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Research Article

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The Impact of Comorbidities on the Treatment Outcome in Patients With Severe Covid-19-Associated Pneumonia

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BACKGROUND A significant role in the course and outcome of COVID-19, alongside other clinical and laboratory factors, is played by comorbidities.

THE AIM OF THE STUDY We studied the impact of comorbidities on the course and outcomes of severe COVID-19-associated pneumonia.

MATERIAL AND METHODS The study was conducted at the Yakut Republican Clinical Hospital. We analyzed treatment outcomes of 450 patients with severe COVID-19-associated pneumonia who were hospitalized in the intensive care unit. An observational case-control study was conducted, in accordance with the research objective, comorbidities were analyzed in detail in two groups of patients: survivors — 144 (32.0%) and deceased — 306 (68.0%). The endpoint of the study was a fatal outcome. The modified Charlson comorbidity index was used to assess the patients' comorbidity status.

RESULTS The study revealed the presence of concomitant pathology in 446 (99.1%) patients. 57 (12.7%) patients had two concomitant diseases, 369 (82%) patients had three or more pathologies. A statistically significant impact on the risk of death for the following combinations of comorbid conditions were found: chronic central nervous system diseases with chronic kidney disease; hypertension with chronic kidney disease; coronary heart disease with chronic kidney disease; severe obesity (class III) with coronary heart disease and chronic kidney disease; severe obesity (class III) with type 2 diabetes mellitus. The mortality rate of patients increases linearly with the growth of the Charlson comorbidity index ($p<0.001$).

CONCLUSION The obtained data indicate a significant increase in the risk of death in patients with severe COVID-19-associated pneumonia in the presence of comorbidities. Therefore, when predicting the outcome and improving the treatment results of this category of patients, one should take into account the patient's comorbidity.

Keywords: new coronavirus infection COVID-19, comorbidity, severe COVID-19-associated pneumonia, mortality, probability of death

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ACS — acute coronary syndrome
ACVA — acute cerebrovascular accident
AH — arterial hypertension
ARDS — acute respiratory distress syndrome
CDCNS — chronic diseases of the central nervous system
CHD — coronary heart disease
CI — confidence interval
CKD — chronic kidney disease
CLD — chronic liver disease
CNS — central nervous system
COPD — chronic obstructive pulmonary disease
CPD — chronic pulmonary disease
CT — computed tomography
CVD — cardiovascular diseases
DARIC — Department of Anesthesiology, Resuscitation and Intensive Care
DM — diabetes mellitus
IQR — interquartile range
Me — median
NCVI — novel coronavirus infection
OD — oncological diseases
OR — odds ratio

INTRODUCTION

The incidence of severe complications, their rapid progression and high mortality in the novel coronavirus infection (NCVI) COVID-19 explain the importance of identifying early risk factors for fatal outcome. Undoubtedly, the factors that significantly influence the course and outcome of any disease include the presence of background and concomitant diseases, and their combination, i.e. the comorbid status of the patient. The term “comorbidity”, first used by A. Feinstein in 1970, refers to the combination of two or more diseases in one patient, pathological syndromes and disorders with a single pathogenetic mechanism of development or observed simultaneously [1].

The most severe category is represented by patients with NCVI COVID-19, whose course of the disease is complicated by the development of pneumonia. The diffuse nature of lung tissue damage in COVID-19-associated pneumonia is similar to the picture of acute respiratory distress syndrome (ARDS), accompanied by severe respiratory failure and requiring invasive mechanical ventilation. The fatality rate in this category of patients varies from 35 to 86.6% [2, 3].

Research devoted to the study of risk factors for severe course and adverse outcome of COVID-19 indicates that, along with age and the use of invasive mechanical ventilation, comorbidities play a significant role. The presence of cardiovascular diseases (CVD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), liver pathology and inflammatory bowel diseases in patients can serve as a factor in the severe course of the disease and higher mortality [4].

Analyzing the published research results, it can be noted that most of them study the effect of individual concomitant pathologies on the course and outcome of the disease, while in practice a combination of two or more diseases is often observed, especially in older patients. At the same time, the presented data are mainly observational and ascertaining in nature. In addition, in many scientific studies, severe concomitant pathology is often a criterion for exclusion from the study, which affects the results obtained, and does not correspond to real clinical practice.

The above explains the relevance of the research topic and the need to study comorbidity in patients with severe COVID-19-associated pneumonia and its impact on the course and outcome of the disease.

The aim was to study the influence of comorbidity on the course and outcome of severe COVID-19-associated pneumonia.

