DOI: https://doi.org/10.17816/brmma626848

Non-lipid genetic predictors of the development of coronary heart disease and myocardial infarction in patients with hypertension

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ABSTRACT

The associations between the main non-lipid genomic biomarkers and coronary heart disease occurrence and the unstable course of the disease with the development of myocardial infarction in 164 patients with stage I–III hypertension were investigated. The study was conducted in two stages. At the first stage, the non-lipid genetic predictors of coronary heart disease were determined without considering the characteristics of its clinical course. At the second stage, the possibility of identifying genetic predictors of the complicated course of coronary heart disease with the development of myocardial infarction was studied. In hypothesis testing, the difference was considered significant at $p < 0.05$. It was found that the presence of coronary heart disease in patients with hypertension was associated with a significant predominance of genetic biomarkers in four single-nucleotide polymorphisms: in the hemostasis system (4G4G *SERPINE 1*), pro-inflammatory cytokines (T allele *IL-1b-511*, C allele *IL-1b-1473*), and innate immunity (FF *TLR3-412*). The development of myocardial infarction was associated with two genetic polymorphisms: pro-inflammatory cytokine system (CC *IL-6-174*) and hemostasis (4G4G *SERPINE 1*). In general, among the single-nucleotide polymorphisms studied, statistically significant results in predicting coronary heart disease were demonstrated by genetic biomarkers of the hemostatic system, pro-inflammatory cytokines, and innate immunity. In relation to myocardial infarction, genetic biomarkers of the hemostatic system and pro-inflammatory cytokines may have prognostic value. The use of genetic biomarker data as unfavorable prognosis predictors in patients with hypertension enables better risk stratification and assessment of the prognosis in these patients, which will significantly reduce the costs of conducting a genome-wide study.

Keywords: coronary heart disease; myocardial infarction; cardiovascular complications; cardiovascular risk; genetic biomarkers; single nucleotide polymorphisms; low-intensity inflammation; non-modifiable risk predictors.

To cite this article

Tyuryupov MS, Shulenin KS, Cherkashin DV, Svyoklina TS, Kutelev GG, Mirzoev NT. Non-lipid genetic predictors of the development of coronary heart disease and myocardial infarction in patients with hypertension. *Bulletin of the Russian Military Medical Academy.* 2024;26(2):197–206. DOI: https://doi.org/10.17816/brmma626848

Received: 13.02.2024 **Accepted:** 13.04.2024 **Published:** 03.06.2024

УДК: 616.12-008.331.1:616.127-005.8-056.7

DOI: https://doi.org/10.17816/brmma626848

Нелипидные генетические предикторы развития ишемической болезни сердца и инфаркта миокарда у пациентов, страдающих гипертонической болезнью

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АННОТАЦИЯ

Анализируются ассоциации основных нелипидных геномных биомаркеров с возникновением ишемической болезни сердца и нестабильным течением заболевания с развитием инфаркта миокарда у 164 пациентов, страдающих гипертонической болезнью I–III стадий. Исследование проходило в 2 этапа. На первом этапе проводился поиск нелипидных генетических предикторов ишемической болезни сердца без учета особенностей ее клинического течения. На втором этапе изучали возможность выделения генетических предикторов осложненного течения ишемической болезни сердца с развитием инфаркта миокарда. Во всех случаях проверки гипотез различие признавалось статистически значимым при $p < 0,05$. Установлено, что наличие ишемической болезни сердца у пациентов, страдающих гипертонической болезнью, было ассоциировано с достоверным преобладанием генетических биомаркеров только в 4 однонуклеотидных полиморфизмах: в системе гемостаза (4G4G *SERPINE 1*), провоспалительных цитокинов (аллель T *IL-1b-511*, аллель C *IL-1b-1473*) и врожденного иммунитета (FF *TLR3-412*). Развитие инфаркта миокарда было ассоциировано с двумя генетическими полиморфизмами: в системе провоспалительных цитокинов (CC *IL-6 -174*) и гемостаза (4G4G *SERPINE 1*). В целом среди изучаемых однонуклеотидных полиморфизмов статистически значимый результат в прогнозировании ишемической болезни сердца продемонстрировали генетические биомаркеры системы гемостаза, провоспалительных цитокинов и врожденного иммунитета. В отношении инфаркта миокарда прогностической ценностью могут обладать генетические биомаркеры системы гемостаза и провоспалительных цитокинов. Использование данных генетических биомаркеров в качестве предикторов неблагоприятного прогноза у пациентов, страдающих гипертонической болезнью, позволит лучше стратифицировать риск, оценить прогноз в этой группе, что значительно снизит затраты на проведение полногеномного исследования.

