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Association of *MIR146A* (rs2910164) and *MIR499A* (rs3746444) gene polymorphisms with markers of thromboinflammation in patients with coronary heart disease after coronary artery bypass grafting

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Abstract

Background. Advances in genomics and proteomics have facilitated the identification of numerous new candidate biomarkers for the diagnosis and prognosis of coronary heart disease (CHD), as well as for predicting adverse cardiovascular events, including post-coronary artery bypass grafting (CABG) outcomes. MicroRNAs represent a promising category of these biomarkers. **Aim**: To investigate the association between the rs2910164 polymorphism in the *MIR146A* gene and the rs3746444 polymorphism in the *MIR499A* gene with adverse cardiovascular events and general inflammation markers in CHD patients post-CABG. **Material and Methods**. This prospective cohort study involved 158 CHD patients with a median age of 63 years [58; 67]. Patients were assessed at three stages: preoperatively, on postoperative days 8–10, and post-discharge. Early in-hospital cardiovascular events were recorded over 8–10 days of hospitalization, and long-term events were tracked for an average of 36.1 ± 10.6 months post-CABG. Comprehensive blood analyses and leukocyte DNA genotyping were conducted preoperatively and on days 8–10 post-surgery. Additionally, flow cytometry and high-sensitivity C-reactive protein (CRP) measurement were performed on a random subset of 102 patients.

Results. The allele frequencies of G and C (rs2910164) were 0.62 and 0.38, respectively, and those of A and G (rs3746444) were 0.83 and 0.17 in the CHD cohort. No significant differences in rare allele prevalence were observed between patients with and without long-term adverse cardiovascular events. Preoperatively, CHD patients with the GG genotype of rs2910164 *MIR146A* displayed higher platelet-platelet aggregate counts. Post-CABG, this genotype group showed significantly elevated values in platelet-platelet aggregate mean fluorescence intensity (MFI) (33.1 [31.5; 35.75] vs. 30.0 [29.0; 33.13], $p = 0.001$), MFI of P-selectin-expressing platelets (4.69 [2.05; 6.77] vs. 1.97 [1.49; 2.53], $p = 0.002$), MFI of P-selectin-expressing platelet–monocyte (6.71 [4.18; 16.4] vs. 4.22 [3.73; 6.14], $p = 0.018$), and MFI of P-selectin-expressing platelet-platelet aggregates (5.17 [2.47; 7.24] vs. 2.56 [1.7; 2.94], $p = 0.003$). The erythrocyte sedimentation rate (ESR) was significantly higher in patients with the C allele preoperatively (60.0 [31.0; 89.0] mm/hr vs. 40.0 [27.75; 57.75] mm/hr, $p = 0.043$). **Conclusions**. The presence of rare alleles in rs2910164 (*MIR146A*) and rs3746444 (*MIR499A*) was not associated with an increased frequency of in-hospital or long-term adverse cardiovascular events. However, CHD patients with the GG genotype of rs2910164 *MIR146A* post-CABG exhibited significantly higher MFI in platelet aggregates expressing P-selectin.

Keywords:	*MIR146A*; rs2910164; MIR499A; rs3746444; coronary artery bypass grafting; platelet activation; P-selectin; coronary artery disease.
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Ассоциация полиморфизмов генов *MIR146A* (rs2910164) и *MIR499A* (rs3746444) с маркерами тромбовоспаления и повышенной активацией тромбоцитов после коронарного шунтирования

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Аннотация

Введение. Достижения в области геномики и протеомики способствовали идентификации множества новых кандидатов в биомаркеры для диагностики и прогнозирования ишемической болезни сердца (ИБС), а также для предсказания неблагоприятных сердечно-сосудистых событий, включая исходы после аортокоронарного шунтирования (КШ). МикроРНК представляют собой перспективную категорию таких биомаркеров.

Цель: выявить ассоциацию полиморфизмов rs2910164 в гене *MIR146A* и rs3746444 в гене *MIR499A* с нежелательными событиями и общеклиническими маркерами воспаления у пациентов с ИБС после КШ.

Материал и методы. В проспективное когортное исследование были включены 158 пациентов с ИБС, медиана возраста составила 63 [58; 67] года. Пациентов наблюдали в трех точках в стационаре: до КШ, на 8–10-е сут после КШ и после выписки из стационара. За 8–10 сут стационарного лечения регистрировали ранние госпитальные нежелательные сердечно-сосудистые события, в период 36,1 ± 10,6 мес. после КШ – отдаленные нежелательные сердечно-сосудистые события. Всем пациентам до КШ и на 8-10-е сут после КШ провели развернутый биохимический анализ крови, генетический анализ ДНК лейкоцитов крови. 102 случайно отобранным пациентам из 158 выполнили проточную цитометрию, определили концентрацию С-реактивного белка (СРБ).