MATERIAL AND METHODS

The study was conducted at the Yakut Republican Clinical Hospital and included an analysis of the treatment results of 450 patients with severe COVID-19-associated pneumonia hospitalized in the Department of Anesthesiology, Resuscitation and Intensive Care (DARIC).

An observational case-control study was conducted and, in accordance with the aim of the work, comorbidities were analyzed in detail in two groups of patients: survivors - 144 (32.0%) and

deceased - 306 patients (68.0%). The endpoint of the study was fatal outcome.

There were 235 female patients (52.2%), 215 male patients (47.8%), the median age was 67 (IQR 60–74) years. In the study groups, patients were comparable in terms of key parameters: age and gender, clinical and laboratory parameters, and intensive care methods. The total duration of hospital treatment was 11 (IQR 6–17) bed-days. The median duration of treatment in the DARIC in the group of deceased patients was 8 (IQR 4–12), in the group of survivors — 4 (IQR 2–7) bed-days.

Diagnosis and treatment of concomitant diseases were carried out in accordance with current clinical recommendations posted on the official website of the Ministry of Health of the Russian Federation [5]. All the patients with concomitant diseases were consulted by medical specialists in the profile of pathology.

To assess the patient's comorbid status, the modified Charlson Comorbidity Index was calculated [6].

The criteria for inclusion of patients in the study were as follows: age over 18 years; hospitalization in the DARIC with diagnoses of U07.1 "COVID-19, virus identified" and U07.2 "suspected COVID-19, virus not identified"; the course of the disease is complicated by severe pneumonia with damage to more than 50% of the lungs (CT-3 and CT-4 according to the results of X-ray computed tomography); treatment in accordance with the Temporary Methodological Recommendations of the Ministry of Health of the Russian Federation that are current at the time of hospital stay; patient consent to participate in the study.

Exclusion criteria: patients who died within 12 hours after hospitalization in the intensive care unit; no confirmation of NCVI COVID-19 (laboratory, clinical, and epidemiological); patients whose treatment for various reasons did not comply with the Temporary Guidelines for the Treatment of Patients with NCVI COVID-19; patients transferred to other hospitals due to the development of acute surgical pathology, acute cerebrovascular accident, acute coronary syndrome; pregnant women and women in the early postpartum period (less than 2 months after delivery); patients without severe pneumonia (according to CT, less than 50% of the lungs are affected); concomitant stage 4 oncological pathology and (or) recent (less than 3 months) treatment for oncological disease - surgery, chemotherapy, radiation therapy; patients who received vaccination against COVID-19; refusal to participate in the study.

The study was carried out in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects" with the amendments of 2008, and the "Rules of Clinical Practice in the Russian Federation" approved by the order of the Ministry of Health of the Russian Federation dated 19.06.2003 No. 266, and approved by the local committee on biomedical ethics of the Medical Institute of M. K. Ammosov North-Eastern Federal University (No. 25 dated 07.10.2020, decision No. 4). Upon inclusion in the study, the essence of the study was explained to the patients and informed voluntary consent was provided.

For statistical processing of the research results, a database was created in the IBM SPSS Statistics program, version 26.0.0.0. The indicators were tested for normal distribution using the excess and asymmetry test (taking into account the sample size, $|Z|<2.58$). As a result of the test, a distribution different from normal was established for all quantitative variables. Accordingly, their descriptive statistics were performed using Me (median) and IQR (interquartile range – Q1;Q3). Comparative nonparametric analysis of quantitative data was performed using the Mann–Whitney U-test for binary populations. The analysis of nominal binary data was performed by constructing a four-field table with calculation of Fisher's exact test or Pearson's $\chi 2$ test depending on the expected minimum number, with calculation of the odds ratio (OR) with a 95% confidence interval (CI) and assessment of the strength of the relationship between the features using the Cramer's V value. The analysis of nominal data with three criteria was performed using the construction of a multifield table and post-hoc analysis. The influence of factors on the risk of death was assessed with the help of survival curves using the Kaplan–Meier method with an assessment of the statistical significance of differences in the log rank (Mantel–Cox) test.

RESULTS OF THE STUDY

The study of comorbidities in patients with severe COVID-associated pneumonia showed that 94.2% of patients had chronic CVD, among which arterial hypertension (AH) (91.8% of patients) and

coronary heart disease (CHD) (75.1% of patients) prevailed. The frequently encountered pathologies were as follows: chronic kidney disease (CKD) — in 48.9% of patients, COPD — in 44.9% of patients, including bronchial asthma in 6.2% of patients, type 2 DM — in 38.2%, and chronic diseases of the central nervous system (CNS) (post-stroke disorders, dementia, Alzheimer's disease, Parkinson's disease, post-traumatic encephalopathy, epilepsy) — in 32.3% of patients. Other concomitant pathologies include chronic liver diseases (8.4%), oncological diseases (7.8%), class III obesity (6.7%) and rheumatic disorders (2.2%) (Table 1).

