

# The Role Of Inflammatory Processes In The Pathogenesis Of Cardiovascular Diseases

David ShirinO'g'li Asanov<sup>1</sup>, Abdul-Malik Movladiyevich Sugaipov<sup>2</sup>, Elizaveta Evgenevna Stebunova<sup>3</sup>, Sultan Shamilevich Lakhialov<sup>4</sup>, Saida Ruslanovna Ataeva<sup>5</sup>, Islam Daudovich Abdulkadyrov<sup>6</sup>, Sakhiba Alibalakzy Kerimova<sup>7</sup>

<sup>1</sup>Branch of the Federal State Autonomous Education Institution of Higher Education "Kazan (Volga region) Federal University" in the city of Jizzakh of Republic of Uzbekistan.

Republic of Uzbekistan, Jizzakh, Jizzaklikmahallya, 295 Sharaf Rashidov street. 130100. Jizzakh Branch of the Republican Specialized Scientific-Practical Medical Center of Cardiology. Republic of Uzbekistan, Jizzakh, 100052, ORCID: 0000-0002-8723-703X, Email:david.asanov.2018@gmail.com

<sup>2</sup>Federal State Budgetary Educational Institution of Higher Education «Kabardino-Balkarian State University named after H.M. Berbekov», 173 Chernyshevsky St., 360004, Email:maliksugaipov5@gmail.com, 0009-0006-3419-8715

<sup>3</sup>Voronezh State Medical University named after N. N. Burdenko, 12 Studencheskaya St., 394036, Email:stebunovaaa@yandex.ru, 0009-0003-6721-2817

<sup>4</sup>Astrakhan state medical university, Bakinskaya Street, 121, 414000, Email:sultan344@bk.ru, 0000-0002-9660-4954

<sup>5</sup>Astrakhan State Medical University, Bakinskaya 121, 414000, s Email:aidasaida10505@gmail.com, 0009-0004-0562-9366

<sup>6</sup>Astrakhan State Medical University, Bakinskaya 121, 414000, 0009-0000-6339-878X, Email:Islamabdulkadyrov502@mail.ru

<sup>7</sup>Astrakhan State Medical University, Bakinskaya 121, 414000, Email:sakhiba.kerimova@mail.ru, 0009-0007-4465-7791

## ABSTRACT

The aim of this study was to evaluate the role of systemic inflammation in the development of cardiovascular risk in patients with atherosclerotic disease and to identify associations between inflammatory marker levels and clinical and functional characteristics.

The study included 130 patients with established atherosclerotic cardiovascular disease. All participants underwent clinical and laboratory examinations, assessment of traditional risk factors, determination of high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6), and calculation of integrated cardiovascular risk.

It was shown that elevated hs-CRP and IL-6 levels were significantly associated with the severity of atherosclerotic lesions and a higher level of cardiovascular risk. Patients with high hs-CRP tertiles were more likely to have advanced coronary artery disease and episodes of disease destabilization. In a multivariate model, hs-CRP and IL-6 retained independent prognostic significance after accounting for age, gender, smoking status, and hypertension.

These results support the concept of inflammation as a key link in the pathogenesis of atherosclerosis and associated clinical events and highlight the usefulness of incorporating inflammatory markers into broader cardiovascular risk stratification.

**Keywords:** systemic inflammation, atherosclerosis, cardiovascular disease, C-reactive protein, interleukin-6, cardiovascular risk, biomarkers.

## INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of death and disability worldwide. Despite significant progress in modifying classic risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking, residual cardiovascular risk remains high, stimulating the search for additional pathogenetic mechanisms and therapeutic targets.

Over the past decades, the concept of atherosclerosis as a chronic inflammatory process of the vascular wall has emerged [11]. Activated immune cells, endothelial cells, and smooth muscle cells produce a wide range of cytokines and inflammatory mediators that promote endothelial activation, impaired lipid metabolism, macrophage migration, and the formation of unstable atherosclerotic plaques. Particular attention is paid to the

role of interleukin-6 (IL-6) as a key cytokine initiating the synthesis of acute-phase proteins in the liver and participating in the modulation of multiple components of the immune response [13].