Результаты. Частоты аллелей G и C (rs2910164) составили 0,62 и 0,38 соответственно, а частоты аллелей A и G (rs3746444) – 0,83 и 0,17 в когорте пациентов с ИБС. Не было выявлено значимых различий в распространенности редких аллелей между пациентами с наличием и отсутствием отдаленных неблагоприятных сердечно-сосудистых событий. До операции у пациентов с ИБС с генотипом GG rs2910164 *MIR146A* наблюдалось большее количество агрегатов тромбоцитов. После КШ у этой группы пациентов были значительно повышены значения средней интенсивности флуоресценции (ИФ) агрегатов тромбоцитов (33,1 [31,5; 35,75] против 30,0 [29,0; 33,13], p = 0,001), ИФ тромбоцитов, экспрессирующих Р-селектин (4,69 [2,05; 6,77] против 1,97 [1,49; 2,53], p = 0,002), ИФ тромбоцитарно-моноцитарных агрегатов, экспрессирующих Р-селектин (6,71 [4,18; 16,4] против 4,22 [3,73; 6,14], p = 0,018), и ИФ тромбоцитарных агрегатов, экспрессирующих Р-селектин (5,17 [2,47; 7,24] против 2,56 [1,7; 2,94], p = 0,003). Скорость оседания эритроцитов (СОЭ) была значительно выше у пациентов с аллелем С до операции (60,0 [31,0; 89,0] против 40,0 [27,75; 57,75] мм/ч, p = 0,043).

Выводы. Наличие редких аллелей rs2910164 (*MIR146A*) и rs3746444 (*MIR499A*) не было связано с увеличением частоты госпитальных или отдаленных неблагоприятных сердечно-сосудистых событий. Однако у пациентов с ИБС с генотипом GG rs2910164 *MIR146A* после КШ наблюдались значительно более высокие значения ИФ в агрегатах тромбоцитов, экспрессирующих Р-селектин.

Keywords:	*MIR146A*; rs2910164; *MIR499A*; rs3746444; коронарное шунтирование; активация тромбоцитов; Р-селектин; ишемическая болезнь сердца.
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Coronary heart disease (CHD) is one of the most prevalent cardiovascular conditions, remaining a significant global health concern with high mortality and disability rates worldwide [1]. Atherosclerosis of the coronary arteries, a primary cause of CHD, is closely associated with innate immunity processes. Macrophages in atherosclerotic plaques synthesize large quantities of cytokines, including pro-inflammatory cytokines [2] such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), both of which play roles in the NF-kB signaling pathway.

Coronary artery bypass grafting (CABG) is a primary surgical treatment for CHD; however, the postoperative period can involve adverse outcomes, including thrombotic and inflammatory complications. Ten years post-CABG, graft failure may reach 39% depending on the type of conduit used [3]. In recent decades, researchers have focused on biomarkers that could serve as predictors of such outcomes.

The advent of genomics and proteomics has introduced numerous novel biomarker candidates for diagnosing and predicting CHD and adverse cardiovascular events, including those following CABG. MicroRNAs (miRNAs) are potential biomarkers of particular interest.

MicroRNAs are a class of regulatory small non-coding RNAs found in nearly all eukaryotes. Their primary function is to suppress gene expression at the post-transcriptional level by binding to untranslated regions of mRNA, leading to mRNA degradation or reversible inactivation [4]. MiRNAs are believed to play critical roles in many physiological and pathophysiological processes by modulating various signaling pathways, making them attractive biomarker candidates. However, single nucleotide polymorphisms (SNPs) in miRNA sequences or their binding sites can affect miRNA-mRNA interactions, potentially leading to dysregulation of target gene expression [5].

MiR-146a, for instance, is involved in the regulation of the NF-kB signaling pathway through negative feedback by suppressing the synthesis of interleukin-1 receptor-associated kinase 1 (IRAK-1) and TNF receptor-associated factor 6 (TRAF-6), thus reducing inflammatory responses and the synthesis of IL-6, IL-8, IL-1β, and TNF-α [6]. Additionally, miR-146a has been implicated in the pathogenesis of atherosclerosis by modulating endothelial activation and dysfunction [7].

