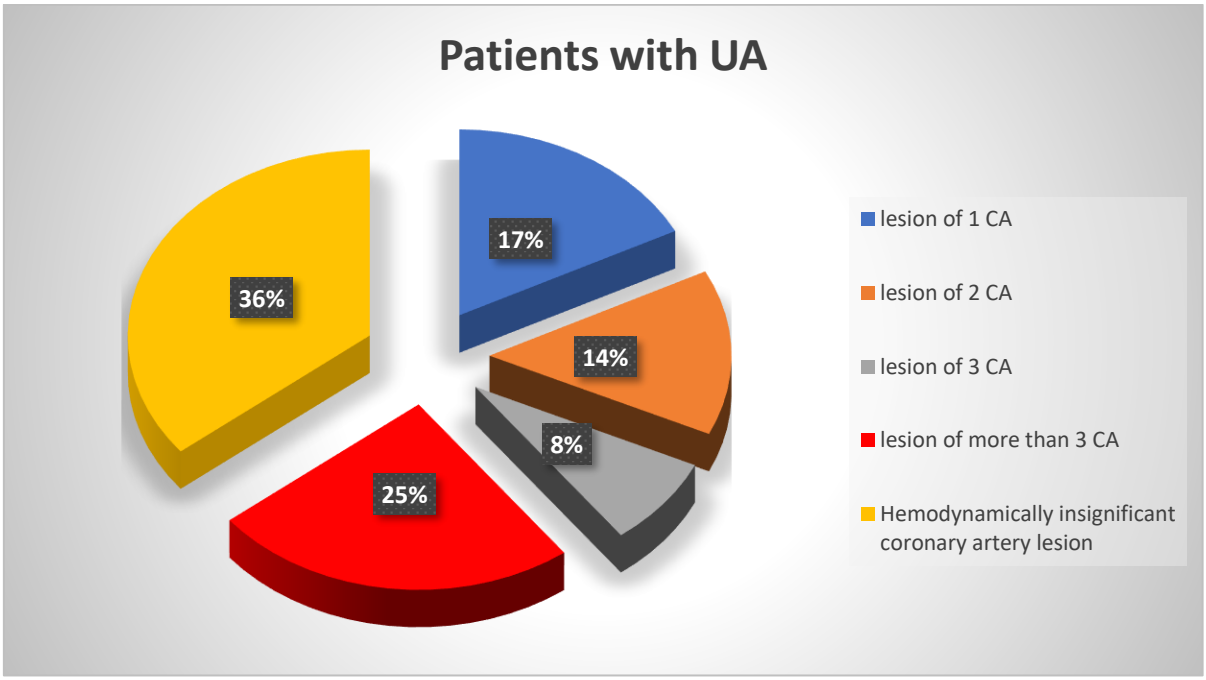
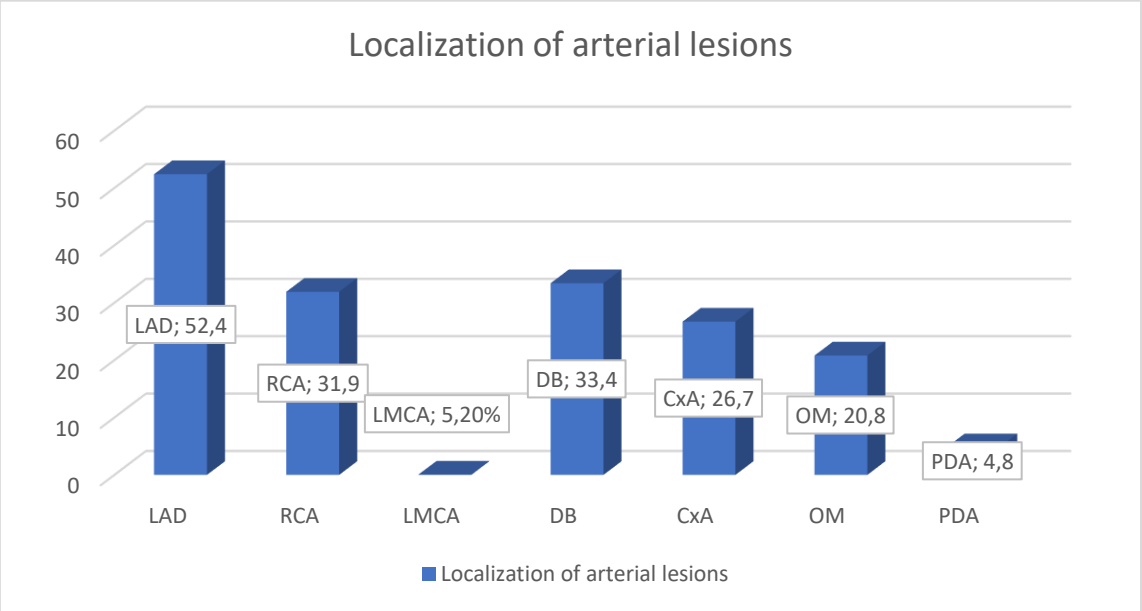



**Figure 2.3.1. Distribution of Patients with Unstable Angina Based on the Number of Affected Coronary Arteries**

It should be noted that the examination of the affected coronary artery branches revealed that the left anterior descending artery (LAD) was the most frequently affected, identified in 141 (52.4%) patients with UA. Lesions of the right coronary artery (RCA) were found in 86 (31.9%) patients, while lesions of the left main coronary artery (LMCA) were detected in only 14 (5.2%) patients. Lesions of the

diagonal branch (DB) were also common and observed in 90 (33.4%) patients. Lesions of the circumflex branch were found in 72 (26.7%) patients, lesions of the obtuse marginal branch in 56 (20.8%) patients, and lesions of the posterior descending artery (PDA) in 13 (4.8%) patients.

**Figure 2.3.2. Localization of Coronary Artery Lesions**

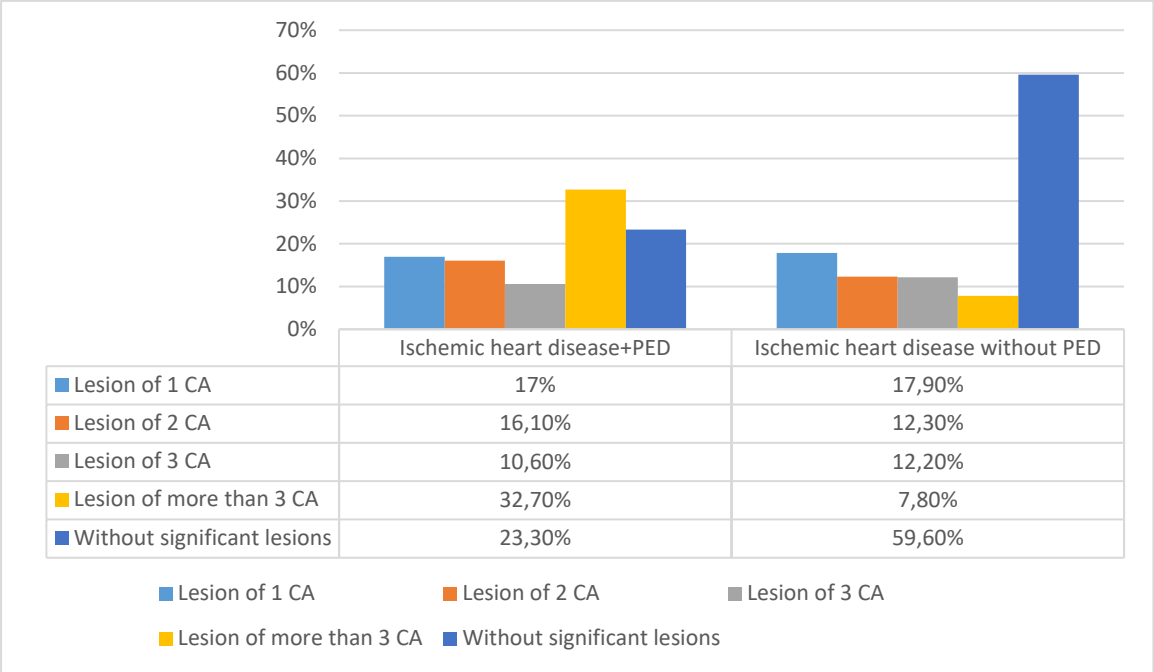



Thus, the most vulnerable coronary arteries were the left anterior descending artery (LAD), the right coronary artery (RCA), as well as the diagonal and circumflex arteries (CxA).

When comparing coronary artery lesions among patients with unstable angina (UA) and psychoemotional disorders (PED) (n=180) and those without PED (n=89), a significantly higher frequency and extent of coronary artery involvement were observed in patients with PED. Specifically, among patients with UA and PED, single-vessel disease (SVD) was found in 31 (17.2%) patients, two-vessel disease (2VD) in 29 (16.1%), three-vessel disease (3VD) in 19 (10.6%), and multivessel disease, defined as the involvement of more than three coronary arteries, in 59 (32.7%) patients.

In contrast, among patients without PED, single-vessel disease was observed in 16 (17.9%) patients, two-vessel disease in 11 (12.3%), three-vessel disease in 2 (2.2%), and multivessel disease in only 7 (7.8%) patients.

These findings indicate a direct correlation between atherosclerotic coronary artery disease and the development of psychoemotional disorders. This relationship requires further investigation to identify the primary etiological factors linking these conditions.




| | Ischemic heart disease+PED | Ischemic heart disease without PED |
|---|---|---|
| Lesion of 1 CA | 17% | 17,90% |
| Lesion of 2 CA | 16,10% | 12,30% |
| Lesion of 3 CA | 10,60% | 12,20% |
| Lesion of more than 3 CA | 32,70% | 7,80% |
| Without significant lesions | 23,30% | 59,60% |

**Figure 2.3.3. Distribution of Patients with UA and PED by the Number of Affected Coronary Arteries**

To identify the relationship between coronary artery lesions and psychoemotional disorders (PED), we decided to analyze both modifiable and non-modifiable risk factors contributing to the progression of ischemic heart disease (IHD) in these patients.

**Table 2.3.1. Prevalence of Risk Factors in Groups of Patients with UA with and without PED**

| Risk Factor | With PED (n=183) | Without PED (n=86) | P-value |
|---|---|---|---|
| Males | 96 (52.4%) | 47 (54.6%) | 0.405 |
| Age (years) | 63.4±11.13*** | 59.4±10.98 | <0.001 |
| Hypercholesterolemia | 130 (71.1%) | 56 (67.4%) | 0.241 |
| Arterial Hypertension | 126 (68.8%)* | 44 (51.1%) | 0.022 |
| Diabetes Mellitus | 48 (26.2%) | 11 (12.7%) | 0.411 |
| Obesity | 88 (48.0%) | 33 (38.4%) | 0.362 |
| Hyperuricemia | 97 (53.0%)*** | 21 (24.4%) | <0.001 |
| Smoking | 40 (21.8%)*** | 22 (25.5%) | <0.001 |
| Family History | 107 (58.4%) | 47 (54.6%) | 0.143 |
| Low Physical Activity | 87 (47.5%) | 22 (25.5%) | 0.295 |
| Number of Combined RFs | 4.6±1.2*** | 3.2±1.5 | <0.001 |

**Note:** *P<0.05, **P<0.01, ***P<0.001 – statistical significance of differences between groups of patients with UA.

Table 2.3.1 presents comparative analysis data between patients with UA and PER and those with UA without PED, respectively. As seen, the prevalence of males was higher among patients with PED (53.3% vs. 52.8%, respectively), but the differences were not statistically significant (p=0.405). Furthermore, no significant association was found between PED and such risk factors as diabetes mellitus (p=0.41), obesity (p=0.36), family history (p=0.14), and physical inactivity (p=0.29). Statistically significant indicators were identified when comparing arterial hypertension (p=0.022), total cholesterol (p<0.001), blood uric acid levels (p<0.001), smoking (p<0.001), and the frequency of combined risk factors (p>0.001).

Despite the lack of statistical significance, obesity was frequently observed in patients with PED—48.8% of cases, while in the group of patients without PER, it was also a common finding at 37.0%. Statistically significant indicators of hypercholesterolemia (p<0.001) and asymptomatic hyperuricemia (p<0.001) were also identified, which is consistent with previously conducted studies. The total cholesterol level was slightly higher in patients with PED compared to those without PED, amounting to 6.9±1.88 mmol/L. The uric acid level in patients with PED was 464.6±150 μmol/L, whereas in patients without PED, it was 348.5±90.5 μmol/L.

When studying the mean arterial pressure levels among patients with and without PED, statistically insignificant indicators were identified. Nevertheless, the mean arterial pressure level was higher in patients with PED compared to those without PED—151.2±25.12 mmHg and 140.5±28.34 mmHg, respectively (p>0.232).

When comparing the prevalence of risk factors and the number of affected coronary arteries, a statistically significant relationship was found in the study of the incidence of arterial hypertension (AH). AH was detected in 21 (12.1%) patients of group 1, 30 (17.3%) patients of group 2, and 51 (29.4%) patients of group 3 (Fig. 3.4). The difference between groups 1 and 2, 2 and 3 was statistically significant (p = 0.01 and p < 0.01, respectively).

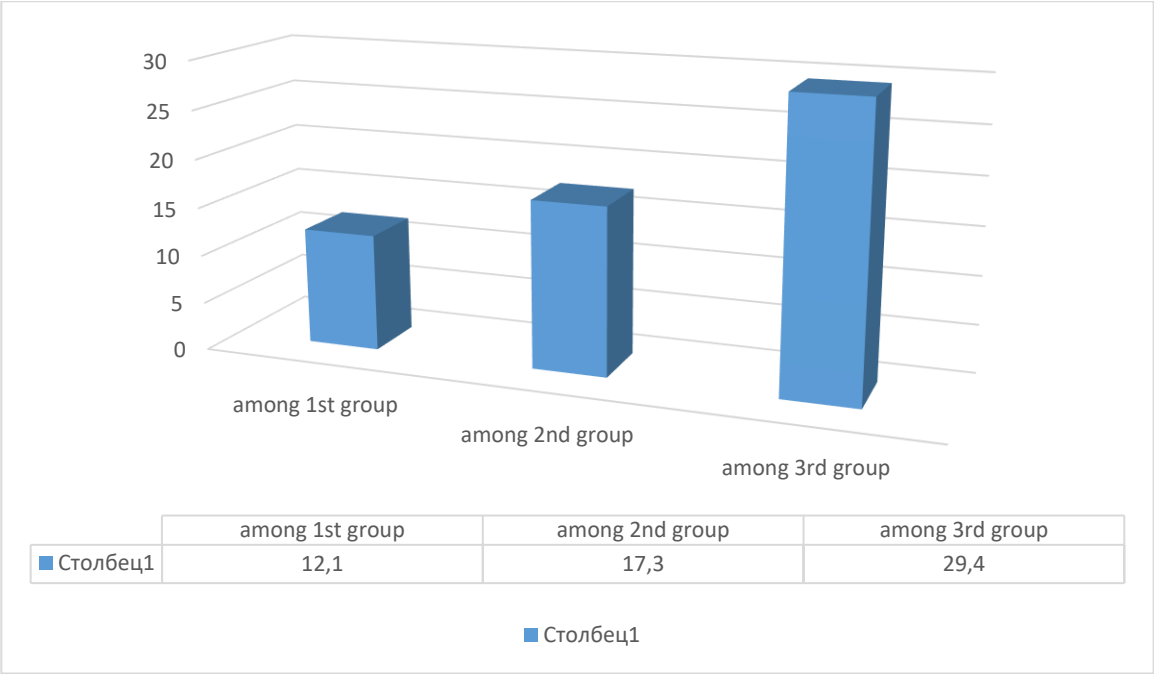



**Figure 2.3.4. Prevalence of Arterial Hypertension Among Patients with UA**

When analyzing the number of coronary artery lesions in relation to risk factors such as male gender, smoking, and low physical activity ($p>0.05$), no significant associations were found. In contrast to these risk factors, diabetes mellitus was significantly more common in patients with multivessel coronary artery disease (5.2%, 6.9%, and 13.3%, respectively).

Additionally, when examining the prevalence of anxiety-depressive syndrome among patients in the three groups, statistically significant differences were identified, with prevalence rates of 17.9%, 16.7%, and 45.1%, respectively (Fig. 2.2.4.).

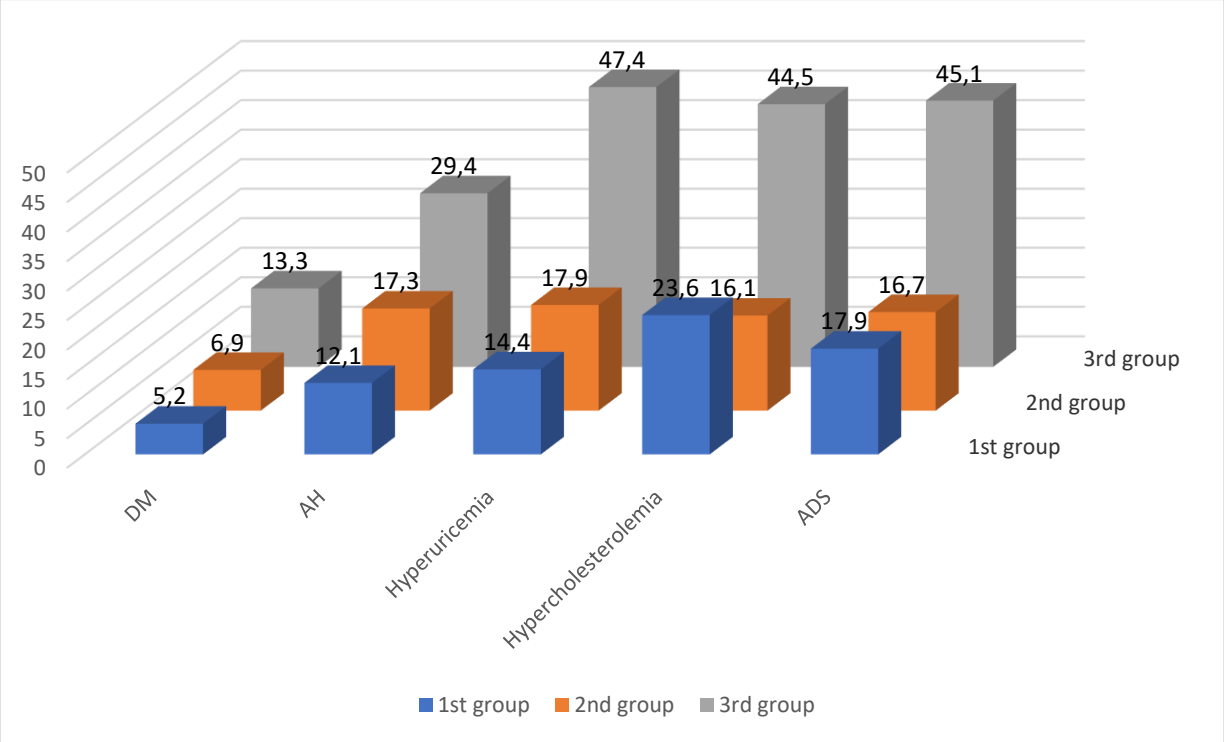



**Figure 2.3.4. Prevalence of Comorbid Conditions Depending on the Number of Affected Coronary Arteries**

Hypercholesterolemia (HC) was significantly more common in patients with three-vessel coronary artery disease, reaching 44.5% (n=77). A minor difference was noted when comparing patients in the first and second groups (Fig. 2.2.4.).

Thus, the study established that among all the analyzed risk factors, arterial hypertension, diabetes mellitus, anxiety-depressive syndrome, asymptomatic hyperuricemia, and hypercholesterolemia showed a significant association with the number of affected coronary arteries. However, the underlying mechanism of this effect remains insufficiently clear.

**Table 2.3.2.**

**Risk Factors Included in the Multivariate Analysis**

| Risk Factor | 1-CA Lesion (n=49) | 2-CA Lesion (n=38) | 3 or More CA Lesions (n=86) | P-value |
|---|---|---|---|---|
| Age (years) | 58±10 | 68.5±12** | 64.8±13 | P=0.007, F(2,85)=5.24 |
| SBP (mmHg) | 138.7±28 | 141±24 | 152±37 | 0.432 |
| DBP (mmHg) | 86±14 | 86±15 | 91±22 | 0.671 |
| Depression (score) | 4.53±1.7 | 4.50±2.12 | 5.25±1.73 | 0.534 |
| Anxiety (score) | 4.26±2.06 | 4.30±1.76 | 4.50±1.69 | 0.948 |

| Risk Factor | 1-CA Lesion (n=49) | 2-CA Lesion (n=38) | 3 or More CA Lesions (n=86) | P-value |
|---|---|---|---|---|
| HC (mmol/L) | 5.99±2.02 | 5.62±2.38 | 5.69±2.27 | 0.828 |
| SUA (μmol/L) | 406.7±21 | 507.2±17 | 547.2±25 | 0.791 |

*Note: *P<0.05, **P<0.01, ***P<0.001 – statistical significance of differences between UA patient groups.*

Multivariate analysis was conducted using a logistic regression model. All risk factors that demonstrated a statistically significant association with the number of affected coronary arteries in preliminary calculations obtained from the study were included in the model. The logistic regression analysis revealed an independent association between three-vessel coronary artery disease and age, the presence of PER, diabetes mellitus, serum uric acid levels, arterial hypertension, and hypercholesterolemia.

## 2.4. ASSESSMENT OF CORONARY ARTERY LESIONS USING THE SYNTAX SCORE CALCULATOR

To assess coronary artery lesions using the SYNTAX Score calculator (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery), 91 patients with hemodynamically significant stenosis were selected.

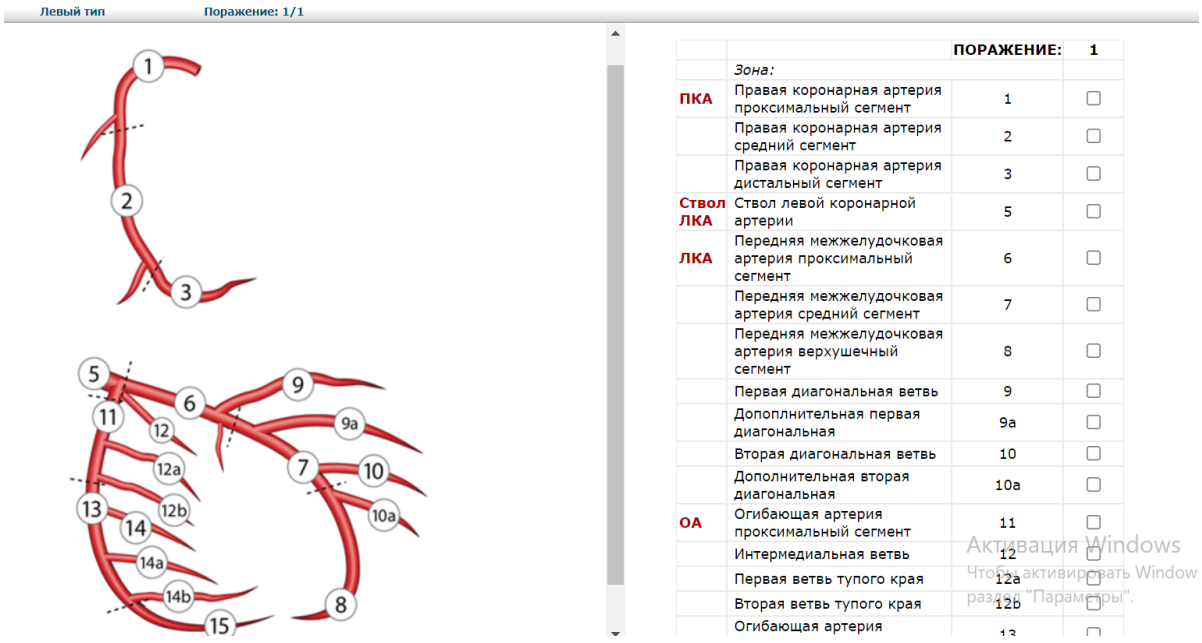



**Figure 2.4.1. SYNTAX Score Calculator**

Using the SYNTAX Score calculator, we were able to assess the anatomical complexity of existing coronary artery lesions in patients, as well as compare the likelihood of developing adverse cardiovascular events (including sudden cardiac death, myocardial infarction, stroke, and repeat revascularization).

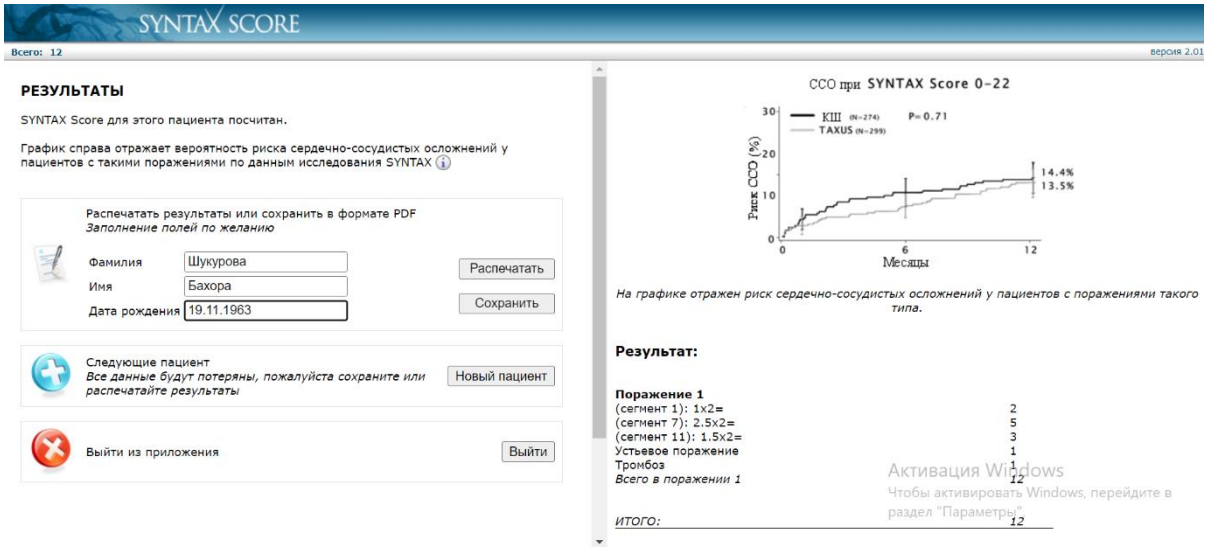



**Figure 2.4.2. Results of Cardiovascular Complication Risk Calculation in Patients with CAD Using the SYNTAX Score Calculator**

Each coronary artery lesion was scored, and the obtained results were summed to interpret the severity of coronary artery disease. Based on the Syntax test results, patients were divided into three groups: Group 1 (n=42) – patients who scored ≤22 points, Group 2 (n=26) – patients who scored 23-32 points, and Group 3 (n=23) – patients who scored ≥33 points. However, our comparative analysis did not reveal significant differences between the groups.

In this regard, we decided to divide the patients into two groups for further comparison of risk factor prevalence: Group 1 (n=42) included patients with moderate coronary artery disease, with a SYNTAX Score of ≤22 points; Group 2 (n=49) included patients with severe coronary artery disease, with a SYNTAX Score above 22 points (Figure 2.3.3).

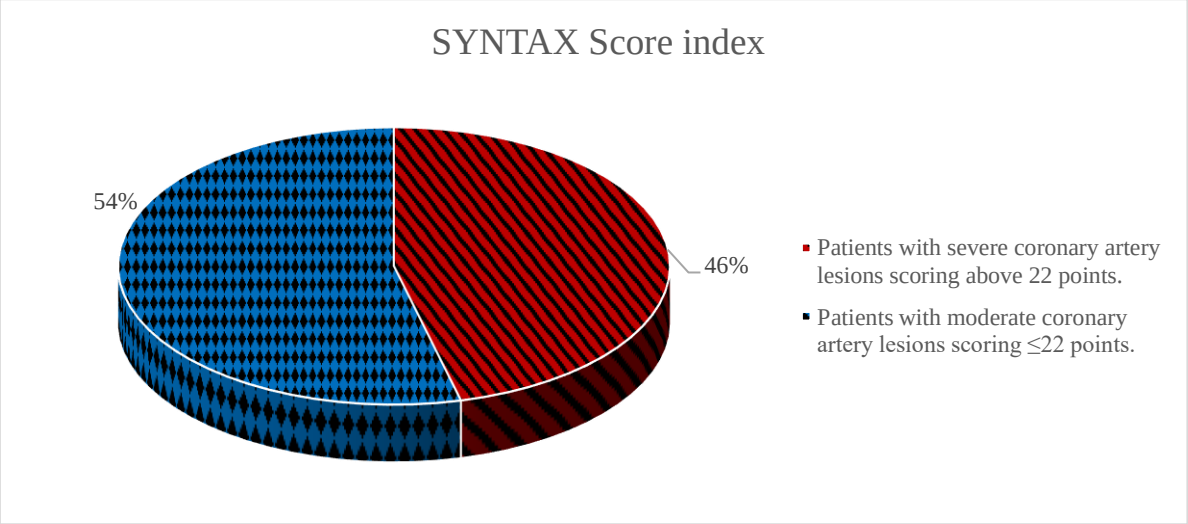



**Figure 2.4.3. Distribution of Patients by Severity of Lesions According to the SYNTAX Score**

When analyzing the association between risk factors and patient groups categorized using the SYNTAX Score calculator, statistically significant indicators were identified among the following risk factors: PED (p=0.001), hypercholesterolemia (p>0.05), blood uric acid (p>0.05), arterial hypertension (p=0.001), and diabetes mellitus (p=0.006) (Table 2.4.1).

When comparing by gender, the prevalence of males in Group 1 (SYNTAX >22) was 28 (66.7%), whereas in Group 2 (SYNTAX ≤22), it was 33 (67.3%). However, analysis using the $\chi^2$ test did not show a statistically significant difference between these groups (p>0.05). The proportion of smokers was higher in Group 1 (47.6%) compared to Group 2, but the difference was not statistically significant (p>0.05). Physical inactivity was found in 23 (54.7%) patients in Group 1 and 29 (59.1%) patients in Group 2, with no significant difference between the groups (p>0.05).

Arterial hypertension was more frequently observed in Group 2 (36 patients, 73.4%) compared to Group 1 (25 patients, 59.5%), and this difference was statistically significant (p=0.001). Psychological and emotional disorders were also more prevalent in Group 2, affecting 38 (77.6%) patients, compared to 26 (61.9%) in Group 1.

