Features of comorbid pathology spectrum and age structure of oxygen-dependent patients with severe coronavirus disease 2019 (COVID-19) depending on outcomes of the disease

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article;
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The aim was to analyze spectrum of comorbid pathology and age structure of oxygen-dependent patients with severe coronavirus disease 2019 (COVID-19) depending on outcomes of the disease.

Materials and methods. The study included 85 oxygen-dependent patients with severe COVID-19. The patients were divided into groups: I – 70 patients with recovery; II – 15 patients in whom the disease was fatal. Statistical data processing was performed in the program Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J).

Results. Among the patients with fatal outcomes of the disease, elderly and senile were dominated – 93.3 % (14 of 15) versus 67.1 % (47 of 70) among patients who recovered (P < 0.05). Analysis of comorbid pathology structure in oxygen-dependent patients with severe COVID-19 showed that patients who died more often had hypertension (93.3 % vs. 30.0 %, P < 0.001), postinfarction cardiosclerosis (26.7 % vs. 2.9 %, P < 0.001), rhythm disturbance as persistent atrial fibrillation (20.0 % vs. 1.4 %, P < 0.01) as compared to those who survived. The patients of group II were more commonly diagnosed with chronic kidney disease (20.0 % vs. 4.3 %, P < 0.05) as the comorbid pathology. The presence of ischemic stroke in COVID-19 infection influenced the disease outcome (20.0 % vs. 4.3 %, P < 0.05). Fatal outcomes in the patients with COVID-19 were associated with a combination of 3 or more comorbid conditions in 46.7 % versus 17.4 % among oxygen-dependent survivors with severe disease (P < 0.01).

Conclusions. Elderly and senile oxygen-dependent patients are more likely to die from severe COVID-19 (P < 0.05). Comorbid hypertension, postinfarction cardiosclerosis, arrhythmia in the form of persistent atrial fibrillation, chronic kidney disease and ischemic stroke or the combination of 3 or more comorbid conditions listed are more common among patients with COVID-19 who died (P < 0.05) as compared to survivors.

Особливості спектра коморбідної патології та вікової структури кисневозалежних хворих із тяжким перебігом коронавірусної хвороби COVID-19 залежно від наслідків захворювання

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Мета роботи – проаналізувати спектр коморбідної патології та вікової структури кисневозалежних хворих із тяжким перебігом коронавірусної хвороби COVID-19 залежно від наслідків захворювання.

Матеріали та методи. У дослідження включили 85 кисневозалежних хворих із тяжким перебігом коронавірусної хвороби COVID-19. Пацієнтів поділили на групи: I – 70 осіб з одужанням; II – 15 пацієнтів, в яких захворювання завершилося летально. Статистичне опрацювання результатів виконали у програмі Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Результати. Серед пацієнтів із летальним наслідком хвороби переважали хворі похилого та старечого віку – 93,3 % (14 із 15) проти 67,1 % (47 із 70) пацієнтів, які одужали (р < 0,05).

Аналіз структури коморбідної патології в кисневозалежних хворих із тяжким перебігом коронавірусної хвороби COVID-19 показав, що у хворих, які померли, частіше, ніж у пацієнтів, які одужали, була гіпертонічна хвороба (93,3 % проти 30,0 %, р < 0,001), постінфарктний кардіосклероз (26,7 % проти 2,9 %, р < 0,001), порушення ритму у вигляді постійної форми фібриляції передсердь (20,0 % проти 1,4 %, р < 0,01). Серед коморбідної патології, що частіше діагностували у хворих II групи, – хронічна хвороба нирок (20,0 % проти 4,3 %, р < 0,05). Наявність ішемічного інсульту на момент розвитку коронавірусної хвороби COVID-19 вплинула на результат захворювання (20,0 % проти 4,3 %, р < 0,05). Серед хворих, в яких коронавірусна хвороба COVID-19 завершилася летально, 46,7 % мали комбінацію трьох і більше коморбідних станів проти 17,4 % кисневозалежних пацієнтів із тяжким перебігом захворювання, які одужали (р < 0,01).

