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International register "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (AKTIV SARS-CoV-2): analysis of 1,000 patients

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COVID-19 is a severe infection with high mortality. The concept of the disease has been shaped to a greater extent on the basis of large registers from the USA, Spain, Italy, and China. However, there is no information on the disease characteristics in Caucasian patients.

Therefore, we created an international register with the estimated capacity of 5,000 patients — Dynamics Analysis of Comorbidities in SARS-CoV-2 Survivors (AKTIV SARS-CoV-2), which brought together professionals from the Russian Federation, Republic of Armenia, Republic of Kazakhstan, and Kyrgyz Republic. The article presents the first analysis of the register involving 1,003 patients. It was shown that the most significant difference of the Caucasian population was the higher effect of multimorbidity on the mortality risk vs other registers. More pronounced effect on mortality of such diseases as diabetes, obesity, hypertension, chronic kidney disease, and age over 60 years was also revealed.

Key words: AKTIV register, SARS-CoV-2, COVID-19, multimorbidity.

Relationships and Activities: none.

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Coronavirus disease 2019 (COVID-19) is a severe infectious disease with a high death risk. At the time of preparing article, according to the World Health Organization (October 25, 2020), the disease has spread to 235 countries and there were 42,512,186 documented cases of infection and 1,147,301 related deaths [1]. The concept of the disease is based on large registries made in the USA, Spain, Italy, and China. However, to date, there is no data on the characteristics of the disease course in Eurasian patients. In this regard, an international AKTIV SARS-CoV-2 register was created, in which specialists from the Russian Federation, the Republic of Armenia, the Republic of Kazakhstan and the Kyrgyz Republic united. The design and prerequisites for register creation are described in article [2]. The main aim of the register with estimated capacity of 5 thousand patients, in addition to assessing the influence of individual risk factors (RFs) (obesity, smoking, hypertension (HTN), age over 60 years) and chronic non-infectious diseases on the risk of severe disease course and death, was the analysis of the infection influence on the course of chronic non-communicable diseases and cancer, as well as on the incidence of new cases of heart failure (HF), diabetes, acute coronary syndrome and cerebrovascular disease within 2 years.

Results

The first analysis of the register included data from 1,003 patients (Table 1): women — 55,2%, mean age — 57,9 [49, 67] years. Patients were hospitalized in 91,6% of cases. The distribution of patients according to the lung damage degree based on computed tomography data is presented as follows: grade 1 — 35,87%, grade 2 — 40,95%, grade 3 — 14,45% and grade 4 — 2,77%. Among hospitalized patients, the mortality rate was 3,8%, in the general cohort — 3,7%. Invasive mechanical ventilation was required in 5,9% of patients, while cytokine storm was observed in 12% of cases. Pulmonary embolism was diagnosed in 0,7% of patients, deep vein thrombosis — in 0,1%.

Impact of prior diseases and RFs. The most common RF was hypertension (Table 1), which occurred in 59,4% and 48,8% of in- and outpatients, respec-

Table 1

Characteristics of in- and outpatients included in the AKTIV register

Parameter	Inpatients	Outpatients	Total
n	919	84	1003
Age, years	58,2 [49, 67,2]	54,1 [44,5, 64,7]	57,9 [49, 67]
Women, %	55,6	51,2	55,2
Deceased patients, %	3,8	2,7	3,7
HTN, %	59,4	48,8	58,5
Obesity, %	42,2	34,2	41,2
Smoking, %	3,9	21,3	5,5
Grade 1, %	35,5	42,0	35,9
Grade 2, %	42,2	20,0	40,9
Grade 3, %	14,9	6,0	14,4
Grade 4, %	2,8	2,0	2,8
CAD, %	21,5	21,5	21,5
Prior MI, %	7,7	2,5	7,3
Type 2 diabetes, %	18,3	12,7	17,9
Class I-II HF, %	12,0	6,3	11,5
Class III-IV HF, %	2,3	0,0	2,1
CKD, %	7,0	19,0	8,0
COPD, %	6,1	1,3	5,7
Cerebrovascular disease, %	3,6	3,8	3,6
Active cancer, %	1,8	5,1	2,1
Type 1 diabetes, %	0,3	1,3	0,4

Abbreviations: HTN — hypertension, CAD — coronary artery disease, MI — myocardial infarction, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, HF — heart failure.

