https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2021-4287

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

An open-label multicenter observational study (registry) of patients recovered from coronavirus disease 2019 (COVID-19) with involvement of the cardiovascular system or with baseline severe cardiovascular diseases: rationale, design, and implications for clinical practice

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The potential impact on cardiovascular morbidity and mortality have become one of the most important issues of the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 may be associated with more frequent development of acute cardiovascular complications, while patients with established cardiovascular diseases are characterized by a higher risk of severe infection and adverse in-hospital outcomes. Due to the spread scale of the pandemic, understanding the long-term cardiovascular consequences of COVID-19 is of no less importance. Inability to extrapolate available international data to the Russian population has led to the initiation of a national multicenter study (registry) of patients recovered from COVID-19 and with concomitant involvement of the cardiovascular system or with baseline severe cardiovascular diseases. The article presents its rationale, design and implications of the results for clinical practice.

Key words: novel CO, COVID-19, SARS-CoV-2, cardiovascular diseases, registry.

Relationships and Activities: none.

Trial ID: ClinicalTrials.gov Identifier NCT04724707.

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Received: 15.01.2021
Revision Received: 17.01.2021
Accepted: 27.01.2021

For citation: Konradi A. O., Villevalde S. V., Duplyakov D. V., Kozlenok A. V., Melnik O. V., Mikhaylov E. N., Moiseeva O. M., Nedoshivin A. O., Solovieva A. E., Fokin V. A., Yakovlev A. N., Arutyunov G. P., Belenkov Yu. N., Shlyakhto E. V. An open-label multicenter observational study (registry) of patients recovered from coronavirus disease 2019 (COVID-19) with involvement of the cardiovascular system or with baseline severe cardiovascular diseases: rationale, design, and implications for clinical practice. *Russian Journal of Cardiology*. 2021;26(1):4287. (In Russ.) doi:10.15829/1560-4071-2021-4287

In conjunction with the incidence scale and direct socio-economic losses, the potential effect of novel coronavirus pandemic (COVID-19) on cardiovascular morbidity and mortality gives cause for particular concern. Testify to the fact that from 15% to 70% of COVID-19 fatal case are recorded in patients with a history of cardiovascular diseases (CVD) [1]. Severe course of COVID-19, higher need for stay in intensive care unit, artificial ventilation, vasopressor or mechanical circulatory support is more often observed in patients with risk factors or established CVD. COVID-19 can lead to cardiovascular complications due to hypoxia and systemic pro-inflammatory effects, but also direct injury to the heart and vascular endothelium [10].

According to recent reports, the COVID-19 pandemic, covering ~3,4 million people, claimed >62 thousand human lives in the Russian Federation in 2020 [11]. The data on epidemiology, course features and CVD outcomes in COVID-19 in the Russian Federation are limited. The conclusions obtained on populations in other countries, certainly, differing from the Russian Federation according to clinical and demographic characteristics of the population, CVD epidemiology and cardiovascular care, cannot be extrapolated to the Russian population. Besides they mainly relate to acute events recorded during hospitalization of patients with COVID-19 [9, 12, 13]. Long-term cardiovascular outcomes after hospital discharge remain understudied.

The need to assess and predict potential medical and socio-economic consequences for population health in the Russian Federation, as well as the importance of optimal tactics and justifying the development of specialized follow-up programs for patients with combination of COVID-19 and CVD promoted the initiation of a selective multicenter study (registry) of patients with damage of the cardiovascular system (CVS) or in the course of severe CVS disease.

Goal of the study: to determine the immediate and long-term prognosis in patients who have undergone COVID-19 with CVS damage, and to form an optimal follow-up system for such patients, including follow-up duration, examination frequency and standards.

Material and methods

Study population. The study is conducted in a population of patients who have been hospitalized with COVID-19 and CVS damage or with severe CVS pathology. The enrollment criteria and the groups that are expected to be monitored dynamically under protocol are presented in Table 1.

Study design and data source. The study (register) is openly observationally researched and is aimed at collecting data from general practitioners, therapists and cardiologists about patients discharged from hospital and meeting the enrollment criteria. Sequential patient enrollment and prospective follow-up for at least 12 months after discharge with the possibility of extension based

on preliminary analysis result is expected. In the absence of an opportunity for in presence visit, the data will be collected by phone.

Any organization in the Russian Federation becomes center-participant in the study in case of declared desire and opportunity to include and monitor at least 30 patients during the year. The patient enrollment is possible either at the phase of discharge from hospital (option with prospective enrollment), or at the stage of the first outpatient visit after discharge (option with retrospective enrollment), which allows center-participants to select patients who survived during hospitalization, have confirmed COVID-19 status and verified CVS damage.

A general electronic individual registration card is formed for each patient included in the study, regardless of CVS damage type. For each enrollment criteria, additional anamnesis and examination data are assumed according to Table 2. The data collection is carried out only in electronic form.