Висновки. Серед кисневозалежних пацієнтів із тяжким перебігом коронавірусної хвороби COVID-19 і летальним наслідком переважають хворі похилого та старечого віку (р < 0,05). У хворих на коронавірусну хворобу COVID-19, які померли, частіше (р < 0,05), ніж у пацієнтів, які одужали, діагностували коморбідну гіпертонічну хворобу, постінфарктний кардіосклероз, порушення ритму у вигляді постійної форми фібриляції передсердь, хронічну хворобу нирок, ішемічний інсульт і поєднання трьох і більше коморбідних станів.

Особенности спектра коморбидной патологии и возрастной структуры кислородзависимых больных с тяжелым течением коронавирусной болезни COVID-19 в зависимости от последствий заболевания

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Цель работы – проанализировать спектр коморбидной патологии и возрастной структуры кислородзависимых больных с тяжелым течением коронавирусной болезни COVID-19 в зависимости от последствий заболевания.

Материалы и методы. В исследование включены 85 кислородзависимых больных с тяжелым течением коронавирусной болезни COVID-19. Больные поделены на группы: I – 70 пациентов, которые выздоровели; II группа – 15 пациентов, у которых заболевание завершилось летально. Статистическая обработка данных проведена в программе Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Результаты. Среди пациентов с летальным исходом болезни преобладали больные пожилого и старческого возраста – 93,3 % (14 из 15) против 67,1 % (47 из 70) пациентов, которые выздоровели (p < 0,05). Анализ структуры коморбидной патологии у кислородзависимых больных с тяжелым течением коронавирусной болезни COVID-19 показал, что у умерших больных чаще, чем у пациентов, которые выздоровели, имели место гипертоническая болезнь (93,3 % против 30,0 %, p < 0,001), постинфарктный кардиосклероз (26,7 % против 2,9 %, p < 0,001), нарушения ритма в виде постоянной формы фибрилляции предсердий (20,0 % против 1,4 %, p < 0,01). Среди коморбидной патологии, которая чаще диагностирована у больных II группы, отмечено наличие хронической болезни почек (20,0 % против 4,3 %, p < 0,05). Наличие ишемического инсульта на момент развития коронавирусной болезни COVID-19 повлияло на исход заболевания (20,0 % против 4,3 %, p < 0,05). Среди больных, у которых коронавирусная болезнь COVID-19 завершилась летальным исходом, 46,7 % пациентов имели комбинацию трёх и более коморбидных состояний против 17,4 % кислородзависимых пациентов с тяжелым течением заболевания, которые выздоровели (p < 0,01).

Выводы. Среди кислородзависимых больных с тяжелым течением коронавирусной болезни COVID-19 и летальным исходом преобладают больные пожилого и старческого возраста (p < 0,05). У больных коронавирусной болезнью COVID-19, которые умерли, чаще (p < 0,05), чем у пациентов, которые выздоровели, имеет место коморбидная гипертоническая болезнь, постинфарктный кардиосклероз, нарушения ритма в виде постоянной формы фибрилляции предсердий, хроническая болезнь почек и ишемический инсульт, а также сочетание трёх и более коморбидных состояний.

In March 2020, the WHO reported a pandemic of the coronavirus disease – 2019 (COVID-19). Literature data indicate that before the outbreak of coronavirus infection SARS-CoV in 2002–2003, coronaviruses were not considered highly pathogenic to humans [1]. However, later in 2012, the outbreak of coronavirus infection was recorded in the Middle East, which was caused by a new MERS-CoV. In December 2019, a new coronavirus SARS-CoV-2 was identified as the causative pathogen of the pandemic and was named COVID-19 [1,2]. Genome structure analysis of the new SARS-CoV-2 revealed that it shares 79.6 % sequence identity with SARS-CoV [3,4]. The coronavirus evolution resulted in N501T mutation, which led to change in the surface spike protein structure and increased the binding affinity of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) receptor by 10-20 times [5].

ACE2 is known as a receptor used by SARS-CoV and SARS-CoV-2 to enter a target cell [6,7]. Even in the study of coronavirus disease caused by SARS-CoV, researchers drew attention to multiple organ damage. Therefore, the study on pathogenesis of COVID-19 gave rise to a question about correlation between viral damage and the receptor ACE2 expression in different human organs. At the tissue level, ACE2 is highly expressed in the lungs, kidneys, heart and vascular endothelium, which, to some extent, explains multiorgan damage by SARS-CoV and SARS-CoV-2 in patients with coronary heart disease [8,9]. Multiorgan damage in severe disease is also derives from the development of a "cytokine storm", which is accompanied by an overproduction of pro-inflammatory cytokines and chemokines such as tumor necrosis factor α, interleukins 1β and 6 by immunocompetent cells and the development of systemic endotheliitis with hypercoagulation [10,11]. Based on the above, considerable attention

is currently being paid to defining the comorbid conditions that can significantly influence the course of SARS-CoV-2.

