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# International register “Dynamics analysis of comorbidities in SARS-CoV-2 survivors” (AKTIV) and the register “Analysis of hospitalizations of comorbid patients infected during the second wave of SARS-CoV-2 outbreak” (AKTIV 2)

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The organizer of the registers "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (AKTIV) and "Analysis of hospitalizations of comorbid patients infected during the second wave of SARS-CoV-2 outbreak" (AKTIV 2) is the Eurasian Association of Therapists (EAT). Currently, there are no clinical registries in the Eurasian region designed to collect and analyze information on long-term outcomes of COVID-19 survivors with comorbid conditions. The aim of the register is to assess the impact of a novel coronavirus infection on long-term course of chronic non-communicable diseases 3, 6, 12 months after recovery, as well as to obtain information on the effect of comorbidity on the severity of COVID-19. Analysis of hospitalized patients of a possible second wave is planned for register "AKTIV 2". To achieve this goal, the register will include men and women over 18 years of age diagnosed with COVID-19 who are treated in a hospital or in outpatient basis. The register includes 25 centers in 5 federal districts of the Russian Federation, centers in the Republic of Armenia, the Republic of Kazakhstan, the Republic of Kyrgyzstan, the Republic of Belarus, the Republic of Moldova, and the Republic of Uzbekistan. The estimated capacity of the register is 5400 patients.