High-sensitivity C-reactive protein (hs-CRP), one of the main acute-phase proteins, acts not only as a marker of systemic inflammation but also as a potential participant in atherogenesis. Numerous studies have shown that elevated hs-CRP levels are associated with an increased risk of myocardial infarction, stroke, and other major cardiovascular events in both patients with established atherosclerosis and individuals without clinically manifest atherosclerosis.

Current evidence suggests that inflammatory markers reflect so-called "residual inflammatory risk," which may persist even when target low-density lipoprotein cholesterol levels are achieved and blood pressure is adequately controlled [12]. This concept has served as the basis for studies evaluating the effects of targeted anti-inflammatory therapy on the incidence of cardiovascular events.

However, in real-world clinical practice, the practical use of inflammatory markers for risk stratification and monitoring remains controversial. Data are needed on the relationship between hs-CRP and IL-6 and the clinical and functional characteristics of specific patient populations, as well as their independent prognostic significance, taking into account traditional risk factors.

Again, it is of interest to study the role of inflammatory processes in the pathogenesis and clinical course of CVD in a sample of patients receiving standard therapy but retaining varying levels of residual risk.

## **MATERIALS AND METHODS**

The analysis included 130 patients aged 40 to 75 years, consecutively hospitalized in the cardiology department for stable coronary artery disease or other clinical forms of atherosclerotic cardiovascular disease (myocardial infarction, angina, atherosclerotic peripheral arterial disease).

Inclusion criteria included documented atherosclerotic cardiovascular disease, patient consent, and the ability to undergo a full clinical and laboratory examination. Exclusion criteria included acute coronary syndrome within the past month, severe chronic inflammatory or autoimmune diseases, active cancer, acute infections, and severe liver or kidney failure, which could significantly affect inflammatory marker levels. All patients underwent a standard clinical examination, including a medical history, assessment of complaints, blood pressure measurement, height, and weight measurement (calculation of body mass index), and recording of traditional risk factors (smoking, diabetes, hypertension, dyslipidemia, and a family history of early CVD). Laboratory tests included determination of total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides, fasting plasma glucose, creatinine, and complete blood count values.

Particular attention was paid to assessing systemic inflammatory markers. hs-CRP levels were determined using a highly sensitive immunoturbidimetry method, with results expressed in mg/L. IL-6 levels were measured using an enzyme-linked immunosorbent assay (ELISA), with results expressed in pg/mL. To further characterize the inflammatory status, the neutrophil-to-lymphocyte ratio was calculated based on complete blood count data. hs-CRP and IL-6 were selected based on their proven association with cardiovascular risk and atherosclerotic inflammatory activity.

The severity of coronary atherosclerotic disease was assessed using coronary angiography data, including the number of affected vessels and the presence of hemodynamically significant stenoses. Additionally, an integrated risk score was calculated based on accepted scales, including age, gender, blood pressure, lipid profile, and the presence of concomitant diabetes.

To analyze associations between inflammatory markers and disease characteristics, patients were stratified by hs-CRP and IL-6 tertiles. Within-group differences in quantitative variables were assessed using parametric and nonparametric tests depending on the distribution, while categorical variables were analyzed using the  $\chi^2$  test. Correlations between hs-CRP, IL-6, and clinical and laboratory parameters were assessed using the Spearman test.

To assess the independent prognostic value of inflammatory markers for advanced atherosclerotic disease and high cardiovascular risk, multivariate logistic regression was used, including age, gender, smoking status, hypertension, and LDL cholesterol levels. Statistical significance was set at  $p < 0.05$ .

## RESULTS AND DISCUSSION

The clinical characteristics of the study group are presented in Table 1. The mean age of patients was  $61.2 \pm 8.5$  years, and 58.5% were men. Hypertension was detected in 78.5% of patients, type 2 diabetes mellitus in 32.3%, and active smoking in 41.5%. The mean body mass index was overweight. According to lipid profile data, dyslipidemia persisted in a significant proportion of the study subjects despite statin use.

