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Evaluation of soluble fms-like thyrosine kinase-1 and anti-endothelial cell antibodies in patients with acute coronary syndrome after COVID-19 infection

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Abstract:
Objective: to evaluate the role of soluble fms-like thyroxine kinase-1 (sFlt-1) and anti-endothelial cell antibodies (AECA) in patients with acute coronary syndrome (ACS) in the post-COVID era.
Materials and Methods. The study included 118 patients (including 57 women, 61 men) with ACS and a history of novel coronavirus infection (NCI). All patients were measured for the levels of sFlt-1and AECA in the blood. The comparison group consisted of 121 patients with ACS without NCI.
Results. Elevated levels of sFlt-1 and AECA were more often detected in the ACS group and group with a history of NCI vs. the comparison group: relative risk (RR)=2.768 [95% confidence interval (CI): 2.0810-3.681], p<0.001; and RR=1.554 [95% CI: 1.216-1.987]; p=0.002), respectively. In the group of patients with ACS and a history of NCI, a more severe course of ACS was also observed: arrhythmia was observed more often (RR=1.372 [95% CI 1.005-1.784]; p=0.032), along with rehospitalization in the first 14 days for cardiovascular diseases (RR=1.475 [95% CI: 1.100-1.977]; p=0.032) and in-hospital mortality (RR=1.610 [95% CI: 1.160-2.233]; p=0.042).
Conclusion. Levels of AECA and sFlt-1 are associated with the risk of developing a severe course of ACS in patients who have previously undergone NCI.

Keywords: acute coronary syndrome, novel coronavirus infection, COVID-19, post-COVID-19 period, soluble fms-like thyrosine kinase-1, anti-endothelial cell antibodies

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Introduction

Diseases of the circulatory system are the leading cause of morbidity and mortality both in the Russian Federation (RF) and worldwide, despite the recent pandemic of the novel coronavirus infection (NCI) [1]. The post-COVID era has made its own adjustments to the course and prognosis of acute coronary syndrome (ACS). The prevalence values of pulmonary embolism, sepsis-induced cardiomyopathy, coronary artery dissections, inflammation of the heart muscle, decompensation of heart failure, complex arrhythmia, along with a special course of ACS, have increased significantly [2]. The World Health Organization (WHO) has identified post-COVID syndrome, which is based on ongoing symptoms, as well as the development of new symptoms within three months after the onset of SARS-CoV-2 infection with a prolongation of symptoms for at least two months and given that these symptoms cannot be explained alternatively [3]. The trigger for ACS in patients in the post-COVID period is an inflammatory substrate that forms a new phenotype of ACS in patients with a history of NCI. This phenotype is associated with systemic inflammation, microvascular dysfunction, endothelial dysfunction, and hypercoagulation [4].

The European Society of Cardiology emphasizes the need for clinical assessment of endothelial function in patients who have undergone NCI to facilitative monitoring and early detection of long-term cardiovascular complications [5].

Soluble fms-like tyrosine kinase-1 (sFlt-1) is a soluble form of vascular endothelial growth factor receptor-1 (VEGFR-1). It has antiangiogenic activity. The main function of sFlt-1 is to bind VEGF, which leads to a reduction in its concentration and inhibition of angiogenesis, making sFlt-1 an important regulatory component of the formation of new blood vessels in various tissues of the body [6].

Currently, the diagnostic significance of sFlt-1 as a marker for the early diagnosis of diseases, the pathogenesis of which is associated with angiogenesis, is under study [7-9]. Many studies investigated an importance of sFlt-1 as a diagnostic marker for assessing the risk of preeclampsia in pregnant women [7]. In their 2022 study, E. Kadife et al. discovered sFlt-1isoforms at different stages of inflammation, considering them as a possible diagnostic marker of sepsis [8]. In the 2022 study by H. Wada et al., an increased level of sFlt-1 in the blood of patients with cardiovascular disease (CVD) and chronic kidney disease was noted [9].

A number of studies were devoted to the role of sFlt-1 in patients with previous NCI [10, 11]. E.g., J. Eguiburu-Jaime et al. (2021) analyzed the diagnostic significance of some biomarkers as predictors of respiratory failure in patients hospitalized with COVID-19 [10]. The best prognostic accuracy was shown for sFlt-1: the area under the receiver operating characteristic curve (AUC-ROC) =0.815 ([95% confidence interval (CI): 0.730-0.882]; p<0.001), sensitivity =82.7%, and specificity =72.9%. Another study observed high levels of circulating sFlt-1 in patients with severe COVID-19 and revealed a correlation between sFlt-1 and a biomarker of endothelial dysfunction, soluble vascular cell adhesion molecule-1 (sVCAM-1) [11].