**Keywords:** SARS-CoV-2, registry, COVID-19, comorbidity, risk, multimorbidity.

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Arutyunov G. P.* ORCID: 0000-0002-6645-2515, Tarlovskaya E. I. ORCID: 0000-0002-9659-7010, Arutyunov A. G. ORCID: 0000-0003-1180-3549, Belenkov Y. N. ORCID: 0000-0002-6180-2619, Konradi A. O. ORCID: 0000-0001-8169-7812, Lopatin Y. M. ORCID: 0000-0003-1943-1137, Rebrov A. P. ORCID: 0000-0002-3463-7734, Tereshchenko S. N. ORCID: 0000-0001-9234-6129, Chesnikova A. I. ORCID: 0000-0002-9323-592X, Hayrapetyan H. G. ORCID: 0000-0002-8764-5623, Babin A. P. ORCID: none, Bakulin I. G. ORCID: 0000-0002-6151-2021, Bakulina N. V. ORCID: 0000-0003-4075-4096, Balykova L. A. ORCID: 0000-0002-2290-0013, Blagonravova A. S. ORCID: 0000-0002-1467-049X, Boldina M. V. ORCID: 0000-0002-1794-0707, Vaisberg A. R. ORCID: 0000-0003-3658-5330, Galyavich A. S. ORCID: 0000-0002-4510-6197, Gomonova V. V. ORCID: 0000-0002-9816-9896, Grigorieva N. U. ORCID: 0000-0001-6795-7884, Gubareva I. V. ORCID: 0000-0003-1881-024X, Demko I. V. ORCID: 0000-0001-8982-5292, Evzerikhina A. V. ORCID: none, Zharkov A. V. ORCID: 0000-0001-6649-0928, Kamilova U. K. ORCID: 0000-0002-5104-456X, Kim Z. F. ORCID: 0000-0003-4240-3329, Kuznetsova T. Yu. ORCID: 0000-0002-6654-1382, Lareva N. V. ORCID: 0000-0001-9498-9216, Makarova E. V. ORCID: 0000-0003-4394-0687, Malchikova S. V. ORCID: 0000-0002-2209-9457, Nedogoda S. V. ORCID: 0000-0001-5981-1754, Petrova M. M. ORCID: 0000-0002-8493-0058, Pochinka I. G. ORCID: 0000-0001-5709-0703, Protasov K. V. ORCID: 0000-0002-6516-3180, Protsenko D. N. ORCID: 0000-0002-5166-3280, Ruzanov D. Yu. ORCID: 0000-0001-5291-4937, Sayganov S. A. ORCID: 0000-0001-7319-2734, Sarybaev A. Sh. ORCID: 0000-0003-2172-9776, Selezneva N. M. ORCID: 0000-0002-3004-2063, Sugraliev A. B. ORCID: 0000-0002-8255-4159, Fomin I. V. ORCID: 0000-0003-0258-5279, Khlynova O. V. ORCID: 0000-0003-4860-0112, Chizhova O. Yu. ORCID: 0000-0002-1716-7654, Shaposhnik I. I. ORCID: 0000-0002-7731-7730, Schukarev D. A. ORCID: none, Abdrahmanova A. K. ORCID: 0000-0002-6332-9503, Avetisian S. A. ORCID: none, Avoyan H. G. ORCID: 0000-0002-3335-7255, Azarian K. K. ORCID: none, Aimakhanova G. T. ORCID: none, Ayipova D. A. ORCID: none, Akunov A. Ch. ORCID: none, Alieva M. K. ORCID: 0000-0002-0763-6111, Aparkina A. V. ORCID: 0000-0001-8463-2379, Aruslanova O. R. ORCID: 0000-0002-6974-2614, Ashina E. Yu. ORCID: 0000-0002-7460-2747, Badina O. Y. ORCID: 0000-0001-9068-8088, Barisheva O. Yu. ORCID: 0000-0001-6317-1243, Batchayeva A. S. ORCID: none, Bitieva A. M. ORCID: 0000-0002-5383-2367, Bikhteyev I. U. ORCID: 0000-0003-0663-3549, Borodulina N. A. ORCID: 0000-0003-1107-5772, Bragin M. V. ORCID: 0000-0003-2308-4887, Budu A. M. ORCID: none, Burygina L. A. ORCID: 0000-0002-2613-8783, Bykova G. A. ORCID: 0000-0003-0823-4605, Varlamova D. D. ORCID: 0000-0002-4015-5109, Vezikova N. N. ORCID: 0000-0002-8901-3363, Verbitskaya E. A. ORCID: 0000-0002-5710-7082, Vilkova O. E. ORCID: 0000-0002-1129-7511, Vinnikova E. A. ORCID: 0000-0002-5948-1561, Vustina V. V. ORCID: 0000-0003-1466-285X, Galova E. A. ORCID: 0000-0002-9574-2933, Genkel V. V. ORCID: 0000-0001-5902-3803, Gorshenina E. I. ORCID: none, Gostishev R. V. ORCID: 0000-0002-2379-5761, Grigorieva E. V. ORCID: 0000-0001-6064-560X, Gubareva E. Yu. ORCID: 0000-0001-6824-3963, Dabylova G. M. ORCID: none, Demchenko A. I. ORCID: none, Dolgikh O. Yu. ORCID: none, Duvanov I. A. ORCID: 0000-0003-0789-429X, Duyshobayev M. Y. ORCID: none, Evdokimov D. S. ORCID: 0000-0002-3107-1691, Egorova K. E. ORCID: 0000-0003-4233-3906, Ermilova A. N. ORCID: 0000-0002-5704-697X, Zheldybayeva A. E. ORCID: none, Zarechnova N. V. ORCID: none, Ivanova S. Yu. ORCID: 0000-0002-0720-6621, Ivanchenko E. Yu. ORCID: 0000-0003-4506-1053, Ilina M. V. ORCID: 0000-0003-2566-1086, Kazakovtseva M. V. ORCID: 0000-0002-0981-3601, Kazymova E. V. ORCID: none, Kalinina Yu. S. ORCID: 0000-0001-6037-5857, Karachenova A. M. ORCID: 0000-0003-1704-490X, Karetnikov I. A. ORCID: 0000-0002-0922-6925, Karoli N. A. ORCID: 0000-0002-7464-826X, Karpov O. V. ORCID: 0000-0001-7909-0675, Karsiev M. Kh. ORCID: 0000-0002-1794-0694, Kaskaeva D. S. ORCID: 0000-0002-0794-2530, Kasymova K. F. ORCID: 0000-0001-8448-6113, Kerimbekova Zh. B. ORCID: none, Kerimova A. Sh. ORCID: 0000-0002-2806-5901, Kim E. S. ORCID: none, Kiseleva N. V. ORCID: 0000-0002-0935-8717, Klimenko D. A.