Already when the first patients with coronavirus disease caused by the new SARS-CoV-2 appeared in China, it was found that one in three among them had comorbid pathology, most often diabetes mellitus (20 %), hypertension (15 %) and other cardiovascular diseases (15 %) [12]. During the spread of pandemic COVID-19, data on risk factors that worsen the disease are intensively studied and constantly updated with the data from different parts of the world.

Particular attention is drawn to patients with severe COVID-19 requiring long-term oxygen support. The role of comorbidity assessment in the disease course is especially relevant for precisely this category of patients. According to Italian researchers, an analysis of the age and comorbid conditions in 1591 patients with COVID-19 admitted to intensive care units, showed the median age of 63 years old with a significant predominance of men (82 %), wherein 68 % patients had at least one comorbid pathology, and hypertension was the most common (49 %). Among 1287 needed respiratory support, 12 % received noninvasive ventilation and 88 % received mechanical ventilation. The mortality rate in these patients was 26 % being significantly higher among persons older than 64 years (36 % vs. 15 %) [13].

However, the analysis of concomitant pathology spectrum, which has substantial impact on the outcomes of COVID-19, provides significantly different data according to various authors, but does reflect the somatic pathology prevalence in the population [12–14]. Thus, American researchers [14] reported that among hospitalized patients, one in two had hypertensive disease, one in three was obese, and one in four was diabetic. The authors of this study suggested that obesity might be a risk factor for respi-

ratory failure requiring mechanical ventilation, while noting that the percentage of patients in this cohort who received mechanical ventilation was 10 times higher as compared to the data of Chinese authors [14,15].

Thus, data on the prognostic value of comorbid conditions in the course of coronavirus infection are currently only being studied, showing different results according to various researches, which determined the direction of our study.

Aim

The aim of the study was to analyze spectrum of comorbid pathology and age structure of oxygen-dependent patients with severe COVID-19 depending on outcomes of the disease.

Materials and methods

The study included 85 oxygen-dependent patients with severe COVID-19, who were treated in the Department of Anesthesiology and Intensive Care of Municipal non-profit enterprise "Regional Infectious Diseases Clinical Hospital" of Zaporizhzhia Regional Council during March–September 2020. The diagnosis of COVID-19 in all patients was confirmed by detection of virus RNA by polymerase chain reaction in the State Institution "Zaporizhzhia Regional Laboratory Center of the Ministry of Health of Ukraine". Patients' age ranged from 37 to 89 years, with the mean of 66.9 ± 1.2 years. There were 40 men (47.1 %) and 45 women (52.9 %). Data on comorbid pathology were obtained from either outpatient cards or discharge summaries when transferring patients to the infectious hospital from therapeutic departments of other hospitals. An age structure of the patients was analyzed using the WHO age classification (2015). Oxygen-dependent patients with severe disease were divided into groups: group I – 70 patients with recovery; group II – 15 patients in whom the disease was fatal.

Statistical data was analyzed using the current patient database in the program Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J). The criterion χ^2 was used to determine the differences between qualitative features. The critical level of significance in testing statistical hypotheses in this study was 0.05.

Results

Based on our study results, it was found that the mean age of oxygen-dependent patients with severe COVID-19 did not differ statistically (P > 0.05) between the studied groups and was (65.1 ± 1.4) years in group I patients and (69.6 ± 2.6) years in group II patients. However, an analysis of age structure revealed a difference, primarily absence of young people and smaller proportion of middle-aged people in the group of patients with lethal COVID-19, compared with the patients of group I: 6.7 % (1 of 15) vs. 28.6 % (20 of 70). Among group II patients with fatal outcomes of the disease, elderly and senile were statistically significantly dominated – 93.3 % (14 of 15) versus 67.1 % (47 of 70) among group I patients (χ^2 = 4.18, P < 0.05) (Fig. 1).

