

УДК 616.379-008.64-06:617.586-021.4-002-073.916-079.4
<https://doi.org/10.20538/1682-0363-2026-1-105-112>

Risk Factors for Cognitive Decline in Patients in Long-term Period of Coronary Artery Bypass Grafting

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ABSTRACT

Aim. To identify risk factors leading to a cognitive decline 5–7 years after CABG, and to develop a model for predicting the development of POCD in patients in the long-term period of CABG.

Materials and methods. The observational prospective study included 146 patients; average follow-up period was 6.4 years. The patients underwent general clinical, neurological, and instrumental examinations 3–5 days before and 5–7 years after surgery. Neuropsychological testing included assessment of psychomotor and executive functions, attention, and short-term memory. The method of binary logistic regression was used to build a predictive model.

Results. Cognitive decline was detected in 67 patients (45.9%) at 5–7 years after CABG. The presence of carotid artery (CA) stenosis ($p = 0.01$), smoking ($p = 0.005$), reduced left ventricular ejection fraction ($p = 0.039$), and high triglyceride levels ($p = 0.011$) were associated with a cognitive decline. The model's sensitivity was 0.61 and specificity was 0.82, indicating a good quality. Results indicate that the model can accurately predict the presence or absence of cognitive decline with a high level of accuracy.

Conclusion. Five to seven years following CABG, 46% of patients experienced a decrease in cognitive functions, manifested in the form of neurodynamic dysfunction, as well as deterioration of short-term memory. The factors included in the prognostic model were CA stenosis, reduced left ventricular ejection fraction, and high triglyceride levels, as well as smoking. The findings indicate the need to improve approaches to postoperative follow-up of patients who have undergone cardiac surgery in order to minimize adverse neurological consequences.

Keywords: cognitive functions, CA stenosis, coronary artery bypass grafting, long-term postoperative period

Source of financing. The study was carried out as part of fundamental research topic No. 0419-2022-0002 “Development of Innovative Models for Management of Cardiovascular Disease Risk Factors and Comorbidities Based on the Study of Fundamental, Clinical, and Epidemiological Mechanisms and Healthcare Management Techniques in the Industrial Region of Siberia”.

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article

Conformity with the principles of ethics. The protocol of the study received approval by the Institutional Review Board of the Federal State Budgetary Institution “Research Institute for Complex Issues of Cardiovascular Diseases” (Minutes No. 20 dated January 25, 2011).

For citation: Syrova I.D., Tarasova I.V., Trubnikova O.A., Sosnina A.S., Ivanov V.I., Barbarash O.L. Risk Factors for Cognitive Decline in Patients in Long-term Period of Coronary Artery Bypass Grafting. *Bulletin of Siberian Medicine*. 2026;26(1):105–112. <https://doi.org/10.20538/1682-0363-2026-1-105-112>.

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Факторы риска когнитивного снижения у пациентов в отдаленном периоде коронарного шунтирования

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РЕЗЮМЕ

Цель. Выявление факторов риска снижения когнитивных функций через 5–7 лет после КШ, а также разработка прогностической модели, способной предсказать вероятность развития ПОКД у пациентов в отдаленном периоде КШ.

Материалы и методы. В наблюдательное проспективное исследование включены 146 пациентов, средний период наблюдения составил 6,4 года. Пациенты прошли общее клиническое, неврологическое и инструментальные обследования за 3–5 дней до и через 5–7 лет после операции. Нейropsychологическое тестирование включало оценку психомоторных и исполнительных функций, внимания и кратковременной памяти. Для построения прогностической модели использовался метод бинарной логистической регрессии.

Результаты. Когнитивное снижение через 5–7 лет после операции выявлено у 67 (45,9%) пациентов. Установлено, что наличие стенозов сонных артерий (СА) ($p = 0,01$), факт курения ($p = 0,005$), низкий уровень фракции выброса левого желудочка ($p = 0,039$) и высокий уровень триглицеридов ($p = 0,011$) были ассоциированы с развитием когнитивного снижения через 5–7 лет после проведения КШ. Уровень чувствительности составил 0,61; специфичности – 0,82, обеспечивая успешное определение наличия или отсутствия снижения когнитивных функций, что говорит о хорошем качестве прогностической модели.