ORCID: none, Klimova A.V. ORCID: 0000-0002-3176-7699, Kovalishena O.V. ORCID: 0000-0002-9595-547X, Kolmakova E.V. ORCID: none, Kolchinskaya T.P. ORCID: none, Kolyadich M.I. ORCID: 0000-0002-0168-1480, Kondriakova O.V. ORCID: 0000-0002-4092-6612, Konoval M.P. ORCID: 0000-0002-8187-6105, Konstantinov D.Yu. ORCID: 0000-0002-6177-8487, Konstantinova E.A. ORCID: 0000-0002-6022-0983, Kordukova V.A. ORCID: none, Koroleva E.V. ORCID: none, Kraposhina A.Yu. ORCID: 0000-0001-6896-877X, Kriukova T.V. ORCID: none, Kuzmina T.Y. ORCID: 0000-0002-0105-6642, Kuzmichev K.V. ORCID: none, Kulchoroeva Ch.K. ORCID: 0000-0003-2801-1994, Kuprina T.V. ORCID: 0000-0002-1176-7309, Kouranova I.M. ORCID: none, Kurenkova L.V. ORCID: none, Kurchugina N.Yu. ORCID: 0000-0003-2988-7402, Kushubakova N.A. ORCID: 0000-0001-6874-7125, Levankova V.I. ORCID: 0000-0002-0788-4449, Levin M.E. ORCID: 0000-0002-9197-1691, Lyubavina N.A. ORCID: 0000-0002-8914-8268, Magdeyeva N.A. ORCID: 0000-0002-6397-3542, Mazalov K.V. ORCID: none, Majseenko V.I. ORCID: 0000-0003-2133-4360, Makarova A.S. ORCID: 0000-0002-0486-9657, Maripov A.M. ORCID: 0000-0003-2801-1994, Marusina A.A. ORCID: 0000-0002-5301-5746, Melnikov E.S. ORCID: 0000-0002-8521-6542, Moiseenko N.B. ORCID: 0000-0003-2072-6370, Muradova F.N. ORCID: 0000-0002-2723-8081, Muradyan R.G. ORCID: none, Musaelian Sh.N. ORCID: none, Nikitina N.M. ORCID: 0000-0002-0313-1191, Ogurlieva B.B. ORCID: none, Odegova A.A. ORCID: 0000-0001-9691-6969, Omarova Yu.M. ORCID: 0000-0002-0942-6070, Omurzakova N.A. ORCID: 0000-0003-3970-9706, Ospanova Sh.O. ORCID: none, Pahomova E.V. ORCID: 0000-0002-8335-4626, Petrov L.D. ORCID: none, Plastinina S.S. ORCID: 0000-0002-0534-5986, Pogrebetskaya V.A. ORCID: none, Polyakov D.S. ORCID: 0000-0001-8421-0168, Ponomarenko E.V. ORCID: none, Popova L.L. ORCID: 0000-0003-0549-361X, Prokofeva N.A. ORCID: 0000-0002-7679-413X, Pudova I.A. ORCID: none, Rakov N.A. ORCID: none, Rakhimov A.N. ORCID: none, Rozanova N.A. ORCID: none, Serikbolkyzy S. ORCID: none, Simonov A.A. ORCID: 0000-0002-7915-3880, Skachkova V.V. 0000-0001-7512-2414, Smirnova L.A. ORCID: 0000-0002-2083-0373, Soloveva D.V. ORCID: 0000-0001-5695-0433, Soloveva I.A. ORCID: 0000-0002-1999-9534, Sokhova F.M. ORCID: 0000-0002-6208-2908, Subbotin A.K. ORCID: none, Sukhomlinova I.M. ORCID: none, Sushilova A.G. ORCID: 0000-0002-7277-5046, Tagayeva D.R. ORCID: none, Titojkina Yu.V. ORCID: 0000-0001-9974-359X, Tikhonova E.P. ORCID: 0000-0001-6466-9609, Tokmin D.S. ORCID: none, Torgunakova M.S. ORCID: 0000-0002-5483-0048, Trenogina K.V. ORCID: 0000-0002-4137-5533, Trostianetckaia N.A. ORCID: none, Trofimov D.A. ORCID: 0000-0001-7613-7132, Tulichev A.A. ORCID: 0000-0002-3157-2218, Tupitsin D.I. ORCID: none, Tursunova A.T. ORCID: none, Tiurin A.A. ORCID: none, Ulanova N.D. ORCID: 0000-0002-5107-6051, Fatenkov O.V. ORCID: 0000-0002-4928-5989, Fedorishina O.V. ORCID: 0000-0002-0155-676X, Fil T.S. ORCID: none, Fomina I.Yu. ORCID: none, Fominova I.S. ORCID: none, Frolova I.A. ORCID: none, Tsvinger S.M. ORCID: 0000-0003-2082-9839, Tsoma V.V. ORCID: 0000-0002-0662-1217, Cholponbaeva M.B. ORCID: none, Chudinovskikh T.I. ORCID: 0000-0002-7515-2215, Shakhgildyan L.D. ORCID: 0000-0003-3302-4757, Shevchenko O.A. ORCID: none, Sheshina T.V. ORCID: none, Shishkina E.A. ORCID: 0000-0001-6965-7869, Shishkov K.Yu. ORCID: 0000-0003-2942-6200, Sherbakov S.Y. ORCID: none, Yausheva E.A. ORCID: none.

