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Analysis of the Impact of Comorbid Cardiovascular Pathology to the Course of COVID-19 and its' Outcomes in Inpatients Admitted to Hospital During the First and the Second Waves of the Novel Coronavirus Infection in the Eurasian Regione

Aim	To study specific features of the clinical course of novel coronavirus infection and the effect of concurrent diseases on the outcome in hospitalized patients with SARS-CoV-2 infection during the first and the second pandemic waves.
Material and Methods	To evaluate features of the course of COVID-19 in the Eurasian region, international registries ACTIV-1 and ACTIV-2 were created during the first and second pandemic waves, respectively. 5397 patients were enrolled to the ACTIV-1 registry from June 29, 2020 through October 29, 2020 and 2665 patients were enrolled to ACTIV-2 from November 01, 2020 through March 30, 2021.
Results	In-hospital mortality decreased during the second pandemic wave to 4.8% vs. 7.6% during the first wave. During the second wave, patients were older, had more concurrent diseases, were admitted in a more severe condition, and had a higher level of polymorbidity. During the second pandemic wave, the incidence of bacterial pneumonia and sepsis increased, but deep vein thrombosis and "cytokine storm" were observed less frequently. The most unfavorable predictors of mortality were the following combinations of concurrent diseases: arterial hypertension (AH) + chronic heart failure (CHF) + diabetes mellitus (DM) + obesity; AH + ischemic heart disease (IHD) + CHF + DM; and AH + IHD + CHF + obesity.
Conclusion	During the second pandemic wave, patients had more extensive damage of the lungs, more frequent febrile fever, higher levels of C-reactive protein and troponin, and lower levels of hemoglobin and lymphocytes. Perhaps, these changes were due to different tactics of hospitalization during the first and second waves in the participant countries that have contributed to ACTIV-1 and ACTIV-2 registries.

Keywords COVID-19; first and second pandemic waves; SARS-CoV-2

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The pandemic of COVID-19, which is caused by the novel strain SARS-CoV-2, demonstrates that outbreaks of new viral infections are a major health concern worldwide [1]. SARS-CoV-2 is a cause of rapidly increasing number of cases and high mortality worldwide [2]. Despite the tropism of SARS-CoV-2 to the lungs, COVID-19 is associated with a high risk of multiple organ system failure [3]. It should be noted that comorbidities aggravate the course of COVID-19 and worsen the long-term prognosis [4].

To assess the peculiarities of the course of COVID-19 in the Eurasian region, international registries were

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established: Analysis of Chronic Non-infectious Diseases Dynamics After COVID-19 Infection in Adult Patients (ACTIV 1) and Analysis of Health Status of Comorbid Adult COVID-19 Patients Hospitalised in Second Wave of SARS-CoV-2 Infection (ACTIV 2) [5].

The main purpose of the registries was to analyze the effects of SARS-CoV-2 infection on the subsequent course of the underlying chronic non-communicable diseases and cancers. It also allows evaluating the effects of multimorbidity as a whole and various combinations of comorbidities, and the following risk factors (RFs): obesity, smoking, arterial hypertension (AH), age over 60 years, on the risk of the severe disease and death.

Objective

The objective of the ACTIV 2 registry was to study the characteristics of the population, comorbidities, treatment regimens during the second wave of the pandemic.

From January 2020 to March 2021, we witnessed two waves of the COVID-19 pandemic. The first wave and the second wave were caused mainly by the Alpha and Beta variants of the virus, respectively [6]. Between the two waves, experience in managing patients was accumulated, which reflected in the guidelines of the Ministry of Health of the Russian Federation. It was of interest to study the clinical course of COVID-19 and the effect of comorbidities on its outcome in hospitalized patients infected with SARS-CoV-2 during the first and second waves of the pandemic.

Material and Methods

The study was approved by the Ethics Committee of the Pirogov Russian National Research Medical University and registered in the ClinicalTrials.gov database as "Analysis of Chronic Non-infectious Diseases Dynamics After COVID-19 Infection in Adult Patients (ACTIV)", NCT ID 04492384, and ACTIV 2 – NCT ID 04709120. Information about the Registry can be found on the website of the Eurasian Association of Therapists or by direct link: https://ACTIV.euat.ru.

The ACTIV 1 and ACTIV 2 registries included male and female patients over 18 years old diagnosed with COVID-19 (nasopharyngeal and oropharyngeal swab tests, SARS-CoV-2 antibody titer, typical CT picture) and treated in hospital, with full respect for anonymity. A total of 5,397 and 2,665 patients are included in the ACTIV 1 and ACTIV 2 registries, respectively. Two groups were analyzed:

- Group 1 – patients included in the ACTIV 1 registry (n=5,397);
- Group 2 – patients included in the ACTIV 2 registry (n=2,665).