Anti-endothelial cell antibodies (AECA) are circulating autoantibodies directed against endothelial cells [12]. By affecting endothelial cells, AECA cause elevated leukocyte adhesion, cytotoxicity, induction of apoptosis, and activation of coagulation and thrombosis. Such antibodies are detected in many autoimmune and inflammatory diseases based on endothelial cell damage [13]. In particular, they were discovered in coronary artery disease associated with unstable angina, as well as clinical relapse and restenosis after percutaneous transluminal coronary angioplasty (PTCA) [14].

The search for possible predictors of the severe course of ACS in patients who have previously undergone NCI is of high interest in contemporary medicine and is of great importance for the healthcare in the RF. Their discovery would allow the transition to personalized, predictive and preventive medicine in compliance with the Decree of the RF President, On the Strategy for Scientific and Technological Development of the Russian Federation, of February 28, 2024 [15].

The goal of our study was to assess the role of sFlt-1 and AECA in patients with ACS and with previous NCI.

Materials and Methods

We conducted a prospective cohort study. The main group included 118 patients (57 women and 61 men). All of them were admitted to the regional vascular center by ambulance with suspected ACS. Then, bypassing the emergency room, all patients, in agreement with a cardiologist, anesthesiologist, intensivist and an endovascular surgeon, were transported in a supine position on a gurney to the X-ray operating room for the purpose of performing PTCA with stenting. A thorough collection of anamneses in the study group revealed a history of COVID-19 (in accordance with the WHO criteria, it was confirmed by elevated immunoglobulin G levels and positive polymerase chain reaction result based on a nasopharyngeal swab in the anamnesis,) [16]. The mean age of women and men was 57.5±6.2 years and 53.7±8.3 years, respectively. The comparison group included 121 patients (62 men and 59 women) with ACS but without a history of COVID-19, which was confirmed by a PCR smear or antibody titer. Both groups were similar in terms of gender, age and the amount of administered treatment.

The study was approved by the local Ethics Committee at Novosibirsk State Medical University of the RF Ministry of Healthcare (protocol No. 152 of May 25, 2023). Each patient signed informed consent to participate in the study in accordance with the ethical requirements of the WHO. The COVID-19 was diagnosed in accordance with the temporary clinical guidelines, Prevention, Diagnosis and Treatment of Novel Coronavirus Infection (COVID-19), version 18 (October 26, 2023), approved by the by the RF Ministry of Healthcare. The diagnosis of ACS was established based on the criteria by the Russian Society of Cardiology, as well as in compliance with the 2020 clinical guidelines, Acute Coronary Syndrome Without ST Segment Elevation of The Electrocardiogram, approved by the RF Ministry of Healthcare [18].

Our study did not include individuals with terminal renal and hepatic failure, in delirium tremens, with mental disorders, as well as terminal patients and patients with oncology (stages III-IV), drug addicts and HIV positive individuals.

The first electrocardiography (ECG) recording was performed by the ambulance team upon arrival to the patient, the second was conducted upon admission to the regional vascular center. ECG was recorded using 12 standard leads with a 6-channel Megacart device (Siemens-Elema AB, Germany) and according to Slopak (in order to clarify the localization of ischemia).

Selective coronary artery angiography (CAAG) was performed according to the 1959 method by F.M. Sones and 1967 method by M. Judkins on days 1-3 of the development of acute myocardial infarction (AMI) symptoms on an angiographic device, CAS-10, by General Electric Optima IGS 330 (USA) with image recording on a computer. All patients were fitted with drug-eluting stents, Everolimus by Abbot, Meril, MedInzh; rapid exchange (RX) delivery system with an inflatable semi-compliant balloon that minimally extends beyond the stent.

Serum for sFlt-1 was obtained from venous blood samples using the electrochemiluminescence immunoassay method using Roche technology; Elecsys sFlt-1 by Roche Diagnostics, Cobas 6000 equipment (Switzerland); fully automated process; and Roche reagent (Switzerland). AECA level was determined in blood serum using the indirect immunofluorescence method, Eurostar II microscope (Germany), and EUROIMMUN reagent (Germany).

Statistical data processing was performed using the SPSS 17.0.5 software. Taking into account their normal distribution, our data are presented as mean values of quantitative variables (M) and their standard deviations (SD). Comparison of groups by qualitative parameters was conducted using Pearson-Fisher $\chi 2$ statistic. The relative risk (RR) with 95% confidence interval (95% CI) for each variable was estimated.

Results

The clinical and demographic characteristics of the patients included in the study are presented in *Table 1*. Patients in both groups were similar in terms of clinical and anamnestic parameters, as well as their gender and age. In the ACS and NCI group, hypertension, dyslipidemia, single-vessel lesion and life-threatening arrhythmia were statistically significantly more common, while in the comparison group smoking and confirmed type 2 diabetes mellitus were observed more frequently.