Table 2

Characteristics of surviving and deceased patients included in the AKTIV register

Parameter	Surviving patients N=975	Deceased patients N=28	p
Age, years	58 [48,75, 66,0]	72 [63,5, 82,0]	0,001
Lymphocytes, %	23,4 [16,0, 31,85]	14,0 [8,45, 19,05]	0,001
CRP, mg/L	29,15 [12,0, 82,70]	98,98 [42,7, 192,5]	0,001

Abbreviation: CRP — C-reactive protein.

tively. The second most common RF was obesity, which was observed in 42,2% and 34,2% of in- and outpatients, respectively. Smoking was more common among outpatients (24,1%) than among hospitalized patients (3,9%). Among chronic noncommunicable diseases in patients with COVID-19, coronary artery disease (CAD) was most common, which was observed with the same frequency in in- and outpatients (21,5%). Prior myocardial infarction was noted in 7,7% of hospitalized patients and only 2,5% of outpatients. Type 2 diabetes occurred in 18,3% of inpatients and 12,7% of outpatients. Class I-II HF was observed in 12,0% and 6,3% of in- and outpatients, respectively. Class III-IV HF occurred only in hospitalized patients (2,3%). Chronic kidney disease (CKD) was diagnosed in 8% of patients — in 7,0% and 19,0 of in- and outpatients, respectively. Chronic obstructive pulmonary disease (COPD) was observed in 6,1% and 1,3% of in- and outpatients, respectively. Prior cerebrovascular disease was in 3,6% and 3,8% of in- and outpatients, respectively. Active cancer was in 1,8% and 5,1% of in- and outpatients, respectively. Type 1 diabetes was observed in 0,3% and 1,3% of in- and outpatients, respectively.

Comparison of survived and deceased patients is shown in Table 2. It was found that the deceased patients were older (72 [63,5, 82,0] vs 58 [48,75, 66,0] years, p=0,001) (Table 2). Age 60 years and older (60+) increased the mortality risk more than 7 times (odds ratio (OR), 7,523 [95% confidence

Table 3

Characteristics of surviving and deceased patients included in the AKTIV register

Parameter	Surviving patients N=975	Deceased patients N=28	p	OR (95% CI)
Men, %	44,6	46,4	NA	
Age 60+, %	44,3	85,7	0,001	7,523 (2,584-21,898)
Grade 3-4, %	15,9	56,5	0,0001	6,880 (2,940-16,099)
HTN, %	57,3	82,1	0,016	3,428 (1,289-9,117)
Obesity, %	38,8	63,6	0,001	2,736 (1,137-6,680)
Obesity, inpatients, %	39,3	70,0	0,01	3,605 (1,362-9,545)
AF, inpatients, %	6,5	19,2	0,04	3,394 (1,220-9,443)
CAD, %	21,6	39,3	0,049	2,345 (1,076-5,109)
Type 2 diabetes, %	15,7	35,7	0,01	2,982 (1,342-6,627)
CKD, %	7,3	28,6	0,0001	5,079 (2,136-12,079)
CKD, patients >60 years of age, %	13,0	33,3	0,02	3,333 (1,344-8,269)
Comorbidities (⩾2), %	46,8	89,3	0,001	9,461 (2,831-31,613)
Comorbidities (⩾2), patients >60 years of age, %	70,2	91,7	0,04	4,673 (1,077-20,263)
Comorbidities (⩾2) and obesity, %	19,0	45,5	0,01	3,544 (1,490-8,427)
Diabetes + obesity + CVD*, %	8,7	41,7	0,001	7,473 (2,076-26,901)
Diabetes + obesity + CVD*, patients >60 years of age, %	13,6	45,5	0,04	5,278 (1,329-20,966)

Note: * — HTN, CAD, MI, cerebrovascular disease, DVT, HF.