The enrollment of patients in the ACTIVE 1 registry began on 29.06.2020 and ended on 29.10.2020. The enrollment of patients in the ACTIVE 2 registry began on 01.11.2020 and ended on 30.03.2021.

The detailed design and the methods of statistical processing have been published earlier [7]. The ACTIV registry was multicenter and included the analysis of the patient's medical examination data during the hospital treatment (hospital chart is the source document). Demographic (age, sex, and ethnicity), clinical (medical history, medication administered at admission, signs and symptoms at hospitalization, and results of physical examination at hospitalization), laboratory findings, computed tomography (CT) data, COVID-19 clinical course in hospital and complications were extracted from electronic hospital charts a standard data collection form. Three committees arranged and managed the registry: organizational and supervisory committees and the committee for the analysis of endpoints and control of filling in case report forms (CRFs). CRFs and document flow were electronic.

Data were collected from 26 medical centers in 7 countries (Russia, Armenia, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Uzbekistan). 140 physicians participated in the data collection. Patient enrollment was limited by the incidence of COVID-19 and local COVID-19 triage regulations given the indications for hospitalization in each region. Whenever the centers provided a set of eligible patients, we tried to get sequential patients. Nosological diagnosis was established based on the ICD-10 criteria.

The following laboratory parameters were collected from hospital charts and included in CRFs: RBCs, hemoglobin, WBCs (lymphocytes and neutrophils), platelets, high sensitivity cardiac troponin T or I, C-reactive protein (CRP), procalcitonin, arterial blood gases (pCO_2, pO_2), aspartate aminotransferase, alanine aminotransferase, bilirubin, glucose, albumin, creatinine to calculate glomerular filtration rate (GFR), serum potassium, serum sodium, D-dimer, ferritin, lactate dehydrogenase, international normalized ratio, fibrinogen, oxygen saturation (SpO_2). Chest CT findings were also included to all CRFs.

Statistical analysis

The data were processed within the registry using SPSS Statistics 25. Categorical variables are represented as percentages. The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to test normality of a distribution. Quantitative variables were described by the means (M) and standard deviations (SD) in the case of a normal distribution. Intergroup differences

were tested using the Student's t-test for normally distributed data and the Mann-Whitney U-test for non-normally distributed data. Percentages were compared using the chi-square test or the Fisher's exact test where appropriate. The differences were statistically significant with p value being less than 0.05. Variables that most significantly affect mortality were identified using logistic regression (univariate analysis).

Results

Comparative analysis of the groups of patients included in the ACTIV 1 and ACTIV 2 registries (Table 1) showed that the mean age of patients who were infected with SARS-CoV-2 in the second wave of the pandemic was higher by 4 years compared to patients infected in the first wave of the disease. Differences in the sex composition of the studied groups are also of interest: the percentage of male patients increased from 46% to 48.3% in the second wave of the pandemic (p = 0.046).

Analysis of the radiological patterns showed that there were less patients without pulmonary tissue involvement (CT0) in the second wave of the COVID-19 pandemic, 6.13% versus 8.12% in the ACTIV 1 registry (p = 0.004), and the percentage of patients with moderate lung lesion (CT1-2) increased from 76.47% in the ACTIV 1 registry to 79.52% in the ACTIV 2 registry (p=0.005). The frequency of detecting severe lung lesion (CT3-4) did not differ significantly and was 15.41% and 14.35% in the ACTIV 1 and ACTIV 2 registries, respectively (p=0.257).

Interestingly, the percentage of patients with febrile fever increased to 23.36% in the ACTIV 2 registry versus 20.69% in the ACTIV 1 registry (p = 0.01).

The analysis of the oxygen status of patients hospitalized with COVID-19 showed that there were more patients with oxygen saturation (pulse oximetry) not less than 95% in the second wave of the pandemic: 92.97% of patients in the ACTIV 2 registry versus 82.03% in the ACTIV 1 registry (p<0.0001). The number of patients with moderate desaturation decreased from 17.63% in the ACTIV 1 registry to 6.54% in the ACTIV 2 registry (p<0.0001), the percentage of patients with severe desaturation did not change statistically significantly and was small, 0.34% and 0.49%, respectively.

Analysis of the laboratory findings of the subjects revealed (Table 2) that the activity of the inflammatory response was higher in the second wave of the COVID-19 pandemic: the levels of C-reactive protein (CRP) were statistically significantly higher in patients of the ACTIV 2 registry than in patients of the ACTIV 1 registry. At the same time, the percentage of patients with a significant increase in serum CRP (>40 mg/L) in the ACTIV 2 registry was greater than in the ACTIV 1 registry, and amounted to 53.97% of the total study cohort (versus 43.87% in the ACTIV 1 registry; p<0.0001).