Ключевые слова: ишемическая болезнь сердца; инфаркт миокарда; кардиоваскулярные осложнения; кардиоваскулярный риск; генетические биомаркеры; однонуклеотидные полиморфизмы; низкоинтенсивное воспаление; немодифицируемые предикторы риска.

Как цитировать

Тюрюпов М.С., Шуленин К.С., Черкашин Д.В., Свеклина Т.С., Кутелев Г.Г., Мирзоев Н.Т. Нелипидные генетические предикторы развития ишемической болезни сердца и инфаркта миокарда у пациентов, страдающих гипертонической болезнью // Вестник Российской военно-медицинской академии. 2024. Т. 26, № 2. С. 197–206. DOI: https://doi.org/10.17816/brmma626848

Рукопись получена: 13.02.2024 **Рукопись одобрена:** 13.04.2024 **Опубликована:** 03.06.2024

DOI: https://doi.org/10.17816/brmma626848

高血压患者冠心病和心肌梗死的非血脂遗传预测因子

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摘要

本文分析了164例高血压 I-III 期患者的主要非血脂基因组生物标志物与冠心病发生的关系，以及冠心病的不稳定病程与心肌梗死发生的关系。研究分两个阶段进行。在第一阶段，寻找冠心病的非血脂遗传预测因素，但不考虑其临床过程的特殊性。在第二阶段，研究了确定缺冠心病复杂病程和心肌梗死发生的遗传预测因素的可能性。在所有假设检验中，当 $p < 0.05$时，差异被认为具有统计学意义。发现高血压患者冠心病的发生与以下4个单核苷酸多态性基因生物标记物的显著流行有关：止血系统（*4G4G SERPINE 1*）、促炎细胞因子（IL-1b T 等位基因-511、*IL-1b* C 等位基因-1473）和先天免疫（FF *TLR3-412*）。心肌梗死的发生与两种基因多态性有关：促炎细胞因子（CC *IL-6 -174*）和止血基因（4G4G SERPINE 1 ）。总体而言，在所研究的单核苷酸多态性中，止血系统、促炎细胞因子和先天性免疫的遗传生物标志物在预测冠心病方面具有显著的统计学意义。对于心肌梗死，止血系统和促炎细胞因子的遗传生物标志物可能具有预后价值。利用这些遗传生物标志物作为高血压患者不良预后的预测因子，可以更好地对这一群体进行风险分层和预后评估，从而大大降低全基因组研究的成本。

关键词：冠心病；心肌梗死；心血管并发症；心血管风险；基因生物标志物；单核苷酸多态性；低强度炎症；不可改变的风险预测因子。

引用本文

Tyuryupov MS, Shulenin KS, Cherkashin DV, Svyoklina TS, Kutelev GG, Mirzoev NT. 高血压患者冠心病和心肌梗死的非血脂遗传预测因子. *Bulletin of the Russian Military Medical Academy.* 2024;26(2): 197–206. DOI: https://doi.org/10.17816/brmma626848

收到： 13.02.2023 **录用：** 13.04.2024 **发布日期：** 03.06.2024

修订： 28.02.2024 **接受：** 01.05.2024

BACKGROUND

Cardiovascular diseases (CVDs) are the leading cause of mortality among adults in the Russian Federation, accounting for 43.8% of the total number of lethal outcomes. In the structure of CVD-related mortality, coronary heart disease (CHD) represents 54.2%, making it an extremely pressing problem[1]. Currently, more than 200 risk factors for CHD have been identified, including genetic factors. For a long time, the emphasis in the search for predictors of CHD was shifted toward lipid biomarkers. However, recent attention has shifted to non-lipid predictors of CHD, particularly low-grade inflammation, an important component of the cardiovascular continuum. Unsurprisingly, levels of pro-inflammatory markers correlate well with cardiovascular risk [1]. A meta-analysis by Y. Li et al. [2], combining results from 14 studies with 83,995 participants, showed a significant relationship between high-sensitivity C-reactive protein (CRP) and the risk of cardiovascular death and death from all causes. More modern works corroborate this relationship [3, 4]. Similar data have also been obtained for other proinflammatory agents. Thus, the STABILITY study, which included 14,611 patients, showed a clear association between the risk of developing major adverse cardiovascular complications and an increased (⩾2 ng/l) level of interleukin-6 (IL-6) in blood serum [5]. This is also true for higher-order proinflammatory cytokines, such as IL-1, the main immunocompetent biomarker that can stimulate the production of both CRP and IL-6 [6].