Заключение. Через 5–7 лет после проведения операции КШ у 46% пациентов наблюдается снижение когнитивных функций, проявляющееся в виде нейродинамических нарушений, а также ухудшения кратковременной памяти. Факторами, вошедшими в прогностическую модель, являлись стенозы СА, низкий уровень фракции выброса левого желудочка и высокий уровень триглицеридов, а также курение пациентов. Это свидетельствует о необходимости совершенствования подходов к послеоперационному наблюдению за пациентами, перенесшими кардиохирургические операции, с целью минимизации неблагоприятных неврологических последствий.

Ключевые слова: когнитивные функции, стенозы СА, коронарное шунтирование, отдаленный послеоперационный период

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

Источник финансирования. Исследование выполнено в рамках фундаментального научного исследования № 0419-2022-0002 «Разработка инновационных моделей управления риском развития болезней системы кровообращения с учетом коморбидности на основе изучения фундаментальных, клинических, эпидемиологических механизмов и организационных технологий медицинской помощи в условиях промышленного региона Сибири».

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование утверждено этическим комитетом ФГБНУ НИИ КПССЗ (протокол № 20 от 25.01.2011).

Для цитирования: Сырова И.Д., Тарасова И.В., Трубникова О.А., Соснина А.С., Иванов В.И., Барбараш О.Л. Факторы риска когнитивного снижения у пациентов в отдаленном периоде коронарного шунтирования. *Бюллетень сибирской медицины*. 2026;26(1):105–112. <https://doi.org/10.20538/1682-0363-2026-1-105-112>.

INTRODUCTION

Coronary artery bypass grafting (CABG) is a cardiac surgical procedure with a high risk of complications like postoperative cognitive dysfunction (POCD) [1]. It can be either short-term or long-term [2]. POCD is associated with an increase in medical care costs, longer hospital stay, and an increase in one-year mortality rate [3]. A significant part of patients referred for myocardial revascularization have chronic cerebral ischemia and are more vulnerable to cognitive decline after surgery [4]. Chronic cerebral circulatory insufficiency and impaired cardiac pumping function are cited as the causes of cognitive impairment in the cohort of patients who are considered as candidates for elective CABG [5].

Identification of modifiable risk factors and mechanisms contributing to the development of POCD can help prevent this dangerous condition and, as a result, improve the effectiveness of patient treatment. There is a large number of studies on the risk factors for cognitive decline in patients in the early postoperative period of cardiac surgery [6–9]. It has been shown that age, cardiopulmonary bypass (CPB) time, and arterial hypertension can be significant predictors of the development of POCD [10]. The role of intraoperative hypoperfusion in the development of POCD is particularly emphasized [7]. The brain and kidneys are the organs most sensitive to changes in blood pressure during CPB, however, optimal cerebral perfusion pressure to maintain stable cerebral blood flow is still a subject of discussion. [11].

The development and aggravation of postoperative cognitive impairment in the long-term period largely negates the success of cardiac surgery, leading to disability, lower quality of life, and higher mortality [12, 13]. The data obtained emphasize the importance of timely identification of patients at high risk of POCD both in the early and long-term period.

However, one should note that studies on the risk factors for the development and aggravation of POCD in the remote postoperative period of CABG are scarce [14, 15]. It has been shown that the patient's age, smoking history, hypertension, diabetes mellitus, heart failure, and preoperative cognitive impairment are predictors of persistent POCD one year after CABG [15]. However, it remains unclear whether these factors will have the same significance in the long term, for example, 5–7 years after surgery. Recurrent strokes and progression of coronary stenosis, development of atrial fibrillation, as well as the level of adherence to treatment can also be considered as possible predictors

of the development of cognitive decline in the remote postoperative period. In this regard, the aim of this study was to identify risk factors for cognitive decline 5–7 years after CABG, as well as to develop a model for predicting the likelihood of developing POCD in patients in the long-term period of CABG.

MATERIALS AND METHODS

The selective observational prospective study was performed to assess the neurological and cognitive status of patients with coronary artery disease (CAD) over a 5–7-year period after CABG, with an average follow-up of 6.4 years. The study included 152 patients with stable CAD who were admitted to an inpatient unit to undergo a surgery. The study was conducted in strict accordance with international standards of Good Clinical Practice and the Declaration of Helsinki (2008). The protocol of the study was approved by the Institutional Review Board of the Research Institute for Complex Issues of Cardiovascular Diseases (Minutes No. 20 dated January 25, 2011). Prior to inclusion in the study, all participants received all the necessary information and provided their consent to participate.