**Table 1. Clinical and demographic characteristics of patients (n = 130)**

Indicator	Meaning
Age, years	$61,2 \pm 8,5$
Men, %	58,5
Arterialhypertension, %	78,5
Type 2 diabetes, %	32,3
Activesmoking, %	41,5
Body mass index, kg/m <sup>2</sup>	$28,6 \pm 4,2$
Totalcholesterol, mmol/L	$5,2 \pm 1,1$
LDL cholesterol, mmol/L	$3,0 \pm 0,9$
HDL cholesterol, mmol/L	$1,1 \pm 0,3$
Triglycerides, mmol/L	$1,8 \pm 0,7$
Previousmyocardialinfarction, %	36,9
Multivesselcoronaryarterydisease, %	44,6

The average hs-CRP level in the overall group was  $3.4 \pm 2.1$  mg/L, and IL-6 was  $4.8 \pm 2.7$  pg/mL. When stratifying patients by hs-CRP tertiles, it was found that the group with the highest values (tertile III) more often had multivessel coronary artery disease, a higher level of integrated cardiovascular risk, and a higher frequency of episodes of destabilization of coronary artery disease over the past year. Similar trends were noted when analyzing IL-6.

**Table 2. Levels of inflammatory markers and signs of disease severity depending on hs-CRP levels**

Indicator	I tertile hs-CRP ( $\leq$ 1.5 mg/l)	II tertile hs-CRP (1.6–3.0 mg/L)	III tertile hs-CRP ( $>$ 3.0 mg/l)	p
Numberofpatients, n	43	44	43	
hs-CRP, mg/L	$0,9 \pm 0,4$	$2,2 \pm 0,4$	$5,4 \pm 1,6$	<0,001
IL-6, pg/ml	$3,1 \pm 1,4$	$4,5 \pm 2,0$	$6,5 \pm 2,5$	<0,001
Multivesseldisease, %	27,9	40,9	62,8	0,004
Highintegratedrisk*, %	34,9	52,3	74,4	<0,001
Episodes of coronary artery disease destabilization per year, %	16,3	27,3	44,2	0,01

\*High integrated risk is the upper quintile of the risk scale in the study sample.

Figure 1 shows the proportion of patients with high cardiovascular risk depending on the hs-CRP tertiles. It is clear that as hs-CRP levels increase, the proportion of patients at high risk increases from 20% in the first tertile to 55% in the third tertile, reflecting a clear gradient relationship between risk and the intensity of the inflammatory response.

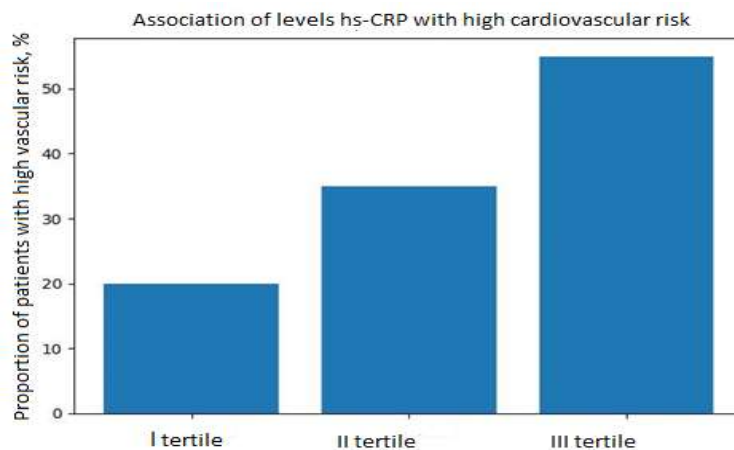


Figure 1. Association of hs-CRP Levels with High Cardiovascular Risk

To assess the independent role of inflammatory markers, a multivariate logistic model was constructed, including age, gender, smoking, hypertension, LDL cholesterol, hs-CRP, and IL-6. The outcome was the presence of severe atherosclerotic disease (multivessel coronary artery disease and/or high integrated risk).