Table 1. Clinical characteristics of patients included in ACTIV 1 and ACTIV 2 registries

Parameter	Patients of the ACTIV 1 registry (n = 5,397)	Patients of the ACTIV 2 registry (n = 2,665)	p
Male, %	45.97	48.33	0.046
Age, years (M ± SD)	56.88 ± 15.05	60.68 ± 14.25	0.000
Age, %			
• < 40 years old	14.26	8.27	0.000
• 40–59 years old	40.36	33.57	0.000
• 60–80 years old	39.35	50.56	0.000
• > 80 years old	6.03	7.59	0.008
Age ≥ 60 years, %			
• Male	19.03	26.13	0.000
• Female	26.35	32.02	0.000
CT, %			
• 0	8.12	6.13	0.004
• 1–2	76.47	79.52	0.005
• 3–4	15.41	14.35	0.257
Body temperature, %			
• < 37.0 °C	14.66	19.14	0.000
• 37.0–38.5 °C	64.66	57.50	0.000
• ≥ 38.6 °C	20.69	23.36	0.010
RR, %			
• < 22 bpm	62.91	64.99	0.097
• 22–29 bpm	33.63	33.69	0.961
• ≥ 30 bpm	3.46	1.32	0.000
SpO_2, %			
• ≥ 95 %	82.03	92.97	0.000
• 75–94 %	17.63	6.54	0.000
• < 75 %	0.34	0.49	0.294

RR, respiratory rate; SpO_2, oxygen blood saturation measured by pulse oximetry; p, statistical significance of differences estimated using the chi-square test.

Attention was drawn to higher frequency of elevated troponin levels evidencing myocardial damage in the ACTIV 2 cohort compared with patients of the ACTIV 1 registry, 43.90% and 18.16%, respectively (p<0.0001). Patients included in ACTIV 2 registry also had lower hemoglobin and lymphocyte levels compared to the ACTIV 1 patients. There were no statistically significant differences between groups in such indicators as the WBC and platelet counts and levels of glucose and fibrinogen.

The comparative analysis of RFs and comorbidities identified statistically significant differences between patients with a history COVID-19 during the first and second waves of the pandemic (Table 3).

AH, obesity, including morbid obesity, coronary artery disease (CAD), including a history of myocardial

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Table 2. Laboratory findings of patients included in the ACTIV 1 and ACTIV 2 registries

Parameter	Patients of the ACTIV 1 registry (n = 5,397)	Patients of the ACTIV 2 registry (n = 2,665)	P
CRP, mg/L (M ± SD)	57.25 ± 78.98	62.89 ± 72.55	0.000
Serum CRP, %			
• ≤ 10 mg/L	24.38	17.36	0.000
• 11–40 mg/L	30.75	28.01	0.017
• > 40 mg/L	43.87	53.97	0.000
Troponin above normal, %	18.16	43.90	0.000
Hemoglobin, g/L (M ± SD)	134.65 ± 19.09	132.71 ± 20.29	0.000
WBCs, $\times 10^9$/L (M ± SD)	6.83 ± 3.72	6.87 ± 4.09	0.310
Lymphocytes, % (M ± SD)	21.65 ± 13.67	21.03 ± 13.08	0.000
Platelets, $\times 10^9$/L (M ± SD)	224.37 ± 89.06	226.76 ± 101.41	0.490
Glucose, mmol/L (M ± SD)	6.56 ± 2.90	6.53 ± 3.01	0.130
Fibrinogen, g/L (M ± SD)	4.66 ± 1.71	4.71 ± 1.91	0.370
Total cholesterol, mmol/L (M ± SD)	4.54 ± 1.29	4.3 ± 1.45	0.000

CRP, C-reactive protein; WBC, white blood cell.

infarction (MI) were more common in the ACTIV 2 cohort. More patients who had been infected with SARS-CoV-2 in the second wave of the pandemic had a history of stroke, the presence of diabetes mellitus (DM) type 2, and active cancer. There are no differences in the prevalence of smoking, atrial fibrillation (AF), chronic kidney disease (CKD), DM type 1, and anemia. Chronic heart failure (CHF) was more common in patients of the ACTIV 2 registry than in the ACTIV 1 subjects. At the same time, the percentage of clinically apparent CHF III–IV FC decreased and the number of patients with the initial stages of CHF increased in the structure of CHF during the second wave of the COVID-19 pandemic.