The analysis showed that among oxygen-dependent patients with severe COVID-19, only 10.6 % had no comor-

bid pathology. Analyzing the comorbid pathology structure in oxygen-dependent patients with severe COVID-19 it was found that most patients had concomitant diseases of the cardiovascular system (81.2 %), in particular, 74.1 % – coronary heart disease, 41.2 % – hypertensive disease, 7.1 % of the patients had previous myocardial infarction with postinfarction cardiosclerosis, 4.7 % of the patients had arrhythmias in the form of persistent atrial fibrillation. Comparing the frequency of distinct cardiovascular pathology in the patients of studied groups, it was revealed that COVID-19 patients who died significantly more often had hypertension (93.3 % vs. 30.0 %, χ^2 = 20.46, P < 0.001), postinfarction cardiosclerosis (26.7 % vs. 2.9 %, χ^2 = 10.67, P < 0.001), arrhythmia in the form of persistent atrial fibrillation (20.0 % vs. 1.4 %, χ^2 = 9.50, P < 0.01) as compared to the patients who recovered (Table 1).

Among the comorbid pathology, which was statistically significantly more common in group II patients, non-dialysis chronic kidney disease stages II-IV was the leading example (20.0 % vs. 4.3 %, χ^2 = 4.65, P < 0.05). Ischemic stroke was followed by COVID-19 in 7.1 % (6 of 85) of cases. The presence of ischemic stroke at the time of severe COVID-19 probably influenced the disease outcome. This comorbid condition was in 20.0 % of group II patients against 4.3 % of group patients I (χ^2 = 4.65, P < 0.05). In 41.2 % of oxygen-dependent patients with severe COVID-19, there was comorbid type 2 diabetes mellitus, incidence of which in patients with fatal disease was 60.0 % versus 37.1 % in patients who recovered, but this difference was not found to be statistically significant (P > 0.05). Chronic obstructive pulmonary disease was the comorbid condition in 17.6 % of patients, but its frequency did not differ statistically (P > 0.05) between the patients of studied groups (Table 1).

The analysis of comorbid conditions in oxygen-dependent patients with severe COVID-19 showed that most patients in both studied groups had a combination of several comorbidities. The presence of two comorbid conditions was noted in 32 (45.7 %) patients in group I and in every third patient in group II (5 – 33.3 %). However, a statistically significant association was found between the combination of 3 or more comorbid conditions and lethal outcome of the disease. Indeed, among all patients in whom COVID-19 was fatal, 46.7 % had combination of 3 or more comorbid conditions versus 17.4 % of severe oxygen-dependent survivors (χ^2 = 6.20, P < 0.01) (Fig. 2).

Discussion

According to the scientific literature published in 2020, the severity and risk for death from SARS-CoV-2 infection are associated with patient age and the presence of comorbid conditions, but the role of each condition is still being assessed [12–14,16], with some studies reporting the most unfavorable course of this infection in men [13]. In our study, when analyzing the comorbid conditions among oxygen-dependent severe COVID-19 patients, who were treated in the intensive care unit, we found the presence of comorbid pathology in 89.4 % (76 of 85) of patients with a dominance of cardiovascular pathology (81.2 %). Such a high frequency of this comorbid condition can be explained by the predominance of elderly and senile patients – 71.7 %
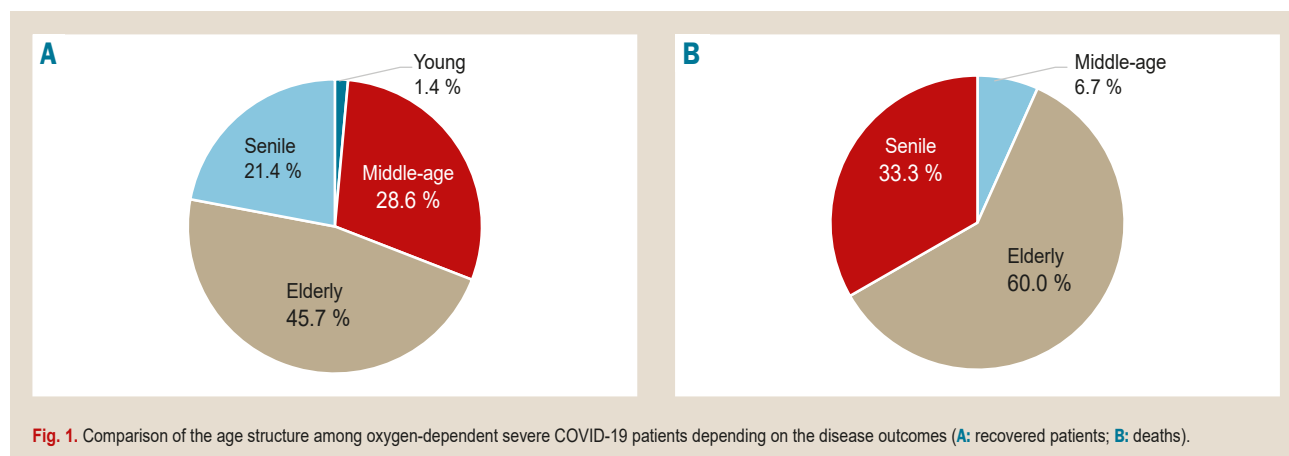
Fig. 1. Comparison of the age structure among oxygen-dependent severe COVID-19 patients depending on the disease outcomes (**A:** recovered patients; **B:** deaths).