**Table 3. Multivariate Analysis of Predictors of Severe Atherosclerotic Disease**

Indicator	Oddsratio (OR)	95 % CI	p
Age (per 10 years)	1,35	1,02–1,79	0,03
Malegender	1,28	0,72–2,29	0,40
Activesmoking	1,81	1,02–3,22	0,04
Arterialhypertension	1,67	0,88–3,15	0,12
LDL cholesterol, mmol/L	1,42	1,05–1,93	0,02
hs-CRP (per 1 mg/L)	1,19	1,05–1,34	0,006
IL-6 (per 1 pg/mL)	1,14	1,02–1,27	0,02

According to the presented model, hs-CRP and IL-6 demonstrate an independent association with severe atherosclerotic disease after accounting for key traditional risk factors. An increase in hs-CRP by just 1 mg/L was associated with a 19% increase in the odds of severe coronary disease, while an increase in IL-6 by 1 pg/mL was associated with a 14% increase. These results are consistent with data from large epidemiological studies, in which higher levels of inflammatory markers were associated with an increased risk of myocardial infarction, stroke, heart failure, and all-cause mortality.

The identified links between hs-CRP, IL-6, and the severity of atherosclerotic disease confirm the pathogenetic role of chronic low-grade inflammation in the progression of CVD. Elevated IL-6 concentrations reflect activation of cellular components of the immune system and the endothelium, leading to increased expression of adhesion molecules, increased prothrombotic potential, and the formation of unstable plaques. hs-CRP, a product of the liver's response to IL-6 stimulation, acts as an integral marker of inflammatory cascade activity.

An important practical aspect is the feasibility of routinely determining hs-CRP and IL-6 in clinical practice. International guidelines and large observational studies indicate that hs-CRP can be used as an additional risk stratification factor, particularly in intermediate-risk patients, and for assessing residual inflammatory risk in patients with established CVD [2].

It should be emphasized that the interpretation of elevated hs-CRP and IL-6 values should be conducted taking into account possible concomitant conditions that can cause a transient increase in markers (infections, injuries, exacerbation of chronic inflammatory diseases). Repeated determinations in cases of questionable or borderline values, as well as an assessment of changes with lifestyle modification and drug therapy, appear optimal. In this context, studies demonstrating a reduction in the incidence of cardiovascular events with anti-inflammatory and immunomodulatory therapy aimed at blocking cytokine pathways, including IL-1 $\beta$ /IL-6, are of interest.

The results of this study confirm the key role of chronic systemic inflammation in the development of residual cardiovascular risk and allow for the formulation of a number of recommendations regarding both further scientific research and the implementation of the obtained data in clinical practice. Of particular importance is the integration of hs-CRP and IL-6 assessment into risk stratification algorithms and the management of patients with atherosclerotic cardiovascular diseases at the level of large specialized centers and in the daily practice of cardiology departments.

Further research should be focused on prospective patient observation with an assessment of the dynamics of inflammatory markers and clinical outcomes. Unlike the cross-sectional design used in this study, a prospective approach will allow for a more precise determination of the causal relationships between hs-CRP and IL-6 levels and the risk of adverse events, as well as the impact of changes in inflammatory status on prognosis. Such studies would be logically conducted at large federal and multidisciplinary cardiology centers, where standardized laboratory monitoring and long-term patient follow-up are available.

The E. I. Chazov National Medical Research Center of Cardiology of the Russian Ministry of Health, located in Moscow, is a leading specialized institution in the country, combining clinical and research activities in the field of cardiovascular diseases.

Randomized trials aimed at assessing the impact of anti-inflammatory interventions on hs-CRP and IL-6 levels and the incidence of cardiovascular events appear promising. Such protocols could utilize both classical anti-inflammatory strategies and targeted approaches targeting individual components of the cytokine cascade [10]. Specialized research institutes and centers with experience in conducting clinical trials and the appropriate infrastructure, including cardiology departments at federal centers and university clinics in Moscow, could be suitable venues for the development and implementation of such studies. The E. I. Chazov National Medical Research Center of Cardiology, with its long-standing tradition of fundamental and clinical research into atherosclerosis and coronary heart disease, appears to be the most logical base for such projects, ensuring a sufficient sample size and a high level of methodological oversight.

