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International register "Analysis of chronic non-infectious diseases dynamics after COVID-19 infection in adult patients (ACTIV SARS-CoV-2)"

Comorbid patients are one of the most vulnerable groups in the COVID-19 pandemic. At present, there are no clinical registries in Russia for collection and analysis of information about delayed consequences of comorbidities in patients after COVID-19. The Eurasian Association of Therapists has initiated creation of a registry for an important scientific and practical task, evaluating the effect of the novel coronavirus infection on long-term dynamics of chronic infectious diseases. This registry was created on the basis of centers in the Russian Federation, the Republic of Armenia, the Republic of Kazakhstan, the Republic of Kyrgyzstan, the Republic of Uzbekistan, the Republic of Belarus, and the Republic of Moldova. The major goal of the registry is evaluating the dynamics of comorbidities in patients after COVID-19 at 3, 6, and 12 months after recovery.

Keywords COVID-19; viral respiratory infection; comorbidities; cardiovascular diseases; chronic noninfectious diseases; polymorbidity; registry

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SARS-CoV-2 ACTIV Registry was initiated by the Eurasian Association of Therapists (EAT). EAT experts believe that the long-term effects of the new coronavirus infection caused by SARS-CoV-2 (COVID-19) on comorbid states has become a healthcare challenge.

This belief is based on data obtained from the analysis of long-term effects in patients infected with SARS-CoV (increased blood lipids and other factors contributing to cardiovascular disease [1]), which is known to be 80% identical to SARS-CoV-2. Absence of population immunity, the rapid spread of the virus, relatively high incidence of severe cases (about 10–20%, especially in elderly people with concomitant diseases), multiple organ injuries, severe systemic inflammatory responses, presence of local vascular lesions, predominantly in microcirculatory vessels; suggests that the infection with SARS-CoV-2 may increase the likelihood of progression of existing concomitant pathologies, including cardiovascular diseases [2, 3].

There were no previous Russian clinical registries designed to collect and analyze information on long-term effects on the course of concomitant conditions in patients with a history of COVID-19. It is of great scientific and practical importance to develop a registry to assess the long-term effects of the new coronavirus infection on the course of chronic non-communicable diseases.

The main task of the registry is to assess the course of comorbid conditions in patients with a history of COVID-19 at 3, 6, and 12 month periods after recovery (the parameters of the register includes those hospitalized, discharge from hospital or discharge after outpatient treatment as well as ambulatory patients).

The following important information will be complied as the Registry is completed:

- incidence of non-communicable diseases (period: 12 months from the moment patients seek health care), percentage of patients with non-communicable diseases of the total number of patients included in the study;
- COVID-19 severity depending on pre-existing conditions (period: 12 months from the moment patients seek health care), the correlation between the number of patients with COVID-19 of any severity and the number of pre-existing conditions and their severity in these groups;establishment/change of disability status (period: 12 months from the moment patients seek health care), the establishment of disability or change of disability status;
- mortality rate (period: 12 months from the moment patients seek health care), the mortality rate among the registered subjects;
- incidence of fatal outcomes depending on a pre-existing disease (period: 12 months from the moment patients seek health care), the correlation between the number of deaths and pre-existing diseases.

In conjunction with the Registry, a pilot project will be carried out, in cooperation with the Smorodintsev Research Institute for Influenza, to study the differences in the virus genome in different regions of the Russian Federation. The data obtained will be used to develop recommendations on the improvement of medication management of patients with a history of COVID-19.

Patient population

Male and female patients with COVID-19 will be anonymously included in the Registry (nasopharynx and oropharynx swab findings, antibody titer, typical computed tomography presentation), whether hospitalized or treated at home.

Registry implementation territory

The Registry is being implemented at 25 sites in 5 federal districts of the Russian Federation, as well as sites in Armenia, Kazakhstan, Kyrgyzstan, Belarus, Moldova, and Uzbekistan. The estimated capacity of the Registry is 5,400 patients.

Definitions

Chronic non-communicable diseases were defined following current clinical guidelines. A patient with two or more diseases was considered comorbid.

Study design

The study design is a close, multi-center registry with two non-intersecting branches (outpatient branch and hospital branch). The CARDIO-ACTIV sub-study is allocated in the hospital branch and will be performed at four sites. Six visits are envisaged (Table 1). The period of follow-up is 12 months. It is planned to analyze inpatient or outpatient medical records retrospectively, outcomes of the disease, and monitor patient condition prospectively (through telephone surveys using the standard questionnaire, or face-to-face visits within the CARDIO-ACTIV study) at 3, 6, and 12 months after recovery from COVID-19.

Registry organization

Recruitment started was on 29 June 2020 and ended on 29 November 2020. The Registry will be completed on 29 November 2021. Three committees working alongside the Registry: organizational, supervisory committees, and the committee analyzing endpoints, and the committee controlling completion of case report forms (CRFs). CRF document circulation is electronic. A total of 140 physicians in 25 sites form the Registry. Monitors are controlling each CRF.