The inclusion criteria were as follows: age 45–69 years, male gender, normal or adjusted to normal vision and hearing, elective primary CABG with CPB. The exclusion criteria were: prior acute cerebrovascular accident (CVA), traumatic brain injury, depression (more than 8 points on the Beck's Depression Inventory), dementia (less than 24 points according to the Mini-Mental State Examination (MMSE)), carotid artery stenosis (CA) greater than 50%, severe respiratory, renal and hepatic insufficiency, and oncological diseases. The clinical and history data of the patients are presented in Table 1.

Table 1

Preoperative Clinical Characteristics of Patients	
Characteristics	Patients, <i>n</i> = 152
Age, years, <i>Me</i> [Q_{25} ; Q_{75}]	57 [53; 61]
Arterial hypertension, <i>n</i> (%)	129 (85)
Carotid artery stenosis, <i>n</i> (%)	56 (37)
Duration of carotid artery stenosis, years, <i>Me</i> [Q_{25} ; Q_{75}]	4 [2; 8]
Coronary artery disease duration, years, <i>Me</i> [Q_{25} ; Q_{75}]	5 [3; 8]
Myocardial infarction in history, <i>n</i> (%)	114 (75)
SYNTAX score, <i>Me</i> [Q_{25} ; Q_{75}]	23 [16; 28]
Number of affected arteries (coronary angiography), <i>Me</i> [Q_{25} ; Q_{75}]	2 [2; 3]
Left ventricular ejection fraction, %, <i>Me</i> [Q_{25} ; Q_{75}]	60 [51; 63]

Comprehensive examinations of patients, including clinical, neurological, and instrumental diagnostics, were conducted both before surgery and 5–7 years after it. MMSE and the Beck’s Depression Inventory were used as screening methods [16–18]. Psychophysiological Complex software was used for complex neuropsychological testing with the determination of indicators of psychomotor and executive functions, attention, and short-term memory [19]. Changes in cognitive functions were calculated using 13 parameters from a common set of tests. Cognitive decline was determined by the “20–20” criterion: postoperative indicators of cognitive functions should be lower by 20% or more compared to preoperative values in 20% of all the indicators used in the study.

The patients were treated in accordance with the general principles of therapy for patients with CAD, chronic heart failure (CHF), and arterial hypertension. The planned procedure was performed with CPB, with normal body temperature and intravenous anesthesia with propofol. The duration of CPB averaged 100.2 ± 28.2 minutes, and the time of aortic cross clamping was 62.8 ± 16.86 minutes. The average number of the grafts was 2.6 ± 0.71 . During the surgical intervention, patients underwent invasive and continuous hemodynamic monitoring and cerebral oximetry (INVOS-3100, SOMANETICS, USA). Outpatient follow-up at the place of residence was conducted for all patients after discharge from the hospital.

Statistical analysis was performed using IBM SPSS Statistics 21 software. When describing the analysis results, continuous variables were expressed as median and interquartile range $Me [Q_1; Q_3]$ and categorical variables were expressed in the form of values and percentages of $n (\%)$, the Pearson’s and Wilcoxon tests χ^2 were used to establish statistical differences.

To build a predictive model, we used the binary logistic regression method and regression coefficients. The regression equation was as follows: $y = a + b_1 \times X_1 + b_2 \times X_2 + \dots + b_i \times X_i$, where y – variable with two values: 0 means no event; 1 stands for an event occurred; a is constant; b_i is regression coefficients; X_i stands for variables. The probability of cognitive decline was determined according to a formula: $P = 1 / (1 + e^{-y})$, where P is predicted probability, e is exponent, the approximate value of which is 2.718. A method based on the percent correctly reclassified and the Somers’D measures were used to assess the validity. The Hosmer–Lemeshow goodness-of-fit test was used to verify the overall consistency of the model with real data. The differences were considered statistically significant at $p < 0.05$.

RESULTS

Analysis of the results of clinical examinations revealed that 5–7 years after CABG, 8 patients (5.3%) had myocardial infarction, and 7 (4.6%) had a stroke. The majority of the study participants had CHF with functional class (FC) no higher than II (Table 2).