The threshold values of sFlt-1 were determined using ROC analysis: a statistically significant association with ACS and NCI was detected at a value of 91 pg/ml. On average, the sFlt-1 level in the main group was 98.9 mg/ml and 79.5 mg/ml in

the comparison group. In 79 (66.9%) people, the concentration of the studied marker was more than 91 mg/ml, while 39 (33.1%) individuals had it below 91 mg/ml.

An elevated AECA exceeding 1:40 (reference values < 1:40) was detected in 35 (29.6%) people, while an AECA titer of less than 1:40 was registered in 83 (70.4%) people.

The probability of detecting sFlt-1 in the ACS and COVID-19 group was 2.7 times higher than in the comparison group (RR=2.768 [95% CI 2.810-3.681]; p<0.001). In the ACS and NCI group, an elevated titer of antibodies to endothelium was more common than in the ACS without NCI group: 35 individuals (29.6%) vs. 16 people (13.5%); RR=1.554 [95% CI 1.216-1.987]; p=0.002). The results are presented in *Table 2*.

In all patients with ACS and previous NCI, the hospital stay endpoints were assessed (*Table 3*): stent thrombosis was observed in 14 (11.8%) patients (6 men and 8 women), early post-infarction angina was detected in 12 (10.1%) patients (7 men and 5 women), arrhythmia was revealed in 32 (27.1%) patients (19 men and 13 women), post-myocardial infarction pericarditis developed in 2 (1.7%) patients (1 man and 1 woman), and recurrent myocardial infarction was established in 7 (5.9%) patients (4 men and 3 women). Vessel dissection was characteristic for 9 (7.6%) patients, including 5 women and 4 men. Rehospitalization for cardiovascular diseases (CVD) within the first 14 days was observed in 18 (15.3%) patients, including 11 men and 7 women. In-hospital mortality was registered in 10 (8.5%) patients, including 6 men and 4 women. It should be noted that in the group of patients with ACS and previous NCI, arrhythmia (RR=1.372 [95% CI 1.005-1.784]; p=0.032), readmission within the first 14 days for CVD (RR=1.475, [95% CI 1.100-1.977]; p=0.032) and in-hospital mortality (RR=1.610 [95% CI 1.160-2.233]; p=0.042) were statistically significantly more common than in the comparison group.

Table 1 . Clinical and anamnestic characteristics of patients in the main group and comparison group

Characteristic	Group				*p*	RR [95% CI]
	Main (with ACS and NCI), *n*=118		Comparison (with ACS, without NCI), *n*=121			
	Counts	%	Counts	%		
Mean age (*M±s*)	55.6±7.5	–	56.5±7.2	–	–	–
Duration of hospital admission: up to 2 h/1 day	101/17	85.6/14.4	98/23	81/19	0.341	RR=1.194 [95% CI 0.812-1.756]
Thrombolysis	12	10.2	16	13.2	0.464	RR=0.853 [95% CI 0.545-1.336]
Previous angina FC 2-3	27	22.8	21	17.3	0.287	RR=1.181 [95% CI 0.883-1.579]
History of AMI	10	91.5	14	11.6	0.426	RR=0.829 [95% CI 0.507-1.356]
History of PCI	13	11.0	10	8.3	0.471	RR=1.163 [95% CI 0.792-1.707]
History of CABG	3	2.5	5	4.1	0.495	RR=0.753 [95% CI 0.305-1.860]
Single-vessel lesion identified by CAAG	72	61.0	68	56.2	0.450	RR=1.107 [95% CI 0.849-1.444];
Multivessel lesion identified by CAAG	46	39.0	52	43.0	0.531	RR=0.919 [95% CI 0.705-1.199]
Hypertension	104	88.1	78	64.5	**p<0.001**	RR=2.327 [95% CI 1.415-3.730]
Confirmed type 2 diabetes mellitus	27	22.9	43	35.5	**0.032**	RR=0.716 [95% CI 0.517-0.993]
Smoking	44	37.3	77	63.6	**<0.001**	RR=0.580 [95% CI 0.441-0.762]
Death of relatives from CVD	27	22.9	24	19.8	0.566	RR=1.094 [95% CI 0.812-1.473]
Dyslipidemia	57	48.3	35	28.9	**0.003**	RR=1.493 [95% CI 1.163-1.917]
Life-threatening arrhythmia	26	22.0	15	12.4	**0.049**	RR=1.365 [95% CI 1.035-1.799]
Killip class > II	22	18.6	24	19.8	0.816	RR=0.962 [95% CI 0.689-1.342]

ACS, acute coronary syndrome; NCI, novel coronavirus infection; RR, relative risk; CI, confidence interval; FC, functional class; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; CAAG, coronary artery angiography; CVD, cardiovascular disease.

