Russian Journal of Cardiology 2021;26(10):4708
doi:10.15829/1560-4071-2021-4708
https://russjcardiol.elpub.ru

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

Clinical features of post-COVID-19 period. Results of the international register "Dynamic analysis of comorbidities in SARS-CoV-2 survivors (AKTIV SARS-CoV-2)". Data from 6-month follow-up

Arutyunov G. P., Tarlovskaya E. I., Arutyunov A. G. on behalf of co-authors#

Aim. To study the clinical course specifics of coronavirus disease 2019 (COVID-19) and comorbid conditions in COVID-19 survivors 3, 6, 12 months after recovery in the Eurasian region according to the AKTIV register.

Material and methods. The AKTIV register was created at the initiative of the Eurasian Association of Therapists. The AKTIV register is divided into 2 parts: AKTIV 1 and AKTIV 2. The AKTIV 1 register currently includes 6300 patients, while in AKTIV 2 — 2770. Patients diagnosed with COVID-19 receiving in- and outpatient treatment have been anonymously included on the registry. The following 7 countries participated in the register: Russian Federation, Republic of Armenia, Republic of Belarus, Republic of Kazakhstan, Kyrgyz Republic, Republic of Moldova, Republic of Uzbekistan. This closed multicenter register with two non-overlapping branches (in- and outpatient branch) provides 6 visits: 3 in-person visits during the acute period and 3 telephone calls after 3, 6, 12 months. Subject recruitment lasted from June 29, 2020 to October 29, 2020. Register will end on October 29, 2022. A total of 9 fragmentary analyzes of the registry data are planned. This fragment of the study presents the results of the post-hospitalization period in COVID-19 survivors after 3 and 6 months.

Results. According to the AKTIV register, patients after COVID-19 are characterized by long-term persistent symptoms and frequent seeking for unscheduled medical care, including rehospitalizations. The most common causes of unplanned medical care are uncontrolled hypertension (HTN) and chronic coronary artery disease (CAD) and/or decompensated type 2 diabetes (T2D). During 3- and 6-month follow-up after hospitalization, 5,6% and 6,4% of patients were diagnosed with other diseases, which were more often presented by HTN, T2D, and CAD. The mortality rate of patients in the post-hospitalization period was 1,9% in the first 3 months and 0,2% for 4-6 months. The highest mortality rate was observed in the first 3 months in the group of patients with class II-IV heart failure, as well as in patients with cardiovascular diseases and cancer. In the pattern of death causes in the post-hospitalization period, following cardiovascular causes prevailed (31,8%): acute coronary syndrome, stroke, acute heart failure.

Conclusion. According to the AKTIV register, the health status of patients after COVID-19 in a serious challenge for healthcare system, which requires planning adequate health system capacity to provide care to patients with COVID-19 in both acute and post-hospitalization period.

Keywords: COVID-19, AKTIV register, cardiovascular diseases, diabetes, post-COVID-19 period.

Relationships and Activities: none.

Trial ID: ClinicalTrials.gov Identifier: NCT04492384.

#Belenkov Y. N., Konradi A. O., Lopatin Yu. M., Rebrov A. P., Tereshchenko S. N., Chesnikova A. I., Hayrapetyan H. G., Babin A. P., Bakulin I. G., Bakulina N. V., Balykova L. A., Blagonravova A. S., Boldina M. V., Vaisberg A. R., Galyavich A. S., Gomonova V. V., Grigorieva N. U., Gubareva I. V., Demko I. V., Evzerikhina A. V., Zharkov A. V., Kamilova U. K., Kim Z. F., Kuznetsova T. Yu., Lareva N. V., Makarova E. V., Malchikova S. V., Nedogoda S. V., Petrova M. M., Pochinka I. G., Protasov K. V., Protsenko D. N., Ruzanau D. Yu., Sayganov S. A., Sarybaev A. Sh., Selezneva N. M., Sugraliev A. B., Fomin I. V., Khlynova O. V., Chizhova O. Yu., Shaposhnik I. I., Shukarev D. A., Abdrahmanova A. K., Avetisian S. A., Avoyan H. G., Azarian K. K., Aimakhanova G. T., Ayipova D. A., Akunov A. Ch., Alieva M. K., Aparkina A. V., Aruslanova O. R., Ashina E. Yu., Badina O. Y., Barisheva O. Yu., Batluk T. I., Batchayeva A. S., Bashkinov R. A., Bitieva A. M., Bikhteyev I. U., Borodulina N. A., Bragin M. V., Budu A. M., Bykova G. A., Vagapova K. R., Varlamova D. D., Vezikova N. N., Verbitskaya E. A., Vilkova O. E., Vinnikova E. A., Vustina V. V., Galova E. A., Genkel V. V., Gorshenina E. I., Grigorieva E. V., Gubareva E. Yu., Dabylova G. M., Demchenko A. I., Dolgikh O. Yu., Duyshobayev M. Y., Evdokimov D. S., Egorova K. E., Ermilova A. N., Zheldybayeva A. E., Zarechnova N. V., Zimina Yu. D., Ivanova S. Yu., Ivanchenko E. Yu., Ilina M. V., Kazakovtseva M. V., Kazymova E. V., Kalinina Yu. S., Kamardina N. A., Karachenova A. M., Karetnikov I. A., Karoli N. A., Karsiev M. Kh., Kaskaeva D. S., Kasymova K. F., Kerimbekova Zh. B., Kerimova A. Sh., Kim E. S., Kiseleva N. V., Klimenko D. A., Klimova A. V., Kovalishena O. V., Kolmakova E. V., Kolchinskaya T. P., Kolyadich M. I., Kondriakova O. V., Konoval M. P., Konstantinov D. Yu., Konstantinova E. A., Kordukova V. A., Koroleva E. V., Kraposhina A. Yu., Kriukova T. V., Kuznetsova A. S., Kuzmina T. Yu., Kuzmichev K. V., Kulchoroeva Ch. K., Kuprina T. V., Kouranova I. M., Kurenkova L. V., Kurchugina N. Yu., Kushubakova N. A., Levankova V. I., Lyubavina N. A., Magdeyeva N. A., Mazalov K. V., Majseenko V. I., Makarova A. S., Maripov A. M., Marusina A. A., Melnikov E. S., Moiseenko N. B., Muradova F. N., Muradyan R. G., Musaelian Sh. N., Myshak A. O., Nekaeva E. S., Nikitina N. M., Ogurlieva B. B., Odegova A. A.,

Omarova Yu. M., Omurzakova N. A., Ospanova Sh. O., Pahomova E. V., Petrov L. D., Plastinina S. S., Pogrebetskaya V. A., Polyakov D. V., Polyakov D. S., Ponomarenko E. V., Popova L. L., Prokofeva N. A., Pudova I. A., Rakov N. A., Rakhimov A. N., Rozanova N. A., Serikbolkyzy S., Simonov A. A., Skachkova V. V., Soloveva D. V., Soloveva I. A., Sukhomlinova I. M., Sushilova A. G., Tagayeva D. R., Titojkina Yu. V., Tikhonova E. P., Tokmin D. S., Tolmacheva A. A., Torgunakova M. S., Trenogina K. V., Trostianetckaia N. A., Trofimov D. A., Trubnikova M. A., Tulichev A. A., Tursunova A. T., Ulanova N. D., Fatenkov O. V., Fedorishina O. V., Fil T. S., Fomina I. Yu., Fominova I. S., Frolova I. A., Tsvinger S. M., Tsoma V. V., Cholponbaeva M. B., Chudinovskikh T. I., Shevchenko O. A., Sheshina T. V., Shishkina E. A., Shishkov K. Yu., Sherbakov S. Yu., Yausheva E. A.