Rs2910164 is a C>G substitution which induces a mispairing in the 3 arm of the hsa-miR-146a precursor (MI0000477) and affects the third base in the seed region of hsa-miR-146a-3p (MIMAT0004608). Increasing evidence suggests that rs2910164 influences the processing and expression of miR-146a. However, there is no consensus regarding the alterations that are induced by either allele of this polymorphism [8]. Low levels of miR-146a may exacerbate vascular injury and atherosclerosis by increasing IRAK-1, TRAF-6, and TNF-α protein levels and by promoting platelet activation [8]. Nevertheless, studies offer divergent views on the role of rs2910164 polymorphism in miRNA regulation and its impact on CHD progression. Interestingly, genotype distribution for this polymorphism varies across populations: in East Asians, the C allele frequency is 0.63[1], while in Europeans, it is 0.76 for the G allele, according to the 1000 Genomes Project.

MiRNA-499a is also implicated in inflammatory processes, regulating the expression of pro-inflammatory cytokines, including TNF-α, C-reactive protein, IL-2, IL-6, and IL-23α [9]. This miRNA has been shown to inhibit apoptosis in cardiomyocytes and exhibit cardioprotective properties [10].

The rs3746444 polymorphism in the miR-499a gene (MIR499A) involves an adenine (A) to guanine (G) substitution in the miRNA seed region. This alteration modifies the stability of the secondary structure of miR-499a, influencing its maturation process and binding affinity with target mRNAs, thereby affecting its anti-apoptotic function [8, 10]. Unlike rs2910164, rs3746444 displays minimal allele

[1] dbSNP (Database of Short Genetic Variations). rs2910164. Available at: https://www.ncbi.nlm.nih.gov/snp/rs2910164#frequency_tab

frequency differences across populations. In the global population, according to data from the 1000 Genomes Project_X30, the distribution of the A and G alleles is 0.82 and 0.18, respectively. The allele frequencies for A[2] and G are 0.74 and 0.26 in East Asia, and 0.81 and 0.19 in Europe, respectively.

To date, there have been no large-scale studies investigating the distribution of rs2910164 in the MIR146A gene and rs3746444 in the MIR499A gene in Siberia, specifically in the Krasnoyarsk region. Likewise, no studies have examined the association of these polymorphisms with adverse events in patients with CHD following CABG.

This study aims to identify the association of rs2910164 in the MIR146A gene and rs3746444 in the MIR499A gene with adverse events and general clinical markers of inflammation in patients with CHD following CABG.

Material and Methods

This prospective cohort study included 158 patients (124 men and 34 women) with CHD, aged 47 to 78 years (median age 63 years [58; 67]). Coronary angiography (CAG) confirmed atherosclerotic lesions in the coronary arteries, and all patients underwent aorto- or mammary CABG at the Federal Center for Cardiovascular Surgery in Krasnoyarsk, Russian Federation.

The study was conducted following the principles of the Declaration of Helsinki, and all participants provided informed consent. The study protocol was approved by the Ethics Committee of the Prof. V.F. Voino-Yasenetsky Krasnoyarsk State Medical University.

Inclusion criteria were as follows: multivessel disease with hemodynamically significant coronary artery stenoses confirmed by CAG, stable angina pectoris (Canadian Cardiovascular Society functional classes II–IV), and signed informed consent. Exclusion criteria included active peptic ulcer disease, chronic kidney disease (estimated glomerular filtration rate less than 60 mL/min/1.73 m²), transaminase levels elevated by 3-fold or more, and intolerance to or inability to take clopidogrel and acetylsalicylic acid (ASA).

Patients were assessed at three time points. In the hospital setting: before CABG, on days 8–10 post-CABG, and after discharge (follow-up by telephone at 36.1 ± 10.6 months post-CABG). Early in-hospital adverse cardiovascular events within 8–10 days of hospitalization included acute myocardial infarction (AMI), stroke, and cardiovascular mortality following CABG. Long-term adverse cardiovascular events recorded over 36.1 ± 10.6 months post-CABG included progression of angina functional class, heart failure, AMI, stroke, repeat myocardial revascularization, and cardiovascular mortality.

The clinical and laboratory characteristics of the patients are presented in Table 1.

Patient groups with CHD, distinguished by the presence or absence of early in-hospital adverse cardiovascular events, did not significantly differ in sex, age, clinical characteristics, or pre-CABG complete blood count parameters. However, there was a trend toward significance in the higher total cholesterol levels in the group with early in-hospital adverse cardiovascular events. Additionally, cardiopulmonary bypass (CPB) duration during CABG was longer in the adverse event group: 104 [66.0; 142.5] minutes, compared to 67.0 [47.5; 88.75] minutes in the event-free group.