*Corresponding author: arut@ossn.ru

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**The organizer of the registers** "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (AKTIV) and "Analysis of hospitalizations of comorbid patients infected **during the second wave** of SARS-CoV-2 outbreak" (AKTIV 2) is the Eurasian Association of Therapists (EAT). EAT experts believe that the impact of a new coronavirus infection caused by SARS-CoV-2 (COVID-19) on the course of comorbid conditions in the long-term period is becoming topical issues for public health. The absence of population immunity, the rapid virus spread, the relatively high frequency of severe disease forms (~10-20% of cases, especially in the elderly with concomitant diseases), the multiple organ nature of the damage, the severity of systemic inflammatory reaction, the presence of a local vascular lesion, with predominant damage to the microcirculatory bloodstream vessels, suggest that SARS-CoV-2 can increase the likelihood of progression of the existing concomitant pathology. Currently, there are no clinical registries in the Eurasian region designed to collect and analyze information on long-term outcomes of COVID-19 survivors with comorbid conditions. The creation of a register to assess the COVID-19 impact on dynamics of chronic non-communicable diseases in the long-term period is an important scientific and practical work.

The main task of the ACTIV registry is to obtain information on the effect of comorbidity on the COVID-19 severity and to assess the dynamics of comorbid conditions in patients who have come through COVID-19, 3, 6, 12 months after recovery (discharge from the hospital or discharge after outpatient treatment). Additionally, at the time of ACTIV creation, it was not clear whether there would be a second wave of the pandemic, but experts assumed a high probability of such an event. Therefore, the question came up: "will the risk factors of infection, the distribution of phenotypes of patients and the outcomes of the disease in the hospitalized patients of the first wave and second wave differ"? Analysis of hospitalized patients of a possible second wave is planned for register ACTIV 2.

The ACTIV register will include both hospitalized patients and those receiving outpatient treatment. When filling out the ACTIV register, the following important information will be received:

- newly emerged non-communicable, infectious and oncological diseases (follow-up period: 12 months from the moment of seeking medical help for COVID-19);
- severity dynamics of pre-existing chronic diseases (follow-up period: 12 months from the moment of seeking medical help for COVID-19);

**Table 1**

**Design of register ACTIV SARS-CoV-2**

| N | Visits | Outpatient branch of the Register | Hospital branch of the Register |
|---|---|---|---|
| 1 | Enrollment | Retrospective data from outpatient medical record | Retrospective data from medical history |
| 2 | 7-12 days | Retrospective data from outpatient medical record | Retrospective data from medical history |
| 3 | Exodus (discharge/death) | Retrospective data from outpatient medical record | Retrospective data from medical history |
| 4 | 3 months after discharge | Phone call | Phone call |
| 5 | 6 months after discharge | Phone call | Phone call |
| 6 | 12 months after discharge | Phone call | Phone call |

• dynamics of traditional risk factors: total cholesterol, low-density lipoprotein cholesterol, triglycerides, blood glucose, blood pressure, body mass index (follow-up period: 12 months after seeking medical help for COVID-19);

• Severity of COVID-19, depending on pre-existing diseases and risk factors for major non-communicable diseases;

• occurrence of new cases of disability/change in the disability degree (follow-up period: 12 months after seeking medical help for COVID-19);

• frequency of deaths (follow-up period: 12 months after seeking medical help for COVID-19).