According to the Eysenck scale, 26.1% of patients in Group 1 and 28.6% in Group 2 exhibited high levels of rigidity, while high levels of aggressiveness were significantly more common, at 45.2% and 65.3%, respectively. The prevalence of hypercholesterolemia was 42.8% in Group 1 and 53.1% in Group 2, with statistical significance (p<0.05). Diabetes mellitus was diagnosed in 8 (19.1%) patients in Group 1 and 17 (34.7%) patients in Group 2. Elevated blood uric acid levels were found in 19 (45.2%) patients in Group 1 and 33 (67.3%) patients in Group 2, with a statistically significant difference (p<0.01).

**Table 2.4.1.**

**Prevalence of Risk Factors Among Patients Categorized Using the SYNTAX Score Calculator (≤22 points – Group 1, >22 points – Group 2)**

| Risk Factors | SYNTAX Score ≤22 (n=42) | SYNTAX Score >22 (n=49) | p-value |
|---|---|---|---|
| **Male Gender (%)** | 28 (66.7%) | 33 (67.3%) | 0.123 |
| **Arterial Hypertension (%)** | 25 (59.5%) *** | 36 (73.4%) | <0.001 |
| **Smoking (%)** | 20 (47.6%) *** | 22 (44.9%) | <0.001 |
| **Hypercholesterolemia (%)** | 18 (42.8%) *** | 26 (53.1%) | <0.001 |
| **Asymptomatic Hyperuricemia (%)** | 19 (45.2%) *** | 33 (67.3%) | <0.001 |
| **Diabetes Mellitus (%)** | 8 (19.1%) *** | 17 (34.7%) | <0.001 |
| **Family History (%)** | 11 (26.1%) | 13 (26.5%) | 0.192 |
| **High Rigidity (%)** | 11 (26.1%) | 14 (28.6%) | 0.09 |
| **Aggressiveness (%)** | 19 (45.2%) *** | 32 (65.3%) | <0.001 |
| **Low Physical Activity (%)** | 23 (54.7%) *** | 29 (59.1%) | <0.001 |

**Note:** ***p<0.001 – statistically significant differences between groups.

Thus, the study conducted using the SYNTAX Score scale demonstrated not only the severity of coronary artery lesions but also their association with the number of affected coronary arteries, arterial hypertension, hypercholesterolemia, asymptomatic hyperuricemia, psycho-emotional disorders, and diabetes mellitus. This study once again confirmed the impact of combined risk factors on the prevalence of coronary artery disease.

# CHAPTER 3. IMMUNOLOGICAL FEATURES OF ISCHEMIC HEART DISEASE DESTABILIZATION DEPENDING ON PSYCHO-EMOTIONAL STATE

## 3.1. ASSESSMENT OF INFLAMMATORY AND ANTI-INFLAMMATORY CYTOKINE LEVELS DEPENDING ON THE PSYCHO-EMOTIONAL STATE IN PATIENTS WITH UNSTABLE ANGINA

An analysis of IL-1β levels among patients with unstable angina (UA) with and without psycho-emotional disorders (PED) revealed that in patients with PED, the TNF-α level was 68.9±2.3 pg/mL, and the IL-1β level was 101.0±4.6 pg/mL. In contrast, in patients without PED, the TNF-α and IL-1β levels were 66.7±2.1 pg/mL and 90.3±3.7 pg/mL, respectively. These differences were statistically significant ($p<0.05$).

**Table 3.1.1.**

**Levels of Certain Cytokines in Patients with CHD and PED**

| Parameter | UA + PED (n=183) | UA (n=126) | SA (n=120) | P-value |
|---|---|---|---|---|
| **TNF-α (pg/mL)** | 68.9 ± 2.3 | 66.7 ± 2.1 | 60.4 ± 2.2 | P = 0.047 |
| **IL-1β (pg/mL)** | 101.0 ± 4.6 | 90.3 ± 3.7 | 77.6 ± 2.1 | P = 0.031 |
| **IL-4 (pg/mL)** | 22.8 ± 1.2 | 23.8 ± 1.0 | 23.7 ± 1.4 | P = 0.154 |
| **IL-10 (pg/mL)** | 12.1 ± 0.6 | 12.7 ± 0.7 | 12.6 ± 0.5 | P = 0.212 |

The levels of anti-inflammatory cytokines IL-4 and IL-10 in patients with PDS were slightly lower compared to patients with UA without PED and CVD. However, these differences were not statistically significant (p = 0.154 and p = 0.212, respectively).

Then, we divided CHD patients with and without PED into two groups based on blood UA levels. We found significantly higher levels of pro-inflammatory cytokines TNF-α (p = 0.004) and IL-1β (p = 0.07) in CHD patients with PED and elevated UA levels (Table 3.1.2).

**Table 3.1.2.**

**Indicators of Certain Interleukins in Patients with CAD With PER Depending on UA Level**

| Parameter | UA without PED(n=126) Patients with elevated UA level (n=33) | UA without PED (n=126) Patients with normal UA level (n=93) | SA (n=120) | P-value |
|---|---|---|---|---|
| **TNF-α (pg/mL)** | 68.2 ± 2.5 | 66.2 ± 2.0 | 60.4 ± 3.4 | 0.020 |
| **IL-1β (pg/mL)** | 91.9 ± 1.7 | 89.3 ± 1.8 | 77.6 ± 2.4 | 0.051 |
| **IL-4 (pg/mL)** | 24.3 ± 2.2 | 23.5 ± 2.8 | 23.7 ± 1.1 | 0.074 |
| **IL-10 (pg/mL)** | 12.8 ± 1.0 | 12.8 ± 1.1 | 12.6 ± 2.5 | 0.018 |
| **UA (μmol/L)** | 443.6 ± 28.3 | 295.1 ± 24.5 | 373.4 ± 17.0 | <0.001 |

Among patients with CAD without PED but with elevated UA levels, pro-inflammatory cytokine levels were significantly higher (p=0.04 and p=0.07) compared to those with normal UA levels. Additionally, when comparing cytokine levels between patients with elevated UA and those with stable angina, TNF-α and IL-1β levels were significantly higher in patients with elevated UA, while anti-inflammatory cytokine levels of IL-4 and IL-10 were significantly reduced (p=0.02 and p=0.05, respectively). Notably, asymptomatic hyperuricemia not only leads to an increase in pro-inflammatory cytokines but also to a decrease in anti-inflammatory cytokines (Table 3.1.3).

**Table 3.1.3.**

**Indicators of Certain Interleukins in Patients with CAD Without PED Depending on UA Level**

| Parameter | UA without PED (n=126)<br>Patients with elevated UA (n=33) | UA without PED (n=126)<br>Patients with normal UA (n=93) | SA (n=120) | P-value |
|---|---|---|---|---|
| **TNF-α (pg/mL)** | 68.2 ± 2.5 | 66.2 ± 2.0 | 60.4 ± 3.4 | 0.020 |
| **IL-1β (pg/mL)** | 91.9 ± 1.7 | 89.3 ± 1.8 | 77.6 ± 2.4 | 0.051 |
| **IL-4 (pg/mL)** | 24.3 ± 2.2 | 23.5 ± 2.8 | 23.7 ± 1.1 | 0.074 |
| **IL-10 (pg/mL)** | 12.8 ± 1.0 | 12.8 ± 1.1 | 12.6 ± 2.5 | 0.018 |
| **Uric Acid (μmol/L)** | 443.6 ± 28.3 | 295.1 ± 24.5 | 373.4 ± 17.0 | <0.001 |

Further, in each group, patients with and without PER were divided into two subgroups based on LDL-C levels in the blood: the first subgroup included patients with low LDL-C levels (less than 4.0 mmol/L), while the second subgroup consisted of patients with high LDL-C levels (more than 4.0 mmol/L) (Table 3.1.4).

**Table 3.1.4.**

**Indicators of Certain Interleukins in Patients with CAD (Stable and Unstable Angina) Depending on LDL-C Levels in the Blood**

| Parameters | UA+PED (n=183) | | SA (n=120) | p-value |
|---|---|---|---|---|
| | Patients with elevated LDL-C (n=117) | Patients with normal LDL-C (n=66) | | |
| TNF-ά pg/ml | 69,9±5.2 | 68,5±3,7 | 60,4±2,7 | 0,01 |
| IL- β pg/ml | 103,7±15.1 | 99,6±7,9 | 77,6±6,2 | 0,025 |
| IL-4 pg/ml | 23,3±3,4 | 24,0±2,9 | 23,7±1,8 | 0,45 |
| IL-10 pg/ml | 12,4±1,5 | 12,4±1,1 | 12,1±1,4 | 0,2 |
| LDL-C mmol/l | 5,1±0,93 | 2,8±0,37 | 4,1±0,62 | <0,001 |

When studying cytokine levels depending on LDL-C levels, it was found that patients with unstable angina and PED, who had high LDL-C levels (greater than 4.0 mmol/L), showed statistically significant values (p=0.01 and p=0.025). Specifically, TNF-α was 69.9±5.2 pg/ml and IL-1β was 103.7±15.1 pg/ml, which was different from patients with stable angina. This indicates a connection between cytokine imbalance not only with elevated UA levels but also with hyperlipidemia in these patients. However, when studying the levels of anti-inflammatory cytokines IL-4 and IL-10, no correlation with hyperlipidemia was found (p=0.45 and p=0.2).

When examining the relationship between LDL-C levels and interleukins in patients without psycho-emotional disorders, significant results were found with TNF-α (67.2±4.9 pg/ml) and IL-1β (91.7±4.9 pg/ml). A significant decrease in IL-4 and IL-10 was observed (p=0.029 and p=0.017), indicating a link between cytokine imbalance not only with PER but also with lipid metabolism disorders.

**Table 3.1.5.**

**Indicators of Cytokines TNF-*α*, IL-1β, IL-4, and IL-10 in Patients with CAD Depending on LDL-C Levels in the Blood**

| Parameters | UA+PED (n=183) | | SA (n=120) | p-value |
|---|---|---|---|---|
| | Patients with elevated LDL-C (n=52) | Patients with normal LDL-C (n=74) | | |
| TNF-ά pg/ml | 69,9±5.2 | 66,5±3,8 | 60,4±3,1 | 0,0047 |
| IL- β pg/ml | 103,7±15.1 | 99,6±7,9 | 77,6±6,2 | 0,039 |
| IL-4 pg/ml | 23,8±2,7 | 23,9±3,0 | 23,7±1,9 | 0,171 |
| IL-10 pg/ml | 12,5±1,1 | 13,2±1,5 | 12,1±1,7 | 0,029 |

| | | | | |
|---|---|---|---|---|
| LDL-C mmol/l | 4,8±0,7 | 2,72±0,36 | 4,1±0,9 | <0,017 |

We aimed to identify the relationship between coronary artery damage and manifestations of imbalance in the endothelial system by studying cytokine imbalance.

When investigating the levels of pro- and anti-inflammatory cytokines in relation to the quantitative damage of coronary arteries (CA), no significant correlations were found. However, in patients with unstable angina (UA) and damage to three or more coronary arteries, the levels of pro-inflammatory cytokines (TNF-α: 73.6±4.1 pg/ml, IL-1β: 103.5±14.1 pg/ml) were higher compared to patients with damage to one or two coronary arteries. Nevertheless, when comparing the levels of UA and LDL-C in the blood with the number of damaged coronary arteries, a significant correlation between coronary artery damage and UA and LDL-C levels was discovered.

Thus, patients with damage to three or more coronary arteries had an average UA level of 547.1±28.4 μmol/L, while patients with damage to one coronary artery had an average UA level of 406.9±27.5 μmol/L ($p<0.001$), which was 140.2±0.9 μmol/L higher compared to those with one coronary artery damage. The LDL-C level in patients with damage to three or more coronary arteries was 4.4±0.4 mmol/L, whereas in patients with damage to one coronary artery, the LDL-C level was 3.9±0.5 mmol/L ($p<0.023$).

**Table 3.1.6.**

**Indicators of Cytokines TNF-α, IL-1β, IL-4, and IL-10 in Patients with CAD Depending on Coronary Artery Damage**

| Indicators | Lesion of 1 coronary artery with UA, n=47 | Lesion of 2 coronary arteries with UA, n=135 | Lesion of 3 coronary arteries with UA, n=87 | P-value |
|---|---|---|---|---|
| TNF-α, pg/ml | 68.6±3.5 | 73.1±4.2 | 73.6±4.1 | 0.752 |
| IL-1β, pg/ml | 99.7±9.7 | 100.1±12.8 | 103.5±14.1 | 0.258 |
| IL-4, pg/ml | 24.6±2.2 | 22.7±2.1 | 24.9±2.6 | 0.214 |
| IL-10, pg/ml | 12.9±1.2 | 11.7±1.2 | 12.5±1.3 | 0.117 |
| UA, μmol/L | 406.9±27.5 | 507.0±29.6 | 547.1±28.4 | 0.013 |
| Total Cholesterol, mmol/L | 6.8±0.6 | 6.3±0.7 | 6.9±0.9 | 0.026 |
| LDL Cholesterol, mmol/L | 3.9±0.5 | 4.3±0.6 | 4.4±0.4 | 0.512 |

| Indicators | Lesion of 1 coronary artery with UA, n=47 | Lesion of 2 coronary arteries with UA, n=135 | Lesion of 3 coronary arteries with UA, n=87 | P-value |
|---|---|---|---|---|
| HADS-D (Depression) | 9.6±1.3 | 10.1±1.4 | 11.6±1.8 | 0.014 |
| HADS-A (Anxiety) | 8.9±0.5 | 9.3±0.6 | 10.7±0.8 | 0.03 |

To confirm the results of our study and identify the stratification of cardiovascular risk, an analysis was conducted comparing the levels of pro- and anti-inflammatory cytokines among patients who had previously been categorized using the SYNTAX Score calculator: those with a SYNTAX Score ≤ 22 (Group 1) and those with a SYNTAX Score ≥ 22 (Group 2).

**Table 3.1.7.**

**Distribution of CAD Patients According to SYNTAX Score Based on Cytokine Levels of TNF-α, IL-1β, IL-4, and IL-10**

| Indicators | SYNTAX Score ≤22, n=42 | SYNTAX Score ≥22, n=49 | P-value |
|---|---|---|---|
| TNF-α, pg/ml | 67.9±8.48 | 71.2±8.9 | 0.021 |
| IL-1β, pg/ml | 100.46±12.5 | 106.8±13.25 | 0.074 |
| IL-4, pg/ml | 24.6±3.0 | 23.6±2.95 | 0.014 |
| IL-10, pg/ml | 12.8±1.6 | 12.5±1.56 | 0.048 |
| UA, μmol/L | 414.8±49.8 | 479.1±59.8 | 0.044 |
| Total Chol, mmol/L | 6.9±0.85 | 6.2±0.8 | 0.039 |
| LDL-C, mmol/L | 4.2±0.5 | 4.6±0.6 | 0.051 |
| HADS-D | 8.9±0.5 | 10.3±0.9 | 0.040 |
| HADS-A | 8.4±0.4 | 10.1±0.9 | 0.032 |

The results of the study showed that in patients with a SYNTAX Score ≥ 22, the levels of pro-inflammatory cytokines were significantly higher than the levels of anti-inflammatory cytokines, further confirming the inflammatory nature of coronary artery damage. The level of uric acid was significantly higher in patients with a SYNTAX Score ≥ 22, which also suggests a correlation between hyperuricemia and the inflammatory process in the vascular endothelium. Considering all of the above, there arose a need to confirm our hypothesis at the molecular-genetic level, taking into account PED.

## §3.2. STUDY OF MOLECULAR-GENETIC MARKERS OF PRO-INFLAMMATORY CYTOKINES PARTICIPATING IN THE DE-STABILIZATION OF CAD ASSOCIATED WITH PSYCHO-EMOTIONAL CONDITION

In this section, we studied the distribution of allele and genotype frequencies of the -308 G/A locus (rs1800629) of the TNF-α gene and the 511 C/T position (rs16944) of the IL-1β gene in patients with CAD and comorbidities to identify the "unfavorable" combination that leads to a high likelihood of disease development in our region.

To establish the link between the progression of coronary artery disease, particularly among patients with PER, we studied the frequency of the C/T alleles at the 511 locus of the IL-1β gene and the 308 G/A position of the TNF-α gene in 198 patients with unstable angina and 80 healthy donors from the Uzbek population, with no clinical manifestations of the disease.

Table 3.2.1 shows that among CAD patients, the T allele of the IL-1β C511T polymorphism occurs 26.1% more frequently than among healthy individuals. The C allele, in contrast to the T allele, is present in 49.5% of patients, whereas it was found in 75.6% of the control group.

**Table 3.2.1.**

**Distribution of Allele Frequencies of the C511T (rs16944) IL-1β Gene Polymorphism and G308A (rs1800629) TNF-α Gene in Patients with Unstable Angina and Healthy Individuals**

| Allele | Frequency (%) | | $\chi^2$ | p-value | OR | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|---|
| | Main group (n=198) | Control (n=80) | | | | | |
| C511T (rs16944) of IL-1β gene | | | | | | | |
| C | 49,5 | 75,6 | 10,8 | <0,001 | 0,19 | 0,08 | 0,46 |
| T | 50,5 | 24,4 | 5,23 | 0,022 | 5,24 | 2,19 | 12,54 |
| G308A (rs1800629) of TNF-α gene | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **G** | **45,5** | **67,5** | **17,13** | **0,031** | **1,018** | **0,981** | **1,218** |
| **A** | **55,1** | **32,5** | **11,32** | **0,715** | **1,541** | **0,995** | **1,913** |

When analyzing the distribution of allele frequencies for the G308A (rs1800629) TNF-α gene polymorphism in patients with unstable angina (UA) and healthy individuals, it was found that the frequency of the major (dominant) G allele in the UA group was 45.5%, compared to 67.5% in the control group. The frequency of the minor (recessive) A allele was 55.1% in the UA group and 32.5% in the control group, respectively.

Upon examining the frequency of various genotypes for the G-308A (rs1800629) TNF-α gene polymorphism, it was discovered that the homozygous G/G genotype occurred 27.7% more frequently in the control group, while the homozygous A/A genotype was found 17.3% more frequently in patients with unstable angina. The heterozygous G/A variant of the G-308A (rs1800629) TNF-α polymorphism was observed in 35.4% of cases in the UA group (Table 3.2.2).

In patients with unstable angina, compared to the control group, the homozygous C/C variant at the C511T IL-1β gene polymorphism position occurred 31.4% less frequently ($\chi2=21.29$; $p<0.001$), while the homozygous T/T variant was 20.9% more common and the heterozygous C/T variant was 10.5% more common ($\chi2=10.87$; $p<0.001$) (Table 3.2.2).

**Table 3.2.2.**

**Distribution of the G-308A (rs1800629) TNF-α Gene and 511 C/T (rs16944) IL-1β Gene Polymorphic Loci in CAD Patients and Healthy Individuals**

| **Allele** | **Frequency (%)** | | **$\chi^2$** | **p-value** | **OR** | **95% CI Lower** | **95% CI Upper** |
|---|---|---|---|---|---|---|---|
| | **Main group (n=198)** | **Control (n=80)** | | | | | |
| C511T (rs16944) of IL-1β gene | | | | | | | |
| **C/C** | **34,8** | **66,2** | **21,29** | **<0,001** | **0,985** | **0,845** | **1,029** |
| **C/T** | **29,3** | **18,8** | **3,27** | **0,071** | **1,127** | **0,915** | **1,284** |
| **T/T** | **35,9** | **15** | **10.87** | **<0,001** | **2,184** | **1,472** | **2,284** |
| G308A (rs1800629) of TNF-α gene | | | | | | | |
| **G/G** | **27,3** | **55,0** | **18,21** | **0,017** | **0,845** | **0,741** | **1,052** |
| **G/A** | **35,4** | **25,0** | **17,14** | **0,715** | **1,122** | **0,989** | **1,239** |
| **A/A** | **37,3** | **20,0** | **24,91** | **0,491** | **0,772** | **0,621** | **0,875** |

An analysis of the IL-1β T/C 511 (rs16944) gene polymorphism was conducted in healthy individuals and patients with unstable angina (UA), depending on the presence of psycho-emotional disorders. Patients with anxiety-depressive syndrome, identified using the HADS-A/D scale, were included in the study.

**Table 3.2.3.**

**Distribution of Allele Frequencies of the C511T (rs16944) IL-1β Gene Polymorphism and G-308A (rs1800629) TNF-α Gene in Patients with Unstable Angina and Healthy Individuals Based on Psycho-Emotional Disorder (PED)**

| Allele | Frequency (%) | $\chi 2$ | P-value | OR | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| **C511T (rs16944) IL-1β gene** | | | | | | |
| C | 18.7 | 18.55 | 0.019 | 0.975 | 0.894 | 1.161 |
| T | 81.3 | 11.74 | 0.715 | 1.612 | 1.225 | 1.842 |
| **G-308A (rs1800629) TNF-α gene** | | | | | | |
| G | 56.7 | 14.91 | 0.011 | 0.815 | 0.711 | 0.981 |
| A | 43.3 | 21.82 | 0.105 | 1.318 | 1.109 | 1.596 |

The study on the distribution of allele frequencies of C and T polymorphism (T511C) of the IL-1β gene in patients with coronary artery disease (CAD) with and without psycho-emotional disorders (PER) compared to healthy controls showed different frequencies for the C and T alleles (Table 3.2.3). The presence of the SNP polymorphism T511C IL-1β in patients with unstable angina (UA) and PER and healthy individuals was also different. Among the patients, the minor allele T predominated with a frequency of 81.3%, while the major allele C was found at a frequency of 18.7%, which is 4 times less frequent compared to the control group ($\chi 2=18.55$; $p<0.001$) (Table 3.2.3).

It was established that among the patients with UA and PER, the carriers of homozygous and heterozygous alleles of the G-308A (rs1800629) TNF-α gene polymorphism had significantly higher levels than the control group. When analyzing the average values based on the anxiety scale in Table 3.2.4, it was observed that patients with homozygous A/A and heterozygous G/A variants of the G-308A (rs1800629) TNF-α gene polymorphism had higher anxiety and depression scores, indicating the correlation between PED and the minor allele A.

**Table 3.2.4**

**Average values of psycho-emotional disorder indicators based on the HADS**

**and Spielberger-Hanin scales depending on the polymorphic locus 511 C/T (rs16944) IL-1β gene and G-308A (rs1800629) TNF-α gene**

| Polymorphic Locus | Genotype | HADS-D (Depression) | HADS-A (Anxiety) | C/T | T/T | P-value |
|---|---|---|---|---|---|---|
| **511 C/T IL-1β** | **C/C** | 7.6±0.95 | 7.3±0.91 | 43.6±4.2 | 42.4±4.1 | 0.017 |
| | **C/T** | 11.8±1.4 | 11.1±1.38 | 53.0±6.62 | 51.3±5.1 | 0.274 |
| | **T/T** | 13.28±1.66 | 13.31±1.7 | 54.7±6.8 | 53.4±4.4 | 0.624 |
| **G308A TNF-α** | **G/G** | 9.37±1.9 | 8.4±1.6 | 51.4±4.4 | 51.1±4.1 | 0.004 |
| | **G/A** | 10.5±2.0 | 10.2±1.8 | 52.9±5.0 | 52.3±4.2 | 0.018 |
| | **A/A** | 12.5±2.1 | 11.3±1.7 | 53.4±5.2 | 53.1±4.4 | 0.148 |

It has been established that in patient groups with unstable angina (UA) and psychoemotional disorders (PED), carriers of both homozygous and heterozygous alleles of the interleukin-1 gene exhibited significantly higher values compared to the control group. In particular, UA patients with PED carrying the homozygous T/T allele variant demonstrated the highest levels of psychoemotional disturbances, with mean scores of 13.28±1.66 on the HADS-D scale and 13.31±1.7 on the HADS-A scale. In patients with the homozygous T/T genotype of the SNP IL-1β (T511C) gene, mean scores on the Spielberger–Hanin scale were 54.7±5.1 for state anxiety (ST) and 53.4±5.2 for trait anxiety (TA).

Eysenck's scale results revealed that 17.5% of carriers of the homozygous T/T genotype exhibited rigidity, whereas among heterozygous C/T carriers, this figure was 8.2%. Notably, no rigidity was detected among carriers of the homozygous C/C genotype.

During the study, we identified a significant correlation between serum uric acid levels and coronary artery disease, prompting an analysis of the relationship between hyperuricemia and the 511 C/T (rs16944) polymorphism of the IL-1β gene, as well as the G-308A (rs1800629) polymorphism of the TNF-α gene, in patients with UA and PED.

**Table 3.2.5.**

**Distribution of Allele Frequencies of the 511 C/T (rs16944) Polymorphism of the IL-1β Gene and the G-308A (rs1800629) Polymorphism of the TNF-α Gene in Patients with UA and Healthy Individuals Depending on Serum Uric Acid Levels**

| Allele | Frequency (%) | | χ2 | P-value | OR | Lower 95% CI | Upper . 95% CI |
|---|---|---|---|---|---|---|---|
| | Uric acid more than 360 mkmol/l (n=123) | Control (n=80) | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **C/T 511 гена IL-1β** | | | | | | | |
| **C** | 50,0 | 75,6 | 14,27 | 0,001 | 0,985 | 0,725 | 1,215 |
| **T** | 50,0 | 24,4 | 20,85 | 0,458 | 1,121 | 0,957 | 1,351 |
| **G/A 308 гена TNF-α** | | | | | | | |
| **G** | 39,9 | 67,5 | 22,71 | 0,041 | 0,751 | 0,512 | 0,971 |
| **A** | 60,1 | 32,5 | 18,11 | 0,728 | 2,417 | 1,843 | 3,111 |
| **Allele** | **Frequency** (%) | | χ2 | P-value | OR | Lower 95% CI | Upper 95% CI |
| | Uric acid more than 360 mkmol/l (n=75) | Control (n=80) | | | | | |
| **C/T 511 of gene IL-1β** | | | | | | | |
| **C** | 48,6 | 75,6 | 23,02 | 0,002 | 0,912 | 0,875 | 0,988 |
| **T** | 51,4 | 24,4 | 24,18 | 0,847 | 2,401 | 1,725 | 2,946 |
| **G/A 308 of gene TNF-α** | | | | | | | |
| **G** | 60,0 | 67,5 | 27,95 | 0,001 | 0,876 | 0,616 | 1,020 |
| **A** | 40,0 | 32,5 | 13,51 | 0,625 | 1,718 | 1,205 | 2,008 |

To study the association between the alleles of the 511 T/C (rs16944) polymorphism of the *IL-1β* gene and uric acid (UA) levels, patients were divided into two groups:

- **Group 1 (n=50):** Patients with elevated uric acid levels (≥360.0 μmol/L).
- **Group 2 (n=47):** Patients with normal uric acid levels (≤360.0 μmol/L).

As demonstrated in **Table 3.2.5**, among patients with elevated uric acid levels, the T allele of the T511C (rs16944) polymorphism of the *IL-1β* gene was found at nearly the same frequency in both normal and elevated uric acid groups—50.0% and 51.4%, respectively.

The results of the molecular genetic study highlight the significance of the polymorphic locus G-308A (rs1800629) of the *TNF-α* gene in the genetic predisposition to coronary artery disease (CAD) associated with asymptomatic hyperuricemia in the Uzbek population. The obtained data suggest that the **TNF-α (A308A) genotype and the -308A allele** serve as markers of increased risk for CAD destabilization associated with asymptomatic hyperuricemia in the Uzbek ethnic population, whereas the **TNF-α (G308G) genotype and the -308G allele** act as protective markers associated with a lower risk.

The study of the association between the *TNF-α* G-308A (rs1800629) polymorphism and the concentration of low-density lipoprotein cholesterol (LDL-C), serum uric acid (UA), and the presence of psycho-emotional disorders in patients

with coronary artery disease (CAD) is of particular interest in understanding the progression of CAD and the atherosclerotic process.

When forming patient groups with unstable angina (UA) based on serum UA concentration, we observed an association between UA levels and the G-308A (rs1800629) polymorphism of the *TNF-α* gene. Specifically, among CAD patients with elevated UA levels, the A allele was found **27.6% more frequently** than in the control group, whereas in patients with normal UA levels, this difference was only **7.5%**. The data presented in **Table 3.2.5** suggest that the presence of the A allele in the *TNF-α* genotype may contribute to impaired purine metabolism.

Patients with the homozygous A/A genotype were more prone to **asymptomatic hyperuricemia**, with a **mean UA level of 542.7±17.0 µmol/L**, whereas patients with the G/G genotype had a significantly lower **mean UA level of 387.2±8.4 µmol/L**.

**Table 3.2.6.**

**Mean Uric Acid Level Depending on the G-308A (rs1800629) Polymorphic Locus of the *TNF-α* Gene**

| **Indicator** | **G/G (n=54)** | **G/A (n=70)** | **A/A (n=74)** | | |
|---|---|---|---|---|---|
| **Uric acid, mkmol/l** | 387,2±8,4 | 484,6±11,0 | 542,7±17,0 | 0,014<br>0,29<br>1,004 | P1<br>P2<br>P3 |

Next, the frequency of occurrence of allele C and T of the T511C (rs16944) polymorphism of the *IL-1β* gene and the G308A (rs1800629) polymorphism of the *TNF-α* gene was studied among patients with unstable angina, depending on the LDL-C level in the blood. Based on LDL-C levels, patients were divided into two groups: the first group included patients with high LDL-C levels (≥4.1 mmol/L), while the second group consisted of patients with normal LDL-C levels (≤4.1 mmol/L). It was found that patients with both elevated and normal LDL-C levels had a significantly high prevalence of allele A—56.5% and 51.6%, respectively ($\chi2$=17.35; P=0.953; OR=1.296 and $\chi2$=19.01; P=0.219; OR=1.085), compared to the control group. Thus, no association between increased LDL-C levels and the polymorphism of this gene was identified.