Table 3. Comorbidities and risk factors of patients included in the ACTIV 1 and ACTIV 2 registries

Parameter, %	Patients of the ACTIV 1 registry (n = 5,397)	Patients of the ACTIV 2 registry (n = 2,665)	P
AH	54.31	63.34	0.000
Smoking	5.22	4.79	0.414
Obesity, BMI ≥ 30 kg/m^2	31.63	34.75	0.005
Obesity, BMI ≥ 40 kg/m^2	3.78	5.31	0.003
AF	6.75	7.59	0.168
CAD without a history of MI	14.66	19.59	0.000
History of MI	5.68	7.71	0.001
CHF	14.22	23.27	0.000
CHF FC I–II	64.65	77.85	0.000
CHF FC III-IV	35.35	22.15	0.000
History of stroke	3.66	5.67	0.000
DM type 2	16.77	18.94	0.017
DM type 1	0.48	0.54	0.721
CKD	7.99	8.28	0.651
COPD	4.56	4.06	0.317
Active cancer	5.09	7.44	0.000
Anemia	22.08	24.08	0.052

CKD, chronic kidney disease;
COPD, chronic obstructive pulmonary disease.

It should be noted that patients included in both the ACTIV 1 and ACTIV 2 registries were highly multimorbid (Table 4).

The absence of comorbidities was a rarer phenomenon in the ACTIV 2 registry: only 19.20% of patients did not have such diseases versus 30.39% in the ACTIV 1 registry ($p < 0.0001$). The percentage of patients with 2–3 comorbidities was statistically significantly higher in the ACTIV 2 registry than in the ACTIV 1 registry, 35.58% and 29.39%, respectively ($p < 0.0001$). Every fifth (21.28%) patient in the ACTIV 2 registry had 4 or more comorbidities (versus 15.67% of patients in the ACTIV 1 registry; $p < 0.0001$). Patients included in the ACTIV 2 registry were more likely to have such combinations of two diseases as AH + CAD, AH + CHF, AH + obesity, more common combinations of three diseases were AH + CAD + CHF, AH + obesity + CAD, and combinations of four diseases included AH + CAD + CHF + obesity, AH + CAD + CHF + DM type 2, AH + DM type 2 + CHF + obesity, than patients included in the ACTIV 1 registry.

COVID-19 was accompanied in some patients by the development of complications (Table 5), and their incidence differed in the patient cohorts in the first and second waves of the pandemic. Attention was drawn to a significant, almost 8 fold increase in the incidence of bacterial pneumonia in the second wave of the pandemic, and an increase, although not as significant, in the incidence of acute respiratory distress syndrome (ARDS). There were fewer cases of deep vein thrombosis (DVT) in patients included in the ACTIV 2 registry and a comparable number of cases of pulmonary embolism. Cytokine storm was reported less often in the ACTIV 2 registry than in ACTIV 1. The incidence of acute kidney injury and cerebrovascular accident occurred was similar and did not exceed 1.50%. Myocarditis was more often observed in the second wave of the COVID-19 pandemic.

In the next stage of the study, we attempted to analyze clinical outcomes in hospitalized patients included in the ACTIV 1 and ACTIV 2 registries and the effects of comorbidities on the risk of death in patients with COVID-19 in the first and second waves of the pandemic.

The mortality rate of hospitalized patients was higher in the ACTIV 1 registry than in the ACTIV 2 registry (7.6% versus 4.8%, respectively; p=0.015). In

the ACTIV 1 registry, deceased patients were older than the survivors, the mean age was 70.87±13.11 years (mean age of the survivors was 56.03±14.65 years; p<0.0001). In the cohort of deceased patients, 55.56% were male.

In the ACTIV 2 registry, the mean age of the deceased patients was also higher the mean age of the survivors (70.51±11.34 and 60.26±14.17 years, respectively; p<0.0001). The mean age of the deceased patients did not differ between the ACTIV 1 and ACTIV 2 registries. There were more male patients among the deceased in the ACTIV 2 registry (62.80%).

A comparative analysis of the predictors of death in hospitalized patients included in ACTIV 1 and ACTIV 2 registries showed that the most powerful predictors were the following in both registries: AF, a history of stroke, CHF, AH, CKD, CAD, DM type 2, anemia, COPD, obesity, and active cancer (Figure 1). The structure of the predictors of death in ACTIV 1 differed from ACTIV 2 by less significance of the age of >80 years in the ACTIV 2 registry (odds ratio (OR) 7.449; 95% confidence interval (CI) 5.601–9.907 and OR 3.073; 95% CI 1.901–4.968, respectively) and less significance of the presence of AH, CKD, and obesity. Anemia, COPD, and cancer had greater negative significance for adverse prognosis in the ACTIV 2 population than in the ACTIV 1 patients. Predictors, such as a history of stroke, CHF, CAD, DM type 2, were equivalent for patients in both registries (see Figure 1).