**Patient population.** The register will include men and women over the age of 18 with COVID-19 diagnosis with the preservation of anonymity (data from the swab analysis of the nasopharynx and oropharynx, antibody titer, a typical picture according to computed tomography), who are being treated in a hospital or receiving treatment at home.

**Territory of register execution.** The register includes 25 centers in 5 federal districts of the Russian Federation, centers in the Republic of Armenia, the Republic of Kazakhstan, the Republic of Kyrgyzstan, the Republic of Belarus, the Republic of Moldova, and the Republic of Uzbekistan. The estimated capacity of the registry is not less than 5400 patients.

**Definitions.** Chronic non-communicable diseases were determined in accordance with current clinical guidelines. A multimorbid patient was considered to have 2 or more verified diseases and received treatment for these diseases.

**Study design.** Study design: multicenter registry with two disjoint branches (outpatient branch and hospital branch). Both branches of the register have 6 visits (Table 1). The follow-up duration is 12 months. It is planned to analyze the patient's medical examination data (the primary document is medical history or outpatient card) and the data obtained by telephone surveys using a standard questionnaire 3, 6, 12 months after recovery from COVID-19.

**Register organization.** Start of patient recruitment on June 29, 2020, end of recruitment on November 29, 2020. Completion of the register on November 29, 2021. 3 committees organize and control the register work: the organizing committee, the supervisory committee, and the committee for analysis of endpoints and control of filling out individual registration cards (IRC). IRC and document management are only electronic. The register is formed by 140 doctors in 25 centers. Each IRC passes monitor control.

**Ethical review.** The ethical review was carried out by the Pirogov Russian National Research Medical University Ethics Committee for centers in the Russian Federation and local ethics committees in other countries participating in the register. Register registration: ID ClinicalTrials.gov: NCT04492384.

**Register's website.** Information on the Register is available on the website of the Eurasian Association of Therapists or by direct link: https://ACTIV.euat.ru, available from fixed and mobile devices.

**Data collection.** If the patient meets the enrollment criteria (see the section "Patient population"), he is included in one of the register branches: either outpatient or hospital. A depersonalized IRC is filled in for the patient with fixing subsequent dates of patient's visits. All information received about the patient, according to the rules of quality clinical practice, is confidential, only the automatically assigned unique number (identifier) of the patient is entered in IRC.

## ACTIV 2 register

**The ACTIV 2** register purpose: to study the differences in populations, comorbidities, and treatment regimens obtained during a statistical comparison of the main indicators of ACTIV and ACTIV 2 in patients during the hospital period.

**Patient population.** The register will include men and women with COVID-19 over 18 years of age with the preservation of anonymity (data from the swab analysis of the nasopharynx and oropharynx, antibody titer, a typical picture according to