Arutyunov G. P. ORCID: 0000-0002-6645-2515, Tarlovskaya E. I.* ORCID: 0000-0002-9659-7010, Arutyunov A. G. ORCID: 0000-0003-1180-3549.

*Corresponding author: etarlovskaya@mail.ru

Received: 29.09.2021
Revision Received: 11.10.2021
Accepted: 13.10.2021

For citation: Arutyunov G. P., Tarlovskaya E. I., Arutyunov A. G. on behalf of co-authors. Clinical features of post-COVID-19 period. Results of the international register "Dynamic analysis of comorbidities in SARS-CoV-2 survivors (AKTIV SARS-CoV-2)". Data from 6-month follow-up. *Russian Journal of Cardiology*. 2021;26(10):4708. doi:10.15829/1560-4071-2021-4708

To study the features of coronavirus disease 2019 (COVID-19) course and changes in comorbid conditions in patients 3, 6, 12 months after recovery from COVID-19 in the Eurasian region, the international register "Dynamic analysis of comorbidities in SARS-CoV-2 survivors (AKTIV SARS-CoV-2)" was created [1], which included specialists from 7 following countries: the Russian Federation, the Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan, the Kyrgyz Republic, the Republic of Moldova, the Republic of Uzbekistan. The AKTIV register was divided into 2 parts: AKTIV 1 and AKTIV 2 [2]. Currently, the AKTIV 1 register includes 6300 patients, while the AKTIV 2 (analysis of the COVID-19 2nd wave) — 2770. In total, 9 fragment analyzes of the register data are planned. This fragment of the study presents the data from 3 and 6-month follow-up of patients after hospitalization due to COVID-19.

Material and methods

The study design and statistical processing methods were published earlier [2]. The register provides 6 visits: 3 in-person visits during the acute period and 3 telephone calls after 3, 6, 12 months. Patient recruitment started on June 29, 2020 and completed on October 29, 2020. Completion of the register on October 29, 2022. ClinicalTrials.

Table 1

Clinical characteristics of patients in the AKTIV register within 6-month follow-up after hospitalization, n=2256

Comorbid disease or risk factor	6-month follow-up
HTN, %	53,0
Obesity, %	27,7
CAD, %	16,4
T2D, %	15,4
HF, %	9,8
CKD, %	6,0
AF, %	4,7
Cancer, %	4,4
Asthma, %	4,4
COPD, %	4,3
Prior myocardial infarction, %	4,2
Prior stroke	2,7
T1D, %	0,5
Hepatitis, %	0,5

Abbreviations: HTN — hypertension, CAD — coronary artery disease, MI — myocardial infarction, T1D — type 1 diabetes, T2D — type 2 diabetes, HF — heart failure, CKD — chronic kidney disease, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease.

Table 2

Persistent symptoms in the post-hospitalization period

Symptom	3 months, n=2185	6 months, n=1208
Weakness, %	30,9	21,1
Shortness of breath, %	28,3	19,0
BP increase, %	18,6	19,1
Heartbeat, %	11,2	5,8
Cough, %	7,9	4,9
Chest pain, %	4,8	3,9
Loss of taste and smell, %	2,9	1,4

Abbreviation: BP — blood pressure.

Table 3

Reasons for seeking unscheduled health care in the post-hospitalization period

Reasons for seeking care	3 months, n1*=638	6 months, n2**=361
Uncontrolled HTN, %	40,2	37,1
T2D decompensation, %	13,2	10,6
CAD destabilization, %	10,3	9,7
Digestive disease, %	7,5	8,4
Cancer, %	4,8	3,8
Asthma exacerbation, %	3,1	1,3
HF decompensation, %	3,1	1,3
Atrial fibrillation, %	2,9	1,9
URTI symptoms, %	2,3	3,9
CKD destabilization, %	1,5	1,9
COPD exacerbation, %	1,5	1,0
Hypothyroidism, %	1,5	1,6
Stroke, %	1,2	0,3
Arthritis, %	1,2	3,9
DVT, %	0,8	0,3
T1D decompensation, %	0,6	0,3
Viral hepatitis, %	0,4	0,0
HIV infection, %	0,4	0,0
PE, %	0,2	0,0
MI, %	0,0	1,0

Note: * — n1, number of patients seeking medical care after 3 months; ** — n2, number of patients seeking medical help after 6 months.
Abbreviations: HTN — hypertension, HIV — human immunodeficiency virus, CAD — coronary artery disease, MI — myocardial infarction, URTI — upper respiratory tract infection, T1D — type 1 diabetes, T2D — type 2 diabetes, DVT — deep vein thrombosis, PE — pulmonary embolism, HF — heart failure, CKD — chronic kidney disease, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease.

gov identifier: NCT04492384. Control telephone interviews were planned for 3500 patients included in AKTIV 1. Control telephone calls were made to 3007 patients after 3 months and 2011 patients after 6 months. Telephone interviews with patients go on. Out of 3000 patients after 3 months, 432 did not answer the control call (14,4%), while 383 (12,8%) answers were regarded as incorrect (during the telephone survey, <50% of the answers were received). Out of 2000 telephone calls made after 6 months, 398 (19,9%) received no response and 394 (19,7%) received incorrect answers. Thus, the analysis is carried out using data from 2185 telephone interviews after 3 months and 1208 — after 6 months. A total of 2256 patients were interviewed, of which 2185 patients were interviewed after 3 months and 1137 of them were re-interviewed after 6 months, while 71 patients were interviewed only after 6 months. A standard form for phone survey is presented at https://activ.euat.ru/documents.

Table 4A

Newly diagnosed diseases in the post-COVID-19 period in relation to the total cohort of patients

Disease	3 months, n=2185	6 months, n=1208
HTN, %	2,3	3,0
T2D, %	1,4	0,7
CAD, %	0,5	1,4
AF, %	0,3	0,3
Arthritis, %	0,3	0,3
Stroke, %	0,2	0,2
Asthma, %	0,2	0,1
Cancer, %	0,1	0,1
HF, %	0,04	0,1
MI, %	0,04	0,2
CKD, %	0,04	0,0
T1D, %	0,04	0,0

Abbreviations: HTN — hypertension, CAD — coronary artery disease, MI — myocardial infarction, T1D — type 1 diabetes, T2D — type 2 diabetes, CKD — chronic kidney disease, HF — heart failure, AF — atrial fibrillation.

Table 4C

Pattern of newly diagnosed diseases in the post-COVID-19 period

Disease	3 months, n=123	6 months, n=77
HTN, %	41,5	46,7
T2D, %	25,2	10,4
CAD, %	9,7	22,1
AF, %	5,7	5,2
Arthritis, %	4,9	5,2
Stroke, %	4,0	2,6
Asthma, %	3,2	1,3
Cancer, %	2,4	1,3
HF, %	0,8	1,3
MI, %	0,8	3,9
CKD, %	0,8	0,0
T1D, %	0,8	0,0

Abbreviations: HTN — hypertension, CAD — coronary artery disease, MI — myocardial infarction, T1D — type 1 diabetes, T2D — type 2 diabetes, CKD — chronic kidney disease, HF — heart failure, AF — atrial fibrillation.