Table 2

Clinical Characteristics of Patients, n (%)			
Characteristics	Patients, n = 152		p
	Before the procedure	After 5 years	
Class I-II angina pectoris	86 (57)	30 (20)	0.0004
Class III angina pectoris	33 (22)	5 (3)	< 0.0001
Class I-II CHF	116 (77)	146 (96)	0.001
Class III CHF	36 (24)	6 (4)	0.0007
Atrial fibrillation	5 (3)	12 (8)	0.1
Type 2 diabetes mellitus	21 (14)	39 (26)	0.002
CA stenosis	56 (37)	86 (57)	0.0001

A total of 146 patients out of 152 participated in a comprehensive neuropsychological testing using the STATUS PF computer program 5–7 years after CABG. Before the operation, three people dropped out due to not scoring enough points on the MMSE and Beck’s Depression Inventory scales; three more patients were unable to undergo comprehensive

neuropsychological testing due to cognitive impairments after stroke and advanced dementia.

Cognitive decline, defined as a $\geq 20\%$ decrease in postoperative cognitive indicators compared to the baseline level in $\geq 20\%$ of tests from the entire test battery, was detected 5–7 years after surgery in 67 (45.9%) patients. Patients were most likely to

exhibit deterioration in postoperative parameters when performing neurodynamic (psychomotor speed and executive functions) and short-term memory tests. In the neurodynamic domain, 60.9% of patients had an increasing number of missed signals. In tests examining short-term memory (memorization of numbers, syllables, words), deterioration occurred in more than 20% of patients (Table 3).

Table 3

Prevalence of More than 20% Cognitive Decline in the Long-term Postoperative Period, <i>n</i> (%)		
Cognitive domain	Parameters	Patients, <i>n</i> = 146
Neurodynamics	Mean reaction time	24 (16.4)
	Errors	57 (39.0)
	Missed signals	89 (60.9)
Attention	The Bourdon test, processed symbols:	
	– on the 1 st minute	12 (8.2)
	– on the 4 th minute	11 (7.5)
Memory	10 numbers memory test	31 (21.2)
	10 syllables memory test	30 (20.6)
	10 words memory test	36 (24.7)

The next stage of the study aimed at identifying the most significant risk factors for cognitive decline 5–7 years after CABG. For this purpose, we selected patients with cognitive decline 5–7 years after surgery (*n* = 67) and without cognitive decline (*n* = 79). The following predictors that could potentially influence the development of cognitive decline were included in the analysis: stroke, old age, smoking, arterial hypertension in history, heart failure with a left

ventricular ejection fraction (LVEF) of less than 50%, CA stenosis, diabetes mellitus, impaired carbohydrate tolerance, atrial fibrillation, compliance with a four-component treatment regimen for CAD, achievement of target blood pressure, indicators of lipid metabolism and glucose in blood serum, and achievement of their target values.

Possible predictors identified both before surgery and during examination 5–7 years after CABG were considered both in their original form and in the form of binomial variables. Using the step-by-step inclusion method, we build the regression model. As a result, the following factors were the most significant in terms of cognitive decline: stroke, CA stenosis present 5–7 years after CABG, preoperative LVEF, smoking before surgery, cholesterol, HDL and triglyceride levels detected during examination 5–7 years after CABG (Table 4).

Analysis of the data presented in Table 4 allow us to conclude that CVA, smoking, CA stenosis, reduced LVEF, and high triglyceride and HDL cholesterol levels detected during examination 5–7 years after CABG increase the likelihood of cognitive decline in patients in the long-term postoperative period.

The developed model correctly predicts the absence of cognitive decline in 82.3% of cases and its presence in 61.2% of cases (Table 5). With the cut-off threshold equal to 0.5, we selected the most effective ratio of sensitivity (0.61) and specificity (0.82), ensuring the successful prediction of both the presence and absence of cognitive decline and good quality of the model.