**Table 2**

**Registers with follow-up period of 1 year or more**

| Register name (No. in article bibliography) | Number of patients/ follow-up period (years) | Register's goal |
|---|---|---|
| Cardiopulmonary Inflammation and Multi-System Imaging During the Clinical Course of COVID-19 Infection in Asymptomatic and Symptomatic Persons | 180/1 | To understand how the COVID-19 virus causes wide differences in how sick one can become from the infection. |
| A Longitudinal Study of COVID-19 Sequelae and Immunity | 900/3 | To learn about any long-term medical problems that people who have recovered from COVID-19 might have, and whether they develop an immune response to SARS-CoV-2 that provides protection against reinfection. |
| Austrian COVID-19 Registry | 1000/2 | The AGMT-COVID-19 Registry is designed as multicenter observational cohort of patients, that are tested positive for SARS-CoV-2. Data will be collected from all sites in Austria willing to participate.<br>Due to the non-interventional nature of the AGMT_COVID-19 registry, only routine data, which has already been recorded in the patient's medical chart, is transferred to the eCRF. |
| Prospective Hospital Registry of Patients With Suspected or Confirmed Coronavirus Infection (COVID-19) and Community-acquired Pneumonia (TARGET-VIP) | 1124/2 | A prospective medical registry of such patients (confirmed or suspected severe COVID-19 or community-acquired pneumonia), hospitalized to National Medical and Surgical Center, is intended to analyze and compare their clinical and instrumental data, co-morbidity, treatment, short-term and long-term outcomes in real clinical practice. |
| COVID-19 Recovered Volunteer Research Participant Pool Registry | 10000/20 | This is a prospective observational registry of COVID-19 recovered patients who are no longer symptomatic.<br>This Registry is intended to serve as a pool of individuals that can participate in studies associated with serological testing, characterization of immunity and immune response, vaccine development, and convalescent plasma donors. |
| Natural History of Post-Coronavirus Disease 19 Convalescence at the National Institutes of Health | 1200/3 | In this study, researchers will use survey data to describe the different ways people experience and recover from COVID-19. They will also use the data to help create future studies to understand why some people do not fully recover. |
| The McMaster Multi-Regional COVID-19 Hospital Case Registry (COREG) | 1500/1 | The McMaster Multi-Regional Hospital Coronavirus Registry (COREG) is a platform that is collecting detailed case data on laboratory confirmed COVID-19 hospital inpatients and outpatients. The COREG platform will provide rapid high-quality evidence to improve the prevention and clinical management of COVID-19 for older adults in Canada, and internationally. The COREG platform will also provide researchers and partners with complete regional level clinical data on COVID-19 cases to inform rapid decision-making and projections, sub-studies, extensions, and linkage for all affected populations. |
| COVID-19 Survivorship Registry | 350/1 | The objectives for this study include providing structural and function information about lung and heart using chest imaging, MRI, Echo, Spirometry, and blood markers in order to assess severity of cardiopulmonary injury and short- and long-term sequelae of COVID-19 infection as well as assess indicators of mental health and quality of life. |
| Innovative Support for Patients With SARS-COV2 Infections (COVID-19) Registry (INSPIRE) | 4800/1,5 | This study will use a digital platform to longitudinally track comprehensive information including patient self-report as well as data that describe the process and outcome of care in the electronic medical record (EMR) of a large representative sample of patients under investigation for SARSCOV2. |

**Table 2. Continuation**

| Register name (No. in article bibliography) | Number of patients/ follow-up period (years) | Register's goal |
|---|---|---|
| Behavior, Environment And Treatments for Covid-19 (BEAT19) | 100000/1 | The purpose of this study is to understand at the population level the symptomatic course of known or suspected COVID-19 patients while sheltering-in-place or under quarantine. Symptoms will be measured using a daily report derived from the CTCAE-PRO as well as free response. Outcomes will be assessed based on the duration and severity of infection, hospitalization, lost-to-follow-up, or death. As a patient-centric registry, patients themselves may propose, suggest, and/or submit evidence or ideas for relevant collection. |
| Analysis of Chronic Non-infectious Diseases Dynamics After COVID-19 Infection in Adult Patients (ACTIV) | 5400/1 | Non-commercial depersonalized multi-centered registry study on analysis of chronic non-infectious diseases dynamics after SARS-CoV-2 infection in cohort of Russian adult patients. Retrospective analysis of medical histories and outcomes in adults with pre-existing conditions after SARS-CoV-2 infection and prospective monitoring of health status during 3, 6 and 12 months after discharge. Comorbidities worsening risk factors measuring through evaluation of range of indicators such as dynamics of diabetes, CKD, COPD, bronchial asthma, incidence of hypertonic crises, vascular events and others. |

computed tomography) who are being treated in a hospital in the period from October 01, 2020.

**Territory of register execution.** Register implementation territory — 18 centers in 5 federal districts of the Russian Federation and in the Republic of Belarus. The estimated register capacity is 2500 patients.

**Study design.** Multicenter register. The follow-up duration — the hospital stay time. Analyzing the history and outcome of the disease retrospectively is planned.