**Table 3.2.7.**

**Distribution of allele frequencies of the 511 C/T (rs16944) polymorphism of the *IL-1β* gene and the G-308A (rs1800629) polymorphism of the *TNF-α* gene in patients with unstable angina and healthy individuals depending on LDL-C levels in the blood.**

| **Allele** | **Frequency (%)** | | **χ2** | **P-value** | **OR** | **Lower 95% CI** | **Upper 95%** |
|---|---|---|---|---|---|---|---|
| | Patients with ≥4,1 | Control (n=80) | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | mmol/l LDL Chol (n=137) | | | | | | **CI** |
| **C/T 511 gene IL-1β** | | | | | | | |
| **C** | 48,5 | 75,6 | 15,11 | 0,001 | 0,758 | 0,612 | 0,984 |
| **T** | 51,5 | 24,4 | 18,08 | 0,729 | 3,801 | 2,791 | 4,195 |
| **G/A 308 gene TNF-α** | | | | | | | |
| **G** | 43,5 | 67,5 | 24,51 | 0,001 | 0,985 | 0,712 | 1,025 |
| **A** | 56,5 | 32,5 | 17,35 | 0,953 | 1,296 | 1,095 | 1,711 |
| **Allele** | Frequency(%) | | χ2 | P-value | OR | Lower 95% CI | Upper 95% CI |
| | Patients with ≤4,1 mmal/l LDL Chol (n=61) | Control(n=80) | | | | | |
| **C/T 511 (rs16944) of gene IL-1β** | | | | | | | |
| **C** | 51,7 | 75,6 | 18,11 | 0,049 | 0,911 | 0,814 | 0,956 |
| **T** | 48,3 | 24,4 | 13,11 | 0,841 | 1,251 | 1,020 | 1,601 |
| **G/A 308 (rs1800629) of gene TNF-α** | | | | | | | |
| **G** | 48,4 | 67,5 | 17,44 | 0,954 | 0,915 | 0,801 | 0,984 |
| **A** | 51,6 | 32,5 | 19,01 | 0,219 | 1,085 | 0,945 | 1,196 |

In addition to all the aforementioned diagnostic methods, a correlation was identified between certain cytokines and the polymorphic locus -511C>T (rs16944) of the *IL-1β* gene, as well as the G-308A (rs1800629) polymorphism of the *TNF-α* gene.

Patients with the homozygous T/T genotype of the T511C (rs16944) polymorphism of the *IL-1β* gene exhibited relatively high concentrations of the cytokine TNF-α (70.5±6.1 pg/mL) and elevated levels of interleukin IL-1β (107.8±8.4 pg/mL). In contrast to pro-inflammatory cytokines, the levels of anti-inflammatory cytokines IL-4 and IL-10 were reduced in patients with the C/T and T/T genotypes of the T511C (rs16944) polymorphism of the *IL-1β* gene, indicating a significant cytokine imbalance in carriers of the *IL-1β* T allele.

**Table 3.2.8.**

**Concentration levels of certain cytokines depending on the -511C>T (rs16944) polymorphic locus of the *IL-1β* gene in patients with unstable angina.**

| Cytokine Concentration Indicators | Genotype IL-1 T/C 511 | | | P-value | |
|---|---|---|---|---|---|
| | C/C, n=69 | | | | |
| | 1 | 2 | 3 | | |
| TNF-ὰ pg/ml | 66,3±3,9 | 68,7±4,2 | 70,5±6,1 | <0,001<br>0,094<br>0,21 | P1<br>P2<br>P3 |
| IL-1 β | 98,0±7,1 | 96,7±6,5 | 107,8±8,4 | 0,001<br>0,103<br>0,856 | P1<br>P2<br>P3 |
| IL-4 pg/ml | 23,6±2,2 | 23,4±2,1 | 24,9±2,5 | 0,502<br>0,529<br>0,311 | P1<br>P2<br>P3 |
| IL-10 pg/ml | 12,5±1,1 | 12,2±1,7 | 12,3±1,9 | 0,014<br>0,194<br>0,830 | P1<br>P2<br>P3 |

To confirm the association between the progression of the inflammatory process in carriers of the T allele of the G-308A (rs1800629) polymorphic locus of the *TNF-α* gene, we studied the mean levels of certain pro- and anti-inflammatory cytokines. As shown in Table 4.8, the levels of pro-inflammatory cytokines TNF-α and IL-1β were statistically higher in patients with the homozygous A/A genotype compared to those with the homozygous G/G and heterozygous G/A genotypes of the G-308A (rs1800629) polymorphic locus of the *TNF-α* gene.

**Table 3.2.9.**

**Cytokine concentration levels depending on the G-308A (rs1800629) polymorphic locus of the *TNF-α* gene in patients with unstable angina**

| Cytokine Concentration Indicators | TNF-ὰ G-308A | | | Level of significance (p)between groups 1, 2, and 3 |
|---|---|---|---|---|
| | G/G | G/A | A/A | |
| | 1 | 2 | 3 | |
| TNF-ὰ pg/ml | 63,4±4,8 | 65,8±3,0 | 69,6±2,9 | 0,05<br>0,105<br>0,524 |
| IL-1 β | 99,1±4,8 | 95,2±5,1 | 106,5±6,3 | 0,008<br>0,018<br>0,405 |
| IL-4 pg/ml | 24,3±2,6 | 23,4±2,1 | 24,9±2,2 | 0,912<br>0,308<br>0,519 |

| | | | | |
|---|---|---|---|---|
| **IL-10 pg/ml** | **12,7±1,3** | **12,2±1,1** | **12,1±1,0** | **0,003**<br>**0,197**<br>**0,752** |

When interpreting the results of coronary angiography among 116 patients with unstable angina depending on the polymorphism of the -511C>T (rs16944) locus of the *IL-1β* gene, it was found that homozygous T/T and heterozygous C/T genotypic carriers had significantly more coronary artery (CA) damage compared to homozygous C/C genotypic carriers. Specifically, 25 homozygous T/T and 22 heterozygous C/T carriers of the -511C>T (rs16944) *IL-1β* gene locus had 3 or more CAs affected, whereas 16 homozygous C/C carriers had damage to 3 CAs.

**Table 3.2.10.**

**Number of Coronary Artery (CA) Damages Depending on the -511C>T (rs16944) Polymorphism of the *IL-1β* Gene, n=116**

| **Genotype IL-1 T/C 511** | **Lesion of 1 CA, n=27** | **Lesion of 2 CA, n=26** | **Lesion of 3 CA, n=63** | **P-value** |
|---|---|---|---|---|
| **C/C** | 16 (59,2%) | 9(34,6%) | 16(25,3%) | 0,021 |
| **C/T** | 5 (18,5%) | 8(30,8%) | 25(39,7%) | 0,041 |
| **T/T** | 6(22,3%) | 9(34,6%) | 22(35,0%) | 0,853 |

In Table 3.2.10, it is shown that among patients with damage to three or more coronary arteries, the number of patients with psychoemotional disorders was significantly higher, suggesting that the coronary artery damage may not be directly associated with the polymorphism of this gene.

**Table 3.2.11.**

**Frequency of coronary artery damage among patients with unstable angina and psychoemotional disorders depending on the polymorphism of the -511C>T (rs16944) IL-1β gene locus, n=104.**

| **Genotype IL-1 T/C 511** | **Lesion of 1 CA, n=20** | **Lesion of 2 CA, n=24** | **Lesion of 1 CA, n=60** | **P value** |
|---|---|---|---|---|
| **C/C, n=32** | 10 (50%) | 7 (29,1%) | 15 (25,0%) | 0,06<br>0,002<br>0,637 |
| **C/T, n=36** | 4 (20%) | 8 (33,3%) | 24 (40,0%) | 0,391 |

| | | | | |
|---|---|---|---|---|
| | | | | 0,056<br>0,917 |
| **T/T, n=36** | 6 (30%) | 9 (37,5%) | 21 (35,0%) | 0,851<br>0,617<br>0,327 |

When analyzing the results of coronary angiography among patients with unstable angina, one coronary artery (CA) damage was found in 22 patients, two CA damages in 22 patients, and three CA damages in 50 patients. Among these, 26 were homozygous for the A/A genotype and 30 were heterozygous for the G/A genotype, while only 10 patients had the homozygous G/G genotype. Therefore, based on these findings, patients with heterozygous G/A and homozygous A/A genotypes of the G-308A (rs1800629) TNF-α gene polymorphism can be classified as high-risk individuals for coronary artery damage (Figure 3.2.1.).

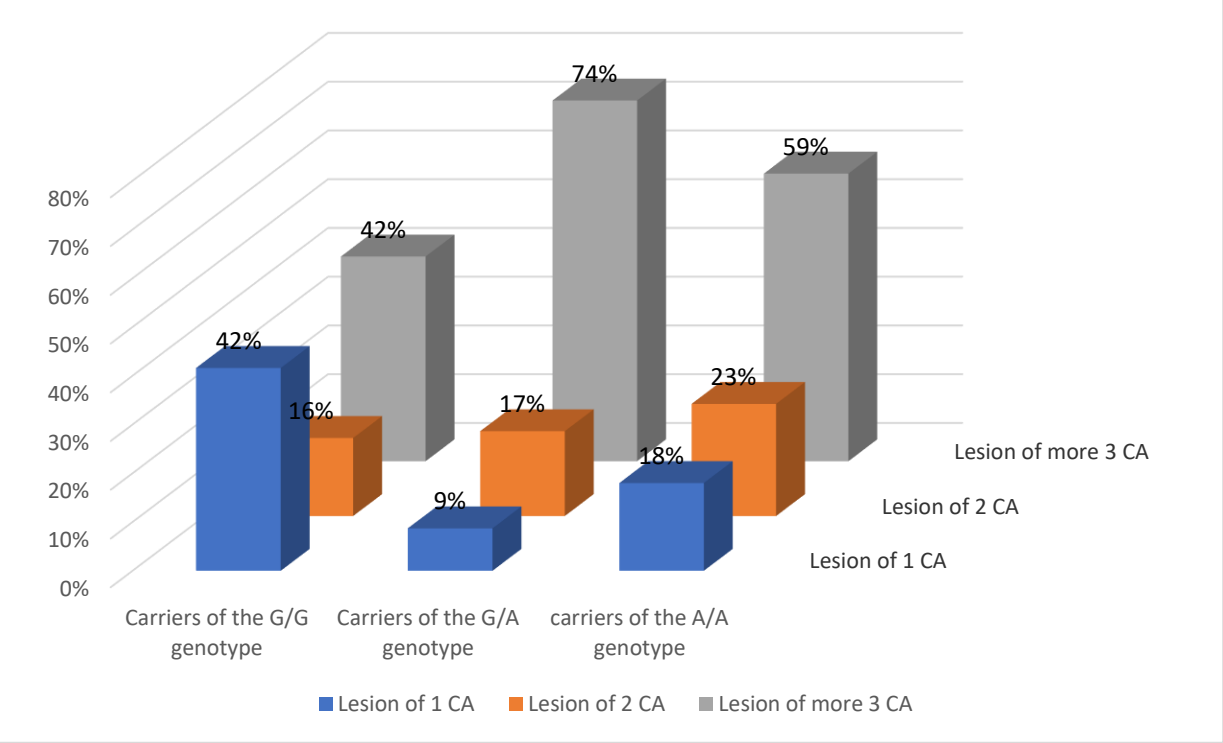



**Figure 3.2.1. Number of coronary artery (CA) damages depending on the polymorphism of the G-308A (rs1800629) TNF-α gene.**

When examining the number of damaged coronary arteries in relation to the presence of a psychological factor, it was found that in patients with psycho-emotional disorders (РЭР), damage to three or more coronary arteries was relatively frequent among all three genotypes. However, it should be noted that among patients with the homozygous G/G genotype, CA damage was observed in 14 (14.5%) patients, while in the heterozygous G/A genotype, it was 42 (43.7%), and among those with the homozygous A/A genotype, 40 (41.7%) patients had CA damage.

These data once again confirm that carriers of the A allele have a higher risk of progression of ischemic heart disease (IHD) with significant coronary artery damage.

**Table 3.2.12.**

**Frequency of coronary artery (CA) damage among patients with unstable angina (UA) and psycho-emotional disorders (Ped) (n=96) depending on the polymorphism of the G-308A (rs1800629) TNF-α gene.**

| G-308A polymorphism (rs1800629) of the TNF-α gene | Lesion of 1 CA, n=14 | Lesion of 2 CA, n=20 | Lesion of 3 CA, n=62 | P-value |
|---|---|---|---|---|
| **G/G, n=14** | 2 (12,5%) | 2 (12,5%) | 10 (62,5%) | 0,01 |
| **G/A, n=42** | 4 (7,4%) | 10 (18,5%) | 28 (51,8%) | 0,319 |
| **A/A, n=40** | 8 (20%) | 8 (20%) | 24 (60%) | 0,864 |

Thus, when identifying the Pearson correlation between the polymorphisms of pro-inflammatory and anti-inflammatory cytokine genes (G-308A (rs1800629) TNF-α gene, -511C>T (rs16944) IL-1β gene, 589C/T (rs2243250) IL-4 gene, 819C/T (rs1800871) IL-10 gene), as well as risk factors such as psycho-emotional disorders (РЭР), hypercholesterolemia, hyperuricemia, and cytokine imbalance, a complex pattern was revealed (Table 3.2.12).

**Table 3.2.13.**

**Pearson correlation between the polymorphisms of some pro-inflammatory and anti-inflammatory cytokine genes and risk factors.**

**Корреляции**

| | | TNF-a 5 308 | Уровень МК до лечения | Общий холестерин до лечения | ЛПВП до лечения | ЛПНП до лечения | А | СТ | ЛТ | IL-1 T/C 511 | IL-4 C/T 589 | IL-10 C/T 819 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TNF-a 5 308 | Корреляция Пирсона | 1 | ,387** | ,138 | -,041 | ,114 | ,179 | ,123 | ,103 | ,314* | -,551** | ,132 |
| | знач. (двухсторонняя) | | <,001 | ,172 | ,683 | ,262 | ,077 | ,227 | ,309 | ,017 | <,001 | ,347 |
| | N | 99 | 99 | 99 | 99 | 99 | 99 | 99 | 99 | 58 | 81 | 53 |
| Уровень МК до лечения | Корреляция Пирсона | ,387** | 1 | ,179* | ,102 | ,219** | ,324** | ,276** | ,237** | ,153 | -,010 | ,418** |
| | знач. (двухсторонняя) | <,001 | | ,011 | ,151 | ,002 | <,001 | <,001 | <,001 | ,056 | ,931 | <,001 |
| | N | 99 | 199 | 199 | 199 | 199 | 199 | 199 | 199 | 158 | 81 | 121 |
| Общий холестерин до лечения | Корреляция Пирсона | ,138 | ,179* | 1 | ,056 | ,124 | ,254** | ,144* | ,119 | ,119 | ,085 | ,041 |
| | знач. (двухсторонняя) | ,172 | ,011 | | ,432 | ,081 | <,001 | ,043 | ,095 | ,136 | ,452 | ,658 |
| | N | 99 | 199 | 199 | 199 | 199 | 199 | 199 | 199 | 158 | 81 | 121 |
| ЛПВП до лечения | Корреляция Пирсона | -,041 | ,102 | ,056 | 1 | -,020 | -,069 | -,069 | -,023 | -,096 | ,062 | ,091 |
| | знач. (двухсторонняя) | ,683 | ,151 | ,432 | | ,775 | ,333 | ,335 | ,752 | ,230 | ,581 | ,320 |
| | N | 99 | 199 | 199 | 199 | 199 | 199 | 199 | 199 | 158 | 81 | 121 |
| ЛПНП до лечения | Корреляция Пирсона | ,114 | ,219** | ,124 | -,020 | 1 | ,128 | ,028 | ,028 | ,207** | ,059 | ,211* |
| | знач. (двухсторонняя) | ,262 | ,002 | ,081 | ,775 | | ,072 | ,693 | ,697 | ,009 | ,603 | ,020 |
| | N | 99 | 199 | 199 | 199 | 199 | 199 | 199 | 199 | 158 | 81 | 121 |
| А | Корреляция Пирсона | ,179 | ,324** | ,254** | -,069 | ,128 | 1 | ,641** | ,576** | ,571** | -,170 | ,311** |
| | знач. (двухсторонняя) | ,077 | <,001 | <,001 | ,333 | ,072 | | <,001 | <,001 | <,001 | ,130 | <,001 |
| | N | 99 | 199 | 199 | 199 | 199 | 199 | 199 | 199 | 158 | 81 | 121 |
| СТ | Корреляция Пирсона | ,123 | ,276** | ,144* | -,069 | ,028 | ,641** | 1 | ,807** | ,657** | -,291** | ,373** |
| | знач. (двухсторонняя) | ,227 | <,001 | ,043 | ,335 | ,693 | <,001 | | <,001 | <,001 | ,008 | <,001 |
| | N | 99 | 199 | 199 | 199 | 199 | 199 | 199 | 199 | 158 | 81 | 121 |
| ЛТ | Корреляция Пирсона | ,103 | ,237** | ,119 | -,023 | ,028 | ,576** | ,807** | 1 | ,660** | -,127 | ,247** |
| | знач. (двухсторонняя) | ,309 | <,001 | ,095 | ,752 | ,697 | <,001 | <,001 | | <,001 | ,260 | ,006 |
| | N | 99 | 199 | 199 | 199 | 199 | 199 | 199 | 199 | 158 | 81 | 121 |
| IL-1 T/C 511 | Корреляция Пирсона | ,314* | ,153 | ,119 | -,096 | ,207** | ,571** | ,657** | ,660** | 1 | -,811** | ,392** |
| | знач. (двухсторонняя) | ,017 | ,056 | ,136 | ,230 | ,009 | <,001 | <,001 | <,001 | | <,001 | <,001 |
| | N | 58 | 158 | 158 | 158 | 158 | 158 | 158 | 158 | 158 | 58 | 104 |
| IL-4 C/T 589 | Корреляция Пирсона | -,551** | -,010 | ,085 | ,062 | ,059 | -,170 | -,291** | -,127 | -,811** | 1 | -,283 |
| | знач. (двухсторонняя) | <,001 | ,931 | ,452 | ,581 | ,603 | ,130 | ,008 | ,260 | <,001 | | ,073 |
| | N | 81 | 81 | 81 | 81 | 81 | 81 | 81 | 81 | 58 | 81 | 41 |
| IL-10 C/T 819 | Корреляция Пирсона | ,132 | ,418** | ,041 | ,091 | ,211* | ,311** | ,373** | ,247** | ,392** | -,283 | 1 |
| | знач. (двухсторонняя) | ,347 | <,001 | ,658 | ,320 | ,020 | <,001 | <,001 | ,006 | <,001 | ,073 | |
| | N | 53 | 121 | 121 | 121 | 121 | 121 | 121 | 121 | 104 | 41 | 121 |

**. Корреляция значима на уровне 0,01 (двухсторонняя).

*. Корреляция значима на уровне 0,05 (двухсторонняя).

A significant correlation was found between the -511C>T (rs16944) polymorphism of the IL-1β gene and anxiety levels as measured by the HADS scale and the Spielberger-Hanin scale (Figure 4.2).

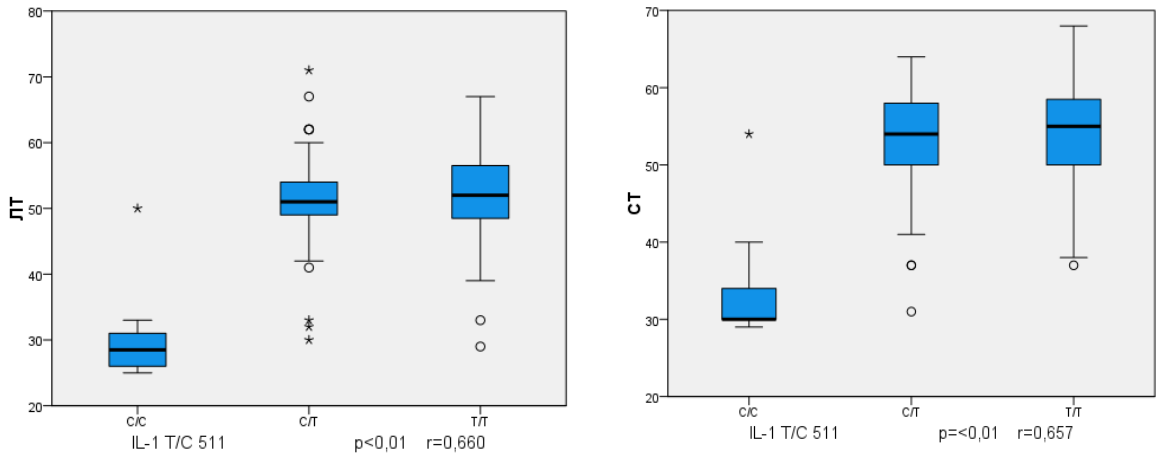



**Figure 3.2.2. Correlation between the -511C>T (rs16944) polymorphism of the IL-1β gene and anxiety levels according to the HADS and Spielberger-Hanin scales.**

The correlation with anxiety levels measured by the HADS scale among carriers of the heterozygous C/T genotype of the -511C>T (rs16944) polymorphism of the IL-1β gene was $r = 0.571$, $p \leq 0.01$. Carriers of the homozygous T/T and

heterozygous C/T genotypes of the -511C>T (rs16944) polymorphism of the IL-1β gene exhibited a strong correlation when assessing both situational anxiety ($r = 0.660$, $p \leq 0.01$) and personal anxiety ($r = 0.657$, $p \leq 0.01$) according to the Spielberger-Hanin scale.

Regarding the G-308A (rs1800629) polymorphism of the TNF-α gene, a moderate correlation ($r = 0.387$, $p \leq 0.01$) was found between carriers of the homozygous A/A genotype and the heterozygous G/A genotype of the G-308A (rs1800629) polymorphism of the TNF-α gene and uric acid levels.

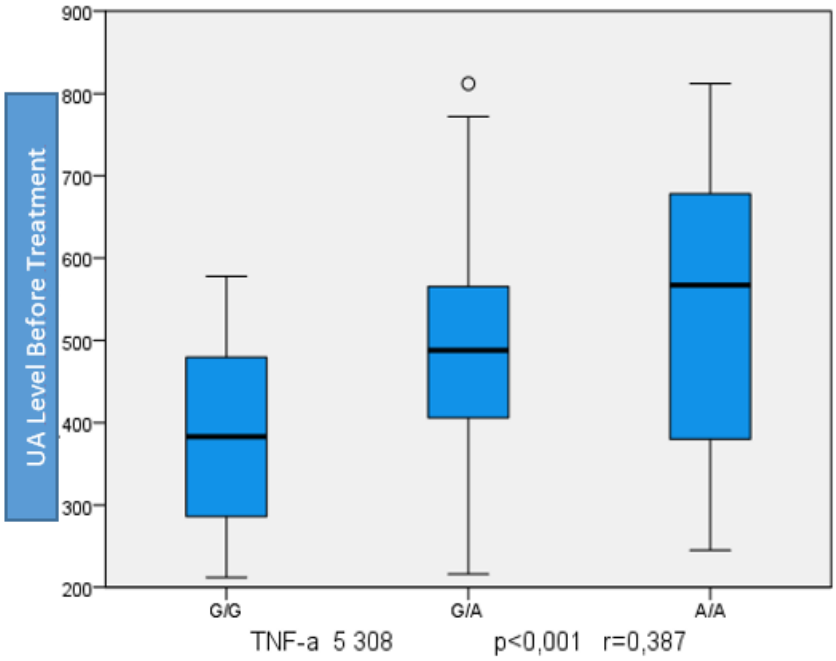



**Figure 3.2.3. Correlation between the G-308A (rs1800629) polymorphism of the TNF-α gene and uric acid levels.**

Thus, patients with the C/T and T/T genotypes of the -511C>T (rs16944) polymorphism of the IL-1β gene are more predisposed to developing psychiatric and emotional disorders, cytokine imbalance, and atherosclerotic changes, as confirmed by coronary angiography results. Specifically, patients with the C/T and T/T genotypes had significant coronary artery (CA) damage, particularly in those with

psychiatric disorders, which in turn worsens the clinical course of the primary disease. This requires more thorough monitoring and treatment of patients to improve the prognosis of coronary heart disease (CHD). It was found that in patients with unstable angina (UA) and psychiatric disorders, carriers of homozygous A/A and heterozygous G/A genotypes of the G-308A (rs1800629) polymorphism of the TNF-α gene had significantly higher levels of anxiety and depression compared to the control group. The distribution of mean scores on the anxiety scales showed that patients with the homozygous A/A and heterozygous G/A genotypes of the G-308A (rs1800629) polymorphism of the TNF-α gene had high anxiety and depression scores, indicating a relationship between psychiatric and emotional disorders and the minor A allele. Moreover, pro-inflammatory cytokine levels of TNF-α and IL-1β were statistically higher in patients with the homozygous A/A genotype compared to those with the homozygous G/G and heterozygous G/A genotypes of the G-308A (rs1800629) polymorphism of the TNF-α gene. A moderate correlation was found between the G-308A (rs1800629) polymorphism of the TNF-α gene and uric acid levels, suggesting a possible link between the progression of CHD and elevated uric acid levels.

## § 3.3. STUDY OF POLYMORPHISM OF ANTI-INFLAMMATORY CYTOKINES IN CORONARY ARTERY DISEASE ASSOCIATED WITH PSYCHOEMOTIONAL STATUS

Interleukin-4 (IL-4) is a key cytokine of the Th2 type and may have a protective effect against depression due to its ability to counteract inflammation and inhibit serotonin transporter activity. In 2017, Simone Wachholz (https://doi.org/10.1016/j.bbr.2017.03.020) used a mouse model with interferon-α to demonstrate that reduced microglial sensitivity to IL-4 was specifically associated with the development of depressive behavior. Additionally, Hyun-ju Lee's study showed that IL-4 is produced by noradrenergic neurons in the locus coeruleus (LC) of the brain, and the release of IL-4 was reduced in response to stress (https://doi.org/10.1155/2016/3501905, Hyun-ju Lee, Hyun-Jung Park, Angela Starkweather, Kyungeh An, and Insop Shim).

Given the impact of IL-4 in counteracting inflammation and inhibiting serotonin activity, we conducted a study to identify the pathogenic polymorphic locus -589 C/T (rs2243250) of the IL-4 gene in patients with coronary artery disease (CAD) and comorbid psychiatric disorders. This may help us predict the development of unstable angina forms. We studied the frequency of the C/T genotype at the 589 locus of the IL-4 gene in 198 CAD patients and 80 healthy donors from the Uzbek ethnic population, who exhibited no clinical disease manifestations. Additionally, IL-10, an anti-inflammatory cytokine, was studied in relation to psychoemotional disorders. Previous research on the relationship between mental health and IL-10 production has been contradictory, showing elevated, unchanged, or reduced IL-10 levels in patients with depression, and differentiating depressive subtypes. It has been suggested that elevated levels of IL-10 might

indicate a compensatory anti-inflammatory response to a generalized inflammatory state due to mental health conditions. In this study, we analyzed the frequency distribution of alleles and genotypes of the -819 C/T (rs1800871) locus of the IL-10 gene in CAD patients with comorbidities to identify "unfavorable" combinations that lead to a high probability of disease development in the Uzbek population. The distribution of alleles and genotypes of the polymorphic variant 819 C/T (rs1800871) of the IL-10 gene was studied in 198 CAD patients and 80 healthy individuals. Genotyping of the polymorphic locus C819T (rs1800871) of the IL-10 gene was conducted in these patients.

The frequency of the major allele C and the minor allele T of the 589 C/T (rs2243250) polymorphism of the IL-4 gene was studied among patients with coronary artery disease (CAD) and the control group, as shown in Table 3.3.1. The table demonstrates that the allele C is found in 62.1% of CAD patients, while in the healthy individuals, allele C was identified in 35.6%. In contrast, allele T is 26.5% more common in the control group. Additionally, when analyzing the frequency of the 819 C/T (rs1800871) polymorphism of the IL-10 gene, it was found that allele T is significantly more common in the main group (35.1%) compared to the control group (22.5%).

**Table 3.3.1.**

**Distribution of allele frequencies of the 589 C/T (rs2243250) IL-4 gene polymorphism and 819 C/T (rs1800871) IL-10 gene polymorphism in CAD patients and healthy individuals.**

| Allele | Frequency (%) | | χ2 | P-value | OR | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|
| | Main group (n=198) | Control group (n=80) | | | | | |
| **C/T 589 (rs 2243250) of gene IL-4** | | | | | | | |
| **C** | 62,1 | 35,6 | 17,25 | 0,001 | 0,985 | 0,879 | 1,026 |
| **T** | 37,9 | 64,4 | 15,87 | 0,173 | 2,328 | 1,919 | 2,549 |
| **C/T 819 (rs1800871) of gene IL -10** | | | | | | | |
| **C** | 64,9 | 77,5 | 11,28 | 0,000 | 0,18 | 0,09 | 0,48 |
| **T** | 35,1 | 22,5 | 11,79 | 0,000 | 5,21 | 2,12 | 12,51 |

The study of genotype polymorphism (Table 3.3.2) revealed that in the group of CAD patients, the frequency of the homozygous T/T variant of the C819T (rs1800871) IL-10 gene polymorphism was significantly higher than in the control group (18.7% vs. 8.8%, respectively, $\chi2=1.02$; $P=0.187$).

The frequency of the heterozygous C/T variant of the C819T (rs1800871) IL-10 gene polymorphism in this group of patients was almost identical to that in the control group. The analysis of allele and genotype frequency distribution of the

C819T (rs1800871) IL-10 gene polymorphism demonstrated statistically significant differences in the T and C alleles, as well as the T/T and C/C genotypes, in the group of CAD patients compared to the control group of healthy individuals (Table 3.3.2).

Table 3.3.2.

**Distribution of the polymorphic locus 589 C/T (rs2243250) of the IL-4 gene and 819 C/T (rs1800871) of the IL-10 gene in CAD patients and healthy individuals.**

| Genotype | Frequency (%) | | χ2 | P | OR | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|
| | UA (n=198) | Control group (n=80) | | | | | |
| **589 C/T (rs 2243250) of gene IL-4** | | | | | | | |
| **C/C** | 54,6 | 72,5 | 3,76 | 0,052 | 0,46 | 0,21 | 1,02 |
| **C/T** | 28,8 | 20 | 1,15 | 0,284 | 1,62 | 0,67 | 3,95 |
| **T/T** | 16,6 | 7,5 | 1,92 | 0,166 | 2,44 | 0,67 | 8,88 |
| **819 C/T (rs1800871) of gene IL-10** | | | | | | | |
| **C/C** | 48,9 | 63,7 | 3,14 | 0,082 | 0,54 | 0,22 | 1,04 |
| **C/T** | 32,8 | 27,5 | 1,18 | 0,316 | 1,88 | 0,76 | 3,11 |
| **T/T** | 18,7 | 8,8 | 1,02 | 0,187 | 2,12 | 0,56 | 8,45 |

When studying the frequency of genotype occurrence among patients with UA in comparison to the control group, it was found that 54.6% of patients carried the homozygous C/C variant at position -589 C/T of the IL-4 gene polymorphism, while in the control group, this figure was 72.5%. The proportion of heterozygous genotype carriers in the main group was 28.8%, compared to 20.0% in the control group. The frequency of the homozygous T/T genotype of the IL-4 gene among patients with UA was 16.6%, whereas in the control group, it was 7.5% (Table 4.2). This indicates that the control group had a significantly higher prevalence of the C allele compared to the main group.