Abbreviations: HTN — hypertension, CI — confidence interval, CAD — coronary artery disease, MI — myocardial infarction, OR — odds ratio, CVD — cardiovascular diseases, DVT — deep vein thrombosis, AF — atrial fibrillation, CKD — chronic kidney disease, HF — heart failure.

Table 4

Hospital mortality (%) of patients depending on drug intake

Drug	Intake+	Intake-	p	OR (95% CI)
ACE inhibitors/ARBs, patients with HTN	2,20	5,50	0,166	0,382 (0,118-1,241)
Statins, patients with CAD	3,50	10,00	0,269	0,397 (0,067-1,603)
Anticoagulants, patients >60 years of age	3,00	10,60	0,049	0,259 (0,078-0,855)

Abbreviations: HTN — hypertension, ARBs — angiotensin receptor blockers, ACE — angiotensin-converting enzyme, CI — confidence interval, CAD — coronary artery disease, OR — odds ratio.

interval (CI), 2,584-21,898] p=0,001) (Table 3). The degree of lung damage significantly influenced the prognosis of the disease. Grade 3-4 increased the risk of death in comparison with grade 1-2 by almost 7 times (OR, 6,880 [95% CI, 2,940-16,099] p=0,0001).

Among comorbidities, CKD had the greatest negative impact on prognosis. The presence of CKD increased the risk of death, regardless of the patient age, by 5 times (OR, 5,079 [95% CI, 2,136-12,079] p=0,0001). The presence of obesity (body mass index ⩾30 kg/m^2) was the RF for death in hospitalized patients (OR, 3,605 [95% CI, 1,362-9,545] p=0,01). Atrial fibrillation (AF), type 2 diabetes, and CAD increased the risk of death in hospitalized patients by 3,4, 3,0 and 2,3 times, respectively (OR, 3,394 [95% CI, 1,220-9,443] p=0,04; OR, 2,982 [95% CI, 1,342-6,627] p=0,01; OR, 2,345 [95% CI, 1,076-5,109] p=0,049).

Among the deceased patients, multimorbidity was significantly more common, which negatively affected the prognosis. Among the deceased patients, 2 or more chronic diseases were observed in 89,3% vs 46,8% among the survivors (p=0,001). The presence of 2 or more comorbidities in comparison with those with no more than 1 disease increased the risk of death by more than 9 times (OR, 9,461 [95% CI, 2,831-31,613] p=0,001). The combination of 2 or more comorbidities with obesity (OR, 3,544 [95% CI, 1,490-8,427] p=0,01) and the combination of diabetes with obesity and cardiovascular disease (OR, 7,473 [95% CI, 2,076-26,901] p=0,001).