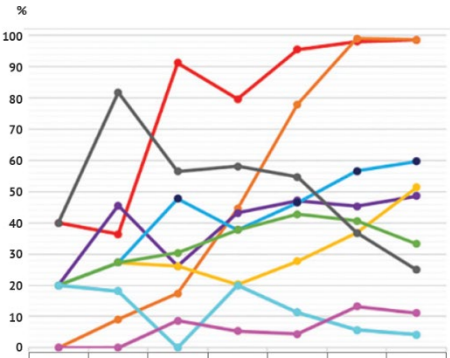
Table 1

Comorbidities in patients with severe COVID-19-associated pneumonia

Diseases	Number of patients, abs. number (%)
Chronic cardiovascular diseases, including: arterial hypertension ischemic heart disease	424 (94.2) 413 (91.8) 338 (75.1)
Chronic kidney disease	220 (48.9)
Chronic pulmonary diseases,	202 (44.9)
including bronchial asthma	28 (6.2)
Type 2 diabetes mellitus	172 (38.2)
Chronic diseases of the central nervous system	145 (32.3)
Chronic liver diseases	38 (8.4)
Oncological diseases	35 (7.8)
Class III obesity	30 (6.7)
Rheumatic disorders	10 (2.2)

The data presented in the table indicate that cardiovascular diseases are the undisputed leaders among concomitant pathologies. The next three most common ranks were CKD, respiratory diseases, and type 2 diabetes.

When analyzing comorbidities, it was noted that the number and severity of comorbidities increased with age, which prompted us to conduct a comparative analysis in different age categories (Fig. 1). As can be seen from the figure, with age, there is a tendency for the proportion of CVD, COPD, chronic CNS diseases, CKD and oncological diseases to increase. For example, 91.3% of patients in the 40–49 age group had hypertension, 78% of patients over 60 had coronary heart disease, and almost all patients over 70 had hypertension and coronary heart disease. It was also noted that the proportion of patients with class III obesity was predominant in the 30–39 age group.



	18–29 лет	30–39 лет	40–49 лет	50–59 лет	60–69 лет	70–79 лет	>80 лет
АГ	40	36,4	91,3	79,7	95,6	98,1	98,6
ИБС	0	9,1	17,4	44,6	78	99,1	98,6
ХЗЛ	20	45,5	26,1	43,2	47,2	45,3	48,6
ХЗЦНС	20	27,3	26,1	20,3	27,7	36,8	51,4
ХБП	20	27,3	47,8	37,8	46,5	56,6	59,7
СД2	20	27,3	30,4	37,8	42,8	40,6	33,3
ХЗП	20	18,2	0	20	11,3	5,7	4,2
ОЗ	0	0	8,7	5,4	4,4	13,2	11,1
Ожирение 3-й ст.	40	81,8	56,5	58,1	54,7	36,8	25

Fig. 1. Incidence of comorbidities in age categories (%)

Notes: АГ — arterial hypertension, ИБС – coronary heart disease, ОЗ — oncological diseases, СД2 — type 2 diabetes, ХБП — chronic kidney disease, ХЗЛ — chronic lung diseases, ХЗП — chronic liver diseases, ХЗЦНС — chronic diseases of the central nervous system

As expected, the age of patients was higher in the group of deceased and amounted to 69 (62; 77) years, versus 62 (55; 69) years in surviving patients ($p < 0.001$). It should be noted that the condition of all patients with severe COVID-19-associated pneumonia upon admission to the DARIC was assessed as severe, reflected in the values of the integral scales and also significantly different in survivors and deceased. Thus, the severity of the condition of survivors according to the APACHE II Score was 15 (12;18) points, according to the SOFA Score - 6 (4;7) points, and in those who died 18 (15;19) and 6 (5;9) points ($p<0.001$), respectively.

The study revealed the presence of comorbidities in 446 patients (99.1%). Moreover, 57 patients (12.7%) had two concomitant diseases, 369 (82%) had three or more pathologies. The most common combinations of concomitant diseases that influence mortality are presented in Fig. 2 and Table 2.