To identify potential associations, an analysis was conducted to explore the relationship between UA associated with psychoemotional disorders (PED) and serum uric acid levels with the C/T polymorphism of the IL-4 and IL-10 genes in the studied population.

When comparing IL-4 gene (C589T) alleles between UA patients and the control group, it was found that the C allele was significantly more frequent among UA patients with elevated uric acid levels (61.0%) compared to the control group (35.6%) ($\chi2=12.95$; $p=0.001$). This suggests a possible association between asymptomatic hyperuricemia and carriage of the C allele of the IL-4 gene (C589T).

When comparing the alleles of the C819T (rs1800871) polymorphism of the IL-10 gene among patients with unstable forms of CHD and asymptomatic hyperuricemia versus healthy individuals, it was noted that the T allele was

significantly more frequent in the group of UA patients with asymptomatic hyperuricemia than in the group of practically healthy individuals (46.3% versus 22.5%, respectively, $\chi 2 = 15.62$; $p = 0.072$) (Table 3.3.3).

Thus, the association of the C819T (rs1800871) polymorphism of the IL-10 gene with the unstable form of the disease in the Uzbek population has been demonstrated, particularly through the T/T genotype combination.

**Table 3.3.3**

**Distribution of allele frequencies of the 589 C/T (rs2243250) polymorphism of the IL-4 gene and the 819 C/T (rs1800871) polymorphism of the IL-10 gene among UA patients and practically healthy individuals, depending on serum uric acid levels.**

| Alleles | Frequency (%) | | χ2 | P | OR | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|
| | Patients with elevated level of uric acid (≥360 mkmol/l (n=123) | Control (n=80) | | | | | |
| **589 C/T (rs 2243250) of gene IL-4** | | | | | | | |
| **C** | 61,0 | 35,6 | 12,95 | 0,001 | 0,823 | 0,703 | 0,914 |
| **T** | 39,0 | 64,4 | 19,07 | 0,348 | 2,260 | 1,783 | 2,876 |
| **819 C/T (rs1800871) of gene IL-10** | | | | | | | |
| **C** | 53,7 | 77,5 | 24.17 | 0.031 | 0.913 | 0.808 | 1.019 |
| **T** | 46,3 | 22,5 | 15.62 | 0.072 | 1.284 | 0.936 | 1.539 |

The results of the molecular genetic study demonstrated the significance of the T allele of the -819 C/T (rs1800871) polymorphism of the IL-10 gene in the genetic predisposition to CHD associated with asymptomatic hyperuricemia in the Uzbek population.

**Table 3.3.4**

**Distribution of allele frequencies of the 589 C/T (rs2243250) polymorphism of the IL-4 gene and the 819 C/T (rs1800871) polymorphism of the IL-10 gene among UA patients and healthy individuals, depending on serum uric acid levels.**

| Allele | Frequency (%) | | χ2 | P-value | OR | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|
| | Patients with normal level of uric acid (less than 360 mkmol/l) | Control (n=80) | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | (n=75) | | | | | | |
| **589 C/T (rs 2243250) of gene IL-4** | | | | | | | |
| **C** | 64,5 | 35,6 | 18,31 | 0,002 | 0,844 | 0,765 | 1,078 |
| **T** | 35,5 | 64,4 | 13,37 | 0,286 | 1,352 | 1,027 | 1,696 |
| **819 C/T (rs1800871) of gene IL-10** | | | | | | | |
| **C** | 50,4 | 77,5 | 26,07 | 0,033 | 0,916 | 0,715 | 1,275 |
| **T** | 49,6 | 22,5 | 19,35 | 0,366 | 1,615 | 1,075 | 2,064 |

The obtained data indicate that the markers of increased risk for CHD destabilization with asymptomatic hyperuricemia in individuals of the Uzbek ethnic population are the IL-10 (T819T) genotype and the T allele, while the markers of reduced risk are the IL-10 (C819C) genotype and the C allele.

When forming groups of UA patients based on serum uric acid concentration, we identified an association between its level and the C819T (rs1800871) polymorphism of the IL-10 gene.

**Table 3.3.5**

**Mean serum uric acid levels depending on the -819 C/T (rs1800871) polymorphism of the IL-10 gene.**

| **Indicator** | **C/C (n=97)** | **C/T (n=64)** | **T/T (n=37)** | | |
|---|---|---|---|---|---|
| **Uric acid, mkmol/l** | 368,8±46,1 | 489,1±61,2 | 514,5±64,3 | <0,384<br><0,030<br><0,839 | $P1_{C/C-C/T}$<br>$P2_{C/C-T/T}$<br>$P3_{C/T-T/T}$ |

The data presented in Table 4.5 indicate that the presence of the T allele in the genotype leads to impaired purine metabolism. Patients with the homozygous T/T genotype were more prone to asymptomatic hyperuricemia, with a mean serum UA level of 514.5±64.3 μmol/L, whereas patients with the C/C genotype had a mean serum uric acid level of 368.8±46.1 μmol/L. Uric acid levels in the T/T genotype group were significantly higher than in patients with the C/C and C/T genotypes ($p<0.03$, $p<0.839$, respectively).

Next, the frequency of the C and T alleles of the -589 C/T polymorphism of the IL-4 gene and the -819 polymorphism of the IL-10 gene was studied among patients with unstable angina, depending on LDL-C levels in the blood.

**Table 3.3.6**

**Distribution of -589 C/T (rs2243250) IL-4 gene and -819 C/T (rs1800871) IL-**

**10 gene allele frequencies in UA patients and healthy individuals depending on LDL-C levels in the blood.**

| Allele | Frequency (%) | | χ2 | P-value | OR | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|
| | Patients with ≥4,1 mmol/l LDL Chol (n=137) | Control (n=80) | | | | | |
| **589 C/T (rs 2243250) of gene IL-4** | | | | | | | |
| **C** | 62,3 | 35,6 | 15,97 | 0,028 | 0,915 | 0,831 | 1,291 |
| **T** | 37,7 | 64,4 | 18,22 | 0,127 | 3,543 | 2,156 | 4,361 |
| **819 C/T (rs1800871) of gene IL-10** | | | | | | | |
| **C** | 48,5 | 77,5 | 22,46 | 0,046 | 0,862 | 0,726 | 0,932 |
| **T** | 51,5 | 22,5 | 19,34 | 0,294 | 0,954 | 0,806 | 1,281 |
| **Allele** | Frequency (%) | | χ2 | P-value | OR | Lower 95% CI | Upper 95% CI |
| | Patients with ≤4,1 mmol/l LDL Chol (n=122) | Control (n=80) | | | | | |
| **589 C/T (rs 2243250) of gene IL-4** | | | | | | | |
| **C** | 61,7 | 35,6 | 25,14 | 0,005 | 0,935 | 0,819 | 1,025 |
| **T** | 38,3 | 64,4 | 22,63 | 0,318 | 1,317 | 0,985 | 1,692 |
| **819 C/T (rs1800871) of gene IL-10** | | | | | | | |
| **C** | 51,7 | 77,5 | 19,85 | 0,028 | 0,769 | 0,602 | 0,914 |
| **T** | 48,3 | 22,5 | 20,84 | 0,375 | 1,165 | 0,905 | 1,572 |

When analyzing the distribution of the C and T alleles of the -589 C/T (rs2243250) IL-4 gene in patients with elevated and normal LDL-C levels, it was found that 62.3% of patients with high LDL-C levels carried the C allele, whereas in the control group, the C allele frequency was 35.6%. However, when examining the frequency of the C and T alleles among patients with LDL-C ≤4.1 mmol/L, a similar pattern was observed, meaning that the frequency of this allele was comparable among patients with both high and normal LDL-C levels (Table 3.3.6).

To determine the association of the -819 C/T (rs1800871) IL-10 gene polymorphism with psychoemotional disorders (PED), allele frequency distributions of the IL-10 gene were analyzed in UA patients with and without PED and in the control group. It was revealed that the C and T alleles of the -819 C/T (rs1800871) IL-10 polymorphism had different frequencies (Table 3.3.6). For a more detailed

analysis of the -819 C/T (rs1800871) IL-10 polymorphism frequency, CAD patients were examined separately based on the presence of PED.

A separate analysis of the -589 C/T (rs2243250) IL-4 polymorphism was conducted among healthy donors and UA patients with different psychoemotional statuses, including those diagnosed with anxiety-depressive syndrome based on the HADS-A/D scale. The distribution of C and T allele frequencies of the -589 C/T IL-4 polymorphism in CAD patients with and without PED and in the control group showed significant differences (Table 4.7). The SNP -589 C/T IL-4 genotype frequencies in UA patients with PED and healthy individuals also varied. Among patients, the minor C allele predominated at a frequency of 61.4%, while the major T allele was found at 38.6%, which was 16.1% less frequent than in the control group ($\chi 2$=16.89; p=0.017) (Table 3.3.7).

**Table 3.3.7.**

**Distribution of allele frequencies of the -589 C/T (rs2243250) IL-4 gene polymorphism and the -819 C/T (rs1800871) IL-10 gene polymorphism in UA patients and healthy individuals depending on psychoemotional disorders (PED).**

| Genotype | Frequency (%) | | χ2 | P | OR | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|---|
| | UA + PED (n=162) | Control(n=80) | | | | | |
| **-589 C/T (rs 2243250) of gene IL-4** | | | | | | | |
| **C** | 61,4 | 35,6 | 16,89 | 0,017 | 0,862 | 0,716 | 0,993 |
| **T** | 38,6 | 64,4 | 20,38 | 0,446 | 1,078 | 0,672 | 1,754 |
| **-819 C/T (rs1800871) of gene IL-10** | | | | | | | |
| **C** | 62,6 | 77,5 | 20,34 | 0,015 | 0,814 | 0,688 | 0,973 |
| **T** | 37,4 | 22,5 | 18,34 | 0,681 | 1,084 | 0,953 | 1,247 |

**Table 3.3.8**

**Average values of anxiety-depressive syndrome indicators on the HADS and Spielberger-Hanin scales depending on the -589 C/T (rs2243250) IL-4 gene polymorphic locus.**

| IL-4 C/T 589 | Аллели | HADS-A | HADS-D | SA | TA | P value |
|---|---|---|---|---|---|---|
| | C/C | 10,2±1,8 | 9,6 ±1,6 | 54,2 ±4,3 | 54,0 ±4,6 | 0,022 |
| | C/T | 12,6 ±1,9 | 11,5 ±1,2 | 53,4 ±4,7 | 52,3 ±4,1 | 0,437 |
| | T/T | 9,8 ±1,5 | 9,1 ±1,1 | 51,2 ±3,9 | 51,3 ±4,9 | 0,374 |

It was found that in the groups of patients with unstable angina (UA) and psycho-emotional disorders (PED), the carriers of homozygous and heterozygous

alleles of the IL-4 gene had significantly higher indicators compared to the control group. Specifically, in patients with UA and PED, those carrying the homozygous C/C variant and the heterozygous C/T genotype had the highest levels of psycho-emotional disturbances. The average score on the HADS-A scale was 12.6±1.9, and on the HADS-D scale, it was 11.5±1.2 for heterozygous C/T genotype carriers. When examining patients with the homozygous C/C genotype of the SNP polymorphism C/T 589 of the IL-4 gene, the average score on the Spielberger-Hanin scale was 54.2±4.3 for ST, and 54.0±4.6 for LT. The results of the Eysenck scale revealed that among 198 patients, 132 showed rigidity, of which 60 (30.3%) were carriers of the C/C genotype, 42 (21.2%) were C/T, and 30 (15.1%) were T/T.

**Table 3.3.9.**

**Average values of anxiety-depressive syndrome indicators on the HADS and Spielberger-Hanin scales depending on the -819 C/T (rs1800871) IL-10 gene polymorphic locus.**

| IL-1 T/C 819 | Alleles | HADS-A | HADS-D | SA | TA | P value |
|---|---|---|---|---|---|---|
| | C/C | 8,8±1,8 | 9,1±1,6 | 48,0±3,5 | 47,1±3,2 | 0,003 |
| | C/T | 10,6±2,1 | 11,4±1,8 | 51,0±3,8 | 49,9±4,5 | 0,027 |
| | T/T | 12,2±2,4 | 12,4±2,4 | 54,4±3,7 | 50,8±4,2 | 0,451 |

To confirm the association between the progression of the inflammatory process in carriers of the T allele of the -819 C/T (rs1800871) IL-10 gene locus, we studied the mean levels of some pro-inflammatory and anti-inflammatory cytokines. As shown in Table 4.10, the levels of pro-inflammatory cytokines TNF-α and IL-1β were statistically higher in patients with the homozygous T/T genotype compared to those with the homozygous C/C and heterozygous C/T genotypes of the -819 C/T (rs1800871) IL-10 gene locus. Additionally, the levels of anti-inflammatory cytokines such as IL-4 and IL-10 in these same patients with the T/T genotype were statistically lower than those in patients with the C/C and C/T genotypes of the -819 C/T (rs1800871) IL-10 gene locus.

**Table 3.3.10.**

**Cytokine concentration levels depending on the -819 C/T (rs1800871) IL-10 gene locus polymorphism in patients with unstable angina (UA).**

| Cytokine concentration levels | C/T 819 of gene IL-10 | | | Significance level (P) between groups 1, 2, 3 |
|---|---|---|---|---|
| | C/C | C/T | T/T | |
| | 1 | 2 | 3 | |
| **TNF-α pg/ml** | 67,0±5,5 | 69,3±5,5 | 71,6±6,2 | <0,001 |

| | | | | |
|---|---|---|---|---|
| | | | | 0,001<br>0,511 |
| **IL-1 pg/ml** | 99,2±6,4 | 102,0±6,7 | 104,7±7,9 | 0,033<br><0,001<br>0,684 |
| **IL-4 pg/ml** | 23,6±2,2 | 23,9±0,8 | 25,3±1,9 | 0,111<br>0,025<br>0,614 |
| **IL-10 pg/ml** | 12,2±0,8 | 12,5±0,7 | 12,8±0,5 | 0,145<br>0,028<br>0,331 |

In the study of the association between the -589 C/T (rs 2243250) IL-4 gene polymorphism and the levels of certain cytokines, the highest levels of pro-inflammatory cytokines TNF-α and IL-1β were found among carriers of the homozygous C/C genotype: 70.1±5.2 and 107.6±7.1 pg/ml, respectively. Additionally, a slightly reduced level of the anti-inflammatory cytokine IL-4 was observed, at 22.3±1.8 pg/ml, compared to the C/T and T/T carriers.

**Table 3.3.11.**

**Concentration levels of certain cytokines depending on the -589 C/T (rs 2243250) IL-4 gene locus polymorphism in patients with unstable angina (UA).**

| Показатели концентрации цитокинов | C/T 589 гена IL-4 | | | P-value | |
|---|---|---|---|---|---|
| | C/C | C/T | T/T | | |
| | 1 | 2 | 3 | | |
| TNF-α пг/мл | 70,1±5,2 | 63,5±5,8 | 63,2±5,5 | 0,071<br><0,001<br>0,246 | P1<br>P2<br>P3 |
| IL-1β пг/мл | 107,6±7,1 | 92,6±6,9 | 95,9±8,4 | 0,024<br>0,031<br>0,349 | P1<br>P2<br>P3 |
| IL-4 пг/мл | 22,3±1,8 | 23,6±1,4 | 24,5±1,8 | 0,815<br>0,01<br>0,547 | P1<br>P2<br>P3 |
| IL-10 пг/мл | 12,3±0,6 | 11,8±0,9 | 13,0±0,7 | 0,784<br>0,371<br>0,679 | P1<br>P2<br>P3 |

Upon examining the results of coronary angiography, we did not find statistically significant data. Among patients with unstable angina (UA), depending on the polymorphism of the -819 C/T (rs1800871) IL-10 gene locus, it was observed that 11.5% of homozygous T/T carriers, 46.1% of heterozygous C/T genotype carriers, and 42.3% of homozygous C/C carriers had damage to two coronary arteries (CA). Damage to three coronary arteries was found in 23.8% of homozygous C/C carriers, 47.6% of C/T carriers, and 28.6% of T/T carriers of the -819 C/T (rs1800871) IL-10 gene polymorphism.

In the study of the number of affected coronary arteries depending on the presence of a mental factor, it was revealed that among patients with psycho-emotional disorders (PED), damage to three or more coronary arteries was more frequently observed in carriers of the heterozygous C/T genotype of the -819 C/T (rs1800871) IL-10 gene polymorphism.

**Table 3.3.12.**

**Frequency of coronary artery (CA) damage among patients with unstable angina (n=103) and psycho-emotional disorders (PED) depending on the -819 C/T (rs1800871) IL-10 gene locus polymorphism.**

| 819 C/T (rs1800871) of gene IL-10 | Lesion of 1 CA, n=19 | Lesion of 2 CA, n=24 | Lesion of 3 CA, n=60 | P-value |
|---|---|---|---|---|
| C/C, n=31 | 7 (36,8%) | 9 (37,5%) | 15 (25,0%) | 0,267<br>0,044<br>0,001 |

| | | | | |
|---|---|---|---|---|
| **C/T, n=49** | 9 (47,4%) | 12 (50,0%) | 28 (46,7%) | 0,347<br>0,629<br>0,025 |
| **T/T, n=23** | 3 (15,8%) | 3 (11,5%) | 17 (28,3%) | 0,614<br>0,581<br>0,649 |

The results of the coronary angiography study showed a significant correlation between coronary artery (CA) damage and the -819 C/T (rs1800871) IL-10 gene locus polymorphism. Among homozygous T/T carriers, 28.3% of patients, as well as 46.7% of heterozygous C/T carriers of the IL-10 gene, exhibited damage to three or more coronary arteries. This confirms that among patients with unstable angina (UA) and psycho-emotional disorders (PED), homozygous T/T and heterozygous C/T carriers show greater coronary artery damage compared to homozygous C/C carriers, indicating the need for special monitoring.

When interpreting the coronary angiography results among patients with UA depending on the polymorphism of the -589 C/T (rs 2243250) IL-4 gene locus, it was revealed that homozygous C/C and heterozygous C/T carriers had significantly more cases of damage to three or more coronary arteries compared to homozygous T/T carriers of the -589 C/T (rs 2243250) IL-4 gene locus. Specifically, multifocal CA damage was found in 32 patients with UA who had the homozygous C/C genotype, 28 patients with the heterozygous C/T genotype, and 12 patients with the homozygous T/T genotype (Table 3.3.13).

**Table 3.3.13.**

**Number of coronary artery (CA) damages depending on the -589 C/T (rs 2243250) IL-4 gene locus polymorphism (n=118).**

| **C/T 589 IL-4** | **Lesion of 1 CA, n=24** | **Lesion of 2 CA, n=22** | **Lesion of 3 CA, n=72** | **P-value** |
|---|---|---|---|---|
| **C/C, n=54** | 12 (22,2%) | 10 (18,5%) | 32 (59,3%) | 0.065<br>0.049<br>0.001 |
| **C/T, n=36** | 2 (5,6%) | 6 (16,7%) | 28 (77,8%) | 0.195<br>0.046<br>0.037 |
| **T/T, n=28** | 10 (35,7%) | 6 (21,4%) | 12 (42,8%) | 0.634<br>0.813<br>0.692 |

Upon studying the -589 C/T (rs 2243250) IL-4 gene locus polymorphism, a relationship was found between the number of coronary artery (CA) lesions and

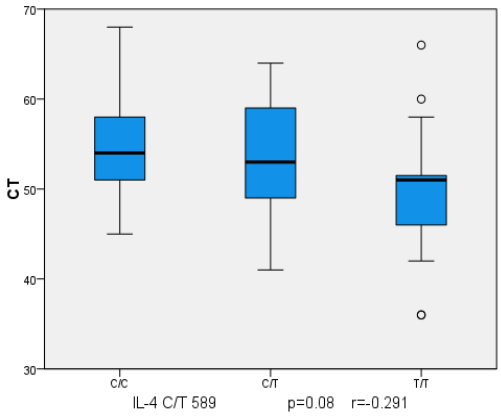
psycho-emotional disorders. Among 92 patients (77.9%) with psycho-emotional disorders (PED), CA lesions were identified (Table 3.3.14).

**Table 3.3.14.**

**Frequency of coronary artery (CA) damage among patients with unstable angina (UA) and psycho-emotional disorders (PED) depending on the -589 C/T (rs 2243250) IL-4 gene locus polymorphism, n=92.**

| C/T 589 IL-4 | Lesion of 1 CA, n=10 | Lesion of 2 CA, n=16 | Lesion of 3 CA, n=66 | P value |
|---|---|---|---|---|
| **C/C, n=42** | 8(80,0%) | 6(37,5%) | 28(42,4%) | 0,011<br>0,018<br>0,001 |
| **C/T, n=36** | 2(20,0%) | 6(37,5%) | 28(43,4%) | 0,349<br>0,735<br>0,084 |
| **T/T, n=14** | 0(0,0%) | 4(25,0%) | 10(15,6%) | 0,068<br>0,497<br>0,618 |

It should be noted that among patients with unstable angina (UA) and psycho-emotional disorders (PED), one coronary artery (CA) lesion was detected in 10 (10.8%) patients, and three or more CA lesions were found in 66 (71.7%) patients. This indicates a direct correlation between CA damage and the development of psycho-emotional disorders. Additionally, a relationship between CA damage and a point mutation, specifically a transition replacing pyrimidine bases (thymine with cytosine), was observed. When analyzing the number of affected coronary arteries in relation to the presence of a mental factor, multifocal damage was more frequently found among carriers of the homozygous C/C genotype and the heterozygous C/T genotype.



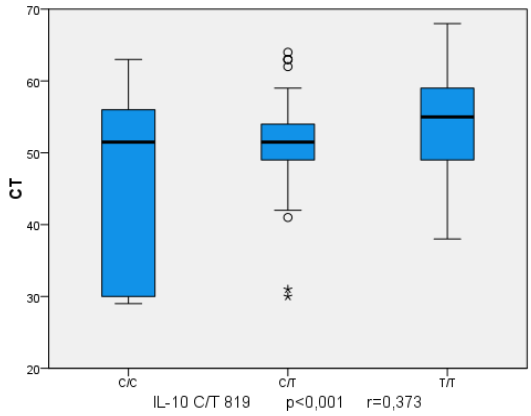



**Figure 3.3.1. Correlation between the polymorphisms -589 C/T (rs 2243250) of the IL-4 gene and -819 C/T (rs1800871) of the IL-10 gene with situational anxiety according to the Spielberger-Hanin scale.**

When studying the relationship between psycho-emotional disorders (PED) and the polymorphisms of the IL-4 and IL-10 genes, a moderate correlation was found between the level of PED and carriers of the homozygous C/C and T/T genotypes of the IL-4 and IL-10 genes, respectively (Figure 3.3.1.). We identified interesting findings when studying the correlation between the IL-10 gene polymorphism and the level of uric acid (UA). It was found that carriers of the heterozygous C/T and homozygous T/T genotypes of the IL-10 gene had a moderate correlation (R=0.418; P≤0.001).

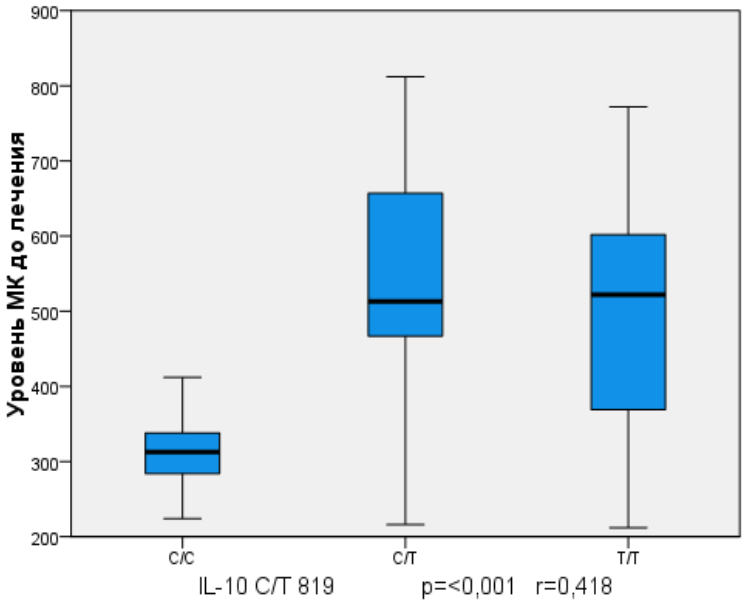



**Figure 3.3.2. Correlation between the polymorphism -819 C/T (rs1800871) of the IL-10 gene and the level of uric acid (UA).**

Thus, in the course of our study, it was found that among patients with unstable angina (UA), the C allele of the IL-4 gene occurred 26.5% more often than in the control group. It was also found that among patients with unstable angina and psycho-emotional disorders (PED), with elevated levels of UA and low-density lipoprotein cholesterol (LDL-C), the C allele in the -589 C/T polymorphism of the IL-4 gene occurred 25.4% and 26.7% more frequently than in the control group. However, it should be emphasized that among patients with normal levels of UA and LDL-C, the frequency of the C allele was also higher than in the control group—28.9% and 26.1%, respectively. This suggests that the polymorphism of this gene may be more related to psycho-emotional disorders rather than disturbances in purine and lipid metabolism, as the results of coronary angiography showed a significantly higher incidence of three or more coronary arteries (CA) lesions among patients with ischemic heart disease (IHD) and PED. This may be because the mutation in the pyrimidine bases sequence potentially suppresses the secretion of

interleukin-4 (IL-4), which could impair the ability to inhibit serotonin transporter activity.

Therefore, when examining the relationship between the -589 C/T (rs 2243250) polymorphism of the IL-4 gene and the -819 C/T (rs1800871) polymorphism of the IL-10 gene with indicators such as hyperuricemia, hypercholesterolemia, PED, and cytokine imbalance, we found a statistically significant strong association between the -589 C/T (rs 2243250) polymorphism of the IL-4 gene and situational anxiety according to the Spielberger-Hanin scale. Carriers of the homozygous C/C genotype of the IL-4 gene had a moderate correlation strength, as measured by Pearson's correlation coefficient.

Thus, when studying the frequency of occurrence and the degree of clinical manifestation of psycho-emotional disorders (PED) in patients with ischemic heart disease (IHD) during periods of stability and destabilization, we found that practically every other patient had PED, with one-third of patients showing clinically significant levels of anxiety and depression.
When comparing the alleles of the G-308A (rs1800629) polymorphism of the TNF-α gene, in the group of patients with unstable IHD and asymptomatic hyperuricemia and healthy individuals, it was noted that the A allele was significantly more frequent in the group of patients with unstable IHD and asymptomatic hyperuricemia compared to the group of practically healthy individuals (56% vs. 27.1%, respectively, $\chi 2 = 11.32$; $p=0.715$).
It was established that in the groups of patients with unstable IHD and PED, carriers of homozygous and heterozygous alleles of the G-308A (rs1800629) TNF-α gene had significantly higher values compared to the control group. When distributing the mean values according to anxiety scales, as seen in Table 4.6, patients with the homozygous A/A and heterozygous G/A genotypes in the G-308A (rs1800629) TNF-α gene polymorphism showed higher levels of anxiety and depression, indicating a correlation between PED and the minor A allele. It was also found that patients with elevated LDL-C levels had significantly higher frequencies of the A allele, 56.5% and 51.6%, respectively, compared to the control group, but no association was found between elevated LDL-C levels and the polymorphism of this gene. Additionally, the levels of pro-inflammatory cytokines TNF-α and IL-1β were statistically higher in patients with the homozygous A/A genotype than in patients with the homozygous G/G and heterozygous G/A genotypes of the G-308A (rs1800629) TNF-α gene polymorphism.

When considering the results of coronary angiography, patients with heterozygous G/A and homozygous A/A genotypes of the G-308A (rs1800629) TNF-α gene can be classified into the high-risk group for coronary artery (CA) damage.

It was found that among patients with ischemic heart disease (IHD), the T allele of the IL-1β gene occurs 36.7% more frequently than in the control group. It was also found that among patients with IHD and psycho-emotional disorders (PED), with elevated levels of metabolic cholesterol (MC) and LDL-C, the T allele

(T511C) rs16944 of the IL-1β gene occurred 27.1% and 23.9% more frequently than in the control group.

When studying the levels of pro-inflammatory cytokines TNF-α and IL-1β among patients with genotypes C/C, C/T, and T/T, it was found that patients with the T/T genotype had statistically higher values compared to those with the homozygous C/C genotype (T511C) rs16944 of the IL-1β gene.

When analyzing the C/T 589 (rs 2243250) polymorphism of the IL-4 gene in healthy donors and patients with ischemic heart disease (IHD), depending on their psycho-emotional state, it was found that the alleles C and T of the IL-4 gene occurred with different frequencies. Among the patients, the minor allele C predominated, with a frequency of 62.6%, while the major allele T had a frequency of 37.4%, which was twice as rare compared to the control group.

In patients with IHD and psycho-emotional disorders (PED), those with the homozygous C/C allele had the highest levels of psycho-emotional disturbances, with an average score of 9.6±1.6 points on the HADS-D scale and 10.2±1.8 points on the HADS-A scale. Among patients with the homozygous C/C allele of SNP C/T 589 IL-4, the average score on the Spielberger-Hanin scale was 54.2±4.3 for ST and 54.0±4.6 for LT. According to the Eysenck scale, rigidity was observed in 132 (66.7%) patients, with the highest frequency observed in homozygous C/C (30.3%), followed by heterozygous C/T (21.2%) and homozygous T/T (15.1%).

The study of the relationship between MC levels and the SNP C/T 589 IL-4 polymorphism showed no significant correlation, which is also supported by a literature review. However, the highest values of pro-inflammatory cytokines TNF-α and IL-1β were found among homozygous C/C genotype carriers, with levels of 70.1 and 107.6 pg/ml, respectively, indicating a close association between the IL-4 gene and inflammation.

When interpreting the coronary angiography results among patients with IHD depending on the polymorphism of the -589 C/T (rs 2243250) IL-4 gene locus, it was found that homozygous C/C and heterozygous C/T genotype carriers had significantly higher occurrences of damage to three or more coronary arteries (CA) compared to homozygous T/T genotype carriers.