(61 of 85) of the studied individuals. There are literature data on a significant predominance of men among patients with COVID-19, namely according to Chinese researchers – 73 % [12], and according to Italian researchers – 82 % of patients treated in the intensive care unit were men [13]. Based on our results of the sex composition analysis of patients who were treated in the intensive care unit during the first six months of the epidemic, the proportion of males was 47.1 % (40 out of 85). The data on the patient sex composition obtained in our study coincide with the American study data, in which the proportion of male patients was 47.7 % (183 out of 383) among hospitalized patients [12].

Considerable attention is currently being paid to analyzing the prognostic role of comorbid cardiovascular pathology in the course of COVID-19. Despite the expression of ACE2 in cardiomyocytes, myocardial injury in SARS-CoV-2 is considered as secondary and systemic manifestations rather than direct damage by the viral action [17]. However, this can lead to decompensation of chronic cardiovascular pathology, as well as to more severe course of coronavirus disease [18]. Our study has found that cardiovascular pathology was not only the most common comorbid condition, but also statistically significantly influenced the disease outcome. Namely, the presence of comorbid hypertension, postinfarction cardiosclerosis, arrhythmias in the form of persistent atrial fibrillation in patients with COVID-19 was statistically significantly associated with the unfavorable course of the disease. The pattern obtained in our study is confirmed by the literature data. According to several estimates [12,16,19], myocardial damage was clearly associated with severe COVID-19 and worse prognosis. For instance, 80 % of patients with elevated blood levels of troponin I above 28 pg/ml required treatment in the intensive care unit [12], as well as the mortality rate during hospitalization was 37.5 % for patients without underlying cardiovascular pathology but elevated troponin T levels, and 69.44 % for those with comorbid cardiovascular pathology and elevated troponin T [16].

In a number of studies, special attention is paid to comorbid renal pathology, namely chronic kidney disease. The results of COVID-19 course analysis in patients with comorbid chronic kidney disease revealed the severe course in 83.9 % of patients, fatal outcomes – in 53.3 % [20]. Based on our study, the presence of comorbid chronic kidney disease was significantly associated with lethal outcome of COVID-19, and it was combined with other

Table 1. Structure of comorbid pathology in COVID-19 patients depending on the disease outcomes, abs (%)

Comorbid pathology	Patients (n = 85)	Patient groups	
		I group (n = 70)	II group (n = 15)
Without comorbid pathology	9 (10.6 %)	8 (11.4 %)	1 (6.7 %)
Cardiovascular pathology, in particular:	69 (81.2 %)	55 (78.6 %)	14 (93.3 %)
Coronary heart disease	63 (74.1 %)	49 (70.0 %)	14 (93.3 %)
Hypertensive disease	35 (41.2 %)	21 (30.0 %)	14 (93.3 %) *
Postinfarction cardiosclerosis	6 (7.1 %)	2 (2.9 %)	4 (26.7 %) *
Arrhythmia	4 (4.7 %)	1 (1.4 %)	3 (20.0 %) *
Type 2 diabetes mellitus	35 (41.2 %)	26 (37.1 %)	9 (60.0 %)
Chronic obstructive pulmonary disease	15 (17.6 %)	13 (18.6 %)	2 (13.3 %)
Chronic kidney disease stages II–IV	7 (8.2 %)	3 (4.3 %)	3 (20.0 %) *
Obesity II–III degrees	7 (8.2 %)	5 (7.1 %)	2 (13.3 %)
Oncopathology	5 (5.9 %)	4 (5.7 %)	1 (6.6 %)
Rheumatoid arthritis	2 (2.4 %)	1 (1.4 %)	1 (6.7 %)
Chronic hepatitis C	1 (1.2 %)	1 (1.4 %)	0
Chronic osteomyelitis	1 (1.2 %)	0	1 (6.7 %)
Epilepsy	1 (1.2 %)	1 (1.3 %)	0
Ischemic stroke	6 (7.1 %)	3 (4.3 %)	3 (20.0 %) *