Multimorbidity was an important predictor of death in COVID-19 for hospitalized patients included in the ACTIV 1 registry and the ACTIV 2 patients. The presence of ≥4 concomitant disease was associated with a 5.7-fold risk of death for patients in the ACTIVE 1 registry and a 4.9-fold risk of death in the ACTIVE 2 registry. Figure 2 shows the most common combinations of comorbidities and their effect on fatal outcome. Of interest, CVDs in combination with AH, DM, and obesity were the main comorbitity. A comparative analysis showed that the negative impact of the combinations including obesity on the mortality decreased in the ACTIV 2 patient population: AH + DM type 2 + CHF + obesity, AH + CAD + CHF + obesity, AH + DM type 2 + obesity, AH + CAD + obesity, AH + obesity. Combinations that did not include obesity were nearly equivalent in effect on the mortality of hospitalized patients, especially, AH + CAD + DM type 2 + CHF.

Table 4. Concomitant cardiovascular diseases in hospitalized patients included in the ACTIV 1 and ACTIV 2 registries

Parameter, %	Patients of the ACTIV 1 registry (n = 5,397)	Patients of the ACTIV 2 registry (n = 2,665)	p
No CDs	30.39	19.59	0.000
1 CD	24.55	23.54	0.347
2–3 CDs	29.39	35.58	0.000
≥4 CDs	15.67	21.28	0.000
AH + CAD	4.29	6.29	0.000
AH + CHF	12.28	21.63	0.000
AH + obesity	21.9	25.04	0.002
AH + CAD + CHF	9.07	14.46	0.000
AH + obesity + DM type 2	7.47	7.78	0.623
AH + obesity + CAD	6.33	8.47	0.000
AH + CAD + CHF + obesity	3.51	4.98	0.002
AH + CAD + CHF + DM type 2	2.84	4.91	0.000
AH + DM type 2 + CHF + obesity	2.02	3.14	0.002

CD, concomitant disease.

Table 5. Complications in patients included in the ACTIV 1 and ACTIV 2 registries

Parameter, %	Patients of the ACTIV 1 registry (n = 5,397)	Patients of the ACTIV 2 registry (n = 2,665)	P
Bacterial pneumonia	4.14	32.22	0.000
ARDS	1.00	5.58	0.000
Cytokine storm	75.43	14.11	0.000
DVT	0.37	0.04	0.008
PE	0.18	0.28	0.363
CVA, %	0.18	0.24	0.568
AKI	1.30	1.32	0.954
Myocarditis	0.16	1.99	0.000
Sepsis	0.06	0.24	0.067

CVA, cerebrovascular accident; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis; PE, pulmonary embolism.

Discussion

It is of great interest to compare data obtained from hospitalized patients with COVID-19 from the ACTIV 1 and ACTIV 2 registries with data from large registries conducted in other countries. In some European, African, and American countries [8–13], attempts were made to compare patients of the first and second waves of the COVID-19 pandemic to identify various features and the possibility of predicting the further course of the infectious process.

According to the ACTIV 2 registry, the patients were older in the second wave of the pandemic than in the first wave, which intrinsically predetermines the higher prevalence of CVDs in this patient cohort, as we observed in our study.

According to a large Brazilian study [14] including 678,235 patients infected with SARS-CoV-2, the mean