Dysregulation of the Toll-like receptor (TLR) system may play a key role in maintaining chronic inflammation and progressing atherosclerosis. Several experimental studies on laboratory animals have convincingly demonstrated the significant role of TLRs in atherogenesis. For instance, a study by A. Kapelouzou et al. [7] demonstrated a high correlation between the expression of TLR types 2, 3, 4, and 8 and the progression of atherosclerosis in the aorta of male rabbits. Additionally, dysregulation of the hemostatic system contributes to the progression of atherosclerotic arterial lesions. Evidence shows that higher levels of plasminogen activator inhibitor 1 and homocysteine are associated with the formation of potentially more "hazardous" coronary plaques (atherosclerotic plaques with thin caps and large atherosclerotic plaques) [8].

However, several limitations prevent using these biomarker levels as reliable predictors of CHD and myocardial infarction (MI). For instance, the expression of inflammatory proteins may change due to persistent infection. Hence, the need arises to search for more reliable non-modifiable risk predictors, which may include genetic polymorphisms. Thus, a study by M. Asif et al. [9] revealed a correlation between the development of CHD and polymorphisms of the protein gene associated with the low-density lipoprotein receptor. The British Heart Foundation database contains 1,122 unique variants of low-density lipoprotein receptors, which are also associated with the development of CHD and are included in genetic screening for homozygous familial hypercholesterolemia (HFHC)[2]. Similar studies are also available regarding the apolipoprotein B-100 protein [10].

There are also studies on polymorphisms of the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes. Polymorphisms of the *PCSK9* genes are known to enhance and inhibit its function. Thus, the T allele of single nucleotide polymorphism rs11206510, which increases its activity, is associated with a high risk of MI in CHD patients [11]. In turn, polymorphisms of the *PCSK9* gene Y142X, C679X, and R46L protect the development of CHD and MI [12]. Low-density lipoprotein receptor adapter protein 1 (*LDLRAP1*) polymorphisms are rarer, namely, 432insA in exon 4 and G65A in exon 1 (p. trp22ter), and they are associated with the development of HFHC [13, 14].

Although there are publications regarding non-lipid genetic biomarkers of CHD, they are much fewer, and the results obtained are quite contradictory. This necessitates new studies to confirm or refute the contribution of any single nucleotide polymorphisms to the development of CHD and MI.

The study aimed to analyze the associations of the main non-lipid genomic biomarkers with the occurrence of CHD and the unstable course of the disease with the development of MI in patients with hypertensive disease (HD).

MATERIALS AND METHODS

The design was a retrospective cohort case-control study. It included 164 patients with stages I–III HD. The median age of patients was 67 (57–74) years; 90 (54.9%) of them were men. A total of 144 (87.8%) patients had dyslipoproteinemia, 101 patients (61.6%) had grades 1–2 abdominal obesity (AO), 84 (51.2%) patients were diagnosed with CHD, 52 (31.74%) patients had prediabetes (impaired glucose tolerance and/or impaired fasting glycemia), 34 (20.7%) patients had chronic kidney disease (CKD) stages C1–C3b. The gender, age, and clinical laboratory parameters of the patients included in the study are presented in Table 1.

[1] Demographic Yearbook of Russia [Internet]. URL: https://rosstat.gov.ru/storage/mediabank/Demogr_ejegod_2023.pdf (access date 03/17/2024).

[2] British Heart Foundation. LDLR Database. [Internet]. URL: http://www.ucl.ac.uk/ldlr/Current/summary.php?select_db=LDLR&show=sum. (access date 01/11/2024).

Table 1. Gender, age and clinical laboratory parameters of patients included in the study at different stages, abs. (%)
Таблица 1. Половозрастные и клинико-лабораторные показатели пациентов, включенных в исследование на разных этапах, абс. (%)

Indicator	Stage 1		*p*	Stage 2		*p*
	CHD, *n* = 84	no CHD, *n* = 80		MI, *n* = 30	no MI, *n* = 54	
Age, years	66	63.5	–	67	72.4	–
Male gender	38 (45.2)	52 (65)	0.01	17 (56.9)	21 (38.9)	0.21
Smoking	46 (54.8)	36 (45)	0.21	20 (66.7)	26 (48.1)	0.1
Dyslipoproteinemia	74 (88.1)	70 (87.5)	0.91	28 (93.3)	46 (85.1)	0.27
Prediabetes	34 (40.5)	18 (22.5)	0.01	12 (40)	22 (40.7)	0.95
CKD	15 (17.9)	19 (23.8)	0.35	7 (23.5)	8 (14.8)	0.33
Abdominal obesity	53 (63.1)	48 (60)	0.68	23 (76.7)	30 (55.6)	0.06