Ethical review

The ethical review was carried out by the ethics committee of the N.I. Pirogov Russian National Research Medical University, for the Russian sites, and local ethics committees in the other countries participating in the Registry. Registry ClinicalTrials.gov ID: NCT04492384. Website of the Registry. Information about the Registry can be found on the website of the Eurasian Association of Therapists or by the direct link: https://activ.euat.ru/, accessible from all computer and mobile devices.

Data collection

Data collection for the Registry is open. All patient information obtained is confidential following the principles of Good Clinical Practice. Only an auto-assigned unique number (ID) of the patient is entered into the CRF. If a patient meets the inclusion/exclusion criteria, he/she is included in one of the Registry branches, and an anonymized CRF is completed based on the required fields of information, with a mandatory follow-up period via visits or over the telephone interviews to monitor the primary and secondary endpoints.

Statistical methodology of the Registry

Statistical processing will include the following steps:

- calculation of the necessary study sample taking into account the hypotheses; expected intergroup differences of the categorical variables and dispersions for the quantitative variables; target levels of accuracy and significance;
- after the data collection: exploratory analysis (identification of the most significant variables,

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Table 1. SARS-CoV-2 ACTIV registry design

#	Visits	Outpatient branch	Hospital branch	
			Study	CARDIO-ACTIV substudy
1	Inclusion	Retrospective data from the outpatient medical record	Retrospective data from the inpatient medical record	Retrospective data from the inpatient medical record
2	Days 7–12	Retrospective data from the outpatient medical record	Retrospective data from the inpatient medical record	Retrospective data from the inpatient medical record
3	Outcome (discharge from hospital or after outpatient treatment/death)	Retrospective data from the outpatient medical record	Retrospective data from the inpatient medical record	Retrospective data from the inpatient medical record
4	Three months after discharge from hospital or outpatient treatment	Phone call	Phone call	Patient in-person visit
5	Six months after discharge from hospital or outpatient treatment	Phone call	Phone call	Patient in-person visit
6	Twelve months after discharge from hospital or outpatient treatment	Phone call	Phone call	Patient in-person visit

anomalies, correlations, distribution analysis, and testing of normality);

- data clearing and transformation: substitution of missing values, removal of omissions, normalization, if necessary, transformations (creation of new variables, grouping of numerical variables, regrouping of categorical variables); if necessary, reduction of the sample (exclusion of observations) to ensure representativeness;
- if necessary, repeat exploratory analysis; formalization of hypotheses applicable to the targets;
- testing of the hypotheses using parametric and non-parametric criteria;
- identification of dependencies (correlation analysis);
- construction of prediction models (for the analysis of multivariate correlations, as well as to cut off individual variables/observational groups);
- testing the effect of omitted variables: erroneous attribution of the effect of some variables to others.

Discussion

Several countries have already established many registries to assess different aspects and manifestations of the disease in patients infected with SARS-CoV-2: COVID-19 DERMATOLOGY REGISTRY [4], ACS COVID-19 Registry [5], NHS COVID-19 Vaccine Research Registry [6], COVID-19 CVD Registry of the American Heart Association [7], ERA-EDTA COVID-19 Registry for Dialysis and Transplant Patients [8], COVID-19 and Cancer Consortium Registry [9], COVID-19 Global Rheumatology Alliance provider registries [10], Pregnancy Corona Virus Outcomes Registry (PRIORITY) [11]. All are reported to have registries of patients. In addition to the international registries, their local registries reflect the unique features of patients in various regions. Such registries, including five or more thousand patients, are located in Spain, Italy, the PRC, and the United States. The prospective cohort observational study (ISARIC/WHO CCP-UK) [12] of hospitalized patients (n = 20,133) determined that elderly males were the most prevalent among all patients. One in three patients had coronary artery disease, one in five had diabetes mellitus, and one in six had chronic kidney disease. About 41% of patients were discharged after recovery, 26% died, 17% required intensive care. The risk of severe course and death during hospitalization was determined by the following risk factors: male sex, severe multimorbidity, and obesity.

The study did not follow up the patients discharged from hospital. Similar values were obtained in a registry (5,700 patients) established on the basis of 12 hospitals in New York. The mean patient observation period was 4–5 days [13]. The retrospective registry based on the Lombardy ICU Network data included 1,591 patients hospitalized in intensive care units. The 30-day observation revealed the same prediction patterns. However, this study did not follow the effects of the infection on the long-term prognosis and the course of comorbidities [14].

The results of a comprehensive examination of 143 patients with a history of COVID-19 have been published. Patients were examined on average in 60.3 (SD 13.6) days after onset of the first symptom of COVID-19. At the time of examination only 18 (12.6%) patients had no symptoms associated with COVID-19, and 32% had one or two symptoms, and 55% of patients had three or more symptoms. No patient had

fever or signs or symptoms of acute illness. The quality of life was reduced in 44.1% of patients. Most of the subjects still reported fatigue (53.1%), shortness of breath (43.4%), joint pain (27.3%), and chest pain (21.7%) [15].

Thus, to optimize the real-life treatment process, there is essentially a need for new information obtained during long-term prospective observation of patients with a history of SARS-CoV-2 infection. This is the main task of the SARS-CoV-2 ACTIV international registry.

No conflict of interest is reported.

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