Sub-study of biomarkers. As part of the study (register), an additional study of biomarker level in blood plasma and serum samples and genetic testing is carried out in the core laboratory.

Imaging sub-study. As part of the study (register), an additional image sub-study is carried out. Video images are provided with the study participant identification number (without specifying the patient's personal data) to a single image processing center. This allows an independent expert to perform an in-depth analysis of imaging data (heart structure and function, coronary artery damage to coronary arteries, lung parenchyma, and pulmonary vascular flow).

Confidentiality and informed consent. All data entered in the online form register, as well as video images and biological samples, are marked in a strictly depersonalized form. Patients included in the study sign an informed consent to participate in the study, take, storage and transfer to third parties video images and biological samples without indicating their personal data. The study protocol and the consent form are approved by the ethics committee(s) of appropriate centers prior to start of patient enrollment.

Study organizer. The study (register) organizer is the Russian Society of Cardiology (RSC). On September 17, 2020, the RSC official website published an advertise for the study (register) initiation and the protocol [14]. Additionally, RSC members were

notified by email. The initial collection, processing and further analysis of biological samples and video images will be carried out on the basis of the Federal State Budgetary Institution "Almazov National Medical Research Centre" of the Ministry of Health of the Russian Federation. The study was approved by the Ethics Committee of the Federal State Budgetary Institution "Almazov National Medical Research Centre" of the Ministry of Health of the Russian Federation (Protocol No. 09-20-01C dated September 11, 2020). The enrollment of new center-participants and communication with researchers is carried out by the coordination group.

Statistical analysis. In statistical processing, the patient clinical and demographic characteristics, COVID-19 severity, CVS damage frequency, quality of life of the enrolled patients, follow-up trajectory of cardiovascular damage course, outcomes (construction of Kaplan-Meier survival curves in subgroups) will be assessed, if the prognostic effect is confirmed, the construction of multivariate Cox regression models will be also assessed.

Discussion

Increasing public awareness and medical aid appealability, maintaining its availability and quality, but also assessing the possible obvious and non-obvious residue of infection, including long-term ones, in convalescents, is of particular significance in patient with COVID-19 and CVD population. The organization of systematic patient follow-up, standardized and coordinated data collection at the domestic level and their timely analysis can have a decisive importance in strategic planning and cardiology service transformation in the present epidemiological conditions. The supplied study (register) will provide information on the spectrum of cardiovascular consequences in the short and long term in hospitalized patients who have come through COVID-19.

The importance of studying the relationship between COVID-19 and CVD is not limited to the high and growing incidence and appalling socio-economic losses that have become a challenge for the health system during the COVID-19 dissemination and have been a persistent problem over the decades in the fight against the burden of chronic non-communicable diseases [15]. The COVID-19 and CVD progression and adverse effects share common pathophysiological mechanisms — inflammation, activation of the sympathetic and renin-angiotensin-aldosterone systems, damage to target organs, their dysfunction and failure [16, 17]. Such general characteristics as elderly age of patients, risk factors (smoking, obesity, arterial hypertension), and high frequency of comorbid conditions emphasize the need to study the features of the COVID-19 and CVD combination. In the study of frequency and outcomes in severe COVID-19 compared with acute respiratory distress syndrome of other etiologies, it was shown that age, gender, and kidney function correcting factor reduces the presumed higher risk of myocardial damage in COVID-19, and additional inclusion of multiple organ dysfunction in a multifactorial model reduces the fatal case associated with myocardial injury [18].

The interpretation of myocardial damage in COVID-19 is ambiguous. In its genesis, along with destabilization of atheromas and development of acute coronary events, damage to microvasculature, appearance or aggravation of an imbalance between oxygen demand and delivery in conditions of acute systemic inflammation and cytokine storm, development of tako-tsubo syndrome, and thrombotic complications may play a role [10]. The design of an algorithm for decision-making tactics (incl. solution to an issue on percutaneous coronary intervention) in each specific situation requires the collection of extensive data and their competent analysis. The importance of examination and careful long-term

Table 1

Criteria for enrollment and list of groups expected to be monitored dynamically within the study (register) framework

1. Hospitalization with COVID-19 with U07.1 or U07.2 code according to the International Classification of Diseases, 10th Edition.
2. CVS damage, defined as*: 1) proven myocarditis or suspected myocarditis; 2) presence of chronic heart failure of grade II or more grade before disease or appearance of heart failure signs associated with COVID-19; 3) combination with acute coronary syndrome or development of acute coronary syndrome associated with infection, including performed endovascular procedures; 4) proven pulmonary artery thromboembolia; 5) hemodynamically relevant arrhythmias (atrial fibrillation, high-grade ventricular extrasystole, paroxysmal ventricular arrhythmias), including associated with prolongation of the QT interval.

Note: * — patient can be enrolled according to one or more criteria of CVS damage.