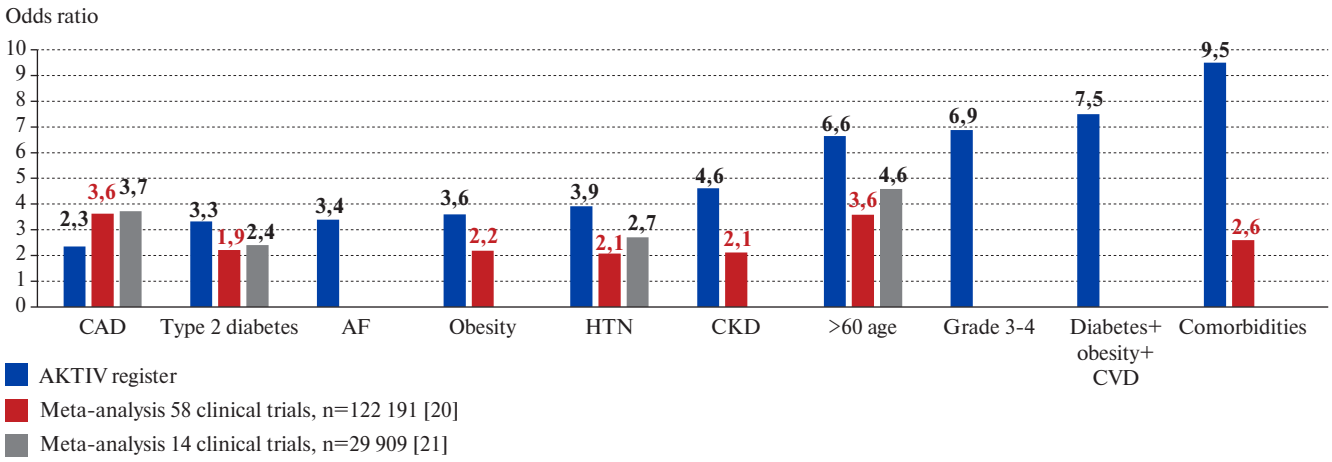

Figure 1. Risk factors for death in hospitalized patients with COVID-19 (ID ClinicalTrials.gov: NCT04492384, https://ACTIV.euat.ru, [20, 21]). **Abbreviations:** HTN — hypertension, CAD — coronary artery disease, CVD — cardiovascular diseases, AF — atrial fibrillation, CKD — chronic kidney disease.

Comparison of a large array of routine laboratory parameters in the population of deceased and surviving patients showed that significant differences were achieved in the levels of C-reactive protein (CRP) (98,98 [42,7, 192,5] vs 29,15 [12,0, 82, 70] mg/l, p=0,001) and the level of lymphocytes. In the population of deceased patients, the level of lymphocytes was significantly lower (14,0 [8,45, 19,05]% vs 23,4 [16,0, 31,85]%, p=0,001).

Analysis of the effect of individual drugs on the risk of death showed that:

– In patients over 60 years of age who received anticoagulant therapy, the death risk was lower than in patients who did not receive it (3,0% vs 10,6%, p=0,049, OR, 0,259 [0,078-0,855]) (Table 4).

– Statin therapy (not adjusted for dose and achievement of target low-density lipoprotein level) did not lead to a decrease in mortality, but significantly reduced the level of CRP by ⩾50% at 7-12 days in 82,9%, while in patients not receiving statins, such CRP changes was observed only in 48,1% (OR, 5,205 [1,634-16,582] p=0,009).

Discussion

Comparison of AKTIV register data with large registers performed in Great Britain, China, Italy, Spain is of great interest. The analysis showed that the patients in the AKTIV register reflecting the Eurasian cohort of patients were 5-15 years younger (mean age, 58 years vs 73 (UK [3]), 64 (China [4]), 63 (USA [5]), 69 (Spain [6]), 63 (Italy [7]). The proportion of women was significantly higher.

Thus, the proportion of women in the AKTIV register was 55%, which exceeds that in UK (40%) [3], China (51%) [4], the USA (40%) [5], Spain (43%) [6] and Italy (18%) [7].