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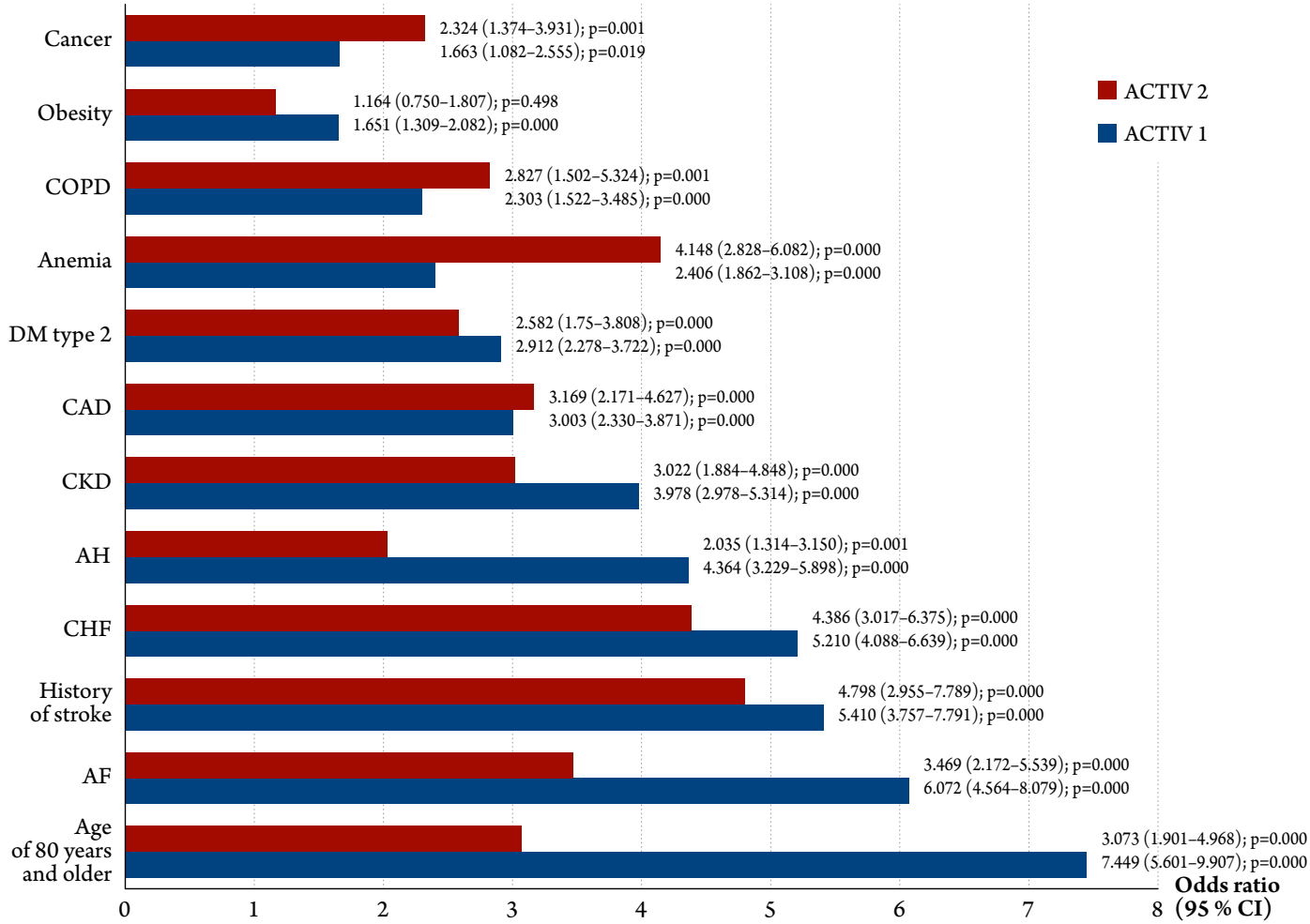
Figure 1. Comparative analysis of death predictors in the ACTIV 1 and ACTIV 2 registries



COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.

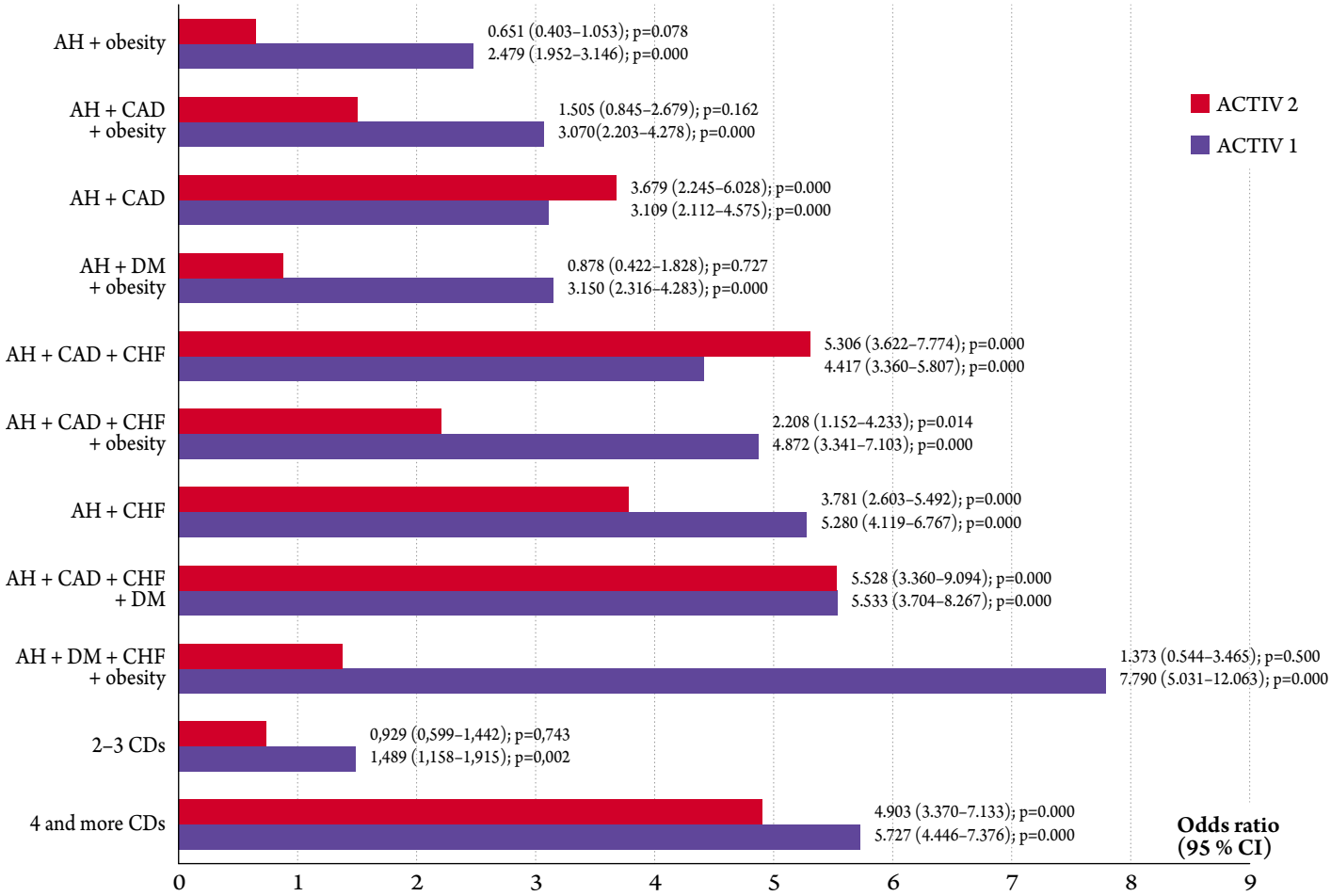
age of patients was the same in the first and second waves (61 [47.0–73.0] and 61 [48.0–72.0] years, respectively; p>0.05).