Table 4B

The incidence of newly diagnosed diseases per 100 thousand population in comparison with the incidence in the Russian population in 2018 [3]

Disease	Incidence 3 months/12 months (recalculation per 100000 population)	Incidence 4-6 months/12 months (recalculation per 100000 population)	Incidence of the Russian population for 12 months in 2018 (newly diagnosed diseases per 100000 population)
HTN (n/100000)	2334,0/9336	2980,0/11920,0	1047,9
CAD (n/100000)	549,2/2196,8	1407,3/5629,2	710,2
MI (n/100000)	45,8/183,2	248,3/993,2	138,2
Diabetes (n/100000)	1464,5/5858,0	662,2/2649,2	251,7
Cancer (n/100000)	137,3/549,2	82,8/331,2	425,5

Abbreviations: HTN — hypertension, CAD — coronary artery disease, MI — myocardial infarction.

The diagnosis was made based on the ICD-10 criteria.

Results

The mean age of patients (n=2256) was 55,27±13,00 years (men, 43,7%). More than half of the patients had hypertension (HTN), almost 1/3 of patients — obesity, almost every sixth patient — coronary artery disease (CAD) and or type 2 diabetes (T2D), every tenth patient — heart failure (HF) (Table 1). There were somewhat less common diseases such as chronic kidney disease (CKD), atrial fibrillation (AF), cancer, asthma, chronic obstructive pulmonary disease (COPD), prior stroke, type 1 diabetes mellitus (T1D) and hepatitis (Table 1).

In the post-hospitalization period, many patients continued to have various complaints (Table 2). After 3-month follow-up, at least 1 symptom persisted in 38,2% of patients, and after 6 months — in 27,7%. The most common symptoms that persisted in patients up to the 3rd and 6th months were weakness and shortness of breath. These symptoms were observed in every third patient after 3 months and every fifth after 6 months. Attention was drawn to the fact that in the first 3 months, many patients (18,6%) with previously effective antihypertensive therapy complained of blood pressure increase, as well as palpitations (11,2%) (Table 2). Less commonly, patients experienced prolonged chest pain and loss of taste and smell.

Table 5

Comparative analysis of patients with and without newly diagnosed diseases, 6-nonth follow-up (n=2256)

Parameter	Patients without newly diagnosed diseases, n=1959	Patients with newly diagnosed diseases, n=297	U-test t-test p-value
Men, %	44,97	42,42	0,410
Age, years M±σ	54,4±14,75	56,14±11,26	0,050
Age <40 years, %	18,13	6,78	0,000
Age of 40-59 years, %	42,39	54,24	0,000
BMI ⩾30 kg/m^2, %	26,39	36,7	0,000
Obesity with age <60 years, %	14,8	25,34	0,000
T <37 in the acute period, 0° C, %	7,61	4,05	0,043
RR of 22-29 bpm in the acute period, %	27,7	34,2	0,042
hsCRP ⩽10 mg/L in the acute period, %	27,59	17,45	0,001
hsCRP >40 mg/L in the acute period, %	38,13	53,62	0,000
Myocarditis in the acute period, %	0,1	1,05	0,002
SpO_2 in the acute period, %, M±σ	95,53±3,41	94,64±3,43	0,000
Lymphocytes in the acute period, %, M±σ	23,28±13,52	17,9±15,85	0,000
hsCRP in the acute period, mg/L, M±σ	48,01±78,69	56,93±51,65	0,000
Glucose in the acute period, mmol/l, M±σ	6,32±2,57	6,64±2,68	0,010
Fibrinogen in the acute period, g/l, M±σ	4,78±1,64	5,33±1,59	0,000

Note: with a standard deviation >30% of the mean, the significance was determined by the nonparametric U-test (Mann-Whitney test).
Abbreviations: hsCRP — high-sensitivity C-reactive protein, BMI — body mass index, T — temperature, RR — respiratory rate, SpO_2 — blood oxygen saturation.

Table 6

Mortality of patients in the 3- and 6- month post-hospitalization period depending on comorbidity

Diseases	3 months, n=2185			6 months, n=1208		
Whole group, n/%	41/1,9			3/0,2		
	+ CVDs	- CVDs	p	+ CVDs	- CVDs	p
CVDs, n/%	34/3,2	7/0,6	0,0001	1/0,2	2/0,17	0,724
Class II-IV HF, n/%	13/8,7	28/1,4	0,0001	0/0,0	3/0,26	0,624
COPD and/or asthma, n/%	4/2,6	2/1,8	0,521	1/1,75	2/0,18	0,020
Cancer, n/%	5/5,7	36/1,7	0,008	0/0,0	3/0,25	0,741

Abbreviations: CVDs — cardiovascular diseases, HF — heart failure, COPD — chronic obstructive pulmonary disease.

Almost a third of patients (29,2%) after hospitalization receive unscheduled health care, and within the first 3 months, at least 2 times. Outpatient health care was sought after 3 and 6 months by 29,2% and 29,9% of patients, respectively. In addition, 4,2% and 4,4% of patients were hospitalized after 3 and 6 months. Also, 2,5% and 2,3% of patients contacted with an ambulance service within 3 and 6 months. In patients who receive unscheduled health care within 3 (n=638) and 6 months (n=361) the most frequent reason for treatment was uncontrolled HTN (40,2% and 37,1%) (Table 3). Almost every tenth patient who applied for medical care complained about chronic CAD and/or type 2 diabetes decompensation. Somewhat less often, the

Table 7

Death causes in patients in the 3- and 6-month post-hospitalization

Death causes	3 months, n=41	6 months, n=3
ACS, %	20,5	
Stroke, %	4,5	
ACF, %	6,8	
Cancer, %	6,8	
Pneumonia, %	9,1	33,4
PE, %	2,3	
Other reasons, %	27,3	66,6
Unknown, %	22,7	

Abbreviations: ACS — acute coronary syndrome, AHF — acute heart failure, PE — pulmonary embolism.