Table 4

The Main Results of Binary Logistic Regression Predicting the Development of Cognitive Decline in Patients in the Long-term Period after Coronary Artery Bypass Grafting					
Step 6	B coefficient	RMSE	Wald	<i>p</i>	Exp (B)
CVA	21.634	16644.068	0.000	0.999	2485603116.578
CA stenosis (5 years)	1.018	0.396	6.625	0.010	2.769
LVEF (before CABG)	-0.925	0.448	4.273	0.039	0.396
Smoking (before CABG)	1.067	0.381	7.841	0.005	2.906
HDL cholesterol (5 years)	1.171	0.617	3.605	0.058	3.226
Triglycerides (5 years)	0.533	0.209	6.527	0.011	1.704
Constant	-2.576	1.208	4.546	0.033	0.076

Table 5

Classification Matrix of the Predictive Model of Cognitive Decline in the Long-term Postoperative Period			
Actual cognitive decline	Predicted cognitive decline		Percent correct classification, %
	Absent	Present	
Absent	65	14	82.3
Present	26	41	61.2
Total percent of correct classification, %			72.6

Note. The cut-off threshold value is 0.5.

DISCUSSION

The results of the study demonstrated that cognitive decline 5–7 years after coronary bypass grafting occurred in 46% of patients and in most cases manifested in the form of neurodynamic dysfunction, and disorders of verbal and symbolic short-term memory.

As previously shown, the pathogenesis of postoperative cognitive impairment is multifactorial [20]. During cardiac surgery, a systemic inflammatory reaction can lead to multiple organ failure, including brain tissue injury. It has been established that some CABG patients suffer blood – brain barrier disruption, accompanied by an increase in systemic inflammation detected in blood plasma, and the development of subacute neuroinflammation [21]. The progression of atherosclerosis is accompanied by changes in the microcirculatory system, resulting in reduced vascular elasticity [22]. In combination with decreased myocardial contractility, patients may experience a deterioration in blood supply to the brain during surgery, which is reflected in the predictive model developed in this study.

Other factors included in the predictive model were smoking and elevated triglyceride levels 5–7 years after CABG, which may indicate low patient adherence to prescribed treatment. There are several known factors that contribute to low patient adherence to prescribed treatment: lack of awareness, tendency to self-medicate, non-compliance with the medication regimen, and, most importantly, the relationship between cognitive impairment and low adherence [14, 23].

CA stenosis turned out to be a significant factor determining the development of cognitive decline 5–7 years after CABG. The progression of carotid stenosis increases the risk of developing cerebral circulatory disorders, and is also an independent factor predicting the likelihood of sudden cardiac death [24]. It has been established that during CABG, the presence of CA stenosis greater than 70% in a patient can lead to ischemic stroke [25, 26]. Studies indicate that patients suffering from cerebral atherosclerosis are at increased risk of decreased blood supply to the brain, atrophy of its tissues and cognitive decline [27]. There is a probability according to which patients with asymptomatic CA stenosis may experience decreased blood flow and microembolization of the brain during surgery, which in turn causes impaired adaptive mechanisms and deterioration of cognitive

functions [28]. Among the factors contributing to the development of CA stenosis, surgical intervention on the coronary arteries can cause an exacerbation of the systemic inflammatory process and endothelial dysfunction. These changes create favorable conditions for the progression of the atherosclerotic process [29].

CONCLUSION

The present study demonstrated that 5–7 years after CABG, 46% of patients experience cognitive decline which manifested in the form of neurodynamic dysfunction and deterioration of verbal and symbolic short-term memory. The factors included in the predictive model are CA stenosis, reduced left ventricular ejection fraction, high triglyceride levels, and smoking in patients. The findings highlight the need to improve approaches to postoperative follow-up of patients who have undergone cardiac surgery in order to minimize adverse neurological consequences.

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Syrova I.D. – drafting of the the manuscript, acquisition and interpretation of data, compilation of database, statistical processing of data, and final approval of the manuscript for publication. Tarasova I.V. – conception and design, drafting of the manuscript, editing of the manuscript, and final approval of the manuscript for publication. Trubnikova O.A. – conception and design, editing of the manuscript, and

final approval of the manuscript for publication. Sosnina A.S. – acquisition and interpretation of the data, compilation of database, and final approval of the manuscript for publication. Ivanov V.I. – statistical processing of data and final approval of the manuscript for publication. Barbarash O.L. – conception and design and final approval of the manuscript for publication.

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Received on August 26, 2025;
approved after peer review on September 11, 2025;
accepted on October 16, 2025