To reduce the risk of hemorrhagic complications, antiplatelet therapy was discontinued five days prior to CABG following the established treatment protocols of the Federal Center for Cardiovascular Surgery in Krasnoyarsk. ASA (100 mg) was resumed on postoperative day 1, and clopidogrel (75 mg) was started on day 2 for those with a history of acute coronary syndrome within the past year. Dual antiplatelet therapy (DAPT) with ASA (100 mg) and clopidogrel (75 mg) was prescribed for 43.0% of patients. Additional therapies included angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, proton pump inhibitors, β-blockers, statins, calcium channel blockers, nonsteroidal anti-inflammatory drugs, and opioid analgesics in the early postoperative period. For patients with diabetes mellitus, hypoglycemic therapy was also administered.

Before CABG and on postoperative days 8–10, all patients underwent comprehensive blood tests, biochemical analysis, and leukocyte DNA genotyping. Flow cytometry and C-reactive protein (CRP) concentration measurements were performed in a randomly selected subset of 102 out of 158 patients.

Platelet-leukocyte aggregates (PLAs) were identified within the total leukocyte fraction using flow cytometry and a panel of monoclonal antibodies (Beckman Coulter, USA and BioLegend, Germany) conjugated with fluorochromes: CD14-FITC (clone RMO52, cat. no. B36297, Beckman Coulter, USA), CD16-PE (clone 3G8, cat. no. A07766, Beckman Coulter, USA), CD41-PC7 (clone P2, cat. no. 6607115, Beckman Coulter), and CD62P (clone AK4, cat. no. 304910, BioLegend, Germany). Erythrocytes were removed from the samples using a no-wash technique with VersaLyse lysing solution (Beckman Coulter, cat. no. A09777) to which 25 µL of IOTest 3 Fixative Solution (Beckman Coulter, cat. no. A07800) was added ex tempore to 975 µL. After incubation, samples were washed once with buffered saline solution (5 min at 400 g), and the cell pellet was resuspended in 400 µL of buffered saline containing 1% neutral paraformaldehyde (cat. no. HT5011, Sigma-Aldrich, USA). Mean fluorescence intensity (MFI) was used to assess CD62P expression and platelet receptor levels within leukocyte aggregates. Sample analysis was performed on a Navios™ flow cytometer (Beckman Coulter, USA) equipped with three diode lasers (405, 488, and 638 nm). Cytometry data were processed using Navios Software v.1.2 and Kaluza™ v.2.2 (Beckman Coulter, USA).

CRP in blood plasma was measured using a latex immunoturbidimetric method. (Sapphire 400, Japan)

Genomic DNA was extracted from leukocytes in whole blood using the “DNA-sorb-B” reagent kit (Amplisense). The DNA was then analyzed for polymorphisms rs2910164 in the *MIR146A* gene and rs3746444 in the *MIR499A* gene. Real-time PCR on the extracted DNA samples was performed using the "PCR Kit" reagent set (Sintol, Russia) with Eva Green. The primer sequences for rs2910164 were taken from K. Agiannitopoulos et al. [5], while primers for rs3746444 were designed independently.

Amplicons were subjected to restriction fragment length polymorphism (RFLP) analysis using restriction endonucleases Psp124B I and TseFI (SibEnzyme, Russia) for rs2910164 and rs3746444, respectively. The length of resulting restriction fragments was determined through

[2] dbSNP (Database of Short Genetic Variations). rs3746444. Available at: https://www.ncbi.nlm.nih.gov/snp/rs3746444