Table 8

Comparative analysis of deceased and surviving patients within 3 months depending on sex and comorbidity

Parameter	Deceased patients, N=41	Surviving patients, N=2144	P	OR (95% CI)
Men, %	36,59	45,2	0,272	0,700 (0,368-1,328)
Age of 40-59 years, %	7,32	44,84	0,000	0,097 (0,030-0,316)
Age of 60-80 years, %	53,66	35,78	0,018	2,078 (1,118-3,864)
Age >80 years, %	39,02	2,62	0,000	23,829 (12,056-47,097)
Male age ⩾60, %	34,15	15,69	0,001	2,785 (1,446-5,367)
Female age ⩾60, %	58,54	22,7	0,000	4,808 (2,562-9,022)
HTN, %	82,93	47,16	0,000	5,442 (2,402-12,330)
HTN, ⩾60 years, %	78,05	28,65	0,000	8,857 (4,202-18,665)
HTN, <60 years, %	4,88	18,47	0,026	0,226 (0,054-0,942)
Smoking, %	7,32	5,3	0,569	1,411 (0,429-4,642)
Obesity, BMI ⩾30 kg/m^2, %	24,39	27,8	0,629	0,838 (0,408-1,720)
Obesity, ⩾60 years, %	21,95	11,2	0,032	2,230 (1,052-4,729)
Obesity, <60 years, %	2,44	16,57	0,015	0,126 (0,017-0,919)
BMI <18,5 kg/m^2, %	8,33	0,53	0,000	17,030 (3,477-83,416)
BMI ⩾40 kg/m^2, %	4,17	3,13	0,772	1,347 (0,179-10,161)
AF, %	19,51	3,93	0,000	5,932 (2,658-13,241)
AF, ⩾60 years, %	19,51	3,13	0,000	7,511 (3,340-16,891)
Coronary artery disease, %	24,39	10,41	0,004	2,777 (1,343-5,742)
History of myocardial infarction, %	12,2	3,36	0,002	3,996 (1,523-10,489)
Class II-IV HF, %	31,71	7,99	0,000	5,343 (2,717-10,508)
Prior stroke, %	12,2	2,18	0,000	6,244 (2,343-16,636)
T2D, %	21,95	13,62	0,125	1,783 (0,842-3,775)
T2D, ⩾60 years, %	19,51	8,67	0,016	2,554 (1,162-5,611)
T2D, <60 years, %	2,44	4,88	0,471	0,487 (0,066-3,580)
CKD, %	21,95	4,54	0,000	5,912 (2,745-12,735)
CKD, ⩾60 years, %	19,51	3,08	0,000	7,631 (3,392-17,169)
CKD, <60 years, %				
GFR ⩾90 ml/min/1,73 m^2, %	5,56	28,49	0,002	0,148 (0,035-0,617)
GFR of 89,9-60 ml/min/1,73 m^2, %	27,78	51,45	0,005	0,363 (0,174-0,757)
GFR 59,9-45 ml/min/1,73 m^2, %	30,56	13,71	0,004	2,770 (1,345-5,705)
GFR 44,9-30 ml/min/1,73 m^2, %	22,22	4,45	0,000	6,133 (2,704-13,914)
GFR 29,9-15 ml/min/1,73 m^2, %	8,33	0,77	0,000	11,692 (3,181-42,980)
COPD, %	4,88	3,36	0,594	1,476 (0,349-6,232)
COPD, ⩾60 years, %	4,88	2,79	0,426	1,784 (0,421-7,561)
Active cancer, %	12,2	3,93	0,008	3,399 (1,300-8,883)
Cancer ⩾60 years, %	12,2	2,46	0,000	5,499 (2,074-14,581)
Anemia, %	50,0	18,69	0,000	4,350 (2,279-8,302)

Abbreviations: HTN — hypertension, CI — confidence interval, CAD — coronary artery disease, MI — myocardial infarction, BMI — body mass index, OR — odds ratio, T2D — type 2 diabetes mellitus, GFR — glomerular filtration rate, AF — atrial fibrillation, HF — heart failure, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease.

reasons for treatment were gastrointestinal disease, cancer, asthma exacerbation, decompensated HF, AF, and upper respiratory tract infection. Even less common were treatment for CKD, COPD exacerbation, hypothyroidism and arthritis. The rarest reasons for seeking medical help were deep

Table 9

Comparative analysis of deceased and surviving patients within 3 months depending on multimorbidity characteristics

	Deceased patients, N=41	Surviving patients, N=2144	P	OR (95% CI)
No comorbidities, %	10,0	39,04	0,001	0,174 (0,052-0,574)
1 comorbidity, %	6,67	28,39	0,009	0,180 (0,043-0,759)
2-3 comorbidities, %	40,0	24,69	0,055	2,033 (0,971-4,258)
⩾4 comorbidities, %	43,33	7,88	0,000	8,938 (4,246-18,814)
No comorbidities, ⩾60 years, %	6,67	5,3	0,742	1,276 (0,299-5,444)
No comorbidities, <60 years, %	3,23	37,05	0,000	0,057 (0,008-0,417)
2-3 comorbidities, ⩾60 years, %	33,33	13,63	0,002	3,170 (1,464-6,861)
2-3 comorbidities, <60 years, %	6,67	11,1	0,442	0,572 (0,135-2,422)
⩾4 comorbidities, ⩾60 years, %	43,33	6,54	0,000	10,937 (5,174-23,118)
HTN+CAD, %	9,76	2,41	0,003	4,373 (1,502-12,728)
HTN+HF, %	31,71	7,28	0,000	5,909 (3,000-11,640)
HTN+CAD+HF, %	24,39	5,72	0,000	5,313 (2,545-11,092)

Abbreviations: HTN — hypertension, CI — confidence interval, CAD — ischemic heart disease, OR — odds ratio, HF — heart failure.

Table 10

Comparative analysis of deceased and surviving patients within 3 months depending on the acute COVID-19 course characteristics

Parameter	Deceased patients, N=41	Surviving patients, N=2144	P	OR (95% CI)
CT 0, %	17,65	10,61	0,190	1,806 (0,737-4,425)
CT 1-2, %	61,76	78,6	0,019	0,440 (0,218-0,888)
CT 3-4, %	20,59	10,8	0,071	2,142 (0,919-4,994)
RR ⩾30 bpm, %	5,88	1,69	0,068	3,630 (0,828-15,918)
SpO_2 ⩾95%, %	78,05	89,26	0,023	0,428 (0,202-0,908)
SpO_2 of 75-94%, %	21,95	10,74	0,023	2,338 (1,102-4,959)
hsCRP ⩽10 mg/L, %	8,11	26,65	0,011	0,243 (0,074-0,795)
hsCRP >40 mg/L, %	62,16	39,64	0,006	2,502 (1,278-4,897)
DVT in the acute period, %	2,44	0,33	0,029	7,471 (0,898-62,153)
AKI in the acute period, %	2,44	0,29	0,017	8,721 (1,026-74,122)

Abbreviations: hsCRP — high-sensitivity C-reactive protein, CI — confidence interval, CT — computed tomography, AKI — acute kidney injury, OR — odds ratio, DVT — deep vein thrombosis, RR — respiratory rate, SpO_2 — blood oxygen saturation.

vein thrombosis (DVT), T1D decompensation, viral hepatitis, HIV infection, pulmonary embolism (PE), and myocardial infarction (MI) (Table 3).

During 3- and 6-month follow-up, 5,6% and 6,4% of patients had newly diagnosed diseases (Tables 4A, 4B, 4C). Incidence rate of newly diagnosed HTN, CAD, myocardial infarction and diabetes in patients after COVID-19 was significantly higher compared to Russian population level in 2018; however, approximately the same level of newly diagnosed cancer incidence rate was revealed (Table 4B) [3].