It was found that among patients with ischemic heart disease (IHD), the T allele (C819T) rs1800871 of the IL-10 gene occurred 12.6% more frequently than in the control group. When examining the alleles of the IL-10 gene depending on the blood MC (monocyte) levels, it was revealed that the T allele was 23.8% more frequent compared to the control group. Among patients with IHD and psycho-emotional disorders (PED), the T allele occurred 16.1% more frequently than in the control group. Additionally, when comparing the average scores on the HADS and Spielberger-Hanin scales, patients with the homozygous variant showed statistically significantly higher scores than those with the C/C and C/T genotypes, indicating a link between this allele and the onset of PED.

Our studies have shown that the development of conditions such as depression, anxiety, frustration, aggressiveness, and rigidity is associated not only with dyslipidemia, hyperuricemia, but also with cytokine imbalance, which

subsequently leads to multi-vessel coronary artery disease, severe progression of the underlying disease, and potentially fatal outcomes.

# CHAPTER 4. EFFECTIVENESS OF COMBINED PHARMACOTHERAPY IN PATIENTS WITH ISCHEMIC HEART DISEASE STABILIZATION ASSOCIATED WITH PSYCHO-EMOTIONAL DISORDERS

## 4.1. ANALYSIS OF THE EFFECTIVENESS OF USING A PROGRAM MODEL FOR RISK GROUP FORECASTING AND THERAPY COMPLIANCE IN IHD PATIENTS

As is well known, one of the objectives of this study was to develop a diagnostic panel of informative genetic markers for predicting ischemic heart disease (IHD) destabilization in patients depending on the psycho-emotional risk factor. In this regard, we developed a software product (No. ECM 14589 “Prediction of Coronary Artery Disease Based on Psycho-Emotional State,” registered on February 14, 2022, in the State Register of Software Products of the Republic of Uzbekistan), which included all risk factors, clinical signs, laboratory indicators (lipid profile, renal-liver indicators, blood glucose levels, cytokine levels in blood), instrumental indicators, including coronary angiography data, ECG and echocardiography, and genetic testing (G-308A (rs1800629) TNF-α gene, T511C (rs16944) IL-1β gene, C589T (rs2243250) IL-4 gene, and C819T (rs1800871) IL-10 gene).

Considering these factors, risk groups among IHD patients were determined.

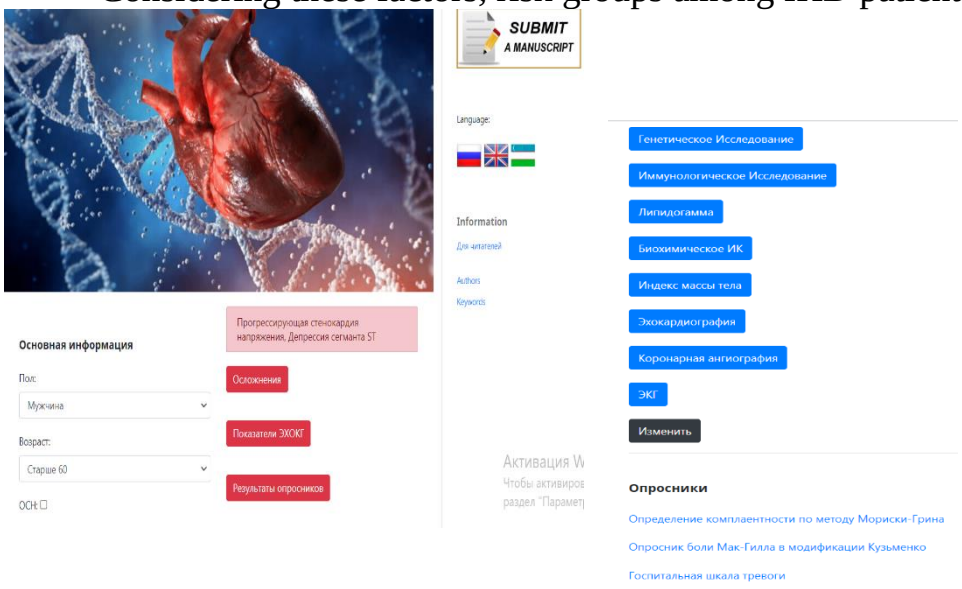



**Figure 4.1.1. Program "Prediction of Coronary Artery Disease Based on Psycho-Emotional State."**

The developed software product interprets data on psycho-emotional status, indicating the presence and severity of depressive, anxious, or anxiety-depressive conditions, which were determined using the HADS-D/A scale. Patients scoring between 8 and 10 points were classified as having subclinical depression and anxiety and received 1 point, while patients scoring above 11 points were classified as

having clinically expressed anxiety/depression and received 2 points. This program allows the assessment of a patient's adherence to therapy at the time of the doctor's visit based on the Morisky-Green test. The main purpose of the software development is to evaluate the psychological, personal, and behavioral components of adherence formation, identifying the risk index for non-adherence in long-term IHD therapy, with subsequent recommendations for comprehensive intervention methods aimed at improving therapy adherence in IHD patients. The program also analyzes the association of adherence with polymorphisms in the G-308A (rs1800629) TNF-α gene, T511C (rs16944) IL-1β gene, C589T (rs2243250) IL-4 gene, and C819T (rs1800871) IL-10 gene.

The software product has been developed in Uzbek, Russian, and English, meaning that the language of the program can be customized according to the doctor's preference. The program operates in online mode and serves as an additional tool for the website https://cardioresp.uz/ru/home/. The language and framework used are Python 3.10 and Django 4, respectively. The architectural template follows MVC (Model View Controller). For calculations, models are used and stored in the website's database. When data is displayed, it undergoes validation before being presented to the user.

The advantage of the software product lies in its ability to provide information about the patient and offer recommendations to doctors regarding personalized behavioral interventions to eliminate factors of non-adherence and psychological barriers. These are given while considering the presence of pathogenic polymorphic variants of the G-308A (rs1800629) TNF-α gene, T511C (rs16944) IL-1β gene, C589T (rs2243250) IL-4 gene, and C819T (rs1800871) IL-10 gene. This approach will help increase the level of treatment adherence in patients with coronary artery disease (CAD).

In the software product, significant attention was given to comorbid conditions such as arterial hypertension, diabetes mellitus, metabolic syndrome, hyperuricemia, and psychoemotional status, all of which were scored from 1 to 3 points. Patients with a history of diabetes mellitus were given 3 points, while those without received 0 points. When determining total cholesterol levels, patients with levels ranging from 5.2–6.5 mmol/L were categorized as having moderate hypercholesterolemia and received 1 point, while those with levels ≥6.5 mmol/L were classified as having high hypercholesterolemia and received 2 points.

Additionally, body mass index (BMI) was taken into account. A normal BMI, ranging from 18.5 to 24.9 kg/m², was scored as 0 points. Overweight individuals, with a BMI of 25–30 kg/m², received 1 point. Obesity (Class I), with a BMI of 30.1–34.9 kg/m², was scored with 2 points. Severe obesity (Class II), with a BMI of 35–40 kg/m², received 3 points, and morbid obesity (Class III), with a BMI over 40 kg/m², was given 4 points.

Smoking, similar to diabetes, was scored as follows: 1 point for patients who smoke, and 0 points for those who do not.

Another factor was the presence of hyperuricemia, which, as previously noted, is directly linked to the destabilization of ischemic heart disease (IHD). Patients with

a uric acid level up to 360 μmol/L received 0 points, those with a level up to 480 μmol/L received 1 point, patients with levels between 481–659 μmol/L received 2 points (indicating moderate hyperuricemia), and patients with a level above 660 μmol/L received 3 points (indicating excessive hyperuricemia).

Next, the results of coronary angiography were included: patients without coronary artery (CA) lesions received 0 points, those with lesions in 1 CA received 1 point, those with lesions in 2 CAs received 2 points, and patients with lesions in 3 or more CAs received 3 points.

The polymorphisms G-308A (rs1800629) of the TNF-α gene, T511C (rs16944) of the IL-1β gene, C589T (rs2243250) of the IL-4 gene, and C819T (rs1800871) of the IL-10 gene were also included and evaluated as follows: homozygous genotype C/C received 1 point, heterozygous C/T received 2 points, and homozygous T/T received 3 points. For both genes, the genotype scoring was identical. For the TNF-α gene (G-308A, rs1800629), carriers of the G/G genotype received 1 point, G/A received 2 points, and A/A received 3 points. For the IL-4 gene (C589T, rs2243250), homozygous T/T carriers received 1 point, heterozygous C/T received 2 points, and homozygous C/C received 3 points.

The clinical signs taken into account included pain syndrome, its duration, intensity, and localization of pain, which were assessed using the McGill Pain Questionnaire (MPQ). The McGill Pain Questionnaire, developed by Melzack and Torgerson in 1971, is a self-report scale designed to allow individuals experiencing severe pain to accurately describe the quality and intensity of their pain to their healthcare provider.

This tool can be used to assess pain locally or track it over time, such as to evaluate the effectiveness of pain-relieving interventions, and can also be used in epidemiological and clinical research. It is the most widely used measurement tool for multidimensional pain assessment in chronic pain conditions.

The version of the questionnaire used in the study consists of three subscales:

1. **Sensory subscale**: This subscale includes 13 sections and 52 word descriptors.
2. **Affective subscale**: This subscale includes 6 sections and 16 word descriptors.
3. **Evaluative subscale**: This subscale corresponds to the 20th section and includes 5 word descriptors.

The participant is required to select the descriptor that best matches their sensations in one section, although it is not necessary to select from each section. Each descriptor is then summed, and the pain sensitivity index is calculated. By analyzing the three subscales, the **Index of Chosen Word Descriptors (ICWD)** is computed—this is the sum of responses from 1 to 20 word descriptors. Additionally, the **Ranked Pain Index (RPI)** is calculated—the sum of the ordinal numbers of the descriptors selected by the patients.

To date, the questionnaire has been used in more than 500 scientific studies and is available in 26 language versions. (https://www.mdapp.co/mcgill-pain-questionnaire-calculator-467/. Date accessed: January 5, 2022).

**Текст опросника боли Мак-Гилла в модификации Кузьменко В.В. и др. (1986).**

**Какими словами Вы можете описать свою боль?**

*1 раздел*
1.1. ❑ пульсирующая
1.2. ❑ схватывающая
1.3. ❑ дергающая
1.4. ❑ стегающая
1.5. ❑ колотящая
1.6. ❑ долбящая

*2 раздел*
2.1. ❑ подобная электрическому разряду, удару тока, выстрелу

*3 раздел*
3.1. ❑ колющая
3.2. ❑ впивающаяся
3.3. ❑ буравящая
3.4. ❑ сверлящая
3.5. ❑ пробивающая

*4 раздел*
4.1. ❑ острая
4.2. ❑ режущая
4.3. ❑ полосующая

*5 раздел*
5.1. ❑ давящая
5.2. ❑ сжимающая
5.3. ❑ щемящая
5.4. ❑ стискивающая
5.5. ❑ раздавливающая

*6 раздел*
6.1. ❑ тянущая
6.2. ❑ выкручивающая
6.3. ❑ вырывающая

*7 раздел*
7.1. ❑ горячая
7.2. ❑ жгучая
7.3. ❑ ошпаривающая
7.4. ❑ палящая

*8 раздел*
8.1. ❑ зудящая
8.2. ❑ щиплющая
8.3. ❑ разъедающая
8.4. ❑ жалящая

*9 раздел*
9.1. ❑ тупая
9.2. ❑ ноющая
9.3. ❑ мозжащая
9.4. ❑ ломящая
9.5. ❑ раскалывающая

*10 раздел*
10.1. ❑ распирающая
10.2. ❑ растягивающая
10.3. ❑ раздирающая
10.4. ❑ разрывающая

*11 раздел*
11.1. ❑ разлитая
11.2. ❑ распространяющаяся
11.3. ❑ проникающая
11.4. ❑ пронизывающая

*12 раздел*
12.1. ❑ царапающая
12.2. ❑ саднящая
12.3. ❑ дерущая
12.4. ❑ пилящая
12.5. ❑ грызущая

*13 раздел*
13.1. ❑ немая
13.2. ❑ сводящая
13.3. ❑ леденящая

**Какие чувства вызывает боль, какое воздействие оказывает на психику?**

*14 раздел*
14.1. ❑ утомляет
14.2. ❑ изматывает

*15 раздел*
15.1. ❑ чувство тошноты, удушья

*16 раздел*
16.1. ❑ чувство тревоги, страха, ужаса

*17 раздел*
17.1. ❑ угнетает
17.2. ❑ раздражает
17.3. ❑ злит
17.4. ❑ приводит в ярость
17.5. ❑ приводит в отчаяние

*18 раздел*
18.1. ❑ обессиливает
18.2. ❑ ослепляет

*19 раздел*
19.1. ❑ боль-помеха
19.2. ❑ боль-досада
19.3. ❑ боль-страдание
19.4. ❑ боль-мучение
19.5. ❑ боль-пытка

**Как вы оцениваете свою боль?**

*20 раздел*
20.1. ❑ слабая
20.2. ❑ умеренная
20.3. ❑ сильная
20.4. ❑ сильнейшая
20.5. ❑ невыносимая

The McGill Pain Questionnaire (MPQ) was used to assess pain, and the factors of risk were summed up to calculate the risk group for each patient. Additionally, the program determined the level of patient compliance with the prescribed treatment. For this, the **Morisky-Green Scale** was utilized, a clinical-psychological test method developed by Morisky D.E., Green L.W., and Levine D.M. in 1985 and published in 1986.

The high-risk group for the destabilization of ischemic heart disease (IHD) was determined based on our observation over 12 months, considering angina attacks over that period, and incorporating factors such as gene polymorphisms, cytokine imbalance, blood glucose levels, signs of asymptomatic hyperuricemia, lipid profile, ECG findings, and coronary angiography results.

It should also be noted that patients with 3 or more affected coronary arteries were undoubtedly classified into the high-risk group for the destabilization of IHD.

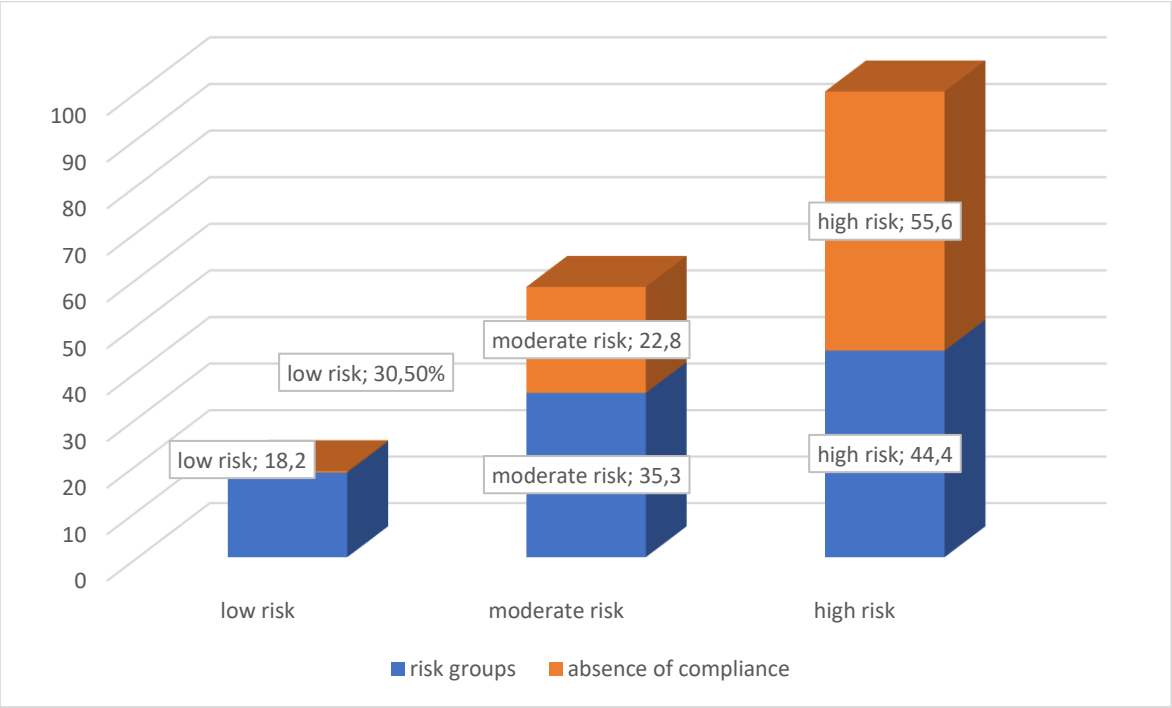



**Figure 4.1.3** Distribution of patients by risk group.

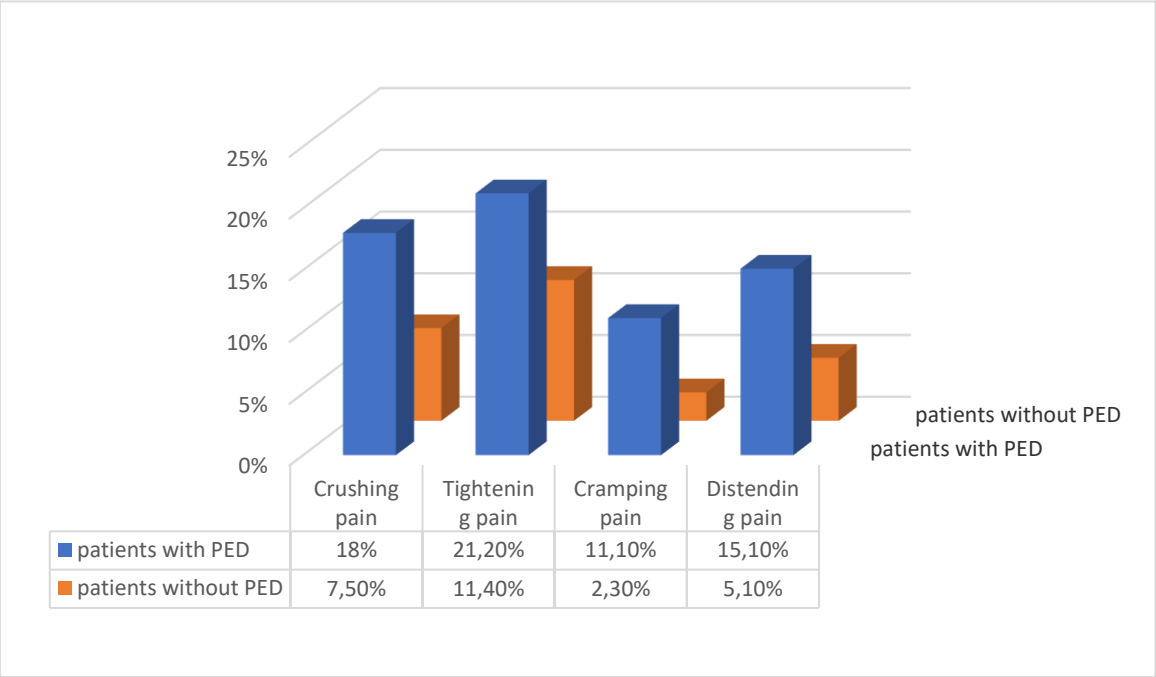
According to the results of the program, it was found that 88 (44.4%) of the 198 patients were classified into the high-risk group. Among them, 54 (61.3%) were carriers of the homozygous genotype T/T 511 T/C (rs16944) of the IL-1β gene, and 28 (14.1%) were carriers of the homozygous genotype T/T polymorphism 819 C/T (rs1800871) of the IL-10 gene. This supports the findings of our study, indicating that these patients had clinically and instrumentally confirmed severe course and frequent angina attacks, which in turn require high-level control and timely treatment to reduce fatal outcomes.

The frequency of the medium-risk group was 35.3% (n=70), and 18.2% (n=36) of patients were classified into the low-risk group.

Out of 198 patients with NCD, 76 (38.3%) were found to have non-compliance with the treatment. Interestingly, 36 (47.3%) of the non-compliant patients had the homozygous T/T 511 T/C (rs16944) genotype of the IL-1β gene, and 64 (84.2%) had psychoneurotic disorders. This once again confirms the connection between the development of compliance with treatment and the presence of psychoneurotic disorders in patients with the T/T genotype of the IL-1β gene.

According to the sensory scale MPQ, patients with PED described their pain syndrome most often using descriptor words with a low ordinal number: 1 or 2. However, words were chosen from almost every row, indicating a variety of pain sensations. Patients without PED described the pain syndrome with a small number of descriptor words (one or two), which also had a low rank, selecting classic characteristics of anginal pain: pressing pain in 36 patients (18.1%), squeezing pain in 42 (21.2%), cramping pain in 22 (11.1%), and tearing pain in 30 (15.1%). Patients with PED had a low pain rank index (PRI) of 18.9±2.78 (with a maximum possible value of 73); this indicator reflects the overall pain intensity. The results for this

indicator in patients with angina without PED were significantly lower ($p<0.001$), indicating a lower pain intensity in this category of patients compared to those with PED.




| | Crushing pain | Tightening pain | Cramping pain | Distending pain |
|---|---|---|---|---|
| patients with PED | 18% | 21,20% | 11,10% | 15,10% |
| patients without PED | 7,50% | 11,40% | 2,30% | 5,10% |

**Figure 4.1.4. Types of pain according to the MPQ scale.**

Patients with psychoemotional disorders (PÉR) when subjectively assessing pain using the three scales of the McGill Pain Questionnaire described the pain syndrome with descriptors of higher rank compared to patients without PÉD. The number of selected descriptors on the McGill Pain Questionnaire scale was also significantly higher ($p<0.001$) in patients with PÉR (9.6±0.7 vs. 6.4±0.8), indicating that patients with PÉR selected a significantly higher number of descriptor words when describing their pain syndrome compared to patients without PÉD.

All of the above allows for the conclusion that there is a direct correlation between the subjective assessment of pain intensity and the degree of psychoemotional disorders in patients with unstable angina. When evaluating the relationship between pain syndrome and the risk group, no statistically significant values were found, but a connection was identified both with psychoemotional disorders and with the homozygous genotype T/T 511 T/C (rs16944) of the IL-1β gene. However, no significant correlation was found with the polymorphism 819 C/T (rs1800871) of the IL-10 gene.

The effectiveness of the software product is characterized not only by an increase in patient adherence (compliance) to medical recommendations but also by the stabilization of coronary artery disease and the improvement in the quality of life for patients with chronic CAD. The developed program "Prediction of Coronary Artery Disease Based on Psychoemotional Status," designed for healthcare providers to assess and predict long-term therapy issues, provides recommendations for a rational treatment strategy. This program aims to preserve public health and

prevent cardiovascular catastrophes, which, in turn, leads to a reduction in social costs by minimizing complications associated with the underlying disease.

## 4.2. THE ROLE OF PERCUTANEOUS CORONARY INTERVENTION IN THE TREATMENT OF CHRONIC CORONARY ARTERY DISEASE AMONG PATIENTS WITH PSYCHOEMOTIONAL DISORDERS

To investigate the role of percutaneous coronary intervention (PCI) in the prognosis of chronic coronary artery disease (CAD) among patients with psychoemotional disorders, we studied 211 cases of emergency stenting of clinically dependent vessels. Complete functional revascularization was performed through PCI using four types of coronary stents: 25.1% of patients received the Resolute Integrity stent (a cobalt alloy stent coated with a thin layer of biocompatible polymer containing zotarolimus), 20.3% received the Resolute Onyx stent (a zotarolimus-coated stent on the RX delivery system), 22.2% received the BioMime TM stent (a third-generation coronary stent eluting sirolimus with an ultra-thin (65 micron) stent shaft), and 32.7% of patients received the Promus Premier stent (a stent coated with everolimus) (Figure 4.4.1). Sixty-eight patients refused stent implantation for various reasons.

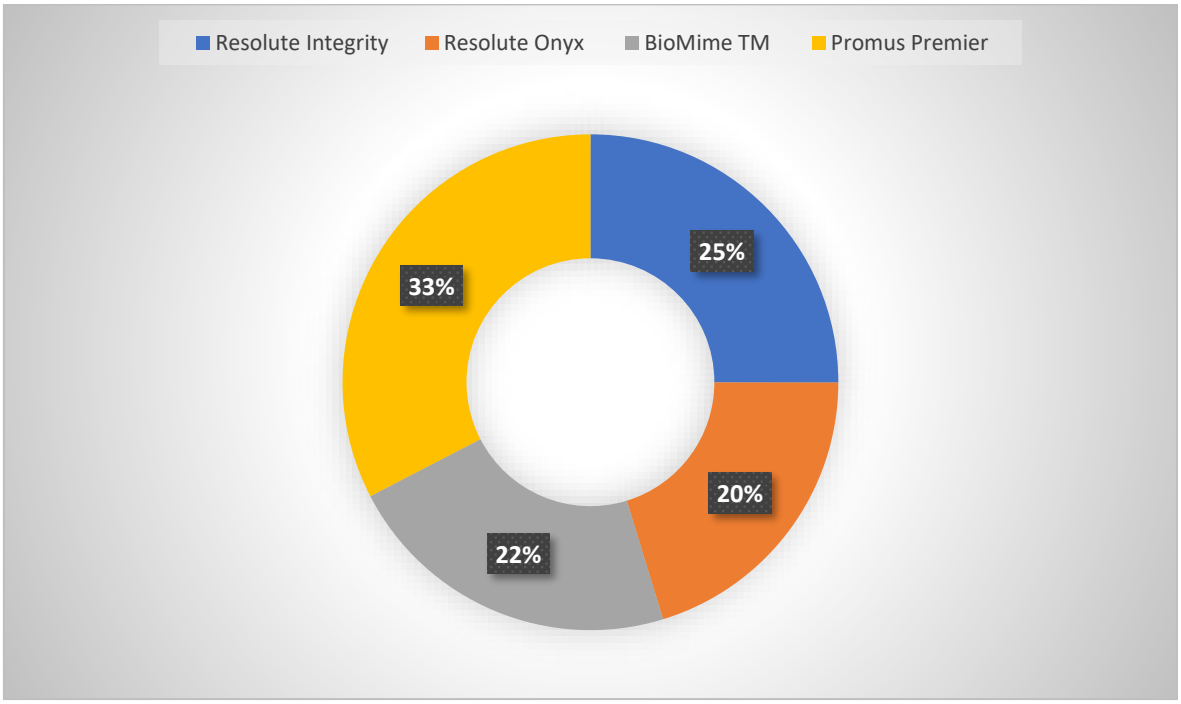


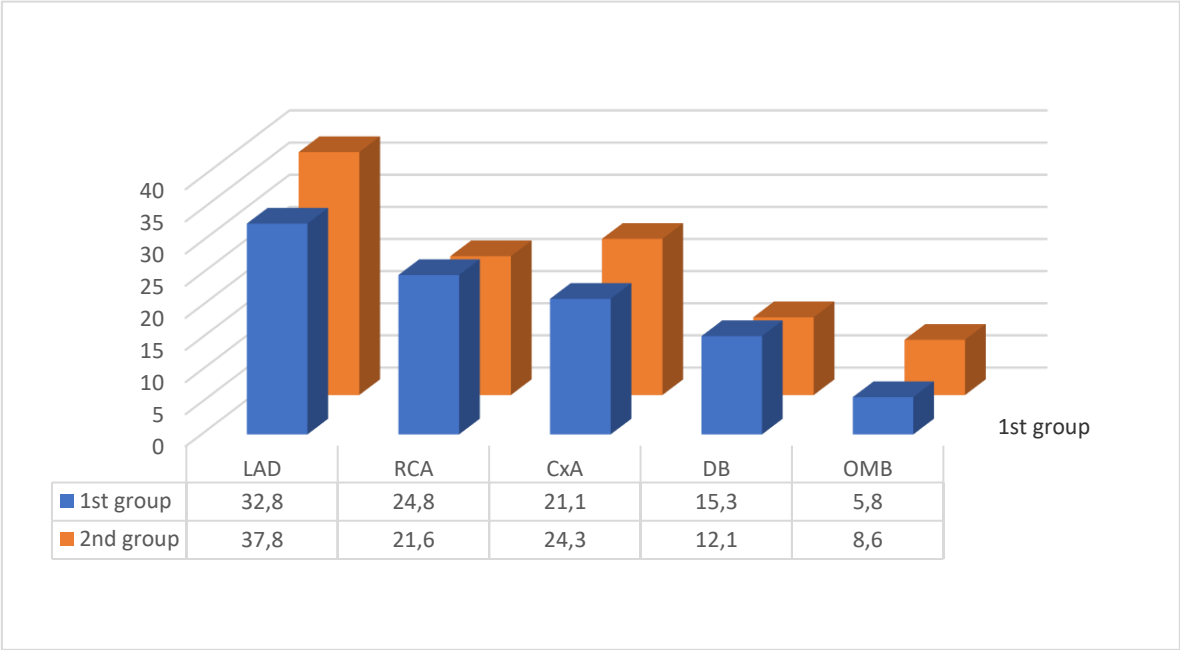

**Figure 4.2.1. Types of Implanted Stents**

Out of 211 patients, psychoemotional disorders (PED) were identified in 137 (64.9%) patients. Based on their psychoemotional state, the patients were divided into two groups: Group 1 included patients with unstable angina (UA) and PED (137 patients, 64.9%), while Group 2 consisted of patients with UA without PED (74

patients, 35%). In these groups, we examined the frequency, severity of coronary artery lesions, and the number of implanted stents.

The number of implanted stents ranged from one to five. When analyzing the number of implanted stents, we found a significantly higher incidence of multiple stent insertions among patients with PED, with an average of 3.3±1.1 stents implanted, compared to an average of 2.4±0.8 stents in patients without PED.

Stenting of the left anterior descending artery (LAD) was performed in 45 (32.8%) patients of the first group and 28 (37.8%) patients of the second group. Stenting of the right coronary artery (RCA) was performed in 34 (24.8%) and 16 (21.6%) patients, stenting of the circumflex artery (CxA) in 29 (21.1%) and 18 (24.3%), stenting of the diagonal branch (DB) in 21 (15.3%) and 9 (12.1%), and stenting of the obtuse marginal branch (OMB) in 8 (5.8%) and 3 (8.6%) patients in Groups I and II, respectively.




| | LAD | RCA | CxA | DB | OMB |
|---|---|---|---|---|---|
| 1st group | 32,8 | 24,8 | 21,1 | 15,3 | 5,8 |
| 2nd group | 37,8 | 21,6 | 24,3 | 12,1 | 8,6 |

**Figure 4.2.2. Frequency of Implanted Stents Depending on Coronary Artery Lesions**

In studying the effectiveness of balloon angioplasty in the compared groups, no statistically significant differences were found. Technical success was achieved in 130 (94.8%) patients of the first group and 71 (95.9%) patients of the second group. Angiographic success was also high, reaching 95.6% (n=131) and 97.2% (n=72), respectively. Complete revascularization was achieved in 81.7% (n=112) of patients with UA+PED and 87.8% (n=65) in patients of the second group, i.e., those with UA without PED.