Table 1. Clinical Characteristics of Patients with IHD Undergoing CABG

Characteristic	Patients with CHD and CABG, *n* = 158	Patients without early in-hospital adverse cardiovascular events, *n* = 143	Patients with early in-hospital adverse cardiovascular events, *n* = 15	*p-value**
Age, years	63 [58; 67]	63 [59; 67]	59 [55,5; 65,5]	0,719
Smoking, %	35,5	33,8	46,6	0,508
Off-pump CABG, %	21,5	23,6	0	0,063
Stable angina, %				
II FC	50,6	51,8	40,0	0,608
III FC	38,6	35,2	53,3	0,441
Arterial hypertension,	100	100	100	1,000
Diabetes mellitus, %	31,0	29,3	40,0	0,547
Post-infarction cardiosclerosis, %	65,1	61,9	72,7	0,691
Obesity, %	43,4	43,6	35,7	0,714
Dual antiplatelet therapy after CABG, %	43,0	41,0	57,1	0,479
CPB time, min	68 [50,25; 99]	67,0 [47,5; 88,75]	104 [66,0; 142,5]	0,040
Platelet count before CABG, 109 cells/l	230,1 [196,5; 269,5]	231,0 [192; 267,0]	203 [180; 237,5]	0,499
Monocyte count before CABG, %	8,2 [6,7; 9,53]	8,15 [6,9; 9,3]	8,8 [7,35; 10,05]	0,280
Neutrophil count, %	60,8 [53,9; 66,0]	59,1 [52,9; 66,0]	58,8 [54,85; 62,45]	0,616
ESR, mm per hour	14,0 8,0; 25,0]	16 [10; 27]	20 [7,5; 25]	0,908
CRP, mg/l				
Before CABG	1 [0,1; 1,9]	1 [0,1; 2,25]	1 [0,4; 1,3]	0,924
After CABG	51,1 [18,7; 95,1]	45,5 [18,7; 92,15]	72,5 [46,75; 107,45	0,537
Total cholesterol level, mmol/l	4,27 [3,67; 5,56]	4,15 [3,68; 5,37]	5,24 [4,09; 6,41]	0,073
LDL level, mmol/l	2,54 [2,06; 3,28]	2,23 [1,99; 2,98]	2,85 [2,7; 4,13]	0,137
Aggregation level with 1 μmol/L Arachidonic acid, %	61 [48; 72]	65 [48; 73]	62 [52,5; 72]	0,945
Aggregation level with 5 μmol/L ADP, %	56 [42; 66]	56 [42; 68]	55,5 [39,5; 60,25]	0,692

Note: *p-values are presented to compare patient groups with and without adverse cardiovascular events. CABG – coronary artery bypass grafting; CHD – coronary heart disease; FC – functional class; CBP – cardiopulmonary bypass; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; LDL – low density lipoprotein.

horizontal agarose gel electrophoresis. In addition to RFLP, single nucleotide polymorphisms (SNPs) were identified using high-resolution melting (HRM) curve analysis with the "Precision Melt Supermix" reagent kit (Bio-Rad, USA).

Statistical processing was performed using SPSS STATISTICS version 20.0. Median (Me) and interquartile range (25th and 75th percentiles) were calculated for descriptive statistics. Qualitative variables were reported as absolute counts and percentages of the total sample or subgroup. The Mann – Whitney *U* test was used to assess differences in continuous variables between independent groups, and the χ^2 test was used for categorical variables. Differences were considered statistically significant at $p < 0.05$.

Results

During the entire follow-up period, 15 patients (9.5%) experienced early in-hospital adverse cardiovascular events. Within the 10 days of hospitalization, 7 cases of perioperative myocardial infarction (MI), 10 cases of stroke, and 1 case of cardiovascular death were recorded. Some patients experienced multiple events concurrently.

At a median follow-up of 36.1±10.6 months post-surgery, 22 patients were identified with adverse cardiovascular events, including: 2 cases of AMI, 1 case of stroke, 12 cases of recurrence or worsening of angina functional class, 4 cases of repeat myocardial revascularization, 2 cases of progression in heart failure functional class, 3 cases of cardiovascular death.

The frequencies of the G and C alleles (rs2910164) in the group of patients with CHD are 0.62 and 0.38. The frequencies of the A and G alleles (rs3746444) in the CHD group are 0.83 and 0.17, respectively (Table 2).

These allele distributions are consistent with general population data and align with the global allele distributions referenced in previous studies[3] [10].

Patients with in-hospital adverse cardiovascular events did not differ in terms of carrying rare alleles of the studied miRNA gene polymorphisms.

102 patients randomly selected out of the 158, underwent flow cytometry to assess the number of intercellular aggregates and MFI among carriers of the rare C allele in the rs2910164 *MIR146*A polymorphism or the rare G allele in rs3746444 *MIR499*, both before and after coronary artery bypass grafting (CABG). Additionally, inflammation markers readily available in clinical practice – such as leukocyte, platelet, and monocyte counts, ESR, and CRP – were evaluated in rare allele carriers both prior to CABG and on postoperative days 8–10.