A Japanese study showed that the second wave of the pandemic affected more young people than the first wave [15]. In Germany, Italy and Belgium, similar results were obtained [16, 17]. However, in Spain, Mollinedo-Gajate et al. [18] showed that patients hospitalized in the second wave were older than patients hospitalized in the first wave, which is consistent with our findings. The Swiss study noted the following features of patients in the second wave of the COVID-19 pandemic compared to the first wave: older age, lower percentage of patients without comorbidities [19]. Thus, the analysis of registries suggests that all age groups were affected in the second wave of the pandemic, as in the first wave, i.e., it is not possible to identify unambiguous age differences in all countries.

According to our study, patients included in the ACTIV 2 registry were hospitalized in a more severe condition than the ACTIV 1 patients: more extensive lung lesion, more frequent febrile fever, higher levels of CRP and troponin, and the lowest values of hemoglobin and lymphocyte count. We attribute this pattern to the different hospitalization norms in the first and second waves of the pandemic in countries that participated in the ACTIV 1 and ACTIV 2 registries: they used a more differentiated approach to the indications for hospitalization in the second wave of the pandemic, giving preference to patients with moderate-to-severe infectious process with RFs [20]. Higher prevalence of elevated troponin levels and myocarditis in the ACTIV 2 cohort compared to the ACTIV 1 patients suggests that there may be more patients at increased risk of heart failure in the post-COVID-19 period after the second wave than after the first wave of the pandemic. However, according to Zeiser et al. [14], the severity of patients at hospitalization did not differ in the first and second waves of the pandemic.

In this study according to the ACTIV 1 and ACTIV 2 registries, hospitalized patients were more likely to have AH, obesity, CAD, a history of MI, a history of stroke, DM type 2, cancer, less likely to have severe CHF (FC III–IV), and were more multimorbid in the second wave of

Figure 2. Comparative analysis of the influence of risk factors, the number of comorbidities and their combinations on the risk of death of patients included in the ACTIV 1 and ACTIV 2 registries



CD, concomitant disease.

the pandemic. These diseases were important predictors of death in COVID-19 in the first and second waves of the pandemic. The ACTIV 2 patients were more likely to have such combinations as AH + CAD, AH + CHF, AH + obesity, AH + CAD + CHF, AH + obesity + CAD, AH + CAD + CHF + obesity, AH + CAD + CHF + DM type 2, AH + DM type 2 + CHF + obesity, than patients included in the ACTIV 1 registry. This is, in part, a reflection of a more severe clinical status of patients, but also suggests a higher incidence of adverse cardiovascular events in the post-hospital period during the second wave of the pandemic. Mollinedo-Gajate et al. [18] note a similar pattern in their study. However, according to Zeiser et al. [14], the degree of polimorbidity and the incidence of comorbidities did not differ in the first and second waves of the pandemic.