Table 2. Levels of soluble fms-like thyroxine kinase-1 (sFlt-1) and anti-endothelial cell antibodies (AECA) in patients of the study groups

Characteristic	Group		*p*
	Main (with ACS and NCI), *n*=118, count (%)	Comparison (with ACS, without NCI), *n*=121, count (%)	
sFlt-1 content (>70 mg/ml)	79 (66.9)	22 (18.2)	<0.001
AECA content (threshold value exceeds 1:40)	35 (29.6)	16 (13.5)	0.002

ACS, acute coronary syndrome; NCI, novel coronavirus infection.

Table 3. Endpoints of the hospital period in patients with acute coronary syndrome (ACS) and novel coronavirus infection (NCI)

Complication	Group		*p*	RR [95% CI]
	Main (with ACS and NCI), *n*=118, count (%)	Comparison (with ACS, without NCI), *n*=121, count (%)		
Stent thrombosis	14 (11.8)	8 (6.6)	0.161	RR=1.328 [95% CI 0.940-1.875]
Early post-infarction angina	12 (10.1)	9 (7.4)	0.456	RR=1.175 [95% CI 0.792-1.744]
Arrhythmia	32 (27.1)	19 (15.7)	**0.032**	RR=1.372 [95% CI 1.005-1.784]
Post-myocardial infarction pericarditis	2 (1.7)	1 (0.8)	0.547	RR=1.358 [95% CI 0.603-3.501]
Recurrent myocardial infarction	7 (5.9)	6 (4.9)	0.741	RR=1.096 [95% CI 0.651-1.845]
Vessel dissection	9 (7.6)	4 (3.3)	0.141	RR=1.435 [95% CI 0.975-2.113]
Rehospitalization for CVD in the first 14 days	18 (15.3)	8 (6.6)	**0.032**	RR=1.475 [95% CI 1.100-1.977]
In-hospital mortality	10 (8.5)	3 (2.5)	**0.042**	RR=1.610 [95% CI 1.160-2.233]

RR, relative risk; CI, confidence interval; CVD, cardiovascular disease.

Discussion

Since recently, sFlt-1 and AECA are employed in cardiology as possible markers for assessing endothelial function in patients who have undergone NCI. Their possible role as predictors for the early detection of long-term cardiovascular complications is being assessed. In our study, we observed an increase in sFlt-1 and AECA levels statistically significantly more often in patients with ACS and a history of NCI than in the comparison group. There are very few Russian and foreign studies on this topic. E.g., Italian scientists investigated the level of sFlt-1 in patients with COVID-19 and their relationship with disease outcome and thrombosis [19]. Factors independently associated with COVID-19 and thrombosis were age, the level of leukocytes in the blood, and sFlt-1. Elevated levels of this marker were significantly associated with thrombosis, especially in the subgroup that did not receive anticoagulant treatment [19].

A Spanish study assessed the impact of post-COVID conditions on the respiratory consequences of severe acute respiratory distress syndrome (ARDS) six months after NCI [20]. It was established that six months after discharge from the intensive care unit, survivors of COVID-19-associated ARDS exhibited a persistent increase in a number of markers of endothelial dysfunction, such as cell adhesion molecule 1, interleukin 8, and endothelin 1, which correlated with the severity of impaired gas exchange. Despite the fact that the authors studied the level of other markers, the study is of interest in terms of assessing the impact of post-COVID-19 conditions not only on cardiovascular complications, but also on the respiratory consequences of severe ARDS by analyzing markers of endothelial dysfunction.

Currently, there are no extensive published studies aimed at examining the levels of sFlt-1 and AECA in patients outside of pregnancy, and there are no comparisons by gender, age and comorbidity, as well as among patients of the pre-COVID era. Results obtained in our research require confirmation on larger patient samples in future studies. We believe that sFlt-1 and AECA are promising markers to investigate, as they can be useful for risk stratification of CVD in the post-COVID era, diagnosis, and treatment. Identification of predictors of severe ACS development in patients who have undergone NCI will reduce morbidity and mortality in this group of patients.

Conclusion

Patients with ACS and previous NCI exhibited elevated levels of sFlt-1 and AECA statistically significantly more often. Besides that, in the studied group of patients, arrhythmia, rehospitalization in the first 14 days for CVD and in-hospital mortality were more often observed as well. The obtained data allows stating that the studied markers are associated with the risk of developing severe ACS in patients who have previously undergone NCI. Thus, AECA and sFlt-1

may be promising markers for assessing the prognosis and predictors of severe ACS course.

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Conflict of interest. None declared by the authors.

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