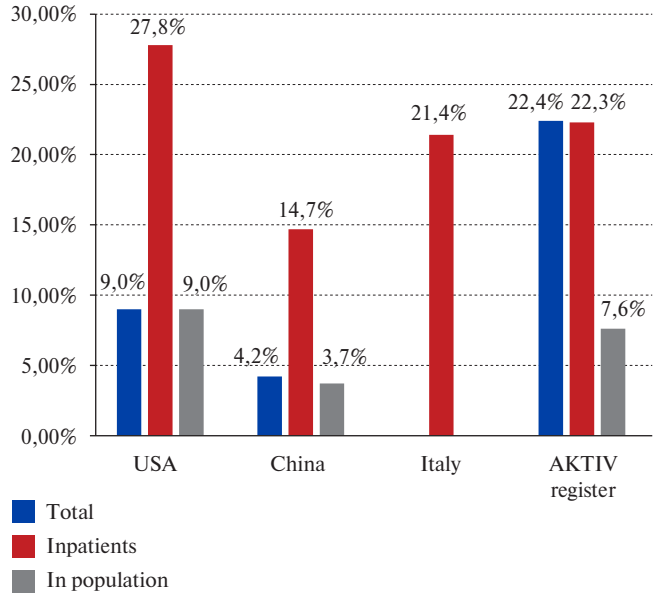

Figure 2. Incidence of CHD in COVID-19 in different regions, depending on the severity of the course [Kang Y, Chen T, Mui D, et al. Cardiovascular manifestations and treatment considerations in COVID-19. Heart. 2020;106(15):1132-41. doi:10.1136/heartjnl-2020-31, [17]).

The mortality rate in the AKTIV register was 3,7% and was lower than in the Italian register (7,2%) [8] and approximately corresponded to the Chinese ones (2,3% and 3,2%) [9, 10] and meta-analysis of Chinese and US studies (4,8%) [11] (Figure 1).

According to various studies, it was found that patients with concomitant diseases such as HTN, CAD, diabetes, HF, CKD, cancer, COPD, asthma, obesity are prone to a more severe course of COVID-19 and have a high death risk [12-16].

According to the AKTIV register, HTN was more common in the Eurasian population (58,5% vs 30,5% (China) [4], 56,6% (USA) [5], 50,9% (Spain) [6] and 49 % (Italy)) [7]. Almost half of the patients in the AKTIV register were obese (41,2%), which coincided with US data (41,7%) [5] and exceeded the obesity rate in the Spanish register (21,2%) [6] almost 2 times.

The CAD rate in patients of the AKTIV register (21,5%) was more than in the population (7,6%) (Figure 2) [17] and was comparable with data from Italian (21%) [7] and Spanish (19,9%) registers [6]. The CAD rate in registers from the USA (11,1%) [5] and China (10,6%) [4] was significantly lower in comparison with AKTIV register.

Diabetes occurred among the patients of the AKTIV register (17,9%) as often as in the register from Italy (17%) [7] and Spain (19,4%) [6] and less frequently than in UK (29, 9%) [3] and US (33,8%) registers [5]. In the Chinese register, diabetes was somewhat less common than in the AKTIV register (14,4%) [4].

The HF prevalence in the AKTIV register (13,6%) was higher than in the US (6,9%) [5] and Spainish (9,2%) registers [6]. In the AKTIV register, class I-II HF was observed in 11,5%, while class III-IV HF — in 2,1%.

CKD in patients of the AKTIV register (8%) was observed approximately as often as in the Spanish register (6,1%) [6] and significantly less frequently than in the UK register (16%) [3]. In registers of USA (5%) [5], China (3,4%) [4] and Italy (3%) [7], CKD was observed somewhat less frequently than in the AKTIV register.

Among patients in the AKTIV register, the COPD rate was small and amounted to 5,7%, which was comparable with data from the USA (5,4%) [5], Spain (5,3%) [6] and Italy (4%) [7]. The prevalence of COPD in UK patients (18,3%) [3] was higher, while in the Chinese ones (2,9%) [4] — lower than in the AKTIV register.

The smoking prevalence among patients of the AKTIV register was also low (5,5%), which is comparable to data from the UK (6,4%) [3] and Spain (5,3%) [6], but significantly lower, than in the US register (15,6%) [5].

The cancer rate in patients of the AKTIV register was low (2,1%) and corresponded to the Russian population (2,56%) [18]. A similar low incidence of cancer was in the Chinese register (2,2%) [4]. In other registries, the cancer prevalence was slightly higher: USA — 6% [5], Italy — 8% [7], Spain — 10,7% [6], Great Britain — 10,8% [3].