Among patients with newly reported diseases after 3- and 4-6-month follow-up, patients with HTN predominated, which accounted for 41,5% and 46,7% in the structure of newly diagnosed diseases. It is noteworthy that the proportion of hypertensive patients increased during 4-6-month follow-up compared with the first 3 months. In addition, the proportion of patients with newly diagnosed CAD during 4-6-month follow-up (22,1%) compared to 3 months (9,7%). For 4-6 months there were more myocardial infarction cases than in the first 3 months (3,9% vs 0,8%). A similar pattern was observed for

Table 11

Comparative analysis of deceased and surviving patients within 3 months depending on the data from acute COVID-19 course

Parameter	Deceased patients, N=41	Surviving patients, N=2144	P
Age, years	73,2±14,38	53,28±13,5	0,000
RR, breaths per minute	21,1±4,77	19,51±3,01	0,020
HR, beats per minute	88,83±14,55	85,31±12,61	0,040
SpO_2, %	92,34±5,26	95,45±3,38	0,000
Hb, g/l	120,68±23,27	135,83±18,18	0,000
Lymphocytes, %	15,64±9,51	22,57±14,03	0,000
hsCRP, mg/L	76,82±65,85	47,3±68,77	0,350
D-dimer, FEU/ml	107,86±287,2	16,94±134,41	0,010
GFR, ml/min/1,73 m^2	53,59±21,2	77,02±20,83	0,000
Troponin I, ng/ml	81,04±141,32	0,32±2,17	0,000
Potassium, mmol/l	3,88±0,51	4,27±0,59	0,000

Abbreviations: hsCRP — high-sensitivity C-reactive protein, GFR — glomerular filtration rate, RR — respiratory rate, HR — heart rate, Hb — hemoglobin, SpO_2 — blood oxygen saturation.

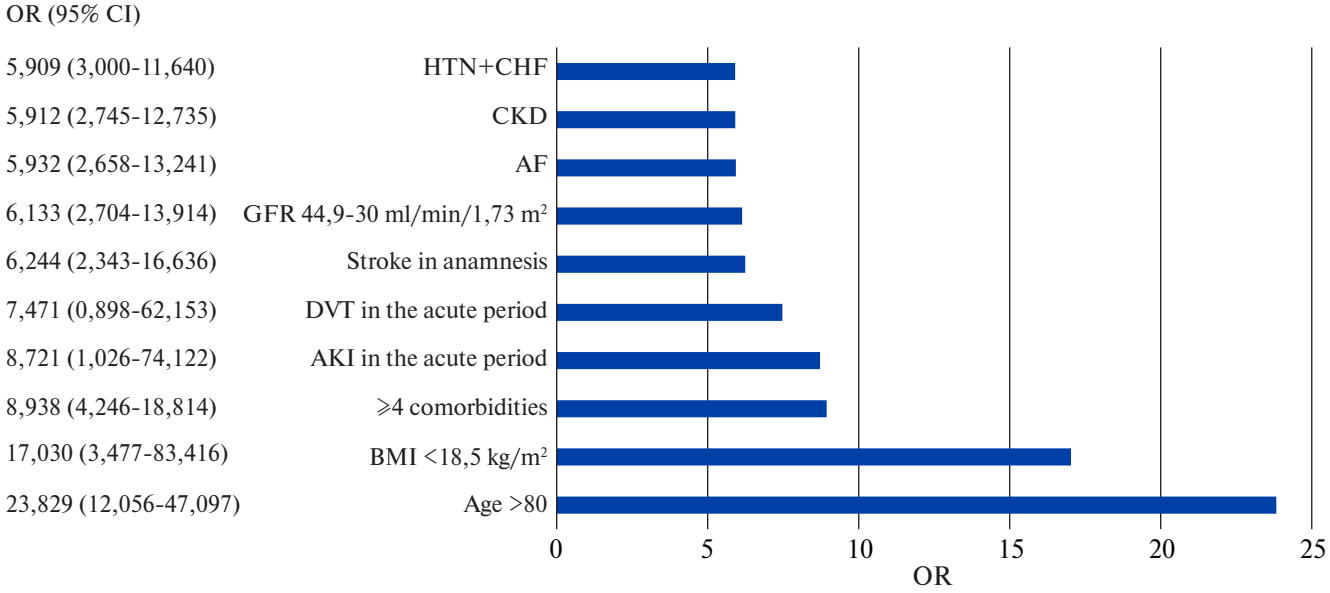

Figure 1. Ten main death RFs in the early 3-month post-hospitalization period.
Abbreviations: HTN — hypertension, CI — confidence interval, BMI — body mass index, AKI — acute kidney injury, OR — odds ratio, GFR — glomerular filtration rate, DVT — deep vein thrombosis, AF — atrial fibrillation, CKD — chronic kidney disease, CHF — chronic heart failure.

arthritis, the proportion of which was higher for 4-6-month follow-up (5,2%) in comparison with the first 3 months (4,9%), as well as for newly diagnosed HF, which was registered in 0,8% in the first 3 months and 1,3% during 4-6-month follow-up. The ratio of other newly diagnosed diseases has changed in the opposite direction. So, the incidence rate of T2D, AF, stroke, asthma, cancer, CKD and type 1 diabetes was lower in the period of 4-6 months compared with the first 3 months (Table 4B).

Despite the fact that patients with newly diagnosed diseases were older than those without them, (Table 5) there were more people aged 40-59 in their group in percentage terms. Obesity was more common in patients with newly diagnosed diseases. It was noteworthy that patients with newly diagnosed diseases suffered from more severe COVID-19 with higher fever, respiratory rate (RR), high-sensitivity C-reactive protein (hsCRP), lymphocyte percentage, glucose and fibrinogen levels. In addition, patients with newly diagnosed diseases were more often diagnosed with myocarditis in the acute COVID-19 period (Table 5).