The comparative analysis of the ACTIV 1 and ACTIV 2 data showed that there was an increase in the incidence of bacterial pneumonia, but less common development of DVT and cytokine storm in the second wave of the pandemic. This may be due to changes in the patient management strategies in the first and second waves of the pandemic [20]. According to the clinical guideline, anticoagulants were administered more often, including in therapeutic doses, in the management of hospitalized patients by the beginning of the second wave. At the same time, widespread use of glucocorticoids began during the second wave of the pandemic, which reduced the incidence of cytokine storm and mortality, but possibly contributed to higher incidence of bacterial complications. Similar results were demonstrated in a nationwide German study [21], which showed that the frequency of admissions to intensive care units for COVID-19 decreased 2-fold during the second wave compared to the first wave of the pandemic. Authors suggested that the new standards of oxygen support and adequate pharmacotherapy, including the use of systemic glucocorticoids, could be the possible reason.

According to our data, the in-hospital mortality rate decreased in the second wave to 4.8% versus 7.6% in the first wave of the COVID-19 pandemic. Fan et al. [12] shows mortality trends in different countries. According to the analysis, 43 of the 53 most affected countries or regions had a clear decrease in mortality, but it increased in the remaining 10 countries. The authors of this study

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discussed some theories of different mortality trends, such as the harvest effect, according to which a large number of elderly people and people with health problems might have died during the first wave, especially in countries with high prevalence of COVID-19. On the contrary, if the first wave was less severe in a country (for example, Hong Kong), then mortality increased during the second wave. The second possible reason is better preparation of the health care system and the introduction of more effective treatments during the second wave of the pandemic. The possibilities of virus mutation and the influence of environmental factors were also discussed.

According to the ACTIV 1 and ACTIV 2 registries, age of 80 years and older, AF, a history of stroke, CHF, AH, CKD, CAD, DM type 2, anemia, COPD, obesity, active cancer, and multimorbidity were the most powerful predictors of death in hospitalized patients. We have previously reported the predictors of unfavorable course of acute infection [4, 22]. Our findings do not contradict the data of other studies of the predictors of unfavorable prognosis of COVID-19 [23–25].

The fundamental difference between the data obtained in our study and the data from other registries is the assessment of the effects of combinations of comorbidities on the risk of death. Our data suggest that AH + CHF + DM type 2 + obesity, AH + CAD + CHF + DM type 2, AH + CAD + CHF + obesity were the most common combinations of comorbidities during the first and second waves of the pandemic. These combinations were associated with an increased risk of death, which should be taken into account in clinical practice. This approach to assessing the risk of death in hospitalized patients with COVID-19 allows makes it possible to increase the efficacy of the management of COVID-19 patients from the very beginning, since it is possible to make a prognosis with high certainty and modify treatment regimen during the collection of anamnesis.

Conclusion

The comparative analysis of the groups of patients included in the ACTIV 1 and ACTIV 2 registries showed that patients who were infected with SARS-CoV-2 in the second wave of the pandemic were older and had more severe condition at admission than patients infected in the first wave. In the second wave of the pandemic, patients had more extensive lung lesion, febrile fever was more common, levels of C-reactive protein and troponin were higher, hemoglobin and lymphocyte counts were lower. This is probably due to the different approaches to hospitalization in the first and second waves of the pandemic in the countries that took part in the ACTIV 1 and ACTIV 2 registries.

During the second wave of the COVID-19 pandemic, hospitalized patients were more likely to have arterial hypertension, obesity, coronary artery disease, a history of myocardial infarction, a history of stroke, diabetes mellitus type 2, cancer, chronic heart failure of functional class I–II, but less likely to have severe chronic heart failure (functional class III–IV), and prevalence of multimorbidity was higher. The incidence of bacterial pneumonia was higher and the incidence of deep vein thrombosis and cytokine storm was lower in the second wave of the pandemic. This can be explained by differences in COVID-19 treatment regimens in the first and second waves of the pandemic.

Despite older age, more severe clinical status, higher prevalence of cardiovascular diseases in the ACTIV 2 patients, the in-hospital mortality decreased in the second wave of the pandemic to 4.8% compared to 7.6% in the first wave, which is probably due to better preparation of the health care system and the introduction of more effective treatment methods during the second wave of the pandemic.

Regardless of the wave of the COVID-19 pandemic the most powerful predictors of death in hospitalized patients are the following: age (80 years and older), atrial fibrillation, a history of stroke, chronic heart failure, arterial hypertension, chronic kidney disease, coronary artery disease, diabetes mellitus type 2, anemia, chronic obstructive pulmonary disease, obesity, active cancer, and multimorbidity.

Arterial hypertension + chronic heart failure + diabetes mellitus type 2 + obesity, arterial hypertension + coronary artery disease + chronic heart failure + diabetes mellitus type 2, arterial hypertension + coronary artery disease + chronic heart failure + obesity were the most common combinations of comorbidities with unfavorable effect on the prognosis of COVID-19 in seven Eurasian countries in the first and second waves of the pandemic.

Limitations

Although the registries included all patients who were successively admitted to hospitals, some selection bias could not be excluded. Our study may have limitations due to the restricted capacity of multicenter registries to verify each patient's data.

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