In deceased patients of the AKTIV register, hypertension was registered in 82,1%, which was more often than among deceased patients in the Italian register (73%) [19]. Among the deceased patients of the AKTIV register, CAD (39,3% vs 30%), CKD (28,6% vs 20%), type 2 diabetes (35,7% vs 33%) were more common than in the Italian register [19]. Comorbidities such as AF (19,2% vs 22%) and prior cerebrovascular disease (10,7% vs 11,2%) were observed in the AKTIV and Italian registers with approximately the same frequency [19]. In the AKTIV register, among the deceased patients, there were fewer patients with COPD (3,6% vs 13,7%) and cancer (10,7% vs 19,5%) than in the Italian register [19].

Comparison of RFs for death in the AKTIV register with the meta-analysis by the Noor FM, et al. [20] with58 studies involving 122,191 patients and the meta-analysis by Parohan M, et al. [21], with 14 studies involving 14,909 patients (Figure 1) found number of differences. Thus, in the AKTIV register, type 2 diabetes, obesity, HTN, CKD, age over 60 and multimorbidity had the most significant negative influence, higher than in above-mentioned meta-analyzes (Figure 1). Multimorbidity had the most significant negative impact on the prognosis in the Eurasian population of COVID-19 patients: 2 or more chronic diseases increased the risk of death by 9,5 times, while in the meta-analysis by the Noor FM, et al. [20], only by 2,6 times.

A number of RFs (male sex, COPD, cancer, asthma, cerebrovascular diseases, chronic liver diseases), which was associated with death in other studies [20, 21], with a pronounced trend, did not achieve significance in the AKTIV register. This can be explained by different sample sizes.

In the AKTIV register, deceased patients had a higher CRP level and a lower lymphocyte count, which is consistent with other studies [22-25].

According to the AKTIV register, the mortality rate was lower in patients over 60 years old who received anticoagulant therapy than in patients who did not receive it. The positive effect of anticoagulant therapy on the severity of COVID-19 course and the death risk was also shown in the study by Paranjpe I, et al. [26]. In this study, long-term anticoagulant therapy was associated with in-hospital mortality reduction by a 14% (hazard ratio, 0,86 [95% CI, 0,82-0,89] p<0,001). According to the study by Lemos AC, et al. [27], therapeutic-dose anticoagulation has advantages over prophylactic doses. The rationale for the widespread use of anticoagulant therapy for COVID-19 patients is the high risk of thrombotic events [28, 29].

Currently, anticoagulant therapy is recommended for COVID-19 pneumonia of any severity [30, 31].

According to the AKTIV register, the statin therapy in CAD patients contributed to a decrease in CRP level in comparison with patients not receiving these drugs. A similar beneficial effect of statins

on inflammatory markers was demonstrated in the study by Zhang XJ, et al. [32]. It is now known that, in addition to the anti-inflammatory effect, statins can inhibit the penetration of SARS-CoV-2 into host cells. Statins, activating autophagy, can regulate viral replication or degradation, providing protective effects in COVID-19 [32, 33]. According to the meta-analysis by the Kow CS and Hasan SS with 8,990 patients [34], the all-cause mortality and/or disease severity in patients with COVID-19 was reduced by 30% in patients taking statins.

Conclusion

The Eurasian population of COVID-19 patients differs from the populations in the European, US and Chinese registers, primarily in terms of the age and sex. The population of the AKTIV register is characterized by a younger age and female predominance. HTN and HF were observed more often than in other registers.

The most significant difference of the Eurasian population was the higher effect of multimorbidity on the mortality risk vs other registers. More pronounced effect on mortality of such diseases as diabetes, obesity, hypertension, chronic kidney disease, and age over 60 years was also revealed.

The mortality rate in the AKTIV register was 3,7%, which is lower than in the Italian register and approximately corresponds to the mortality rate in the Chinese and US registers.

Relationship and Activities: none.

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