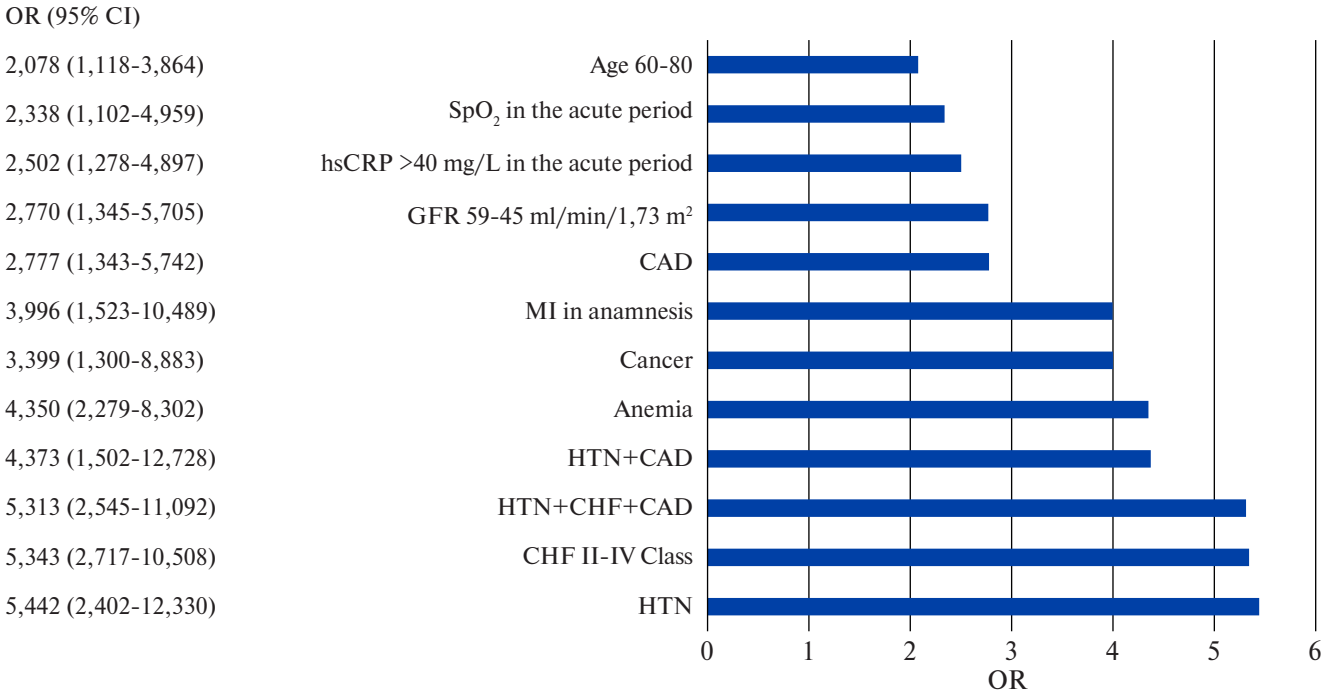

Figure 2. Death RFs in the early 3-month post-hospitalization period.
Abbreviations: HTN — hypertension, hsCRP — high-sensitivity C-reactive protein, CI — confidence interval, CAD — coronary artery disease, MI — myocardial infarction, BMI — body mass index, OR — odds ratio, GFR — glomerular filtration rate, CHF — chronic heart failure, SpO_2 — oxygen saturation.

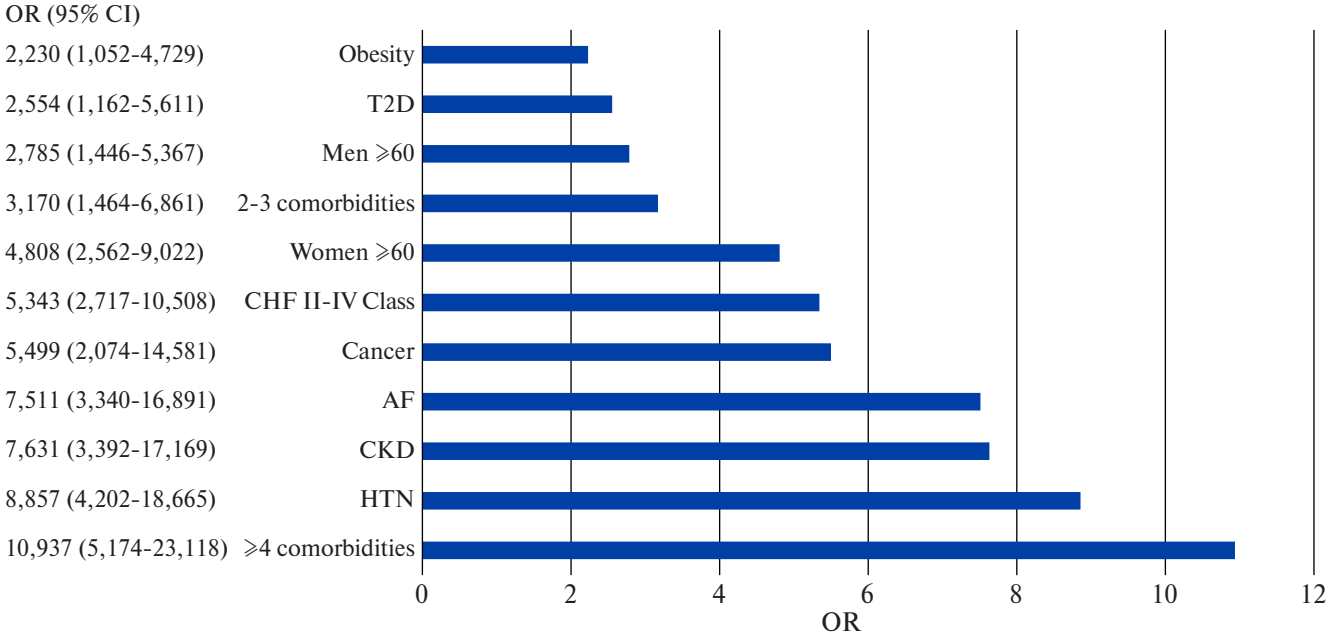

Figure 3. Death RFs in the early 3-month post-hospitalization period in patients aged ⩾60.
Abbreviations: HTN — hypertension, CI — confidence interval, OR — odds ratio, T2D — type 2 diabetes, GFR — glomerular filtration rate, AF — atrial fibrillation, CKD — chronic kidney disease, CHF — chronic heart failure.

The mortality rate of patients in the post-hospitalization period was 1,9% in the first 3 months and 0,2% during 4-6-month follow-up (Table 6). According to a differentiation analysis of mortality, depending on the type of comorbidity, the highest mortality rate was observed in the first 3 months in the group of patients with class II-IV HF, as well as in patients with cardiovascular diseases (CVDs) and

cancer. The presence of COPD and asthma did not affect the mortality of patients.

In the pattern of death causes in the post-hospitalization period, the following CVDs predominated (31,8%): acute coronary syndrome, stroke, acute heart failure (Table 7). In addition, pneumonia, cancer and pulmonary embolism were among the known causes of death.

Patients who died in the post-hospitalization period were significantly different from those who survived. The deceased patients were older. Age >60 years was associated with an increased risk of death by 3,324 and 4,765 times for men and women, respectively (Table 8). Patients who died in the post-hospitalization period differed from the survivors in comorbidity rates. HTN was associated with an increased risk of death, which was most pronounced in the group of patients >60 years old (Table 8). The following factors was associated with the death risk: body mass index (BMI) <18,5 kg/m^2, AF, especially in patients >60 years old, and CAD, especially with prior myocardial infarction. For patients ⩾60 years old, obesity was a risk factor (RF) for death. One of the strongest risk factors for lethal outcome was class II-IV HF, the presence of which was associated with an almost 5-fold increase in risk. A strong risk factor for lethal outcome was a history of stroke and CKD. The risk of death increased as the glomerular filtration rate (GFR) decreased. So, GFR of 59,9-45 ml/min/1,73 m^2 was associated with an increased risk of death by 2,770 times, GFR of 44,9-30 ml/min/1,73 m^2 — 6,133 times, and GFR of 29,9-15 ml/min/1,73 m^2 — 11,692 times. The presence of cancer, especially for patients ⩾60 years of age, and anemia were associated with an increased risk of death.

Patients who survived and died in the post-hospitalization period differed in multimorbidity severity (Table 9). Among the survivors, there were significantly more patients with no concomitant diseases or with only 1 comorbidity. The presence of 2-3 and especially 4 comorbid diseases was associated with an increased death risk. This was especially important for patients ⩾60 years old. Among the combinations of comorbid diseases, the most common were combinations of CVD and RF, such as HTN, CAD, HF, and obesity. The combination of HF with hypertension and/or CAD was a strong risk factor for lethal outcome in the post-hospitalization.