The study was conducted in two stages. At stage 1, a search was performed for non-lipid genetic predictors of CHD without taking into account the characteristics of its clinical course. For this purpose, all patients were distributed into two groups depending on the presence or absence of CHD. All patients underwent genetic typing of innate immunity (human leukocyte antigen class 2 (*HLA-DRB1*), TLRs type 3 (*TLR3*-412 L/F)), inflammatory cytokines (*IL-6* (-174 C/G, rs1800795), *IL-1b* (-511 T/C, -1473 G/C), *IL-10* (-1082 G/A, rs1800896), tumor necrosis factor α (-308 G/A), blood pressure regulatory systems (angiotensin-converting enzyme (ACE) (*ACE* Alu I/D, rs 4646994), angiotensin 2 (-235 M/T), hemostatic system (type 1 plasminogen activator inhibitor (*SERPINE 1* (*PAI-1*)-675 5G/4G), coagulation factor 13 (*F13A1-35* V/L), integrin beta 3 (*ITGB3-33* L/P), folate cycle of methylenetetrahydrofolate reductase (*MTHFR*) -677 C/T, rs 1801133), methionine synthase reductase (*MTRR-66* A/G, rs 1801394), and apoptosis inducers, namely, ataxia-telangiectasia mutation (*ATM-185* Asp/Asn, rs 1801516). At stage 2, the possibility of identifying genetic predictors of the complicated course of CHD with the development of MI was studied.

Peripheral blood from patients was used for genetic typing and collected in ethylenediaminetetraacetic acid tubes upon discharge. Deoxyribonucleic acid (DNA) extraction was performed using the GS-Genetics kit, and DNA was amplified using the DT-Prime device from DNA Technology (Russia).

The study was conducted as part of the Virus research project and adhered to the provisions of the Declaration of Helsinki. It was approved by the ethics committee of the S.M. Kirov Military Medical Academy (Protocol No. 271, November 22, 2022). All patients signed informed, voluntary consent for medical intervention, personal data processing, and study participation.

When describing data for numerical normally distributed variables, the mean and standard deviation *M* (*SD*) were used, whereas the median and interquartile range *Me* [Q_1–Q_3] were used for non-Gaussian variables. Descriptive statistics used the number of occurrences of each value and the proportion of each value relative to the entire sample *n* (*m*%) for nominal and ordinal data. The search for differences was performed by testing statistical hypotheses. For normal samples, the Student's *t*-test was used; for non-Gaussian samples, the Mann – Whitney *U* test was used. Nominal and ordinal samples were compared using the chi-square test, and Fisher's exact test was used for small samples (at least one of the expected values less than 10). In all hypothesis testing cases, the difference was considered statistically significant at $p < 0.05$. Calculations were performed in the statistical package *R*, version 4.3.1.

RESULTS AND DISCUSSION

It was established that the presence of CHD in HD patients was associated with a significant predominance of genetic biomarkers in only four single-nucleotide polymorphisms: the hemostatic system (4G4G *SERPINE 1*), proinflammatory cytokines (T allele *IL-1b-511*, C allele *IL-1b-1473*), and innate immunity (FF *TLR3-412*) (Fig. 1).

The development of MI was associated with two genetic polymorphisms, namely, in the system of proinflammatory cytokines (CC *IL-6-174*) and hemostasis (4G4G *SERPINE 1*) (Fig. 2).

The association of genotype 4G4G polymorphism of the *SERPINE 1* gene of the hemostasis system with a high risk of developing both CHD and MI in CHD patients was demonstrated. Thus, in the group of CHD patients, this genotype was significantly more common (40% vs. 9.5%; $p = 0.007$, odds ratio (OR) 11.4, 95% CI 2.24–89.2). A similar effect of this polymorphism was also demonstrated on the risk of MI occurrence. In the group of patients with a history of MI, it was significantly more common (66.7% vs. 20.7%; $p = 0.026$, OR = 14, 95% CI 1.85–296.1).