The issue of integrating hs-CRP and IL-6 assessment into clinical practice in the daily work of cardiology hospitals and outpatient departments deserves special attention [1]. Based on the data obtained, it is advisable to consider hs-CRP determination as an additional element of an expanded risk assessment in patients with intermediate and high cardiovascular risk, as well as in patients with established coronary heart disease, when planning secondary prevention. Large city multidisciplinary hospitals with cardiology departments and functional and laboratory diagnostics departments, as well as specialized cardiology centers in Moscow, could be selected for the implementation of this approach. In these circumstances, it is possible to implement standard diagnostic panels including hs-CRP, with subsequent integration of this indicator into local patient management protocols.

An important area of research is the development of a patient routing system for patients with a high residual inflammatory risk [7]. Patients who, upon repeated measurements, show persistently elevated hs-CRP and IL-6 levels despite seemingly adequate correction of traditional risk factors can be considered candidates for more intensive monitoring, more frequent laboratory testing, and assessment of the need for therapy modification. To implement such a routing system, it is advisable to utilize the structure of regional vascular centers, cardiologist offices in city clinics, and specialized outpatient departments of federal centers. In Moscow, a similar approach could be tested in the cardiology clinic of a large multidisciplinary center or in the consultative and diagnostic units of the National Medical Research Center of Cardiology, which include outpatient consultations and post-inpatient follow-up.

Clinical units and research groups. To ensure comparability of results and accurate data interpretation, it is necessary to standardize methods for determining hs-CRP and IL-6, unify blood collection and sample storage conditions, and ensure regular internal and external quality control [6]. These tasks can best be addressed in large centers where laboratories have sufficient research capacity and participate in external quality assessment programs [4]. Furthermore, the results obtained at the federal level can be translated into smaller clinics and outpatient clinics using standard guidelines.

A promising direction for future research is to study the relationship between inflammatory markers and new biomarkers of vascular remodeling, thrombo-inflammation, and endothelial dysfunction [8]. The combination of hs-CRP and IL-6 with markers reflecting the state of the coagulation system and microvascular bed may enable

the development of more accurate multi-biomarker risk stratification models applicable both at the primary prevention stage and in patients with established coronary artery disease. Such projects require the participation of interdisciplinary teams, including cardiologists, clinical pharmacologists, laboratory diagnostic specialists, and biostatisticians. Therefore, it is logical to initiate them at academic and university centers in Moscow and other major cities, with the possibility of subsequently expanding the geographic scope of the study.

Equally important is the development of educational programs for physicians of various specialties aimed at deepening the understanding of the role of inflammation in the pathogenesis of CVD and the practical aspects of interpreting hs-CRP and IL-6 [3]. Conducting continuing professional education courses, master classes, and schools for cardiologists, internists, and general practitioners will increase awareness of the concept of residual inflammatory risk and promote the broader and more informed use of inflammatory markers in clinical practice. Such programs can be organized by federal centers and specialized departments of medical universities, including departments based at the National Medical Research Center of Cardiology and other leading Moscow clinics, which have experience conducting educational events and access to modern evidence.

Table 4 below presents recommendations for further research and implementation of inflammatory marker assessment.