Table 2

Schedule of visits (telephone contacts) and list of necessary examinations

	Enrollment	1 month* ± 1 week	3 months ± 1 week	6 months ± 2 weeks	12 months ± 2 weeks
Detailed analysis of documentation and CRF filling	+				
Structured complaints analysis	+	+*	+	+	+
Objective data	+	+*	+	+	+
Informed consent	+ during prospective enrollment		+ during retrospective enrollment		
EchoCG	+[&]	+*	+*[#]	+	+
Biochemical examination data (special examination by subgroups)	+		+ (during in presence visit)	+	+
Blood collection for biobanking, including genetic analysis	+ during prospective enrollment		+ during retrospective enrollment	+ (except for genetics)	+ (except for genetics)
Analysis of therapy	+		+	+	+
Analysis of hospitalization			+	+	+
Endpoint analysis			+	+	+
Quality of life questionnaire (KCCQ)	+ (when check-out)		+	+	+
Contrast-enhanced cardiac MRI*	+		+		
Endomyocardial biopsy*	+		+		
Daily ECG monitoring*		+	+		
MSCT pulmonary angiography[#]	+[#]		+ (if control study was performed)[#]		
CA results[&]	+ (if performed)				

Note: * — only for the criterion "proven myocarditis or suspected myocarditis", additional visit of 1 month — only in case of severe course; [#] — only for the criterion "proven pulmonary artery thromboembolia"; [&] — only for the criterion "combination with acute coronary syndrome or development of acute coronary syndrome associated with COVID-19", all EchoCG protocols performed during hospitalization are downloaded.

Acronyms and abbreviations: CRF — clinical report form, CA — coronary angiography, MRI — magnetic resonance imaging, MSCT — multispiral computed tomography, ECG — electrocardiography, EchoCG — echocardiography, KCCQ (Kansas City Cardiomyopathy Questionnaire) — Kansas questionnaire for patients with cardiomyopathy.

follow-up of patients with myocardial damage associated with COVID-19 is emphasized by described clinical cases of myocarditis and identification of SARS-CoV-2 virus particles in cardiomyocytes by electron microscopy [19-21]. The study of the results of magnetic resonance imaging of the heart, showing signs of distant changes in the myocardium in patients coming through COVID-19 stirs particular control [22]. Whether these changes are the consequence of background risk factors and comorbid conditions, or a direct result of COVID-19, remains to be determined in the prospective follow-up of patients enrolled upon the criteria for confirmed myocarditis or suspected myocarditis, with subsequent image interpretation by an independent expert.

A separate group for enrollment is patients with hemodynamically significant heart rhythm disorders. Along with the increased risk of arrhythmias associated with infectious process (irrespective of the presence of structural and functional changes in myocardium), the interest in these complications comes from the potential cardiotoxicity of drugs that are widely used empirically as COVID-19 therapy. With insufficient scientifically grounded data on the management of patients, most approaches rely on the experts' opinion. This also applies to the choice of drug and the dosage regimen of anticoagulants in patients hospitalized with COVID-19. The study of routine clinical practice will allow to assess the frequency of thrombotic and thromboembolic complications, primarily pulmonary artery thromboembolia, as well as their outcomes, including the risk of hemorrhagic complications, depending on the chosen therapeutic strategy.

Since dispensary observation of patients who have undergone COVID-19 is not yet regulated by

orders and procedures for providing assistance, and rehabilitation programs mainly expect rehabilitation after pneumonia, it is critically important to collect data on recovery time, possible separated risks in patients with clinically significant CVS damage associated with COVID-19, as well as to assess the prognosis of patients who initially had serious heart damage, chronic heart failure, in whom the transferred infection could affect its further course. The detected changes in the biomarker level may contribute to understanding the COVID-19 pathogenesis, as well as be additional factors that can be used in stratifying patients by the CVD damage risk or adverse outcomes.

Study limitations. In a situation of continuing tense epidemiological situation, participation in the study (register) may be an additional workload on medical organizations' staff. A greater readiness to participate in patient enrollment from research centers and clinics at institutes, rather than urban hospitals that are restructured to provide assistance to patients with COVID-19 can be expected, which potentially limits the sample representativeness. However, data from more than 30 centers of different regions that are currently registered as participants can provide a picture that is more corresponded to actual practice than data obtained from a single institution.

The study design retains the limitations inherent in observational studies, and to obtain more solid evidence, it may be necessary to use the results of registers and observational studies performed in the Russian Federation before COVID-19 pandemic development.

Conclusion

By the aid of the join forces of specialists-participants in studies from different cities of the Russian Federation, it is expected that the data obtained on features of clinical manifestations of the COVID-19 and CVD combination, management in real clinical practice and outcomes in the future will justify approaches to the prevention of complications, the introduction of new treatment methods and determine optimal management for such patients.

Relationships and Activities: none.

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