Surviving and deceased patients differed depending on the severity of infection during hospitalization or outpatient treatment in the acute period. The deceased patients suffered from more severe COVID-19 than the survivors (Tables 10, 11). They more often had severe shortness of breath with a respiratory rate of ⩾30 bpm, a decrease in SpO_2 within 75-94%, serum hsCRP >40 mg/L, which was associated with a significant increase in the death risk. Strong RFs were complications of the acute period of infection, such as acute renal injury and deep vein thrombosis (DVT) (Table 10). In addition, deceased patients in the acute infection period had higher heart rate, D-dimer levels, and troponin I levels, as well as lower hemoglobin, lymphocyte proportion, GFR and potassium levels (Table 11).

Thus, there were following 10 strongest RFs of lethal outcome in the early post-hospitalization period (3 months) in decreasing order of factor value (Figure 1): age >80 years, BMI <18,5 kg/m^2, ⩾4 comorbid conditions, acute renal injury and DVT in the acute period, prior stroke, GFR of 44,9-30 ml/min/1,73 m^2, presence of AF, CKD, and a combination of HTN+HF.

In addition, significant death RFs were as the factor value decreased (Figure 2): HTN, class II-IV HF, HTN+CAD+HF combination, HTN+CAD combination, anemia, cancer, prior myocardial infarction, CAD, GFR of 59,9-45 ml/min/1,73 m^2, hsCRP >40 mg/l in the acute period, SpO_2 of 75-94% in the acute period, and the age of 60-80 years.

For patients ⩾60 years old, the main risk factors for lethal outcome were in decreasing order of factor value (Figure 3): ⩾4 comorbidities, HTN, CKD, AF, cancer, class II-IV HF, 2-3 comorbidities, T2D and obesity. It was noteworthy that the combination of age ⩾60 years and female sex was associated with a 4,808-fold increased risk of death.

Discussion

The incidence of comorbidities in patients after COVID-19 generally corresponds to the population levels in a similar age [3, 4], as well as data from other observational studies of patients after hospitalization. So, according to Günster C, et al. [5] the most common comorbidities in patients discharged from the hospital were HTN (56,7%), diabetes (uncomplicated — 22%; complicated — 8,5%), cardiac arrhythmias (27,3%), CKD (23,0%) and HF (19,0%).

According to the AKTIV register, 38,2% of patients after COVID-19 had long-term persistence of symptoms. Most often, patients complained of weakness, shortness of breath, chest pain, increased blood pressure and palpitations. Other researchers demonstrate similar data. Thus, according to Huang C, et al. from Wuhan [6] with 6-month follow-up of 1733 patients after discharge from hospital, the most common persisting symptoms were fatigue or muscle weakness (63% of patients), as well as sleep problems (26%) and anxiety and/or depression (23%). According to the National

Institute for Health and Care Excellence (NICE) guidelines for long COVID [7], about one in five people had symptoms that lasted ⩾5 weeks, and 1 in 10 people had symptoms that lasted ⩾12 weeks. Most often, patients complained of chronic cough, shortness of breath, chest tightness, cognitive dysfunction, and extreme fatigue. Many publications on tachycardia in patients after COVID-19 have appeared recently [8-10]. Ståhlberg M, et al. [8] in their review emphasize the presence of tachycardia in long COVID and introduce a new term "post-COVID-19 tachycardia syndrome", considering it as a special phenotype of long COVID, which is defined as symptoms after COVID-19 infection persisting for 4-12 or >12 weeks [7].

One of the most significant results of data from the AKTIV register is information on an increase in the incidence of newly diagnosed diseases in patients after COVID-19. The incidence rate of HTN, CAD, MI and diabetes significantly exceeds that in the general Russian population (Table 4B). Other authors cite similar data. According to a retrospective study by Ayoubkhani D, et al. [11], patients after hospitalization due to COVID-19 were diagnosed with following diseases more often than in the corresponding control group: 3,0 (2,7-3,2) times for CVDs, 2,8 (2,0-4,0) times for chronic liver disease, 1,9 (1,7-2,1) times for CKD and 1,5 (1,4-1,6) times for diabetes.

According to the AKTIV register, more often newly diagnosed diseases developed in patients aged 49-50 years. According to the study by Ayoubkhani D, et al. [11], more often newly diagnosed diseases in the post-hospitalization period developed in patients under 70 years of age in comparison with patients in older age groups. Newly diagnosed diseases in patients with a low death risk from COVID-19 was studied in a prospective cohort observational study by Dennis A, et al. [12]. The study found that 70% of middle-aged patients without pronounced comorbidity after COVID-19 develop *de novo* damage to one or more organs 4 months after COVID-19 onset, which, according to the authors, should have serious consequences for society and the health system as a whole.

Rehospitalizations and increased mortality in the first 3-6 months are a serious problem in the post-hospitalization period. After hospitalization, according to our data, almost 1/3 of patients sought unscheduled health care (outpatient, inpatient), and during the first 3 months, at least 2 times. In addition, mortality of patients within 6 months amounted to 2,1%. An analysis of >100 thousand hospitalized patients with COVID-19 in the United States showed that 6 months after discharge, the readmission rate to the same hospital was 9%, while 1,6% was hospitalized >1 time. The presence of prior lung diseases, HF, T2D, CKD and age ⩾65 years increased the risk of readmission [13].

The UK retrospective cohort study by Ayoubkhani D, et al. [11] with 47780 patients showed that during an average follow-up period of 140 days, almost a third (29,4%) of those discharged from the hospital after an acute COVID-19 were rehospitalized (n=14060), and 12,3% (n=5875) died early after discharge (first 90 days). A study of 1775 US veterans hospitalized for COVID-19 found that 20% were readmitted and 9% died within 60 days of discharge [14]. According to the study by Leijte WT, et al. [15] with 769 patients after COVID-19 found that the all-cause mortality rate after discharge was 6,4%, and the re-hospitalization rate was 11,7%. The main reasons for readmission were respiratory failure (31%), arterial and venous thrombotic events (16%), or events associated with decompensated comorbidity (14%). Mortality was significantly higher in the cohort of elderly patients and patients with acute delirium. According to the study by Chopra V, et al. (n=1250) [16], 6,7% of patients died 60 days after discharge from the hospital. The observational study by Günster C, et al. with 8679 patients from Germany [5] showed that 26,8% of patients were re-hospitalized within 180 days, while the 90- and 180-day mortality rate was 27,9% (n=2425) and 29,6% (n=2566), respectively. For patients aged ⩾80 years, the 180-day mortality rate was 52,3% (n=1472). The RFs for 180-day all-cause mortality were HF, CKD, diabetes, cancer, liver disease, coagulopathy, BMI ⩾40 kg/m^2, and age. For patients with symptomatic HF, the 180-day all-cause mortality was 49,8%, for patients with CKD — 47,2%, for patients with complicated diabetes — 45,4%.

Ninety-day follow-up of severe COVID-19 patients after hospitalization has been reported in various observational studies, a large percentage of which had single-center design. The 90-day mortality rate ranged from 11% in Spain [17] to 29% in Denmark [18] (single-center studies), 27% in Sweden [19], 31% in Belgium, France and Switzerland [20]. In the multicenter study from 3 countries above, which included 4643 patients with severe COVID-19, the early independent predictors of 90-day mortality were old age, immunosuppression, severe obesity, HTN, diabetes, CKD, CVD, and severe acute respiratory distress syndrome.