Early PCI complications were identified in 14 (10.2%) patients of the first group and 4 (5.5%) patients of the second group. The complications included arrhythmia in 3 patients with PED and 1 patient without PED, contrast agent allergy

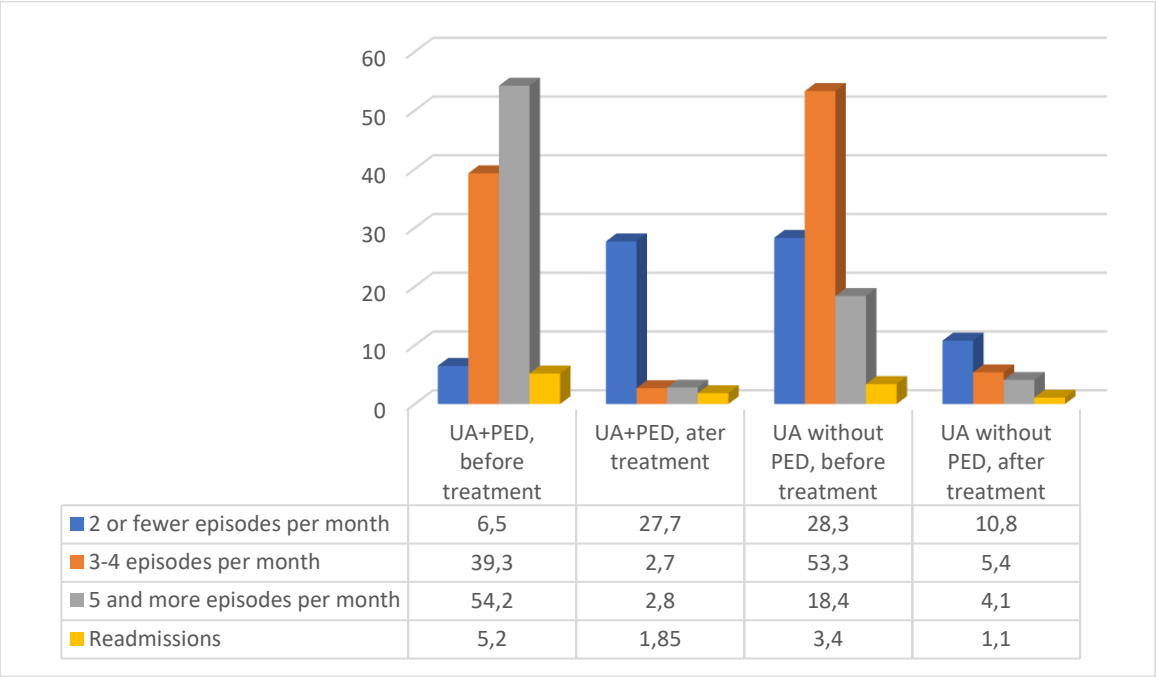
in 4 patients with UA+PED and 2 patients with UA without PED, hematomas in 4 patients of the first group and 1 patient of the second group, and restenosis in 1 patient of the first group. Fatal outcomes were recorded in three patients of the first group, while no deaths were reported in the second group.

**Table 4.2.1.**

**Combined Endpoints During the Follow-Up Period in Patients with CAD After PCI**

| Outcomes | Patients with UA+PED (Group 1), n=137 | Patients with UA without PED (Group 2), n=74 | P value |
|---|---|---|---|
| Myocardial infarction with Q wave | 3 (2.1%) | 0 | 0.028 |
| Myocardial infarction without Q wave | 5 (3.64%) | 1 (1.3%) | 0.031 |
| Thrombosis of a previously implanted stent | 2 (1.4%) | 0 | 0.257 |
| New atherosclerotic lesion | 4 (2.9%) | 2 (2.7%) | 0.118 |
| Restenosis | 3 (2.1%) | 1 (1.35%) | 0.047 |
| CABG | 3 (2.1%) | 0 | 0.028 |
| Mortality | 3 (2.1%) | 0 | 0.028 |
| Transition to stable angina | 114 (83.2%) | 70 (94.5%) | 0.001 |
| Rehospitalizations | 3.4±0.68 | 1.2±0.24 | 0.072 |

The combined long-term endpoints of PCI in patients with CAD were also analyzed. A significantly higher frequency of complications was observed in patients with PED, including myocardial infarction with a Q wave (2.1%) and without a Q wave (3.64%), restenosis (2.1%), mortality (2.1%), as well as cases of rehospitalization (3.4±0.68, P=0.072). Among patients without PED, the transition to stable angina was observed in 94.5% of cases (P≤0.001).




| | UA+PED, before treatment | UA+PED, ater treatment | UA without PED, before treatment | UA without PED, after treatment |
|---|---|---|---|---|
| 2 or fewer episodes per month | 6,5 | 27,7 | 28,3 | 10,8 |
| 3-4 episodes per month | 39,3 | 2,7 | 53,3 | 5,4 |
| 5 and more episodes per month | 54,2 | 2,8 | 18,4 | 4,1 |
| Readmissions | 5,2 | 1,85 | 3,4 | 1,1 |

**Figure 4.2.3. Structure of Angina Syndrome Before and After Treatment in Patients with UA with and without PED**

Angina attacks were significantly more frequent in patients with PED. For example, five or more angina attacks per week were reported in 54.2% of patients with UA and PED, whereas in patients without PED, such frequent attacks occurred in only 24.4% of cases, indicating a direct relationship between the occurrence of angina attacks and PED. After the therapy, the frequency of angina attacks significantly decreased in both patient groups.

As an antidepressant, 98 out of 137 patients with UA+PED (Group 1) were prescribed Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) with thymoanaleptic and stimulating effects. The remaining 39 patients with UA+PED (Group 2) received traditional therapy, as did patients with UA without PED (Group 3). To compare the positive effects of stenting and Fluoxetine treatment, hemodynamic, biochemical, and immunological parameters were evaluated at 3, 6, and 12 months of follow-up.

**Table 4.2.2.**

**Dynamics of EchoCG indicators before and after stent implantation in patients with UA + PED**

| Dynamics of Echocardiographic Parameters Before and After Stent Implantation in Patients with UA+PED | Patients with UA + PED (Group 1), n=98 TrT + Fluoxetine | | | | P value | Patients with UA + PED (Group 2), n=39 TrT | | | | P value |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before treatment | After 3 month | After 6 month | After 12 month | | Before treatment | After 3 month | After 6 month | After 12 month | |
| EDD LV, mm | 5,8±1,1 | 4,9±0,5 | 4,8±0,4 | 4,5±0,4 | 0,241<br>0,106<br>0,040 | 5,7±1,0 | 4,9±0,7 | 5,1±0,7 | 5,3±0,7 | 0,103<br>0,052<br>0,018 |
| ESD LV, mm | 5,3±0,8 | 4,8±0,6 | 4,5±0,5 | 4,3±0,4 | 0,116<br>0,064<br>0,022 | 5,2±0,7 | 4,6±0,6 | 4,8±0,6 | 5,0±0,7 | 0,328<br>0,227<br>0,027 |
| LVPW, mm | 1,3±0,2 | 1,2±0,2 | 1,1±0,2 | 1,1±0,1 | 0,074<br>0,081<br>0,028 | 1,29±0,3 | 1,1±0,3 | 1,16±0,2 | 1,2±0,2 | 0,211<br>0,079<br>0,015 |
| IVS, mm | 1,3±0,3 | 1,2±0,3 | 1,12±0,2 | 1,1±0,1 | 0,128<br>0,054<br>0,018 | 1,26±0,3 | 1,12±0,3 | 1,17±0,2 | 1,2±0,2 | 0,097<br>0,034<br>0,026 |
| LVEF,% | 51,1±8,2 | 54,1±7,5 | 55,3±7,1 | 56,4±6,8 | 0,087<br>0,027<br>0,019 | 51,3±8,0 | 55,1±7,5 | 53,6±7,1 | 52,8±6,5 | 0,059<br>0,047<br>0,014 |

Table 4.2.3 demonstrates that echocardiographic hemodynamic parameters such as LV EDD, LV ESD, and LVEF showed a significantly positive trend three months after PCI in patients with UA+PED who received only traditional therapy. However, after 12 months of follow-up, these parameters noticeably returned to their baseline values before treatment: LVEF decreased to 52.8±6.5%, while the dimensions of LVPW and IVS increased to 1.2±0.2 mm and 1.2±0.2 mm, respectively.

In contrast to patients who received only traditional therapy, those who received TrT+Fluoxetine exhibited positive and stable dynamics in nearly all hemodynamic parameters, even in the long-term follow-up period.

**Table 4.2.3.**

**Dynamics of Echocardiographic Parameters Before and After Stent Implantation**

| Parameter | Before Treatment | After 3 Months | After 6 Months | After 12 Months | P value (3M) | P value (6M) | P value (12M) |
|---|---|---|---|---|---|---|---|
| LV EDD (mm) | 5.6±0.9 | 5.1±0.8 | 4.9±0.7 | 4.8±0.6 | 0.115 | 0.071 | 0.032 |
| LV ESD (mm) | 5.2±0.7 | 4.8±0.6 | 4.6±0.6 | 4.6±0.5 | 0.121 | 0.094 | 0.039 |
| LVPW (mm) | 1.29±0.3 | 1.16±0.3 | 1.13±0.2 | 1.1±0.2 | 0.274 | 0.206 | 0.371 |
| IVS (mm) | 1.24±0.2 | 1.19±0.2 | 1.15±0.2 | 1.1±0.1 | 0.069 | 0.225 | 0.193 |
| LVEF (%) | 51.9±9.0 | 53.4±8.7 | 55.1±8.5 | 55.6±8.2 | 0.075 | 0.037 | 0.001 |

When analyzing hemodynamic parameters in patients with UA without signs of psychoemotional disorders, a positive dynamic was observed in almost all indicators, confirming the effectiveness of the chosen treatment method.

**Table 4.2.4.**

**Dynamics of Immunological Parameters Before and After Stent Implantation in Patients with UA+PED**

| Indicator | Patients with UA + PED (Group 1), n=98 TrT + Fluoxetine | | | | | Patients with UA + PED (Group 2), n=39 TrT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before stent implantation | After 3 month | After 6 month | After 12 month | P-value | Before stent implantation | After 3 month | After 6 month | After 12 month | P-value |
| **TNF-α пг/мл** | 69,6±6,2 | 67,3±5,7 | 55,7±5,1 | 45,2±4,2 | 0,135<br>0,061<br>0,025 | 68,9±2,3 | 66,2±6,1 | 58,4±5,3 | 52,5±5,1 | 0,111<br>0,043<br>0,012 |
| **IL-1β пг/мл** | 100,7±10,3 | 94,2±9,5 | 76,3±7,5 | 53,1±5,8 | 0,245<br>0,181<br>0,037 | 101±4,6 | 93,4±4,1 | 81,5±3,9 | 76,3±3,4 | 0,142<br>0,033<br>0,022 |
| **IL-4 пг/мл** | 22,2±2,2 | 21,1±2,0 | 22,4±2,0 | 24,3±1,8 | 0,813<br>0,264<br>0,195 | 22,8±1,2 | 20,3±1,1 | 21,4±1,0 | 23,7±0,9 | 0,482<br>0,246<br>0,162 |
| **IL-10 пг/мл** | 12,7±1,1 | 12,9±1,0 | 14,4±1,1 | 15,3±1,1 | 0,310<br>0,174<br>0,084 | 12,1±0,6 | 13,2±0,5 | 13,4±0,4 | 14,6±0,4 | 0,137<br>0,085<br>0,039 |

The levels of pro-inflammatory cytokines **TNF-α** and **IL-1β** significantly decreased after 12 months in both groups: patients with **UA+PED** who received Fluoxetine in combination with traditional therapy (**45.2±4.2; 53.1±5.8**, respectively) and those who received only traditional therapy (**52.5±5.1; 76.3±3.4**, respectively). However, it is important to note that the levels of pro-inflammatory interleukins were significantly lower in patients who underwent combination therapy compared to those who received only traditional therapy (**P≥0.001**).

**Table 4.2.5.**

**Dynamics of Immunological Parameters Before and After Stent Implantation in Patients with UA without PED (Group 3)**

| Indicator, pg/ml | Before implantation | After 3 month | After 6 month | After 12 month | P-value |
|---|---|---|---|---|---|
| **TNF-α** | 68,9±2,3 | 56,3±2,1 | 44,7±2,0 | 38,7±1,7 | 0,311<br>0,218<br>0,037 |
| **IL-1β** | 101±4,6 | 84,8±4,1 | 67,2±3,5 | 52,5±3,1 | 0,529<br>0,019<br>0,001 |
| **IL-4** | 22,8±1,2 | 23,4±1,1 | 23,1±1,0 | 24,7±0,9 | 0,324<br>0,318<br>0,294 |
| **IL-10** | 12,1±0,6 | 12,7±0,6 | 13,5±0,5 | 13,8±0,4 | 0,813<br>0,293<br>0,127 |

Thus, in patients with UA without PED, the levels of TNF-α and IL-1β (38.7±1.7; 52.5±3.1, respectively) also significantly decreased. However, it is important to note that none of the groups achieved target levels, particularly patients with UA+PED who did not receive the anxiolytic drug Fluoxetine.

A comparative analysis of blood lipid profile indicators at 3, 6, and 12 months showed that in patients of the second group, treatment resulted in an insignificant reduction in lipid profile parameters and uric acid levels. In contrast, the analysis of indicators in patients of the first and third groups after treatment revealed a significant reduction in lipid profile parameters.

**Table 4.2.6.**

**Comparative Analysis of Blood Lipid Profile and Uric Acid Levels in Patients with UA+PED**

| | Patients with UA + PES (Group 1), n=98 TrT + Fluoxetine | | | | | Patients with UA + PES (Group 2), n=39 TrT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Indicators** | Before treatment | After 3 month | After 6 month | After 12 month | P-value | Before treatment | After 3 month | After 6 month | After 12 month | P-value |
| **Total Cholesterol, mmol/l** | 6,7±0,6 | 5,9±0,5 | 5,1±0,4 | 4,2±0,3 | 0,254<br>0,139<br>0,025 | 6,8±0,6 | 6,1±0,5 | 5,4±0,5 | 4,8±0,4 | 0,685<br>0,374<br>0,062 |
| **HDL-C, mmol/l** | 0,85±0,04 | 0,94±0,05 | 1,2±0,06 | 1,3±0,6 | 0,624<br>0,347<br>0,043 | 0,86±0,03 | 0,93±0,02 | 1,1±0,01 | 1,2±0,01 | 0,924<br>0,073<br>0,025 |
| **LDL-C, mmol/l** | 4,30±0,3 | 3,6±0,3 | 3,1±0,3 | 2,4±0,2 | 0,627<br>0,237<br>0,033 | 4,33±0,5 | 3,8±0,4 | 3,3±0,3 | 2,9±0,3 | 0,374<br>0,236<br>0,035 |
| **TG, mmol/l** | 2,36±0,2 | 2,2±0,2 | 1,87±0,2 | 1,7±0,1 | 0,291<br>0,188<br>0,048 | 2,4±0,3 | 2,3±0,2 | 2,0±0,2 | 1,93±0,1 | 0,578<br>0,253<br>0,075 |
| **AC** | 6,88±0,8 | 5,27±0,7 | 3,25±0,4 | 2,23±0,3 | 0,086<br>0,022<br>0,001 | 6,9±0,7 | 5,5±0,5 | 3,9±0,4 | 3,0±0,3 | 0,521<br>0,084<br>0,001 |
| **Uric acid** | 446,3±40,2 | 422,4±41,3 | 408,7±39,4 | 388,5±37,6 | 0,349<br>0,282<br>0,029 | 458,7±40,2 | 432,3±39,8 | 425,6±36,4 | 412,8±35,1 | 0,412<br>0,325<br>0,109 |

### Analysis of Lipid Profile Indicators in Groups 1 and 3 After Treatment

In Group 1, total cholesterol (TC) decreased to **4.2±0.3 mmol/L**, LDL-C to **2.4±0.2 mmol/L**, triglycerides (TG) to **1.7±0.1 mmol/L**, and the atherogenic coefficient (AC) reached the target level of **2.23±0.3 U**. Uric acid (UA) levels decreased to **388.5±37.6 µmol/L**.

In Group 3, total cholesterol (TC) decreased to **4.2±0.4 mmol/L**, LDL-C to **2.5±0.3 mmol/L**, triglycerides (TG) to **1.73±0.1 mmol/L**, and the atherogenic coefficient (AC) reached the target level of **2.2±0.2 U**. Uric acid (UA) levels dropped to **321.5±28.7 µmol/L**.

**Table 4.2.7.**

**Comparative Analysis of Lipid Profile and Uric Acid Levels in Patients with UA Without PEP (Group 3)**

| Indicators | Before treatment | After 3 month | After 6 month | After 12 month | P-value |
|---|---|---|---|---|---|
| **Total Cholesterol, mmol/l** | 5,9±0,6 | 5,3±0,5 | 4,8±0,5 | 4,2±0,4 | 0,321<br>0,019<br>0,011 |
| **HDL-C, mmol/l** | 0,91±0,09 | 0,98±0,09 | 1,2±0,1 | 1,4±0,1 | 0,067<br>0,019<br>0,001 |
| **LDL-C, mmol/l** | 3,93±0,4 | 3,4±0,4 | 2,9±0,3 | 2,5±0,3 | 0,359<br>0,217<br>0,177 |
| **TG, mmol/l** | 2,1±0,2 | 1,9±0,2 | 1,8±0,2 | 1,73±0,1 | 0,108<br>0,098<br>0,015 |
| **AC** | 5,48±0,6 | 4,4±0,5 | 3,0±0,3 | 2,2±0,2 | 0,637<br>0,037<br>0,001 |
| **UC** | 348,1±31,2 | 332,1±30,6 | 326,3±30,8 | 321,5±28,7 | 0,218<br>0,192<br>0,084 |

The study of psychoemotional state indicators among patients in the second group at 3, 6, and 12 months revealed no significant changes and even an increase

in anxiety and depression scores on both the HADS scales and the Spielberger-Khanin scale at 3 months after stent implantation. This indicates a deterioration in the psychoemotional state of patients, which may affect their overall condition.

**Table 4.2.8.**

**Comparative analysis of psychoemotional state indicators before and after treatment**

| Indicators | Patients with UA + PES (Group 1), n=98 TrT + Fluoxetine | | | | | Patients with UA + PES (Group 2), n=39 TrT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before treatment | After 3 month | After 6 month | After 12 month | P-value | Before treatment | After 3 month | After 6 month | After 12 month | P-value |
| **HADS-D** | 11,8±1,1 | 10,4±1,0 | 8,8±0,9 | 7,6±0,8 | 0,211<br>0,069<br>0,025 | 11,1±1,1 | 12,3±1,2 | 11,6±1,2 | 10,8±1,0 | 0,352<br>0,210<br>0,069 |
| **HADS-A** | 10,6±1,0 | 10,1±1,0 | 8,9±0,8 | 7,4±0,7 | 0,136<br>0,095<br>0,016 | 10,48±1,0 | 11,6±1,1 | 10,7±1,0 | 10,1±1,0 | 0,265<br>0,129<br>0,018 |
| **SA** | 53,4±5,2 | 50,2±5,1 | 44,7±4,2 | 40,1±4,0 | 0,384<br>0,026<br>0,018 | 53,1±5,1 | 55,4±5,2 | 54,7±5,3 | 53,4±5,2 | 0,628<br>0,423<br>0,325 |
| **TA** | 53,1±5,1 | 50,7±5,0 | 46,8±4,5 | 41,7±4,3 | 0,261<br>0,037<br>0,004 | 52,5±5,1 | 54,8±5,2 | 53,4±5,1 | 53,8±5,2 | 0,684<br>0,295<br>0,158 |

Patients in the first group who received Fluoxetine as part of a comprehensive treatment alongside traditional therapy showed positive dynamics. By the 12th month of observation, anxiety and depression levels had decreased to a subclinical level: HADS-D was 7.6±0.8, HADS-A was 7.4±0.7, SA was 40.1±4.0, and TA was 41.7±4.3 points. The results obtained confirm the effectiveness of our chosen treatment approach.

## 4.3. ASSOCIATION OF PRO-INFLAMMATORY POLYMORPHISMS G-308A TNF-α, 511 T/C IL-1β AND ANTI-INFLAMMATORY POLYMORPHISMS 589 T/C IL-4, 819 C/T IL-10 WITH THE TREATMENT OF UNSTABLE ANGINA DEPENDING ON PSYCHOEMOTIONAL STATE

In this subsection of the dissertation, we examined the effectiveness of therapy for ischemic heart disease (IHD) associated with psychoemotional disorders, depending on the presence of specific pro-inflammatory and anti-inflammatory cytokine polymorphisms.

All patients received standard therapy, which included nitrates, β-blockers, Ca+2 channel blockers, ACE inhibitors, AII receptor antagonists, antiplatelet agents, statins, and diuretics.

Drug dosages were titrated based on disease severity and patient risk group.

**Table 4.3.1.**

**Prescription of medications for UA+PED depending on the overall condition of patients, mg/day**

| Genes | Genotype | Nitrates, mg | β-adreno blockers, mg | $Ca^{+2}$ channel blockers, mg | ACE inhibitors, mg | Angiotensin II receptor blockers (ARBs), mg | Antiplatelets, mg | Statins, mg | Diuretics, mg | SSRI (Fluoxetine), mg | P-Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C511T (rs16944) of gene IL-1β | C/C | 19,8±4.2 | 5,7±1.5 | 5,4±1.6 | 5,4±1.2 | 80,3±8.6 | 187,4±12.9 | 13,8±2.1 | 33,4±3.8 | 33,2±4.5 | 0.084 |
| | C/T | 20,2±4.5 | 6,3±1.7 | 5,8±1.5 | 6,8±1.8 | 85,7±8.2 | 193,1±14.1 | 14,6±3.2 | 37,8±4.1 | 35,1±2.9 | 0.215 |
| | T/T | 28,3±3.5 | 8,4±1.8 | 5,4±0.9 | 8,3±1.4 | 91,5±8.1 | 200,3±18.2 | 18,8±2.8 | 43,2±3.8 | 47,9±4.2 | 0.044 |
| G-308A (rs1800629) of gene TNF-α | G/G | 19,2±3.5 | 4,3±1.1 | 5,3±1.6 | 5,3±1.4 | 76,4±8.4 | 188,2±20.3 | 15,4±4.8 | 35,3±3.9 | 37,1±5.9 | 0.349 |
| | G/A | 19,7±4.8 | 5,2±1.6 | 5,5±1.7 | 6,5±2.1 | 87,7±8.8 | 196,2±21.3 | 16,3±4.9 | 36,7±4.5 | 35,8±5.8 | 0.412 |
| | A/A | 24,3±3.5 | 9,2±1.8 | 5,5±1.3 | 8,4±1.7 | 91,3±7.8 | 200,8±18.8 | 18,3±3.8 | 45,7±4.7 | 48,2±6.6 | 0.013 |
| 589 C/T (rs 2243250) of gene IL-4 | C/C | 26,7±3.4 | 8,8±1.7 | 5,4±1.2 | 8,2±1.5 | 92,3±7.1 | 204,9±19.2 | 14,3±2.7 | 43,5±4.4 | 34,1±5.1 | 0.019 |
| | C/T | 22,1±2.4 | 6,7±1.5 | 5,3±1.1 | 6,4±1.6 | 85,6±6.2 | 198,2±16.8 | 16,8±2.6 | 36,4±4.1 | 36,8±4.9 | 0.367 |
| | T/T | 18,4±1.8 | 4,3±1.7 | 5,3±1.5 | 4,3±1.2 | 80,1±5.9 | 184,3±14.7 | 16,4±2.1 | 46,4±4.7 | 42,2±4.3 | 0.295 |
| 819 C/T (rs1800871) of gene IL-10 | C/C | 21,3±1.7 | 5,8±1.4 | 5,1±1.5 | 4,7±1.1 | 82,3±5.8 | 197,4±15.1 | 17,3±2.3 | 36,4±3.9 | 35,2±3.6 | 0.472 |
| | C/T | 22,4±1.9 | 7,3±1.8 | 5,2±1.6 | 6,2±1.5 | 88,4±7.6 | 198,6±14.8 | 16,7±2.2 | 41,5±3.7 | 36,3±3.5 | 0.523 |
| | T/T | 25,2±1.4 | 7,8±1.3 | 5,5±1.5 | 8,5±1.4 | 93,3±6.4 | 203,8±18.8 | 18,7±2.7 | 43,6±3.7 | 42,7±3.8 | 0.001 |

In Table 5.1, it can be seen that carriers of the homozygous T/T genotype of the **IL-1β** gene were prescribed higher doses of nitrates (28.3±3.5 mg), β-blockers (8.4±1.8 mg), and Fluoxetine (47.9±4.2 mg) compared to carriers of the homozygous C/C genotype and the heterozygous C/T genotype. A similar pattern was observed in carriers of the homozygous A/A genotype of the **TNF-α** gene, the homozygous C/C genotype of the **IL-4** gene, and the homozygous T/T genotype of the **IL-10** gene.

We have studied detailed indicators (psychoemotional state parameters, frequency of angina attacks over the year, EchoCG parameters, uric acid, LDL-C, total cholesterol, TG, and cytokine concentration dynamics during treatment), which were analyzed to assess the impact of the polymorphisms of the studied genes on the success of therapy in patients with IHD.

To determine the potential influence of the studied genes on myocardial dimensions during treatment, patients with IHD associated with psychoemotional disorders underwent EchoCG, followed by an evaluation of the following parameters: **LV EDD, LVPW, IVS, and LVEF**. The results are presented in Tables **4.3.1 – 4.3.2**.

**Table 4.3.2.**

**Dynamics of EchoCG parameters before and after treatment depending on the allelic variant G-308A (rs1800629) of the TNF-α gene.**

| Echocardiography indicators | G-308A (rs1800629) гена TNF-α | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Alleles | | | | | | |
| | GG, n=27 | | GA, n=36 | | AA, n=35 | | |
| | Before | After | Before | After | Before | After | |
| **EDD LV, mm** | 55,4±13,0 | 53,2±12,0 | 56,3±13,0 | 55,2±8,0 | 57,1±15,0 | 54,2±9,0 | 0,001<br>0,029<br>0,132 |
| **LVPW, mm** | 11,9±3,0 | 11,2±2,7 | 12,1±2,5 | 11,4±2,4 | 12,2±2,6 | 11,4±2,2 | 0,274<br>0,895<br>0,215 |
| **IVS, mm** | 11,7±3,2 | 11,4±3,0 | 12,6±3,6 | 11,7±2,5 | 12,7±3,4 | 11,5±2,9 | 0,014<br>0,025<br>0,793 |
| **LVEF,%** | 49,3±7,0 | 52,2±7,0 | 48,1±6,0 | 51,3±6,0 | 46,4±5,8 | 51,5±5,4 | 0,001<br>0,05<br>0,038 |

Echocardiographic parameters in carriers of the mutant homozygous A/A genotype of the G-308A (rs1800629) TNF-α gene were as follows: left ventricular end-diastolic dimension (LV EDD) – 54.2±9.0 mm, left ventricular posterior wall thickness (LVPW) – 11.4±2.2 mm, interventricular septum thickness (IVS) – 11.5±2.9 mm, and ejection fraction (EF) – 51.5±5.4%. A positive trend was observed in terms of left ventricular ejection fraction and relative wall thickness, calculated using LVPW and IVS values, in patients carrying the A/A homozygous variant of the G-308A (rs1800629) TNF-α gene. In contrast, carriers of the G/G homozygous genotype showed a positive dynamic not only in left ventricular ejection fraction but also in LV EDD, which decreased to 53.2±12.0 mm (P=0.001).

**Table 4.3.3.**

**Dynamics of EchoCG parameters before and after treatment depending on the allelic variant G-308A (rs1800629) of the TNF-α gene.**

| **Indicators of echocardiography** | **511T/C (rs16944) гена IL-1β** | | | | | | **P value** |
|---|---|---|---|---|---|---|---|
| | Alleles | | | | | | |
| | CC, n=28 | | CT, n=23 | | TT, n=47 | | |
| | Before | After | Before | After | Before | After | |
| **LV EDD, mm** | 57,2±4,8 | 55,4±4,8 | 57,8±5,1 | 55,1±4,0 | 58,1±4,8 | 54,4±4,4 | 0,001<br>0,024<br>0,351 |
| **LVPW, mm** | 11,8±0,9 | 11,4±0,7 | 12,3±0,9 | 11,1±0,7 | 12,4±0,7 | 11,8±1,5 | 0,038<br>0,065<br>0,195 |
| **IVS, mm** | 11,7±0,7 | 11,2±0,6 | 12,8±0,7 | 11,5±0,6 | 12,7±0,9 | 11,9±1,3 | 0,033<br>0,037<br>0,077 |
| **LVEF, %** | 48,4±3,9 | 52,5±4,3 | 48,1±4,1 | 50,3±4,7 | 47,8±4,2 | 50,3±4,2 | 0,006<br>0,001<br>0,037 |

Depending on the polymorphic variants of **511 T/C (rs16944) of the IL-1β gene**, the average EchoCG parameters for the group with the pathogenic T/T genotype were as follows: **EDD LV – 54.4±4.4 mm, LVPW – 11.8±1.5 mm, IVS – 11.9±1.3 mm, and LVEF – 50.3±4.2%**. A positive trend was observed in terms of **EDD LV** and the relative thickness of the LV walls in patients carrying the **T/T homozygous variant of the 511 T/C (rs16944) IL-1β gene**.