**Register organization.** Patient recruitment starts on October 01, 2020, and ends on March 30, 2021.

**Register registration:** ID ClinicalTrials.gov: NCT04709120.

**Register's website.** Information on the Register is available on the website of the Eurasian Association of Therapists or by direct link: https://ACTIV.euat.ru, available from fixed and mobile devices.

**Methods of statistical analysis of registers ACTIV and ACTIV 2.** Data processing within the register will be performed using the IBM SPSS Statistics 25 statistical package. The work will be carried out in several stages.

Stage 1. Data preparation. The main stage 1 is the cleaning of quantitative follow-up (results of laboratory and instrumental diagnostics, drug dosages, etc.) from input errors and the use of different scales (for example, ng/ml, mcg/ml, mcg/l for the D-dimer). During this stage, new features will also be constructed, such as presence of specific polymorbidity variants of interest, presence of significant negative dynamics of individual indicators (computed tomography data, D-dimer and C-reactive protein), and calculation of combined variables (body mass index, glomerular filtration rate, etc.). Finally, for the purposes of modeling and clustering (stage 4), the quantitative variables will be regularized by the Z-scaling method.

Stage 2. Exploratory analysis. First of all, the quantitative variables will be checked for normality using the Shapiro-Wilk agreement test (p=0,05) and graphical analysis. The vast majority of numeric variables do not have a normal distribution, so stage 3 (see below) will be implemented primarily using nonparametric tests.

Using logistic regression (first one-factor, then multi-factor by step-by-step construction), the variables that most significantly affect the outcomes of interest (mortality rate, artificial ventilation transfer, cytokine storm development, etc.) will be identified.

Finally, to avoid multicollinearity and incorrect interpretation of relationships, correlation matrices and multi-input frequency tables will be constructed. Based on these data and the results of logistic regression, the final hypothesis adjustment within the register will be carried out.

Stage 3. Hypothesis testing. The vast majority of hypotheses will be tested using nonparametric criteria:

• Hypotheses about relationship of quantitative variables-using the Pearson rank correlation;

• Hypotheses about difference in quantitative indicators of the groups of interest (clinical parameters, degree of oxygenation) — using the Craskell-Wallis test/Mann-Whitney test;

• Hypotheses about different frequency of events in the groups (mortality rate, hospitalization, etc.) — using the Pearson Chi-Square test. In 2×2 groups with a small number of follows-up — using the Yates continuity correction.

The odds ratio will be calculated for all hypotheses. In a number of cases, the odds ratio was adjusted for significant concomitant factors identified in stage 2: age, number of diseases in anamnesis, and so on, using multivariate logistic regression.

All hypotheses were tested at a significance level of p=0,05. A posteriori inter-group comparisons were performed using the Bonferroni correction.

Stage 4. Modeling and clustering. At the final stage of the register, the following is planned:

A) Modeling of adverse patient outcomes: logistic regression by step-up method with control of predictor collinearity and iterative construction (bagging).

B) Clustering of patients by demographic (gender-age) parameters and anamnesis (concurrent diseases) with further comparison of outcomes between clusters: "phenotyping" of patients who have been infected with SARS-CoV-2. It is planned to use both the K-means method and hierarchical clustering methods.

## Discussion

Over the past 20 years, four major outbreaks of viral infectious diseases have caused a large number of deaths worldwide: SARS, H1N1 influenza, MERS, and COVID-19. All of them are initially clinically manifested as upper and lower respiratory tract infections, but can progress to multiple organ failure [1]. In a study by Chu KH, et al., the long-term effect of SARS infection on kidney function was studied: among 536 patients with SARS, 36 (6,7%) developed impaired renal function, which was manifested on average 20 days (range of 5-48 days) after the onset of viral infection, despite the initial normal plasma creatinine level [2]. According to a study by Wu Q, et al, patients who had recovered from SARS-CoV, disorders of lipid and glucose metabolism with elevated levels of phosphatidylinositol and lysophosphatidylinositol were found [3]. Another study by Yang JK, et al. shown that SARS coronavirus can cause damage to the kidneys, heart, lungs, and endocrine part of the pancreas [4]. In a study by Leow MK, et al., 39,3% of patients showed signs of hypocorticism out of 61 patients who had SARS-CoV. Dysfunction of hypothalamus-pituitary-adrenal axis in the majority was resolved within a year. Two (3,3%) of the cohort of patients with hypocorticism had transient subclinical thyrotoxicosis, and four (6,7%) had biochemical hypothyroidism [5]. There are a small number of studies analyzing the damage to the cardiovascular system as a result of SARS-CoV-1 and MERS infections. This is how acute coronary syndrome, transient diastolic dysfunction, hypotension, bradycardia, and transient cardiomegaly are described [6-11]. Thus, the problem of long-term changes in patients who have been infected with coronaviruses becomes an urgent problem of modern medicine, the study of which, undeniably, should begin with registers.