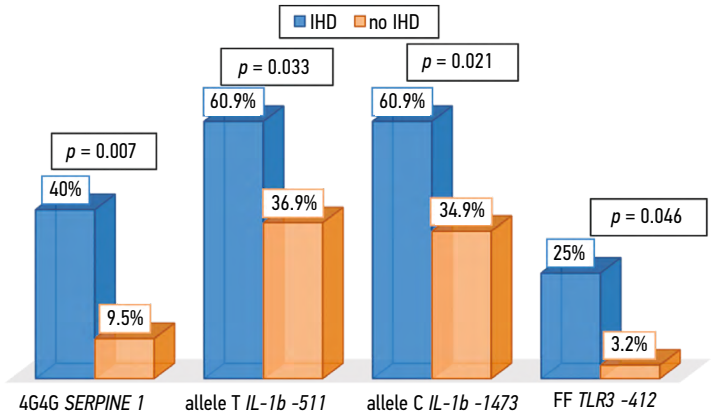

Fig. 1. Frequency of occurrence of genetic biomarkers in patients with hypertension associated with the development of coronary heart disease
Рис. 1. Частота встречаемости генетических биомаркеров у пациентов, страдающих ГБ, ассоциированных с развитием ИБС

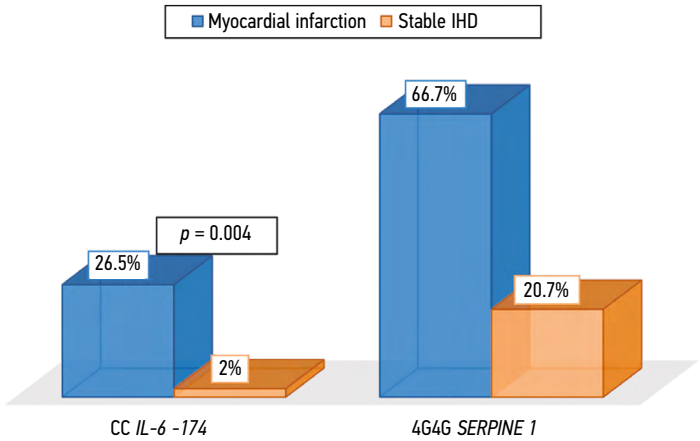

Fig. 2. Frequency of occurrence of genetic biomarkers in patients with stable ischemic heart disease and post-myocardial infarction
Рис. 2. Частота встречаемости генетических биомаркеров у пациентов со стабильным течением ИБС и перенесших ИМ

A meta-analysis by Y. Liu et al. [15], which included almost 150,000 people from different ethnic populations, demonstrated an association between the polymorphism of this gene and the development of atherosclerotic diseases. The study by A.L. Gonchar et al. [16] showed an almost twofold excess of the occurrence of the 4G4G genotype in patients with a history of MI (41.2% vs. 28.7%; p = 0.01). A more modern study by A. Bayramoglu [17] demonstrated the negative contribution of this genotype to the development of coronary atherosclerosis. This adverse effect may be attributed to the higher expression of tissue plasminogen activator type 1 in its carriers [18]. It has long been known that it is a potent antifibrinolytic enzyme [19]. In this regard, the progression of atherosclerotic lesions in the coronary vessels in carriers of this genotype can be due to the high potential for thrombogenesis resulting from the low activity of the antifibrinolytic system.

Our study also showed an association between polymorphisms of proinflammatory cytokine genes and the development of CHD and MI. Specifically, the T allele of the *IL-1b-511* gene polymorphism was associated with the presence in CHD patients (60.9% vs. 36.9%; p = 0.033, OR = 2.66, 95% CI = 1.09–6.78). However, there are contradictory opinions regarding the association of this allele with the risk of developing CHD. For example, a meta-analysis by L. Zhou [20] found that this polymorphism has no association with the development and progression of atherosclerotic lesions of the coronary arteries. Conversely, the study by H. Rai [21] showed the protective function of the T allele and the negative function of the C allele of this gene. According to their data, carriage of the C allele significantly increases the risk of CHD (p = 0.041, OR = 1.36). Additionally, E.A. Zakharyan and O.Yu. Gritskevich [22] revealed an association between the TT genotype and the development of CHD in Caucasians. In their study, this genotype increased the risk of CHD by two times (OR = 2.2, 95% CI = 1.3–3.6). It is most logical to explain such heterogeneity in the results of researchers by ethnic differences in the studied groups of

patients. All this again confirms the need for new research and reassessment of the contribution of this polymorphism to the development of cardiovascular pathology. An association with CHD was also revealed for the C allele of the *IL-1b-1473* gene polymorphism. This allele was noted significantly more often in the group of CHD patients (60.9% vs. 34.9%; $p = 0.021$, OR = 2.9, 95% CI = 1.97–7.4). Currently, there is no convincing information about the effect of this polymorphism on cardiovascular pathology.