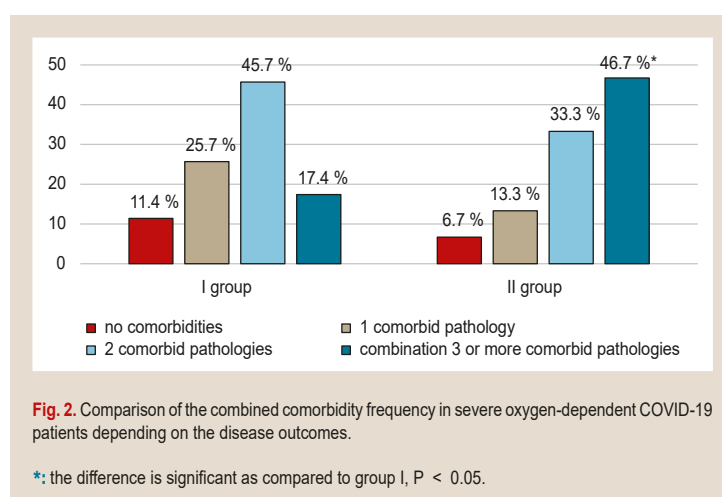***:** the difference is significant as compared to group I (P < 0.05).

Fig. 2. Comparison of the combined comorbidity frequency in severe oxygen-dependent COVID-19 patients depending on the disease outcomes.

*: the difference is significant as compared to group I, P < 0.05.

comorbid conditions in all the cases. Our data are consistent with the results of other studies assessing the risk factors for critical course of the disease. Thus, a study [21] showed that lethal outcome of COVID-19 was associated with combinations of such comorbid conditions as chronic kidney

disease, chronic heart failure, chronic obstructive pulmonary disease, diabetes, obesity and others in 86 % of patients.

It was estimated [14] that among patients with severe COVID-19, who underwent artificial lung ventilation, 54 % had concomitant hypertension, 43 % – obesity, 28 % – diabetes mellitus, 19 % – coronary heart disease. The authors of this study suggested that obesity might be one of the main risk factors for respiratory failure requiring for mechanical ventilation, noting that the proportion of patients in this cohort was 10 times higher than that reported by Chinese authors [14,15]. Given the ongoing pandemic, information continues to collect outlining the role of comorbid conditions in COVID-19.

Conclusions

1. Among oxygen-dependent patients with severe COVID-19 and fatal outcome, elderly and senile patients statistically significantly dominated – 93.3 % vs. 67.1 % of patients who recovered ($\chi^2 = 4.18$, $P < 0.05$).

2. In the structure of comorbid pathology among oxygen-dependent patients with severe COVID-19, cardiovascular diseases were prevailed (81.2 %). Non-survivors with COVID-19 more often ($P < 0.05$) than survivors had comorbid hypertension (93.3 % vs. 30.0 %), postinfarction cardiosclerosis (26.7 % vs. 2.9 %), arrhythmia in the form of persistent atrial fibrillation (20.0 % vs. 1.4 %), chronic kidney disease (20.0 % vs. 4.3 %) and ischemic stroke (20.0 % vs. 4.3 %).

3. The combination of comorbid conditions in oxygen-dependent patients with severe COVID-19 had some effect on the disease outcomes. In the patients with lethal outcome, the combination of 3 or more comorbid conditions frequency was higher than in the patients who recovered (46.7 % vs. 17.4 %, $P < 0.01$).

Prospects for further research. In our opinion, the revealed relationships between comorbid pathology spectrum in oxygen-dependent patients and severe COVID-19 outcomes necessitated further study on immunopathogenetic features.

Conflicts of interest: authors have no conflict of interest to declare.
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