Brieghel C, et al. [18] found that the risk of 90-day mortality increased in proportion to the patient age and the Charlson comorbidity index. In the study by Zettersten E, et al. [19], 3-month mortality depended on the patient's sex (older in men), age,

presence of COPD, asthma, immunodeficiency and active treatment of cancer.

Thus, the patients included in the AKTIV register were found to have comorbidities comparable to those cited above, which led to an increase in readmission rates and mortality in the post-hospitalization period. Apparently, the predominance of CVDs in patients after COVID-19 is universal in all countries. The AKTIV registry working group suggests that the post-hospitalization problems of COVID-19 can be explained by the destabilization of comorbid diseases due to COVID-19 [21], direct damaging effects of the virus on tissues and organs [22], expressed by the health system overload [23].

Study limitations. An insufficiently accurate assessment of the mortality rate in the post-hospitalization period is possible. This is due to the fact that no answer to the phone call cannot rule out the death of a patient. The accuracy of data presented is limited by the fact that they were obtained by contact with patients or their relatives, and not by the analysis of medical documents.

Conclusion

According to the AKTIV register and other studies, the health status of people after COVID-19 is a serious problem for the health care system in all countries. These patients are characterized by common seeking for health care, including rehospitalizations, worsening of existing disease course, high mortality rate, and diagnosis of "new" diseases in the post-hospitalization period.

The accumulated information on the frequency and RFs of rehospitalization and the development of *de novo* diseases allows the working group of the AKTIV register to suggest the formation of a new phenotype of patients. We believe that in a routine clinical practice, a new patient phenotype has appeared — a patient after a severe COVID-19, which required hospitalization. This patient is characterized by a high risk of progression of HTN, T2D, atherosclerosis and associated complications, as well as the development of *de novo* HF and/or progression of prior HF.

Discussion on this issue will allow, in our opinion, to optimize the solution of such priority tasks as health care capacity planning to provide care to patients with COVID-19 in both acute and post-hospitalization periods and can influence decision-making both at the local and national levels.

Relationships and Activities: none.

References

1. Arutyunov GP, Tarlovskaya EI, Arutyunov AG, et al. International register "Analysis of Chronic Non-infectious Diseases Dynamics After COVID-19 Infection in Adult Patients (ACTIV SARS-CoV-2)". Kardiologiia. 2020;60(11):31-4. (In Russ.) doi:10.18087/cardio.2020.11.n1398.
2. Arutyunov GP, Tarlovskaya EI, Arutyunov AG, et al. International register "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (ACTIV) and the register "Analysis of hospitalizations of comorbid patients infected during the second wave of SARS-CoV-2 outbreak" (ACTIV 2). Russian Journal of Cardiology. 2021;26(3):4358. (In Russ.) doi:10.15829/1560-4071-2021-4358.
3. Healthcare in Russia. 2019: Statistical digest. Rosstat. Moscow, 3-46 2019. 170 p. (In Russ.)
4. Badin YuV, Fomin IV, Belenkov YuN, et al. EPOCHA-AH 1998-2017. Dynamics of prevalence, awareness of arterial hypertension, treatment coverage, and effective control of blood pressure in the European part of the Russian Federation. Kardiologiia. 2019;59(1S):34-42. (In Russ.) doi:10.18087/cardio.2445.
5. Günster C, Busse R, Spoden M, et al. 6-month mortality and readmissions of hospitalized COVID-19 patients: A nationwide cohort study of 8,679 patients in Germany. PLoS One. 2021;16(8):e0255427. doi:10.1371/journal.pone.0255427.
6. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-32. doi:10.1016/S0140-6736(20)32656-8.
7. Venkatesan P. NICE guideline on long COVID. Lancet Respir Med. 2021;9(2):129. doi:10.1016/S2213-2600(21)00031-X.
8. Ståhlberg M, Reistam U, Fedorowski A, et al. Post-Covid-19 Tachycardia Syndrome: A distinct phenotype of Post-acute Covid-19 Syndrome. Am J Med. 2021:S0002-9343(21)00472-1. doi:10.1016/j.amjmed.2021.07.004.
9. Johansson M, Ståhlberg M, Runold M, et al. Long-Haul Post-COVID-19 Symptoms Presenting as a Variant of Postural Orthostatic Tachycardia Syndrome: The Swedish Experience. JACC Case Rep. 2021;3(4):573-80. doi:10.1016/j.jaccas.2021.01.009.
10. Shouman K, Vanichkachorn G, Cheshire WP, et al. Autonomic dysfunction following COVID-19 infection: an early experience. Clin Auton Res. 2021;31(3):385-94. doi:10.1007/s10286-021-00803-8.
11. Ayoubkhani D, Khunti K, Nafilyan V, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021;372:n693. doi:10.1136/bmj.n693.
12. Dennis A, Wamil M, Alberts J, et al.; COVERSCAN study investigators. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open. 2021;11(3):e048391. doi:10.1136/bmjopen-2020-048391.
13. Lavery AM, Preston LE, Ko JY, et al. Characteristics of Hospitalized COVID-19 Patients Discharged and Experiencing Same-Hospital Readmission — United States, March-August 2020. MMWR Morb Mortal Wkly Rep. 2020;69(45):1695-9. doi:10.15585/mmwr.mm6945e2.
14. Donnelly JP, Wang XQ, Iwashyna TJ, Prescott HC. Readmission and Death After Initial Hospital Discharge Among Patients With COVID-19 in a Large Multihospital System. JAMA. 2021;325(3):304-6. doi:10.1001/jama.2020.21465.
15. Leijte WT, Wagemaker NMM, van Kraaij TDA, et al. Sterfte en heropname na ziekenhuisopname met COVID-19. [Mortality and re-admission after hospitalization with COVID-19]. Ned Tijdschr Geneeskd. 2020;164:D5423. Dutch.
16. Chopra V, Flanders SA, O'Malley M, et al. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. Ann Intern Med. 2021;174(4):576-8. doi:10.7326/M20-5661.
17. Garcia-Vidal C, Cózar-Llistó A, Meira F, et al. COVID-19-researcher group. Trends in mortality of hospitalised COVID-19 patients: A single centre observational cohort study from Spain. Lancet Reg Health Eur. 2021;3:100041. doi:10.1016/j.lanepe.2021.100041.

18. Brieghel C, Ellekvist P, Lund ML, et al. Prognostic factors of 90-day mortality in patients hospitalised with COVID-19. Dan Med J. 2021;68(3):A09200705.
19. Zettersten E, Engerström L, Bell M, et al. Long-term outcome after intensive care for COVID-19: differences between men and women-a nationwide cohort study. Crit Care. 2021;25(1):86. doi:10.1186/s13054-021-03511-x.
20. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47(1):60-73. doi:10.1007/s00134-020-06294-x.
21. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020;8:546-50. doi:10.1016/S2213-8587(20)30152-2.
22. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. Circulation 2020;142:68-78. doi:10.1161/CIRCULATIONAHA.120.047549.
23. Masroor S. Collateral damage of COVID-19 pandemic: delayed medical care. J Card Surg 2020;35:1345-7. doi:10.1111/jocs.14638.