**Table 4.3.5.**

**Dynamics of EchoCG parameters before and after treatment depending on the polymorphic variant C/T -589 (rs2243250) of the IL-4 gene.**

| Indicators of echocardiography | IL-4 C/T -589 (rs 2243250) | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Genotypes | | | | | | |
| | CC, n=44 | | CT, n=30 | | TT, n=24 | | |
| | Before | After | Before | After | Before | After | |
| **EDD LV, mm** | 56,1±9 | 54,8±8 | 56,8±8 | 55,5±7 | 57,8±7 | 54,2±7 | 0,022<br>0,019<br>0,039 |
| **LVPW, mm** | 11,7±3 | 11,2±2 | 12,1±3 | 11,7±3 | 12,8±4 | 11,2±3 | 0,001<br>0,852<br>0,318 |
| **IVS, мм** | 11,9±3 | 11,1±2 | 12,7±3 | 11,5±3 | 12,9±4 | 11,8±4 | 0,015<br>0,037<br>0,043 |
| **LVEF, %** | 47,8±7 | 51,8±6 | 48,3±7 | 53,3±7 | 47,4±6 | 55,1±7 | 0,027<br>0,05<br>0,033 |

For the **mutant homozygous C/C genotype of the C589T (rs2243250) polymorphism of the IL-4 gene**, a positive trend was observed in **LV EDD and LVEF**, along with a slight decrease in the relative thickness of the **PWLV and IVS**. After **12 months of therapy**, patients with the **C/C homozygous genotype** had the following values: **LV EDD – 54.8±8 mm, LVEF – 51.8±6%, PWLV – 11.2±2 mm, and IVS – 11.1±2 mm**.

Although carriers of the **T/T homozygous genotype** had a **LVEF of 47.4±6% before treatment**, after **12 months, LVEF significantly improved to 55.1±7% (P=0.033)**, confirming the effectiveness of the chosen treatment approach.

**Table 4.3.6.**

**Dynamics of EchoCG parameters before and after treatment depending on the polymorphic variants C819T (rs1800871) of the IL-10 gene.**

| Indicators of echocardiography | C819T (rs1800871) of gene IL-10 | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Genotypes | | | | | | |
| | CC, n=50 | | CT, n=28 | | TT, n=20 | | |
| | Before | After | Before | After | Before | After | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **LV EDD, mm** | 57,8±5,2 | 55,9±4,8 | 57,1±4,3 | 55,1±3,2 | 58,6±3,7 | 56,4±2,0 | 0,025<br>0,346<br>0,017 |
| **PWLV, mm** | 11,8±0,8 | 11,1±0,8 | 12,2±0,9 | 11,4±0,7 | 12,4±0,7 | 11,2±0,4 | 0,238<br>0,033<br>0,624 |
| **IVS, mm** | 11,7±0,9 | 11,4±0,7 | 12,7±0,8 | 11,8±0,3 | 12,8±0,6 | 11,9±0,5 | 0,319<br>0,022<br>0,046 |
| **LVEF, %** | 51,4±4,1 | 52,5±2,1 | 50,1±3,0 | 53,3±2,3 | 48,1±3,7 | 50,2±3,5 | 0,001<br>0,001<br>0,028 |

For the **C/C homozygous genotype of the C819T (rs1800871) polymorphism of the IL-10 gene**, a significant decrease in **LV ED**Dwas observed (**p=0.025**), along with a significant increase in **LVEF** (**p=0.001**).

Carriers of the **T/T mutant homozygous genotype** in the **C819T (rs1800871) polymorphism of the IL-10 gene** showed a significant decrease in **LV EDD** (**p=0.017**) and **IVS thickness** (**p=0.046**), as well as a significant increase in **LVEF** (**p=0.028**).

The results of our study demonstrated that the administration of **rosurvastatin** as part of a comprehensive therapy contributed to a decrease in **uric acid levels** by influencing **cytokine imbalance**. After treatment, **uric acid levels** reached the target range in carriers of the **G/G homozygous genotype** and the **G/A heterozygous genotype** of the **G-308A (rs1800629) polymorphism of the TNF-α gene**. However, despite the ongoing therapy, carriers of the **A/A homozygous genotype** failed to achieve the target **uric acid level**.

**Table 4.3.7.**

**Difference in uric acid levels before and after treatment depending on the G-308A (rs1800629) polymorphism of the TNF-α gene.**

| Gene | Genotype | Uric acid Before treatment | Uric acid After treatment | P-value |
|---|---|---|---|---|
| G-308A TNF-α | G/G, n=27 | 387,2±13,4 | 294,8±10,3 | 0,03 |
| | G/A, n=36 | 484,6±22,5 | 346,5±17,1 | 0,006 |
| | A/A, n=35 | 542,7±26,1 | 409,4±206 | 0,642 |

Individuals with the **C/T heterozygous variant** of the **511 T/C (rs16944) polymorphism of the IL-1β gene** had an average uric acid **level of 437.0±34.7 µmol/L before treatment**, which decreased to **317.3±21.3 µmol/L** after **12 months of therapy** (**p=0.074**).

In patients with the **T/T homozygous variant**, the decrease in uric acid **levels** was statistically significant (**p=0.035**), reaching **307.4±17.9 µmol/L**. Meanwhile, patients with the **C/C homozygous genotype** of the **511 T/C (rs16944) polymorphism of the IL-1β gene** had an MK level of **301.2±15.3 µmol/L** (**p=0.025**).

**Table 4.3.8.**

**Difference in uric acid levels before and after treatment depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene.**

| Gene | Genotype | Uric acid level before treatment | Uric acid level after treatment | | P-value |
|---|---|---|---|---|---|
| T511C IL-1β | C/C, n=28 | 330,5±18,4 | 301,2±15,3 | 29,3 | 0,025 |
| | C/T, n=23 | 437,0±34,7 | 317,3±21,3 | 119,3 | 0,074 |
| | T/T, n=47 | 434,1±28,5 | 307,4±17,9 | 126,7 | 0,035 |

Carriers of the **C/C homozygous genotype** of the **589 C/T polymorphism of the IL-4 gene** had an average **uric acid level of 525.4±31.0 µmol/L before therapy**, which decreased to **404.4±21.3 µmol/L** after treatment.

In contrast, carriers of the **C/T heterozygous genotype** and the **T/T homozygous genotype** of the **IL-4 gene** reached the **target uric acid level**, with values of **320.2±14.3 µmol/L** and **301.6±12.5 µmol/L**, respectively.

**Table 4.3.9.**

**Difference in uric acid levels before and after treatment depending on the 589 C/T polymorphism of the IL-4 gene.**

| Gene | Genotype | Uric acid before treatment | Uric acid after treatment | P-value |
|---|---|---|---|---|
| IL-4 C589T | C/C, n=44 | 525,4±31,1 | 404,4±21,3 | 0,025 |
| | C/T, n=30 | 448,8±21,7 | 320,2±14,3 | 0,038 |
| | T/T, n=24 | 425,3±20,2 | 301,6±12,5 | 0,172 |

During the treatment, individuals with the **T/T mutant homozygous genotype** of the **819 C/T (rs1800871) polymorphism of the IL-10 gene** had an average **uric acid level of 596.0±27.3 µmol/L before medication**, which decreased to **367.8±23.7 µmol/L** after treatment (**p=0.071**).

**Table 4.3.10.**

**Difference in uric acid levels before and after treatment depending on the 819 C/T (rs1800871) polymorphism of the IL-10 gene.**

| Gene | Genotype | Uric acid before treatment | Uric acid after treatment | P-value |
|---|---|---|---|---|
| C819T IL-10 | C/C, n=50 | 316,2±21,4 | 294,7±19,7 | 0,024 |
| | C/T, n=28 | 452,3±20,3 | 311,3±21,3 | 0,033 |
| | T/T, n=20 | 596,0±27,3 | 367,8±23,7 | 0,071 |

The **reduction in serum uric acid levels** can be explained by the **anti-inflammatory effects of rosuvastatin**. Furthermore, **major studies such as JUPITER and ANDROMEDA** have demonstrated this effect in their research, which aligns with the results of our study.

**Table 4.3.11.**

**Difference in lipid profile parameters before and after treatment depending on the G-308A (rs1800629) polymorphism of the TNF-α gene.**

| Indicator | GG, n=27 | | GA, n=36 | | AA, n= 35 | | P value |
|---|---|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment | |
| Total Chol, mmol/l | 6,2±1,2 | 5,9±1,1 | 6,7±1,4 | 5,5±1,2 | 6,9±1,4 | 5,6±0,3 | 0,018<br>0,005 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 0,037 |
| HDL-C, mmol/l | 0,87±0,02 | 1,02±0,1 | 0,87±0,17 | 0,96±0,1 | 0,84±0,12 | 1,0±0,1 | 0,038<br>0,017<br>0,084 |
| LDL-C, mmol/l | 4,4±0,4 | 4,0±0,3 | 4,1±0,7 | 3,9±0,4 | 4,8±0,5 | 3,9±0,3 | 0,073<br>0,039<br>0,276 |
| TG, mmol/l | 2,4±0,3 | 2,2±0,2 | 2,8±0,3 | 2,4±0,3 | 3,1±0,3 | 2,5±0,2 | 0,011<br>0,026<br>0,128 |
| AC | 6,1±0,8 | 4,8±0,4 | 6,7±0,6 | 4,7±0,4 | 7,2±0,8 | 4,6±0,4 | 0,036<br>0,049<br>0,425 |

**Table 4.3.12.**

**Difference in lipid profile parameters before and after treatment depending on the T511C (rs16944) polymorphism of the IL-1β gene.**

| Indicators | CC, n=28 | | CT, n=23 | | TT, n=47 | | P value |
|---|---|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment | |
| Total Chol, mmol/l | 6,5±0,23 | 5,2±0,24 | 7,3±0,5 | 5,6±0,6 | 7,7±0,8 | 5,8±0,6 | 0,035<br>0,029<br>0,285 |
| HDL-C, mmol/l | 0,9±0,03 | 1,24±0,03 | 0,9±0,03 | 1,2±0,2 | 0,8±0,05 | 1,4±0,04 | 0,019<br>0,027<br>0,095 |
| LDL-C, mmol/l | 3,8±0,14 | 3,2±0,15 | 4,3±1,3 | 3,2±0,4 | 4,0±0,2 | 3,2±0,1 | 0,037<br>0,022<br>0,324 |
| TG, mmol/l | 2,2±0,09 | 2,1±0,10 | 2,8±1,3 | 2,5±0,8 | 3,2±0,2 | 2,6±0,1 | 0,081<br>0,015<br>0,038 |
| AC | 6,2±0,16 | 3,2±0,24 | 7,1±0,6 | 3,7±0,4 | 8,6±0,6 | 3,1±0,1 | 0,031<br>0,014 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 0,036 |

In Tables 5.9-5.10, a significant reduction in LDL-C levels was demonstrated among carriers of the homozygous G/G genotype (p=0.073) and the heterozygous G/A genotype (p=0.039) of the G-308A (rs1800629) polymorphism of the **TNF-α** gene, as well as among carriers of the heterozygous C/T genotype and the homozygous T/T genotype of the 511 T/C (rs16944) polymorphism of the **IL-1β** gene, with reductions of 1.1±0.9 mmol/L and 1.2±0.1 mmol/L, respectively. Total cholesterol (TC) levels were significantly reduced in carriers of the homozygous T/T genotype (p=0.029) and the heterozygous C/T genotype (p=0.035) of the 511 T/C (rs16944) polymorphism of the **IL-1β** gene.

**Table 4.3.13**

Difference in lipid profile levels before and after treatment depending on the **589 C/T** polymorphism of the **IL-4** gene.

| Indicators | CC, n=44 | | CT, n=30 | | TT, n=24 | | P value |
|---|---|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment | |
| Total Chol, mmol/l | 6,5±0,6 | 5,2±0,4 | 6,9±0,6 | 5,8±0,4 | 6,4±0,4 | 6,3±0,3 | 0,011<br>0,031<br>0,627 |
| HDL-C, mmol/l | 0,9±0,1 | 1,0±0,08 | 0,86±0,03 | 1,0±0,07 | 0,9±0,03 | 0,9±0,03 | 0,281<br>0,318<br>0,627 |
| LDL-C, mmol/l | 4,6±0,4 | 3,8±0,7 | 4,1±0,5 | 3,9±0,1 | 4,6±0,3 | 4,2±0,3 | 0,376<br>0,048<br>0,552 |
| TG, mmol/l | 2,3±0,4 | 2,1±0,1 | 2,7±0,1 | 2,3±0,1 | 3,3±0,2 | 2,7±0,1 | 0,017<br>0,035<br>0,215 |
| AC | 6,2±0,7 | 4,2±0,3 | 7,0±0,6 | 4,8±0,3 | 6,1±0,5 | 6,0±0,5 | 0,031<br>0,022<br>0,183 |

In **Table 4.3.14**, a significant reduction in total cholesterol (TC) levels can be observed among carriers of the homozygous **C/C** genotype, heterozygous **C/T** genotype, and homozygous **T/T** genotype of the **819 C/T (rs1800871) polymorphism** of the **IL-10** gene, with reductions of **5.22±0.4, 5.7±0.6, and 5.4±0.4 mmol/L**, respectively. Additionally, a non-significant decrease in LDL-C levels was observed, with reductions of **2.7±0.3, 2.6±0.1, and 3.1±0.2 mmol/L**, respectively.

**Table 4.3.14**

Difference in lipid profile levels before and after treatment depending on the **819 C/T (rs1800871) polymorphism** of the **IL-10** gene.

| Indicators | CC, n=50 | | CT, n=28 | | TT, n=20 | | P value |
|---|---|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment | |
| Total chol, Mmol/l | 6,7±0,6 | 5,22±0,4 | 7,4±0,8 | 5,7±0,6 | 7,2±0,8 | 5,4±0,4 | 0,018<br>0,021<br>0,351 |
| HDL-C, mmol/l | 0,89±0,03 | 1,3±0,06 | 0,86±0,07 | 1,21±0,1 | 0,95±0,03 | 1,27±0,1 | 0,038<br>0,043<br>0,102 |
| LDL-C, mmol/l | 3,65±0,2 | 2,7±0,3 | 3,5±0,4 | 2,6±0,1 | 3,9±0,2 | 3,1±0,2 | 0,029<br>0,024<br>0,36 |
| TG, mmol/l | 2,2±0,09 | 2,1±0,1 | 2,8±0,2 | 2,5±0,1 | 3,2±0,2 | 2,6±0,3 | 0,041<br>0,124<br>0,137 |
| AC | 6,7±0,5 | 3,0±0,2 | 7,6±0,9 | 3,7±0,2 | 6,6±0,5 | 3,2±0,2 | 0,023<br>0,029<br>0,538 |

The presented data demonstrate that carriers of the **homozygous T/T genotype of the IL-10 gene** and the **homozygous C/C genotype of the IL-4 gene** in both genes exhibited significant resistance to correction. Therefore, **long-term and careful monitoring** is recommended for these patients.

When analyzing the levels of **pro- and anti-inflammatory cytokines** in patients with **unstable angina**, significantly **elevated levels of pro-inflammatory cytokines** and **variable levels of anti-inflammatory cytokines** were observed.

**Table 4.3.15**

Cytokine status levels before and after treatment depending on the **G-308A (rs1800629) polymorphism** of the **TNF-α** gene.

| **Cytokine profile indicators** | **G-308A of gene TNF-α** | | | | | | **P-value** |
|---|---|---|---|---|---|---|---|
| | G/G, n=27 | | G/A, n=36 | | A/A, n=35 | | |
| | Before | After | Before | After | Before | After | |
| **TNF-α, pg/ml** | 63,4±3,1 | 33,7±3,7 | 65,8±2,8 | 33,4±2,9 | 69,6±5,8 | 33,2±2,8 | 0,031 |
| | | | | | | | 0,018 |
| | | | | | | | 0,057 |
| **IL-1β, pg/ml** | 99,1±6,2 | 43,9±4,0 | 95,2±5,3 | 42,9±3,8 | 106,5±8,2 | 42,7±3,7 | 0,001 |
| | | | | | | | 0,021 |
| | | | | | | | 0,003 |
| **IL-4, pg/ml** | 24,3±2,2 | 22,8±2,1 | 23,2±2,1 | 21,5±2,5 | 24,9±1,7 | 21,8±0,8 | 0,174 |
| | | | | | | | 0,927 |
| | | | | | | | 0,753 |
| **IL-10, pg/ml** | 12,7±0,9 | 15,7±1,3 | 12,3±1,1 | 15,3±0,9 | 12,1±0,7 | 15,1±0,8 | 0,371 |
| | | | | | | | 0,810 |
| | | | | | | | 0,391 |

**P1, P2, P3** – statistical significance of differences in cytokine level changes (**TNF-α, IL-1β, IL-4, IL-10**) between **G/G and G/A, G/G and A/A, G/A and A/A**, respectively.

Patients with the **heterozygous G/A genotype** and **homozygous A/A genotype** in the **G-308A polymorphism of the TNF-α gene** had **statistically higher levels of pro-inflammatory cytokines TNF-α and IL-1β before treatment** compared to patients with the **homozygous G/G variant** of the **G-308A TNF-α polymorphism**. After **comprehensive therapy**, these levels significantly decreased but **did not reach target values** (**Table 4.3.16**).

**Table 4.3.16**

Cytokine status levels before and after treatment depending on the **511 T/C (rs16944) polymorphism** of the **IL-1β gene**.

| **Cytokine profile indicators** | **T/C 511 гена IL-1β** | | | | | | **P-value** |
|---|---|---|---|---|---|---|---|
| | CC, n=28 | | CT, n=23 | | TT, n=47 | | |
| | Before | After | Before | After | Before | After | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **TNF-α, pg/ml** | 62,9±4,5 | 35,2±3,6 | 77,5±6,2 | 33,0±2,1 | 74,5±6,3 | 31,8±2,4 | 0,022 |
| | | | | | | | 0,001 |
| | | | | | | | 0,327 |
| **IL-1 β, pg/ml** | 78,8±6,2 | 45,2±4,0 | 98,9±8,2 | 42,3±3,6 | 100,5±8,9 | 37,6±2,8 | 0,017 |
| | | | | | | | 0,001 |
| | | | | | | | 0,828 |
| **IL-4, pg/ml** | 19,74±1,2 | 22,4±2,7 | 18,2±1,6 | 22,4±1,8 | 18,1±1,6 | 22,4±2,1 | 0,043 |
| | | | | | | | 0,029 |
| | | | | | | | 0,685 |
| **IL-10, pg/ml** | 13,6±1,1 | 15,75±1,2 | 12,7±1,3 | 15,6±1,9 | 12,04±1,1 | 15,9±1,7 | 0,015 |
| | | | | | | | 0,004 |
| | | | | | | | 0,845 |

**P1, P2, P3** – statistical significance of differences in cytokine level changes (**TNF-α, IL-1β, IL-4, IL-10**) between **C/C and C/T, C/C and T/T, C/T and T/T**, respectively.

All **patients with unstable angina** had significantly high levels of **pro-inflammatory cytokines**. Patients with the **heterozygous C/T genotype** and **homozygous T/T genotype** had **statistically higher levels of pro-inflammatory cytokines TNF-α and IL-1β before treatment** compared to patients with the **homozygous C/C variant (T511C) rs16944 of the IL-1β gene**. After **comprehensive therapy**, these levels significantly decreased.

**Table 4.3.17**

Cytokine status levels before and after treatment depending on the **589 C/T polymorphism** of the **IL-4 gene**.

| **Cytokine profile indicators** | **C/T 589 гена IL-4** | | | | | | **P-value** |
|---|---|---|---|---|---|---|---|
| | Genotype | | | | | | |
| | C/C, n=44 | | C/T, n=30 | | T/T, n=24 | | |
| | Before | After | Before | After | Before | After | |
| **TNF-α pg/ml** | 70,1±6,7 | 33,4±2,8 | 63,5±5,7 | 33,1±2,7 | 63,3±5,4 | 33,9±2,6 | 0,02 |
| | | | | | | | 0,041 |
| | | | | | | | 0,037 |
| **IL-1β pg/ml** | 107,6±8,7 | 43,0±3,7 | 92,7±8,1 | 42,0±3,8 | 95,9±6,9 | 44,5±3,7 | 0,001 |
| | | | | | | | 0,039 |
| | | | | | | | 0,043 |
| **IL-4** | 24,9±2, | 21,9±1, | 22,6±1, | 21,8±1, | 24,5±2 | 22,3±1, | 0,382 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **pg/ml** | 1 | 8 | 9 | 8 | ,1 | 7 | 0,613 |
| | | | | | | | 0,738 |
| **IL-10 pg/ml** | 12,3±1,6 | 15,6±1,3 | 11,8±0,8 | 15,4±0,9 | 13,0±0,9 | 14,7±0,9 | 0,069 |
| | | | | | | | 0,831 |
| | | | | | | | 0,382 |

P1, P2, P3 represent the statistical significance of differences in cytokine level changes (TNF-α, IL-1β, IL-4, IL-10) between C/C and C/T, C/C and T/T, and C/T and T/T, respectively.

Significantly high levels of pro-inflammatory cytokines were observed in carriers of the homozygous C/C genotype in the C/T 589 polymorphism of the IL-4 gene: before treatment, TNF-α was 70.1±6.7 pg/mL, and IL-1β was 107.6±8.7 pg/mL. After 12 months, the levels of pro-inflammatory cytokines decreased to 33.4±2.8 pg/mL and 43.0±3.7 pg/mL, respectively.

**Table 4.3.18**

**Cytokine status levels before and after treatment depending on the 819 C/T (rs1800871) polymorphism of the IL-10 gene**.

| **Cytokine profile indicators** | **C/T 819 гена IL-10** | | | | | | **P-value** |
|---|---|---|---|---|---|---|---|
| | Genotype | | | | | | |
| | CC, n=50 | | CT, n=28 | | TT, n=20 | | |
| | Before | After | Before | After | Before | After | |
| **TNF-α pg/ml** | 65,0±5,8 | 34,6±2,4 | 77,7±6,2 | 34,1±2,8 | 83,2±7,6 | 35,6±2,9 | 0,028 |
| | | | | | | | 0,038 |
| | | | | | | | 0,019 |
| **IL-1β pg/ml** | 81,7±7,2 | 42,9±3,5 | 103,9±8,6 | 45,0±4,6 | 112,4±1,1 | 45,5±3,8 | 0,01 |
| | | | | | | | 0,001 |
| | | | | | | | 0,017 |
| **IL-4 pg/ml** | 19,7±1,3 | 22,6±1,8 | 19,2±1,8 | 22,1±1,9 | 14,1±1,2 | 22,0±2,0 | 0,842 |
| | | | | | | | 0,621 |
| | | | | | | | 0,082 |
| **IL-10 pg/ml** | 13,3±0,8 | 15,5±1,1 | 12,7±1,1 | 15,7±1,4 | 10,6±0,9 | 17,0±1,5 | 0,310 |
| | | | | | | | 0,083 |
| | | | | | | | 0,719 |

P1, P2, P3 represent the statistical significance of differences in cytokine level changes (TNF-α, IL-1β, IL-4, IL-10) between C/C and C/T, C/C and T/T, and C/T and T/T, respectively.

In the study of pro-inflammatory cytokine levels (TNF-α and IL-1β) among patients with different genotypes of the IL-10 gene, it was also observed that patients with the homozygous T/T genotype of the IL-10 gene showed a significant difference in cytokine levels after 12 months of therapy. The difference was 47.6±4.7 pg/mL and 66.9±7.2 pg/mL, respectively (Table 4.3.18).

## 4.4. PHARMACOGENETIC ASPECTS OF INDIVIDUALIZED TREATMENT OF PSYCHOEMOTIONAL STATE IN PATIENTS WITH UNSTABLE ANGINA

According to WHO data, as of today, patients suffering from psychoemotional disorders account for more than 70%. It is well known that by 2023, the role of psychoemotional disorders in the development and progression of coronary artery disease has become a leading factor. By 2030, this condition is expected to become the primary cause of disability worldwide. In this regard, our objective was to study the pharmacogenetic characteristics of personalized treatment for patients with coronary artery disease who also had psychoemotional disorders.

As an antidepressant, we included Fluoxetine, a drug from the selective serotonin reuptake inhibitor (SSRI) group. This medication possesses thymoleptic and stimulating properties. It selectively blocks the neuronal reuptake of serotonin (5-HT) in the synapses of central nervous system neurons. Inhibition of serotonin reuptake leads to an increase in the concentration of this neurotransmitter in the synaptic cleft, enhancing and prolonging its action on postsynaptic receptor sites. By enhancing serotonergic transmission, Fluoxetine inhibits neurotransmitter metabolism through a negative feedback mechanism. With prolonged use, Fluoxetine suppresses the activity of 5-HT1 receptors. It has little effect on the reuptake of norepinephrine and dopamine.

Fluoxetine does not directly affect serotonin, muscarinic cholinergic, H1-histamine, or alpha-adrenergic receptors. Unlike most antidepressants, it does not reduce the activity of postsynaptic beta-adrenergic receptors. It does not cause orthostatic hypotension, has no sedative effects, and is not cardiotoxic. A stable clinical effect is achieved after 1–2 weeks of treatment. The medication was prescribed for 4–5 weeks. Its effectiveness was assessed after one month, with a final evaluation conducted at 12 months.

To assess the impact on the success of therapy in patients with unstable angina associated with psychoemotional disorders, we evaluated the difference between the scores of the HADS-A/D and Spielberger-Khanin scales before treatment initiation and after 12 months of follow-up.

**Table 4.4.1.**

**HADS scale scores depending on the G-308A (rs1800629) polymorphism of**

**the TNF-α gene before and after Fluoxetine administration in patients with coronary artery disease.**

| Gene | Genotype | HADS-A | | P-value |
|---|---|---|---|---|
| G-308A TNF-α | | Before | After | |
| | G/G, n=27 | 8,4±1,2 | 6,5±0,9 | 0,037 |
| | G/A, n=36 | 11,3±1,1 | 7,1±0,8 | 0,042 |
| | A/A, n=35 | 10,2±1,2 | 7,9±0,7 | 0,813 |
| Gene | Genotype | HADS-D | | P-value |
| G-308A TNF-α | | Before treatment | After treatment | |
| | G/G, n=27 | 9,37±1,3 | 6,1±0,6 | 0,001 |
| | G/A, n=36 | 12,5±1,5 | 7,0±0,8 | 0,034 |
| | A/A, n=35 | 10,5±1,3 | 7,9±0,5 | 0,316 |

**Table 4.4.2.**

**Spielberger-Khanin scale scores depending on the G-308A (rs1800629) polymorphism of the TNF-α gene before and after Fluoxetine administration in patients with coronary artery disease.**

| Gene | genotype | SA | | P-value |
|---|---|---|---|---|
| G-308A TNF-α | | Before | After | |
| | G/G, n=27 | 51,4±4,1 | 36,3±3,2 | 0,001 |
| | G/A, n=36 | 52,9±3,8 | 38,5±3,0 | 0,039 |
| | A/A, n=35 | 53,4±3,2 | 49,6±3,1 | 0,072 |
| Gene | Genotype | TA | | P-value |
| G-308A TNF-α | | Before | After | |
| | G/G, n=27 | 51,0±4,4 | 36,9±3,7 | 0,001 |
| | G/A, n=36 | 52,3±4,1 | 37,7±3,3 | 0,219 |
| | A/A, n=35 | 53,1±4,7 | 48,9±3,1 | 0,411 |

Anxiety and depression scores after the conducted therapy among all three genotypes of the G-308A TNF-α gene successfully reached target values, with carriers of the homozygous G/G genotype responding better to correction (p=0.001). For example, the HADS-A score before treatment was 8.4±1.2 points, which decreased to 6.5±0.9 points after treatment (p=0.037). The HADS-D score was 9.37±1.3 points and decreased to 6.1±0.6 points (p=0.001). Anxiety scores

according to the Spielberger-Hanin scale were also significantly reduced in this category of patients (p=0.001).

After 12 months of therapy, the HADS-A anxiety scores in patients with the C/T and T/T genotypes of the IL-1β gene decreased to 7.6±0.3 and 8.4±0.6 points, respectively, but did not reach target values, in contrast to carriers of the C/C genotype of the IL-1β gene. Depression scores on the HADS-D scale in these patients decreased to 6.9±0.5 and 7.7±0.9 points, respectively (Table 4.4.3).

**Table 4.4.3.**

**Difference in HADS scores before and after Fluoxetine administration depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene**.

| Gene | Genotype | HADS-A | | P-value |
|---|---|---|---|---|
| T/C 511 IL-1β | | Before treatment | After treatment | |
| | C/C, n=28 | 4,4±0,3 | 4,2±0,2 | 0,001 |
| | C/T, n=23 | 11,5±0,7 | 7,6±0,3 | 0,047 |
| | T/T, n=47 | 13,3±0,9 | 8,4±0,6 | 0,672 |
| Gene | Genotype | HADS-D | | P-value |
| T/C 511 IL-1β | | Before treatment | After treatment | |
| | C/C, n=28 | 4,2±0,4 | 4,1±0,3 | 0,028 |
| | C/T, n=23 | 11,6±0,7 | 6,9±0,5 | 0,005 |
| | T/T, n=47 | 13,3±1,5 | 7,7±0,9 | 0,014 |

**Table 4.4.4.**

**Difference in Spielberger-Hanin scale scores before and after Fluoxetine administration depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene.**

| Gene | Genotype | SA | | P-value |
|---|---|---|---|---|
| T/C 511 IL-1β | | Before | After | |
| | C/C, n=28 | 32,8±3,8 | 32,7±3,0 | 0,219 |
| | C/T, n=23 | 54,6±4,5 | 44,5±2,1 | 0,038 |
| | T/T, n=47 | 54,8±5,8 | 44,7±4,0 | 0,084 |
| Gene | Genotype | TA | | P-value |
| T/C 511 IL-1β | | Before | After | |
| | C/C, n=28 | 29,6±2,0 | 29,1±1,8 | 0,394 |
| | C/T, n=23 | 51,7±3,2 | 41,4±2,8 | 0,019 |

| | | | | |
|---|---|---|---|---|
| | T/T, n=47 | 53,4±4,8 | 43,6±3,2 | 0,046 |

When studying the indicators of trait anxiety (TA) and state anxiety (SA) according to the Spielberger-Hanin scale after the conducted therapy, patients with the C/T genotype, in contrast to patients with the T/T genotype, reached target values: 41.4±2.8 and 44.5±2.1, respectively (P=0.038; P=0.019). This once again confirms the severe course of anxiety-depressive syndrome among patients with the homozygous T/T variant in the 511 (rs16944) polymorphism of the IL-1 T/C gene (Table 4.4.4).

When assessing the effectiveness of Fluoxetine therapy in patients with coronary artery disease (CAD) associated with psychoemotional disorders, depending on different allelic variants of anti-inflammatory cytokines—IL-4 in the C/T -589 (rs2243250) polymorphism and IL-10 in the C/T 819 (rs1800871) polymorphism—a follow-up survey of patients using the HADS-A/D and Spielberger-Hanin scales was conducted after 12 months of treatment.