In patients with CHD and the homozygous GG variant of rs2910164 *MIR146A*, there were no significant differences in intercellular aggregate levels, CRP, leukocyte count, or platelet count compared to carriers of the GC + CC genotypes before CABG. However, the count of platelet-platelet aggregates was significantly higher in CHD patients with the GG genotype prior to CABG. Post-CABG, patients with the GG genotype demonstrated significantly elevated

[3] dbSNP (Database of Short Genetic Variations). rs3746444. Available at: https://www.ncbi.nlm.nih.gov/snp/rs3746444

Table 2. The prevalence of genotype variants of polymorphisms rs2910164 in *MIR146A* and rs3746444 in *MIR499A* among patients with CHD who underwent CABG, divided into groups based on the presence or absence of in-hospital adverse cardiovascular events

Polymor-phism, gene	Genotype variant	Patients with CHD and CABG, *n* = 158	Patients without early in-hospital adverse cardiovascular events, *n* = 143	Patients with early in-hospital adverse cardiovascular events, *n* = 15	OR [95% CI]	**p-value*
		Prevalence, *n* (%)				
rs2910164 MIR146A	GG	79 (50,0)	70 (49,0)	9 (60,0)	1,878 [0,599–5,877]	0,279
	GC	37 (23,4)	33 (23,1)	4 (26,7)	1,245 [0,372–4,169]	0,356
	CC	42 (26,6)	40 (28,0)	2 (13,3)	0,632 [0,135–2,962]	0,560
	GC + CC	79 (50,0)	73 (51,0)	6 (40,0)	0,639 [0,216–1,889]	0,418
rs3746444 MIR499A	AA	105 (66,5)	95 (66,4)	10 (66,7)	1,011 [0,3270–3,123]	0,986
	AG	51 (32,3)	46 (32,2)	5 (33,3)	1,054 [0,341–3,262]	0,927
	GG	2 (1,3)	2 (1,4)	0	1,826 [0,084–39,781]	0,702
	AG + GG	53 (33,5)	48 (33,6)	5 (33,5)	0,989 [0,320–3,058]	0,986

Note: CABG – coronary artery bypass grafting; CHD – coronary heart disease; OR – odds ratio; CI – confident interval; * *p-value* compare the frequencies of genotypes carriage among patients with CHD with and without adverse cardiovascular events.

MFI of platelet-platelet aggregates (33.1 [31.5; 35.75] vs. 30.0 [29.0; 33.13], $p = 0.001$), MFI of P-selectin-expressing platelets (4.69 [2.05; 6.77] vs. 1.97 [1.49; 2.53], $p = 0.002$), MFI of platelet-monocyte aggregates expressing P-selectin (6.71 [4.18; 16.4] vs. 4.22 [3.73; 6.14], $p = 0.018$), and MFI of P-selectin-expressing platelet-platelet aggregates (5.17 [2.47; 7.24] vs. 2.56 [1.7; 2.94], $p = 0.003$). ESR levels were significantly higher in carriers of the rare C allele before CABG (60.0 [31.0; 89.0] mm/h vs. 40.0 [27.75; 57.75] mm/h, $p = 0.043$). These results suggest that the GG genotype can enhance the inflammatory response, potentially in reaction to major surgical intervention, and can increase intercellular aggregate activity.

Patients with CHD who had AG + GG genotypes of the rs3746444 MIR499 polymorphism showed no significant differences from those with the AA genotype in levels of intercellular aggregates, P-selectin, ESR, CRP, leukocyte count, or platelet count both prior to CABG and on postoperative days 8–10.

Discussion

Thrombosis and inflammation are interconnected processes that play a crucial role in the development of atherosclerosis and its complications. Research over recent decades has highlighted a complex relationship between platelet activation, a primary component of thrombosis, coagulation, and innate immunity – collectively referred to as immunothrombosis [11]. The link between inflammation, thrombosis, and adverse cardiovascular events has been well-documented [12]; however, the precise molecular and cellular mechanisms, as well as definitive markers for cardiovascular events, remain unclear.

Recent studies indicate that microRNAs (specifically inflamma-miRs), including miR-146a and miR-499a, contribute to the regulation of inflammatory status in the development of cardiovascular pathology and thromboinflammation [13]. This study aimed to investigate the association of polymorphisms rs2910164 in the *MIR146A* gene and rs3746444 in the *MIR499A* gene with the risk of adverse cardiovascular events in patients with CHD following CABG, as well as with widely accessible clinical markers of inflammation.

Despite previous studies demonstrating the role of microRNAs in modulating inflammatory processes and thrombosis, our data did not reveal statistically significant differences in genotype frequencies of the studied polymorphisms between patients who experienced adverse cardiovascular events and those who did not, both in the early and late postoperative periods.