**Table 4. Practical recommendations and potential implementation sites.**

Direction	Content of the recommendation	Level of implementation	Possible site (example)
Scientific research (prospective cohort observations)	Organization of prospective studies with long-term observation of patients with atherosclerotic CVD with regular determination of hs-CRP and IL-6 and registration of clinical outcomes to clarify the prognostic significance of markers	Federal and large regional cardiology centers, university clinics	National Medical Research Center of Cardiology named after Academician E. I. Chazov (Moscow)
Randomized clinical trials	Design and implementation of randomized trials evaluating the impact of anti-inflammatory therapy on hs-CRP, IL-6 levels, and cardiovascular event rates in high-risk patients	Research institutes, clinical trial centers, cardiology departments of multidisciplinary hospitals	Institute of Clinical Cardiology of the National Medical Research Center of Cardiology, clinical sites of the cardiology departments of Moscow medical universities
Implementation of hs-CRP into clinical protocols	Inclusion of hs-CRP determination in expanded algorithms for assessing cardiovascular risk in patients with intermediate and high risk and in secondary prevention, with subsequent consideration of the indicator when choosing the volume of therapy	Cardiology departments of city and regional hospitals, specialized centers, outpatient departments	Cardiology departments of multidisciplinary hospitals in Moscow, consultative and diagnostic departments of the National Medical Research Center of Cardiology
Routing of patients with high residual inflammatory risk	Formation of routes for patients with persistently elevated hs-CRP and IL-6: more frequent monitoring, in-depth examination, possible consultation at a highly specialized center	Regional vascular centers, cardiology offices of outpatient clinics, federal centers	City vascular centers, outpatient services of the National Medical Research Center of Cardiology and other cardiology clinics in Moscow
Standardization of laboratory diagnostics	Unification of methods for determining hs-CRP and IL-6, standardization of conditions for collecting and storing samples, participation of laboratories in external quality control programs	Laboratories of large hospitals, interlaboratory centers	Central Clinical Diagnostic Laboratory of the National Medical Research Center of Cardiology, reference laboratory of Moscow
Educational programs for doctors	Development of DPO courses, schools and seminars for cardiologists, therapists and general practitioners on the role of inflammation, interpretation of hs-CRP and IL-6 and the concept of residual inflammatory risk	Federal centers, departments of cardiology and therapeutic disciplines of medical universities, professional societies	Cardiology departments at the National Medical Research Center of Cardiology, leading Moscow clinics, and the Russian Society of Cardiology in collaboration with Moscow centers

Thus, recommendations for further research and implementation of inflammatory status assessments can be logically divided into several levels. At the level of basic and clinical research, prospective and interventional studies aimed at clarifying the role of hs-CRP and IL-6 and assessing the effectiveness of anti-inflammatory

therapy remain a priority. At the level of medical care organization, the inclusion of hs-CRP in expanded risk scores and the creation of pathways for patients with high residual inflammatory risk are key. At the educational level, it is advisable to develop programs aimed at developing a robust understanding of the concept of inflammation in cardiology among physicians. The E. I. Chazov National Medical Research Center of Cardiology, which has the necessary clinical, laboratory, and research facilities, could serve as a specific platform for piloting these approaches in Moscow, with subsequent dissemination of the developed algorithms to city hospitals and clinics. The results of this study demonstrate that integrating inflammatory markers into a cardiovascular risk assessment system allows for a more precise identification of a subgroup of patients with advanced atherosclerotic disease and a poor prognosis. These patients may be candidates for more aggressive management strategies, including intensification of lipid-lowering and antithrombotic therapy, and, potentially, targeted anti-inflammatory interventions. However, these data should be considered illustrative of the approach; definitive conclusions require larger prospective studies with hard clinical endpoints.

## CONCLUSION

Chronic systemic inflammation plays a key role in the pathogenesis of atherosclerosis and the clinical manifestation of cardiovascular disease. In a sample of 130 patients, higher levels of hs-CRP and IL-6 were associated with a greater degree of atherosclerotic coronary artery disease, higher integrated cardiovascular risk, and a higher frequency of episodes of disease destabilization. In a multivariate analysis, hs-CRP and IL-6 retained independent prognostic significance after accounting for age, gender, and traditional risk factors, confirming their role as markers of residual inflammatory risk.

These data support the concept of inflammation as a central component of CVD pathogenesis and substantiate the inclusion of inflammatory markers in expanded cardiovascular risk stratification algorithms, particularly in patients with atherosclerotic disease and intermediate risk.

These recommendations demonstrate that hs-CRP and IL-6 assessment can serve as a practical tool for advanced cardiovascular risk stratification and the identification of patients with high residual inflammatory risk. Implementation of these approaches is most appropriate in large federal and city cardiology centers, including the National Medical Research Center of Cardiology in Moscow, where standardized testing, patient routing, and updated protocols can be implemented. A comprehensive combination of research projects, clinical practice, and educational programs provides the basis for the gradual inclusion of inflammatory markers in the routine care of patients with atherosclerotic cardiovascular diseases.

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