According to the site Trials.gov, there are currently 91 registries in the world dedicated to analysis of patients with COVID-19. The registers classification is a complex and difficult task, but it is necessary in order to know what clinically significant questions we can expect answers in the near future. It seems appropriate to divide the registers according to the following principle: ***those studying the course*** of ***COVID-19 in special patient populations*** (patients with oncological diseases [12], patients with chronic obstructive pulmonary disease [13], patients with onco-hematological diseases [14], patients with rheumatological diseases [15] and patients with cardiovascular diseases [16]); ***those studying complications recorded in patients with COVID-19*** (pulmonary artery thromboembolia [17], myocarditis [18], cardiac arrhythmias [19], with acute heart failure [20], with arterial and venous thrombosis [21]); ***studying the effect of individual drugs and effects on the course of COVID-19*** (aerobic exercise [22], various drug therapy regimens [23]); ***studying the changes in patients who have come through COVID-19*** (state of immune system [24], quality of life [25]).

A separate type of registry consists of studies that assess the clinical condition dynamics of polymorbid patients who have come through COVID-19. Without disputing the value for real practice of the data that are planned to be obtained in short-term registers lasting up to 1 year [26] and small (up to 1 thousand patients [27]), from 1 thousand to 3 thousand patients [28] — we believe that the initial versatility of polymorbid patients and difficulties in assessing the initial state dynamics require both a larger number of patients (for example, assuming the inclusion of >5 thousand patients) and longer follow-up periods (Table 2). Register ACTIV, presented by us, is an international one, including data on patients from 7 countries of the Eurasian region, and is designed to

include at least 5400 patients whose status severity required either hospitalization or allowed the patient to be left for outpatient treatment. Within the register, prospective follow-up of patients is planned for a year, while the possibility of extending the study remains with the appropriate decision of the supervisory committee. The publication of data obtained during the follow-up of patients for 12 months is mandatory. Such indicators as the need for emergency and planned medical treatment, the need for hospitalization, the occurrence of disability, the analysis of comorbid disease course, the incidence of non-communicable diseases (for example, myocardial infarction, stroke, diabetes mellitus, decompensation of heart failure) will be assessed, which will allow to form an idea of the dynamics of existing chronic diseases and assess the prognosis of these patients in post-COVID-19 period. For comparison, the COVID-19 Recovered Volunteer Research Participant Pool Registry (USA) [29] provides only periodic serological test of recovered patients. The Behavior, Environment And Treatments for Covid-19 (BEAT19) register (USA) [30] suggests follow-up only for non-hospitalized patients with COVID-19. The Innovative Support for Patients With SARS-COV2 Infections (COVID-19) Registry (INSPIRE) (USA) [31], which is expected to include 4800 patients, is supposed to analyze the incidence of myalgic encephalomyelitis/chronic fatigue syndrome, as well as the frequency of outpatient and inpatient medical care and mortality, but does not provide an analysis of comorbid disease course and non-communicable disease incidence. Equally important is the issue: does the course of COVID-19 during the first wave (spring — early autumn 2020) differ from the second wave (autumn-winter 2020-2021)? The ACTIV 2 register is devoted to clinical features comparison of disease course during the first and second waves in hospitalized patients.

Thus, in order to optimize the treatment process in real practice, fundamentally new information obtained during long-term prospective follow-up of patients who have come through SARS-CoV-2 is required. This task is the main one in international register ACTIV. Register ACTIV 2 will allow to compare the clinical course features of the first and second waves of COVID-19 in hospitalized patients.

**Relationships and Activities:** none.

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