According to the literature, a study by Qu J.Y. et al., conducted on 1,139 ischemic stroke patients and 1,585 controls, found no significant association between the rs2910164 polymorphism in *MIR146A* and the risk of ischemic stroke (OR = 1.00; 95% CI = 0.80–1.24; $p = 0.985$). However, prospective follow-up of these patients over 4.5 years revealed that the presence of this polymorphism was associated with a 1.56-fold increase in the risk of recurrent stroke (HR = 1.56; 95% CI = 1.10–2.20; $p = 0.013$) and a 2.13-fold increased risk of death from cardiovascular causes or stroke (HR = 2.13; 95% CI = 1.31–3.46; $p = 0.002$). Thus, the rs2910164 polymorphism appears to be a significant predictor of stroke prognosis, though not of its initial development [14].

In another study, X.R. Qiao et al. found that the rs2910164 polymorphism in *MIR146A* significantly increased the risk of acute coronary syndrome (ACS) (dominant model: OR = 1.270, $p = 0.049$; recessive model: OR = 1.402, $p = 0.039$). Moreover, patients with the G allele of rs2910164 exhibited elevated levels of inflammatory factors, which may contribute to the activation of the NF-kB signaling pathway. In patients who underwent percutaneous coronary intervention (PCI), carriage of the G allele was associated with a heightened risk of adverse cardiovascular events (OR = 1.405, $p = 0.038$). The authors concluded that the AG+GG variant of the rs2910164 polymorphism in *MIR146A* is closely linked to the risk of developing ACS in Han Chinese individuals. Patients carrying the G allele of rs2910164 may experience more severe pathological changes and poorer outcomes post-PCI, possibly due to oxidatively modified miR-146a, which aberrantly binds to the 3'-untranslated region of the IKBA gene, activating NF-kB inflammatory pathways [15].

The rs2910164 polymorphism in *MIR146A*, which influences both the structure and expression of miR-146a, plays a crucial role in inflammation regulation through the NF-kB pathway according to multiple studies [15]. Theoretically, this polymorphism could impact the risk of thrombotic and inflammatory complications in post-CABG patients. In our study, the frequency of the rare C allele was 40% and 51% among CHD patients with and without adverse events post-CABG, respectively. Carriage of this allele was not associated with an increased risk of early or late cardiovascular events. However, in patients with the homozygous GG genotype, there was a postoperative increase in the expression of platelet activation markers, such as P-selectin and

intercellular aggregates, potentially indicating an enhanced inflammatory response to surgical intervention.

M.P. Boldin et al. published a seminal study demonstrating that NF-kB induced miR-146a expression as part of a negative feedback loop, resulting in reduced levels of IL-1 receptor-associated kinase (IRAK1) and TNF receptor-associated factor 6 (TRAF6) [16]. The authors showed that bacterial components activated NF-kB via a MyD88-dependent pathway, which, in turn, elevated miR-146a levels. Notably, the increase in miR-146a subtly regulates inflammatory cytokine production rather than completely suppressing this pathway. Subsequently, the same research group characterized the role of miR-146a in immune and inflammatory responses using a mouse model [16]. Deletion of miR-146a in mice led to heightened inflammation in response to endotoxin exposure. As these mice aged, they developed multi-organ inflammation, myeloid cell proliferation, and cancer, ultimately leading to premature death [16]. These findings suggest an additional pathway linking inflammation with cardiovascular disease.

The functional role of miR-146a in ischemia/reperfusion (I/R) injury has also been documented. L. Xiao et al. administered mimic miR-146a in a mouse model prior to I/R injury, which preserved cardiac function, reduced infarct size and fibrosis, and decreased the inflammatory response [17]. The rs3746444 polymorphism in *MIR499A*, which also influences inflammatory processes through miR-499a, did not show a significant effect on the incidence of cardiovascular complications in the postoperative period. Although miR-499a exhibits cardioprotective properties, our study data do not support an association between this polymorphism and clinical outcomes in CHD patients post-CABG.

In a Chinese population, the homozygous GG genotype was associated with a significantly increased risk of CHD (OR 2.87, 95% CI 1.63–5.04, $p < 0.001$) [18]. In Egypt, researchers not only confirmed the association between rs3746444 and predisposition to AMI and CHD but also demonstrated that patients with AMI exhibited a high relative expression of miR-499a (over a 100-fold increase, $p < 0.001$), while in healthy controls and hypertensive patients, this expression was almost undetectable [19].