**Table 4.4.5.**

**HADS scale scores depending on the C/T 589 (rs2243250) polymorphism of the IL-4 gene before and after Fluoxetine administration in patients with coronary artery disease**.

| Gene | Genotype | HADS-A | | P-value |
|---|---|---|---|---|
| C/T 589 IL-4 | | Before | After treatment | |
| | C/C, n=44 | 10,1±0,7 | 8,2±0,5 | 0,009 |
| | C/T, n=30 | 11,1±0,9 | 7,1±0,4 | 0,013 |
| | T/T, n=24 | 8,9±0,7 | 5,8±0,4 | 0,197 |
| Gene | Genotype | HADS-D | | P-value |
| C/T 589 IL-4 | | Before | After treatment | |
| | C/C, n=44 | 11,0±1,4 | 8,2±0,8 | 0,001 |
| | C/T, n=30 | 12,0±0,8 | 6,9±0,4 | <0,001 |
| | T/T, n=24 | 9,3±0,6 | 5,6±0,5 | 0,072 |

According to Table 4.4.5, it can be seen that only carriers of the homozygous T/T genotype in the C/T -589 polymorphism of the IL-4 gene successfully reached the target levels for both anxiety (HADS-A) and depression (HADS-D), although anxiety and depression scores among carriers of the homozygous C/C genotype and the heterozygous C/T genotype were significantly reduced.

Thus, in the study of the C/T -589 polymorphism of the IL-4 gene before treatment, carriers of the homozygous C/C genotype and the heterozygous C/T genotype exhibited clinically significant anxiety and depression, which, after 12

months of therapy, transitioned to subclinical anxiety and depression. However, it should be noted that this category of patients required higher doses of Fluoxetine (60–80 mg/day).

**Table 4.4.6.**

**Spielberger-Hanin scale scores depending on the C/T -589 (rs2243250) polymorphism of the IL-4 gene before and after Fluoxetine administration in patients with coronary artery disease**.

| Gene | Genotype | SA | | P-value |
|---|---|---|---|---|
| C/T -589 IL-4 | | Before | After | |
| | C/C, n=44 | 54,0±4,9 | 48,9±3,0 | 0,006 |
| | C/T, n=30 | 53,0±4,1 | 38,7±3,1 | <0,001 |
| | T/T, n=24 | 49,6±3,8 | 36,9±2,8 | 0,062 |
| Gene | Genotype | TA | | P-value |
| C/T -589 IL-4 | | Before | After | |
| | C/C, n=44 | 52,9±6,3 | 48,4±2,4 | 0,038 |
| | C/T, n=30 | 52,8±4,8 | 37,6±2,8 | 0,049 |
| | T/T, n=24 | 50,5±5,2 | 37,5±3,3 | 0,032 |

In the study of trait anxiety (TA) and situational anxiety (SA) using the Spielberger-Hanin scale after treatment, carriers of all three genotypes of the C/T -589 (rs2243250) polymorphism of the IL-4 gene showed a significant reduction in scores and successfully reached the target level.

**Table 4.4.7.**

**HADS scale scores depending on the 819 C/T (rs1800871) polymorphism of the IL-10 gene before and after Fluoxetine administration in patients with coronary artery disease.**

| Gene | Genotype | HADS-A | | P-value |
|---|---|---|---|---|
| C/T 819 IL-10 | | Before | After | |
| | C/C, n=50 | 8,5±0,9 | 6,5±0,5 | <0,001 |
| | C/T, n=28 | 11±0,9 | 7,4±0,6 | 0,318 |
| | T/T, n=20 | 13,7±1,2 | 8,6±0,6 | 0,017 |
| Gene | Genotype | HADS-D | | P-value |
| C/T 819 | | Before | After | |

| | | | | |
|---|---|---|---|---|
| IL-10 | C/C, n=50 | 8,4±0,7 | 6,1±0,3 | 0,007 |
| | C/T, n=28 | 11,1±1,2 | 6,3±0,4 | 0,013 |
| | T/T, n=20 | 13,5±1,8 | 7,7±0,4 | 0,043 |

The study revealed that patients with the heterozygous C/T variant of the (C819T) rs1800871 polymorphism of the IL-10 gene, as well as those with the homozygous T/T variant, exhibited clinically significant anxiety and depression, in contrast to patients with the C/C genotype, who had subclinically expressed anxiety and depression. After 12 months of therapy, the HADS-A scores decreased to 7.4±0.6 and 8.6±0.6 points (P<0.001) in carriers of the heterozygous C/T genotype and the homozygous T/T genotype of the IL-10 gene, respectively, while the HADS-D scores decreased to 6.3±0.4 and 7.7±0.4 points (P<0.001), respectively. Notably, in carriers of the homozygous T/T genotype, despite antidepressant therapy, it was not possible to reduce anxiety and depression levels to the target values.

**Table 4.4.8.**

**Spielberger-Hanin scale scores depending on the 819 C/T (rs1800871) polymorphism of the IL-10 gene before and after Fluoxetine administration in patients with coronary artery disease**.

| Gene | Genotype | SA | | P-value |
|---|---|---|---|---|
| | | Before | After | |
| C/T 819 IL-10 | C/C, n=50 | 43,9±4,7 | 33,7±2,1 | 0,027 |
| | C/T, n=28 | 50,7±4,6 | 40,6±3,7 | 0,032 |
| | T/T, n=20 | 55,1±4,9 | 45,1±3,7 | 0,162 |
| Gene | Genotype | TA | | P-value |
| | | Before | After | |
| C/T 819 IL-10 | C/C, n=50 | 42,0±3,3 | 32,1±1,3 | 0,001 |
| | C/T, n=28 | 48,9±3,4 | 38,8±1,5 | 0,001 |
| | T/T, n=20 | 51,3±4,2 | 41,2±2,8 | 0,028 |

Upon repeated assessment using the Spielberger-Hanin scale, we found that carriers of the homozygous T/T genotype of the IL-10 gene exhibited clinically significant (high) situational and trait anxiety, with scores of 55.1±4.9 and 51.3±4.2 points, respectively. After 12 months of therapy, we successfully reduced the anxiety levels to a subclinical (moderate) level—45.1±3.7 and 41.2±2.8 points, respectively. Among carriers of the homozygous C/C genotype and the heterozygous C/T genotype of the IL-10 gene, moderate and high anxiety levels were observed before

treatment. However, after 12 months of therapy, anxiety levels decreased to a low level, indicating the rational selection of this treatment (Table 4.4.8).

Given that chronic coronary artery disease (CAD) is a multifactorial pathology, we examined changes in immune status, dyslipidemia, hyperuricemia, and psycho-emotional disorders, which can be classified as biopsychosocial issues leading to endothelial dysfunction and disease destabilization. To predict CAD destabilization in patients based on various risk factors, we developed a software product (No. DGU 14589, "Prediction of Coronary Artery Disease Based on Psycho-Emotional Status," registered on 14.02.2022 in the State Register of Software Products of the Republic of Uzbekistan). This software incorporates all risk factors, clinical signs, laboratory parameters (lipid profile, renal and hepatic function markers, uric acid and blood glucose levels, interleukin levels in blood), instrumental findings from coronary angiography, ECG, and echocardiography, as well as molecular-genetic studies (G-308A (rs1800629) polymorphism of the TNF-α gene, 511 (rs16944) polymorphism of the IL-1β gene, C/T -589 (rs2243250) polymorphism of the IL-4 gene, and C/T -819 (rs1800871) polymorphism of the IL-10 gene). Taking these factors into account, we identified risk groups among CAD patients.

We conducted traditional therapy over 12 months for patients with coronary artery disease (CAD). Positive hemodynamic changes were observed in left ventricular ejection fraction (LVEF) and relative left ventricular wall thickness, depending on the polymorphisms of the G-308A (rs1800629) TNF-α gene, 511 (rs16944) IL-1β gene, C/T -589 (rs2243250) IL-4 gene, and C/T -819 (rs1800871) IL-10 gene, considering mutant variants.

As the study results showed, lipid profile and cytokine status did not reach control levels after treatment, considering the polymorphic variants of the studied genes.

In assessing psycho-emotional disorders after correction with the selective serotonin reuptake inhibitor fluoxetine hydrochloride (Fluoxetine), it was found that all three genotypes of the G-308A (rs1800629) TNF-α gene achieved control levels. Additionally, carriers of the homozygous T/T genotype in the C/T -589 polymorphism of the IL-4 gene reached control levels for both anxiety (HADS-A) and depression (HADS-D).

The study revealed that patients with the heterozygous C/T variant of the C819T (rs1800871) IL-10 gene polymorphism, as well as those with the homozygous T/T variant, had clinically significant anxiety and depression, unlike patients with the C/C genotype, who exhibited subclinical anxiety and depression. After 12 months of Fluoxetine therapy, HADS-A scores decreased to 7.4±0.6 and 8.6±0.6 points ($P<0.001$) in carriers of the heterozygous C/T and homozygous T/T genotypes of the IL-10 T/C 819 polymorphism, respectively. HADS-D scores decreased to 6.3±0.4 and 7.7±0.4 points ($P<0.001$), respectively.

It should be noted that despite antidepressant therapy, carriers of the homozygous T/T genotype did not achieve control levels for anxiety and depression.

Upon repeated assessment using the Spielberger-Hanin scale, it was found that carriers of the homozygous T/T genotype of the IL-10 T/C 819 polymorphism exhibited clinically significant (high) situational and trait anxiety. After 12 months of therapy, we successfully reduced anxiety levels to a subclinical (moderate) level, indicating the appropriate selection of the treatment.

## SUMMARY

Ischemic heart disease (IHD), also known as coronary artery disease, is a broad term referring to the accumulation of a waxy substance called plaques in the coronary arteries. This buildup disrupts coronary circulation, impairing the adequate supply of blood to the heart muscle and surrounding tissues—a phenomenon that can lead to myocardial infarction (MI).

Mental disorders also contribute significantly to the global burden of disease. For instance, more than 300 million people of all ages worldwide suffer from anxiety and depression, and by 2030, this condition is expected to become the leading cause of disability globally. According to a recent meta-analysis, 14.3% of all deaths worldwide—approximately 8 million deaths annually—are associated with mental disorders.

There is an intriguing link between mental disorders and IHD. A higher prevalence of mental disorders has been observed in patients with diabetes mellitus. Conversely, individuals with mental disorders appear to have an increased risk of developing ischemic heart disease. Furthermore, shared pathophysiological mechanisms may connect both conditions.

However, the relationship between psychoemotional state and the degree of coronary atherosclerosis, as assessed by coronary angiography, as well as the association of ischemic heart disease with impaired purine metabolism and the polymorphism of pro-inflammatory cytokines such as G-308A TNF-α and 511 T/C IL-1β, or anti-inflammatory cytokines such as C/T -589 IL-4 and C/T -819 IL-10, is often overlooked by many researchers and remains an understudied issue.

All the above highlights that ischemic heart disease, when associated with comorbid conditions, remains a pressing issue in both national and international healthcare across most developed and developing countries.

In our study, we investigated the relationship between several risk factors and psychoemotional state, as well as their role in the destabilization of ischemic heart disease (IHD), particularly in atherosclerotic coronary artery disease, hypercholesterolemia, diabetes mellitus, hyperuricemia, cytokine imbalance, and the polymorphism of pro- and anti-inflammatory cytokine genes (G-308A (rs1800629) TNF-α, 511 (rs16944) IL-1β, C/T -589 (rs2243250) IL-4, C/T -819 (rs1800871) IL-10). We analyzed the correlation between these parameters, anxiety indicators, and the production of immunoregulatory cytokines.

It is important to note that hypercholesterolemia, psychoemotional disturbances, and the polymorphism of pro- and anti-inflammatory cytokine genes—specifically, the presence of the homozygous A/A genotype of the TNF-α gene, the T/T genotype of the IL-1β gene, the C/C genotype of the IL-4 gene, and the T/T

genotype of the IL-10 gene—were identified as factors significantly associated with hemodynamically significant coronary artery disease.

Additionally, our data analysis revealed a significant relationship between the prevalence of psychoemotional disorders among patients with ischemic heart disease and high coronary artery disease severity scores according to the Syntax Score.

In recent years, considerable attention has been focused on identifying effective methods for the early detection of severe depressive disorders in patients with ischemic heart disease (IHD) at both the clinical and biological levels using specific markers. However, there are currently no sufficiently informative and reliable laboratory diagnostic tests based on potential biomarkers specifically for the verification of psychoemotional disorders (PED). Due to the lack of an objective diagnostic method, more than half of patients with PED remain undiagnosed and do not receive effective treatment [74,78].

Based on the comprehensive data presented above, this study aimed to evaluate specific biomarkers of severe depressive and anxiety-depressive disorders in patients with ischemic heart disease. To achieve this, we conducted immunological (IL-1β, IL-4, IL-10, TNF-α) and genetic studies (G-308A (rs1800629) TNF-α, 511 (rs16944) IL-1β, C/T -589 (rs2243250) IL-4, C/T -819 (rs1800871) IL-10) that have a direct association with the destabilization of IHD in patients with PED.

The study findings revealed that patients with unstable angina exhibited elevated serum levels of IL-1β and TNF-α. However, in patients with unstable angina and comorbid conditions such as PED and generalized anxiety disorder (GAD), these levels were slightly higher than in patients with unstable angina without comorbid pathology.

The influence of cytokines on the dopaminergic system has recently been reviewed (Treadway et al., 2019; Felger and Treadway, 2017; Capuron et al., 2012). Relevant mechanisms that may elevate cytokine activity in the brain to pathological levels include psychological and physical stressors. However, it remains unclear how the same cytokine can exert opposite effects on neuronal function depending on the context. It has been suggested that the source and combination of cytokines determine their impact on brain function.

In the field of neuroinflammation, primary attention has been given to central cytokines, whereas peripheral cytokines undoubtedly contribute to behavioral effects. Evidence suggests that blocking peripheral cytokines is sufficient to prolong PED, and that preventing PED disruption is enough to produce an antidepressant effect (Cheng et al., 2018; Menard et al., 2017).

There are several well-documented pathways through which peripheral cytokines reach the brain, similar to immune cells:

1. Through "leaky" areas of the PED, such as organs located around the ventricles, or through disease-induced PED disruption (Quan and Banks, 2007; Vitkovic et al., 2000);
2. Via the neuronal pathway through afferent cytokine receptors on nerve fibers, which transmit signals to the brain parenchyma;

3. Through infiltration of immune cells that produce cytokines after being attracted by a chemokine gradient into the brain parenchyma (Lewitus et al., 2008). This chronology highlights the origins of psychoneuroimmunology and the theory of immune system hyperactivation.

The conducted studies demonstrated that cytokine imbalance was associated not only with PED but also with elevated uric acid levels, as the average uric acid level among patients with PED was 462.2±7.42 μmol/L, whereas in patients without PED, these values were 348.5±5.38 μmol/L.

The results of this study are of significant importance for practical medicine as they reveal essential pathogenetic mechanisms of CAD development. The crucial practical significance of determining pro- and anti-inflammatory cytokine levels and anxiety levels using two scales (Spielberger-Hanin Scale and HADS) has been established as additional differential diagnostic criteria for disease instability. It should be emphasized that such clinical-immunological studies of cytokine status in relation to uric acid and PED in patients with unstable angina have been conducted for the first time in our study.

The development of such comorbid conditions is influenced not only by environmental factors but also by genetic factors.

Due to the significant contribution of heredity to depression vulnerability, it has been suggested that the physiology of immune function in depression may be partially predicted by genetic mechanisms. Over the past few years, the number of samples in genome-wide association studies (GWASs) has grown to hundreds of thousands, with multiple gene variants contributing only minimally to depression vulnerability [81,145].

Polymorphisms in genes encoding IL-1β, IL-6, IL-10, TNF, MCP1/CCL2, CRP, and phospholipase-A2 (PLA2) have been among the most common findings in PED. However, determining their exact contribution remains challenging. For instance, the IL-1β promoter polymorphism at position 511 has been linked to more severe depression symptoms, regardless of whether the polymorphism is associated with increased IL-1β production (511T allele) or decreased IL-1β production (511C allele) [145]. Similar findings have been observed in the promoters of TNF, CRP, and CCL2.

Crawford et al. (2018) argue that this discrepancy may be due to the fact that not all patients with depression exhibit inflammation, and environmental factors and gene-environment interactions are likely more critical than purely genetic factors in explaining depression. Moreover, these same genetic variants also increase the risk of inflammation-related metabolic diseases.

Overall, these findings support the view that epigenetic profiles of inflammatory genes in PED may provide valuable insights into the immune biology of PED.

Moreover, mental disorders such as anxiety and depression have become increasingly prevalent. The World Health Organization (WHO) recommends that Central Asian countries integrate mental health care into primary care services to improve access to psychiatric care.

On April 25–26, 2023, the Ministry of Health of Uzbekistan and the WHO Regional Office for Europe held an interregional policy dialogue in Tashkent on strengthening mental health services and reducing stigma. During the event, it was noted that mental disorders are widespread, with approximately 1 in 7 people suffering from a mental illness. Recent events, including stress caused by the COVID-19 pandemic and the current cost-of-living crisis, have further impacted people's mental well-being (https://www.gazeta.uz/ru/2023/04/25/mental-health/).

According to a study by Golimbeta V.I. et al. [15,16], the (C-589T) polymorphism of the IL-4 gene is more strongly associated with depression than with ischemic heart disease (IHD). However, major studies have shown that the (C-589T) polymorphism of the IL-4 gene is more commonly associated with IHD than with depression. In the studies by Golimbeta V.I. et al. [16], no association was found between TNF-α and CRP genes and depression, although some immunological studies suggest a possible link.

Studies conducted by Bing-Jian Wang and colleagues have shown that the C/T 819 polymorphism of the IL-10 gene is more frequently observed in patients with ischemic heart disease (IHD), hypertension, hyperuricemia, diabetes mellitus, peptic ulcer disease, and liver diseases. Additionally, researchers noted that cases of this polymorphism are more common in patients over the age of 57.

Research by Huang et al. demonstrated that the presence of the 511T allele in the promoter region of human IL-1 is associated with the development of arterial hypertension [145]. Furthermore, Kanae Oda et al. stated that the -511T allele of the IL-1β gene is linked to increased IL-1β protein production, according to ex vivo blood stimulation analysis, and that the -511T allele is a risk factor for atherogenesis in the subclavian artery. However, data on the relationship between polymorphisms in the G-308A TNF-α, 511 T/C IL-1β, C/T -589 IL-4, and C/T -819 IL-10 genes in patients with unstable angina and asymptomatic hyperuricemia, depending on the presence of anxiety-depressive syndrome, remain unexplored.

In studies by Kazemi E et al., it was found that the frequency of G-308A TNF-α AA or AG genotypes was significantly lower in patients classified as having IHD, with obstruction of ≥ or <50% in at least one coronary artery, compared to the control group. They observed that IHD patients with ≥50% stenosis and the AA genotype had a higher risk of IHD, with an odds ratio (OR) of 3.56 (95% CI: 1.02–12.41; P = 0.046) in multivariate analysis [146].

A.B. Smulevich et al. [52] proposed a model of depression that expands the search for biological determinants of this condition, considering the complexity of its etiology and pathogenesis. According to this model, genetic predisposition plays a key role not only in the functioning of the neurotransmitter system but also in the response to stress factors, taking into account the immune response.

For the first time, V. Smith [198] and T.V. Lezhayko [37] established a link between depression and cytokine imbalance, including IL-1. When IL-1, IL-6, and TNF-α were administered to animals, the development of behavioral disturbances resembling depressive reactions was observed.

In our study, we analyzed the distribution of allele and genotype frequencies of polymorphic variants in pro- and anti-inflammatory cytokine genes, such as G-308A TNF-α, 511 T/C IL-1β, C/T -589 IL-4, and C/T -819 IL-10, which may contribute to the hereditary susceptibility to IHD associated with anxiety-depressive disorders (ADD) and asymptomatic hyperuricemia (AHU).

As a result of our own clinical and laboratory study, the following distribution of allele frequencies and genotypes of the T/C polymorphism of the IL-1ß gene in patients with UA with AHU and PED was revealed: markers of an increased risk of developing UA with AHU and PER are the A/A genotype of the G-308A polymorphic locus of the TNF-a gene and the T/T genotype of the IL-10 gene. Important results were also obtained in the study of the relationship between G-308A of the TNF-a gene, 511 T/C of the IL-1B gene, C/T -589 of the IL-4 gene, C/T -819 of the IL-10 gene with the level of uric acid, the level of anxiety, Total LDL-C, proinflammatory and anti-inflammatory cytokines, the association of which is of significant importance in the progression of cardiovascular diseases.

Thus, the results of the conducted study, state that polymorphism G-308A (rs1800629) of the TNF-a gene, 511 (rs16944) of the IL-1ß gene, C/T-589 (rs2243250) of the IL-4 gene, C/T-819 (rs1800871) of the IL-10 gene in NS with PER, as well as without PER, apparently, can allow us to speak about these genes not as candidates, but as precursor genes in the formation of hereditary predisposition to the development and destabilization of coronary heart disease.

Currently, one of the most promising tools for clinical practice and an applied instrument of personalized medicine is pharmacogenetic testing. There is significant interpatient variability in drug response, most of which has a genetic basis. In particular, genotype can influence drug metabolism, drug transport, and individual sensitivity to a drug. Pharmacogenetics involves the application of DNA sequence data to predict drug response and inform drug discovery and development. To date, cardiovascular pharmacogenetics has primarily focused on genetic variants relevant to existing treatments. However, examples of pharmacogenetic applications for the discovery and development of cardiovascular drugs are beginning to emerge. The recent creation of the Encyclopedia of DNA Elements (ENCODE), which describes the biochemical functions of 80% of the components in the human genome, is expected to deepen our understanding of the genetic contribution to the pharmacokinetics and pharmacodynamics of cardiovascular drugs and lead to new targets for drug development.

Pharmacogenetics enables the prediction of drug response based on a person's DNA and facilitates appropriate treatment, or personalized medicine. Pharmacogenetic testing identifies variations in pharmacological response associated with patients' genetic characteristics [5]. Genetic traits arise due to nucleotide substitutions in the DNA molecule, which play different roles in the pharmacodynamics or pharmacokinetics of drugs [36]. Identifying such substitutions allows for the prediction of pharmacological response and, consequently, a personalized approach to selecting the drug and its dosage [13].

The use of pharmacogenetic testing is considered appropriate when the frequency of polymorphisms in the studied gene exceeds 20% of cases [15].

Ultimately, it may become possible to apply pharmacogenetics on a broader scale to determine the best combination of drugs for treating complex diseases such as heart failure; however, pharmacogenetics in this regard is still in its early stages. Therefore, the safety and efficacy of pharmacotherapy remain a pressing and unresolved issue today. All the aforementioned aspects have served as the main prerequisites for conducting this study.

It is important to emphasize that, for the first time in our region, the influence of allele variants G-308A (rs1800629) of the **TNF-α** gene, 511C/T (rs16944) of the **IL-1β** gene, -589C/T (rs2243250) of the **IL-4** gene, and -819C/T (rs1800871) of the **IL-10** gene on the course of ischemic heart disease (IHD) associated with psycho-emotional disorders and without them has been studied.

The results of our pharmacogenetic studies indicate that the efficacy of pharmacotherapy with standard therapy + Fluoxetine is generally higher in patients with unstable angina (UA) associated with psycho-emotional disorders who are carriers of the heterozygous **C/T** and homozygous **T/T** variants of the -511C/T (rs16944) polymorphic locus of the **IL-1β** gene, the homozygous **A/A** genotype of the **G308A** (rs1800629) polymorphism of the **TNF-α** gene, as well as the heterozygous **C/T** and homozygous **T/T** variants of the -819C/T (rs1800871) polymorphic locus of the **IL-10** gene, compared to carriers of the normal **C/C** homozygous genotype. This suggests a pronounced pharmacodynamic effect on the synthesis of pro-inflammatory cytokines, which, in turn, contribute to the development of endothelial dysfunction and left ventricular myocardial remodeling. In conclusion, as part of our study, we have developed an innovative approach—a computer program titled **"Prediction of Coronary Heart Disease Based on Psycho-Emotional State"**—designed for assessing and managing patients with ischemic heart disease (IHD). This program enables a multifactorial assessment of the interconnected influence of socio-anamnestic, psycho-emotional, laboratory (specifically immunological and atherosclerotic) factors, as well as cardiovascular risk, on the level of adherence to primary therapy in IHD patients with various risk factors.

The practical application of the study's findings, in the form of implementing this software in hospitals, has the potential to enhance both economic efficiency and personalized therapy for IHD patients seeking medical care. This is expected to contribute to an increase in life expectancy by reducing the incidence of diseases and their complications.

## CONCLUSIONS

1. The analysis of the prevalence of cardiovascular disease (CVD) risk factors showed that independent psycho-emotional risk factors, such as anxiety and depression in patients with ischemic heart disease (IHD), are often associated

with smoking (69 cases, 27.4%), hyperuricemia (118 cases, 47.0%), high-grade arterial hypertension (172 cases, 68.5%), and excess body weight (164 cases, 65.3%). These associations contribute to a decrease in patients' quality of life and a significant worsening of the clinical course of IHD.

2. A detailed analysis of psycho-emotional status using the HADS questionnaire revealed psycho-emotional disorders (PED) in 58.5% of cases, indicating a high prevalence of affective conditions in cardiac pathology. Assessment of PED severity using the HADS scale identified 44.2% of cases with subclinical depression, 55.7% with clinical depression, 35.5% with subclinical anxiety, and 59.0% with clinical anxiety among patients with unstable angina (UA) and PED, emphasizing the need for strict monitoring and timely detection of PED in every CVD patient.
3. A direct relationship was established between atherosclerotic coronary artery disease and the development of PED. When comparing coronary artery (CA) lesions in patients with UA and PED (n=180) versus those with UA without PED (n=89), three or more CA lesions were found in 59 patients (32.7%) with PED, compared to only 10 patients (11.2%) without PED.
4. Lack of treatment compliance was identified in 38 UA patients, among whom 18 non-compliant patients carried the homozygous **T/T** genotype of the **511 T/C (rs16944)** polymorphism of the **IL-1β** gene. Additionally, 32 patients had psycho-emotional disorders, indicating that the homozygous **T/T** genotype of the **511 T/C (rs16944)** polymorphism of the **IL-1β** gene poses a potential risk for cardiovascular complications.
5. The use of **Fluoxetine** in addition to standard therapy for patients with unstable angina combined with anxiety and depression is associated with improved clinical and functional status, enhanced quality of life, and a significant reduction in the risk of hospitalization due to angina destabilization. A 3–4 week course of Fluoxetine does not affect high-resolution electrocardiographic parameters or structural-functional myocardial parameters. Improvement in psycho-emotional state was observed. The drug is well tolerated by patients, with no occurrence of severe or potentially dangerous adverse effects.

6. The analysis of pro- and anti-inflammatory cytokine genes revealed a high frequency of the mutant **T** allele in the **C511T (rs16944)** polymorphism of the **IL-1β** gene (50.5%), the **A** allele in the **G308A (rs1800629)** polymorphism of the **TNF-α** gene (55.1%), the **C** allele in the **C589T (rs2243250)** polymorphism of the **IL-4** gene (62.1%), and the **T** allele in the **C819T (rs1800871)** polymorphism of the **IL-10** gene (35.1%). These genetic variations contributed to the destabilization of coronary heart disease.
7. A strong correlation was established between carriers of the **T/T** homozygous and **C/T** heterozygous genotypes of the **511C>T (rs16944)** polymorphism of the **IL-1β** gene and the levels of situational (**r=0.660, p≤0.01**) and trait anxiety (**r=0.657, p≤0.01**) on the Spielberger-Khanin scale. A moderate correlation

was found between carriers of the **-589C/T (rs2243250)** polymorphism of the **IL-4** gene and the **-819C/T (rs1800871)** polymorphism of the **IL-10** gene.

8. The developed software identified **44.4%** of patients as being at high risk for the destabilization of ischemic heart disease. Among them, **54 patients (61.3%)** were carriers of the **T/T** homozygous genotype in the **511 T/C (rs16944)** polymorphism of the **IL-1β** gene, and **28 patients (14.1%)** carried the **T/T** genotype in the **819 C/T (rs1800871)** polymorphism of the **IL-10** gene. This category of patients exhibited both clinically and laboratory-confirmed severe disease progression with frequent angina attacks, necessitating strict monitoring and timely treatment to reduce fatal outcomes.

## PRACTICAL RECOMMENDATIONS

1. Patients with ischemic heart disease (IHD) are recommended to undergo screening using the **HADS** and **Spielberger-Khanin** scales to identify psycho-emotional disorders, ensuring timely diagnosis, prevention of IHD destabilization, and reduction of cardiovascular complications.
2. Individuals with **chronic coronary heart disease** who, during routine examination, are found to have clinically significant anxiety or depression scoring **more than 10 points on the HADS scale** and **more than 40 points on the Spielberger-Khanin scale** should be classified as a high-risk group for psycho-emotional disorders, with a potential risk of IHD destabilization and the development of cardiovascular complications.
3. In **patients with unstable angina**, those with severe psycho-emotional disorders exceeding **12 points on the HADS scale** and **55 points or more on the Spielberger-Khanin scale** are more likely to experience **cardiovascular complications** and more severe **anginal attacks**, which are difficult to manage with standard therapy. This should be considered when planning patient management strategies, including the necessity of performing **coronary angiography within 24 hours of hospitalization**.
4. Given the **critical role of psycho-emotional status** in the pathogenesis of unstable angina, it is essential to include **psycho-emotional disorder correction** in the treatment regimen. In addition to standard therapy, the **selective serotonin reuptake inhibitor (SSRI) Fluoxetine** is recommended for patients with psycho-emotional disorders. Its inclusion enhances treatment efficacy for unstable angina by **reducing the number and duration of ischemic episodes**.
5. A **personalized treatment approach** for patients with unstable angina associated with anxiety-depressive syndrome, or isolated unstable angina, should consider **genetic testing results**, specifically:
    - **G308A (rs1800629) of the TNF-α gene**
    - **C/T 511 (rs16944) of the IL-1β gene**

- **C/T 589 (rs2243250) of the IL-4 gene**
- **C/T 819 (rs1800871) of the IL-10 gene**
  The presence of **T/T homozygous polymorphism of the IL-1β gene**, **C819T polymorphism of the IL-10 gene**, **A/A homozygous variant of the TNF-α gene**, and **C/C genotype of the IL-4 gene** is considered **mutant**, requiring special monitoring during treatment.

6. The developed **software model** is recommended for use in **clinical cardiology and therapy practice** to improve early diagnosis of **IHD destabilization, treatment effectiveness, prevention strategies, and overall quality of life**, particularly in the presence of **psycho-emotional disorders**.

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