Our study also revealed a correlation of the CC genotype of the *IL-6-174* C/G gene polymorphism, rs 1800795, with the development of MI in patients with stable CHD. This genotype was detected significantly more often in patients with a history of MI (26.5% vs. 2%, $p = 0.004$, OR = 25.7, 95% CI = 3.85–520.71). A number of studies have noted a similar correlation between the carriage of this genotype and the risk of developing thrombosis in various locations, including the coronary arterial bed. Thus, a meta-analysis of about 30.000 patients convincingly demonstrated the association of this genotype with the risk of MI and other arterial thrombosis [23]. This can be due to a higher level of IL-6 expression in carriers of this polymorphism [24].

We also established an association between polymorphism of the *TLR* gene, related to the innate immune system, and the occurrence of CHD. Thus, in the group of CHD patients, the FF genotype of the *TLR3-412* gene polymorphism was significantly more common (25% vs. 3.2%; $p = 0.046$, OR = 10.33, 95% CI = 1.1–119.58). There are currently no studies regarding the contribution of this polymorphism to the course of CVDs, particularly CHD. However, a number of publications assess the association of this polymorphism with negative and protective effects in relation to a number of other nosologies. Currently, an association of this polymorphism with some autoimmune and oncological diseases has been established [25–28]. *TLR3* is known to bind double-stranded ribonucleic acid (RNA) of viruses, bacteria, fungi, and messenger RNA isolated from necrotized cells [29].

An interesting study was conducted by G. Cooke et al. [30] demonstrated an association of the FF genotype with an enhanced proliferation potential of fibroblasts. This may well explain the progression of atherosclerotic lesions of the coronary arteries in patients carrying this genotype.

Overall, we have obtained data on the influence of the main non-lipid genetic biomarkers on the development of CHD and MI in patients with HD. CHD predictors include the 4G4G genotype of the *SERPINE 1* gene polymorphism, the TT genotype of the *IL-1b-511* gene polymorphism, the C allele of the *IL-1b-1473* gene polymorphism, and the FF genotype of the *TLR3-412* gene polymorphism. The negative impact of the 4G4G genotype of the *SERPINE 1* gene polymorphism and the CC genotype of the *IL-6-174* C/G, rs 1800795 gene polymorphism has been proven in relation to the risk of developing MI in individuals with a stable course of CHD. The use of these genetic biomarkers as predictors of poor prognosis in patients with HD will allow for better risk stratification and assessment of the prognosis in this group, which will significantly reduce the costs of conducting a genome-wide study.

CONCLUSIONS

Carriage of the 4G4G genotype of the *SERPINE 1* gene, associated with the potential for hypercoagulation, increases the risk of CHD by four times.

Carriage of alleles and genotypes of proinflammatory cytokines associated with their higher expression also increases the risk of CHD and MI significantly more often, namely, the TT genotype of the *IL-1b-511* gene polymorphism by more than two times, the C allele of the *IL-1b-1473* gene polymorphism by almost three times. Carriage of the CC genotype of the *IL-6-174* C/G gene polymorphism increases the risk of occurrence of MI in CHD patients by more than 10 times.

Polymorphisms of the TLR system genes are also associated with the risk of CHD occurrence. Thus, in the group of CHD patients, the FF genotype of the *TLR3-412* gene polymorphism was eight times more common.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

The contribution of each author. M.S. Tyuryupov — development of the general concept, study design, article writing, data analysis; K.S. Shulenin — development of the general concept, study design, article writing, data analysis; T.S. Sveklina — review of publications, writing the article; T.G. Mirzoev — review of publications, writing the article; G.G. Kutelev — collection of clinical material, database compilation, statistical processing, article writing; D.V. Cherkashin — collection of clinical material, database compilation, statistical processing, article writing.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Вклад каждого автора. М.С. Тюрюпов — разработка общей концепции, дизайн исследования, написание статьи, анализ данных; К.С. Шуленин — разработка общей концепции, дизайн исследования, написание статьи, анализ данных; Т.С. Свеклина — обзор публикаций, написание статьи; Т.Г. Мирзоев — обзор публикаций, написание статьи; Г.Г. Кутелев — сбор клинического материала, составление базы данных, статистическая обработка, написание статьи; Д.В. Черкашин — сбор клинического материала, составление базы данных, статистическая обработка, написание статьи.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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