A meta-analysis by Y. Yang et al., which included studies from PubMed, EMBASE, ISI Web of Science, and Scopus databases, evaluated associations between miRNA polymorphisms and AMI susceptibility: it involved 2,507 AMI patients and 3,796 healthy controls and analyzed 9 miRNA genes. The study found that miR-146a rs2910164 and miR-499 rs3746444 were significantly associated with susceptibility to AMI (rs2910164: GG/CC, OR 1.40, 95% CI 1.05–1.74, $p < 0.001$; rs3746444: AA + AG/GG, OR 2.04, 95% CI 1.37–2.70, $p < 0.001$) [20].

The absence of an association between the rs2910164 genotype in *MIR146A* and rs3746444 in *MIR499A* with the development of both hospital and long-term adverse events in our study may indicate that, in addition to the presence of polymorphisms, other genetic and epigenetic factors could determine individual inflammatory and thrombotic responses post-surgery.

In summary, our study results do not confirm a significant impact of the rs2910164 and rs3746444 polymorphisms on the risk of cardiovascular complications post-CABG. However, these findings may prove valuable for further exploration of inflammatory and thrombotic mechanisms in the context of CHD and CABG, as well as for the development of more individualized approaches to patient management.

Conclusion

The allele frequencies of G and C (rs2910164) in the group of CHD patients were 0.62 and 0.38, respectively. For alleles A and G (rs3746444) in the CHD group, frequencies were 0.83 and 0.17, respectively. Among CHD patients carrying the rare C allele of the rs2910164 polymorphism in *MIR146A*, the incidence of in-hospital and long-term adverse cardiovascular events did not differ significantly from that in patients with the GG homozygous genotype. Similarly, in CHD patients carrying the rare G allele of the rs3746444 polymorphism in *MIR499*, the incidence of adverse cardiovascular events was comparable to that in patients with the AA homozygous genotype. Additionally, CHD patients with the rare G allele of rs3746444 *MIR499* showed no significant difference in intercellular aggregate levels, ESR, CRP, leukocyte, and platelet counts compared to those with the AA homozygous genotype before and 8–10 days after CABG. Following CABG, patients with the GG homozygous genotype for rs2910164 *MIR146A* exhibited significantly elevated levels in MFI of platelet-platelet aggregates, MFI of P-selectin-expressing platelets, MFI of P-selectin-expressing platelet-monocyte aggregates, and MFI of P-selectin-expressing platelet-platelet aggregates. ESR was significantly higher among patients with the rare C allele of rs2910164 *MIR146A* prior to CABG. The findings suggest that genotyping for the *MIR146A* rs2910164 polymorphism could help identify CAD patients at risk for heightened platelet activation following CABG. For carriers of the GG genotype, more rigorous monitoring of platelet function and perhaps tailored antiplatelet therapy regimens could be considered to potentially mitigate the risk of thrombotic complications.

Study Limitations

When interpreting these findings, it is important to consider that this was a single-center study with a limited sample size, which may have impacted the statistical significance of the results.

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Information on author contributions

Grinshtein Yu.I., together with Subbotina T.N., developed the study concept and protocol, supervised data collection, and edited the final version of the manuscript. Subbotina T.N. oversaw the quality of genetic analysis. Kosinova A.A., together with Mongush T.S., formed the patient cohort, monitored them during therapy, and collected endpoint data. Kosinova A.A., together with Semashchenko K.S., performed statistical data processing, analyzed the data, and wrote the initial draft of the manuscript. Makarova D.Yu. and Shaleva A.A. conducted the genetic analysis and assisted Kosinova A.A. and Semashchenko K.S. in the analysis of literature data. The translation of the manuscript into English was carried out by Kosinova A.A.

All authors approved the final version of the manuscript for submission and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

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Гринштейн Ю.И., Субботина Т.Н. разработали концепцию и протокол исследования, курировали сбор данных и редактировали окончательную версию рукописи; Субботина Т.Н. контролировала качество генетического анализа; Косинова А.А., Монгуш Т.С. формировали когорту пациентов, наблюдали за ними в ходе терапии и собирали данные по конечным точкам; Косинова А.А., Семащенко К.С. провели статистическую обработку данных, проанализировали их и написали первоначальный вариант рукописи; Макарова Д.Ю., Шалева А.А. выполнили генетический анализ, помогали Косиновой А.А. и Семащенко К.С. в анализе литературных данных; Косинова А.А. перевела рукопись на английский язык.

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