Table 2

The impact of comorbidity on mortality

Comorbidity	Fatality rate, n (%)		*p-value*	OR (95% CI)	Cramer's V
	Absence of factor	Presence of factor			
CDCNS +CKD, n=87	237 (65.2)	69 (79.3)	0.011*	2.04 [1.16–3.58]	0.212
AH+CKD, n=212	144 (60.5)	162 (76.4)	0.015*	2.11 [1.40–3.19]	0.180
AH+ 2DM, n=166	195 (68.7)	111 (66.9)	0.693	–	–
CHD +CKD, n=179	159 (58.7)	147 (82.1)	<0.001*	3.24 [2.06–5.09]	0.246
Obesity+CHD+CKD, n=84	237 (64.8)	69 (82.1)	0.002*	2.5 [1.38–4.55]	0.145
Obesity+CHD+ 2DM, n=72	248 (65.6)	58 (80.6)	0.013*	2.17 [1.17–4.04]	0.117
AH+CHD+CKD+ 2DM, n=134	211 (66.8)	95 (70.9)	0.391	–	–

Note: p – statistical significance (Pearson's chi-squared test), * – differences are statistically significant, OD – odds ratio, CI – confidence interval, AH — arterial hypertension; CHD — coronary heart disease; 2DM — type 2 diabetes; CKD — chronic kidney disease; CDCNS — chronic diseases of the central nervous system

As can be seen from Figure 2, the vast majority of patients had a combination of hypertension and CKD, hypertension and type 2 diabetes, and coronary heart disease with CKD. The study of their impact on the risk of death is presented in Table 2.

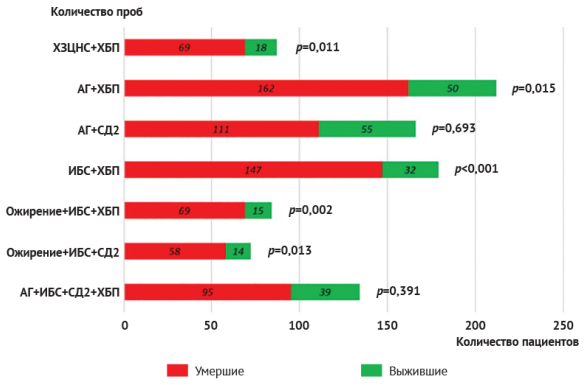


Fig. 2. Combination of comorbidities in groups of deceased and surviving patients

Notes: АГ — arterial hypertension, ИБС — ischemic heart disease, СД2 — type 2 diabetes, ХБП — chronic kidney disease, ХЗЦНС — chronic diseases of the central nervous system

A statistically significant effect on the risk of fatal outcome was revealed for the following combinations of comorbidities: chronic CNS diseases with CKD — 87 patients (mortality — 79.3%; OR=2.04; 95% CI: [1.16–3.58]; p=0.011; Cramer's V 0.212); AH with CKD — 212 patients (mortality — 76.4%; OR=2.11; 95% CI: [1.40–3.19]; p=0.015; Cramer's V 0.180); CHD with CKD — 179 patients (mortality — 82.1%; OR=3.24; 95% CI: [2.06-5.09]; p<0.001; Cramer's V 0.246); class III obesity with CHD and CKD — 84 patients (mortality — 82.1%; OR=2.50; 95% CI: [1.38-4.55]; p=0.002; Cramer's V 0.145); class III obesity with CHD and type 2 diabetes mellitus - 72 patients (mortality - 80.6%; OR = 2.17; 95% CI: [1.17-4.04]; p = 0.013; Cramer's V 0.117).

The risk of death was not affected by the combination of AH and type 2 DM (166 patients, mortality rate 66.9%; p=0.693), and AH with CHD, type 2 DM and CKD (134 patients, mortality rate 70.9%; p=0.391) (Table 2).

It can be noted that the presented concomitant diseases have common pathogenetic mechanisms and are interrelated - AH, CKD, obesity, type 2 DM, that is, in reality, we observe comorbidity. From this perspective, the Charlson Comorbidity Index was calculated to assess the comorbid status of the patients and predict mortality.

At the next stage, we studied the relationship between mortality and the patient's comorbid status, which is presented in Table 3.

The Charlson Comorbidity Index used to assess the comorbid status of the patients studied was: 1–2 points in 47 patients (10.4%), of whom 22 (46.8%) died; 3–4 points in 108 patients (24%), 69 (63.9%) died; more than 5 points in 291 patients (64.7%), 215 (73.9%) died (Table 3). The presented data show that the number of adverse outcomes is statistically significantly associated with an increase in the number of comorbidities and an increase in the Charlson Comorbidity Index.

Table 3

Mortality depending on the Charlson comorbidity index

Charlson Comorbidity Index, points (n, number of patients)	Number of deceased patients		*p-value*
	abs. number	%	
0 (*n*=4)	0	0	*p*<0.001*
1–2 балла (*n*=47)	22	46.8	p_{2-4}<0.001*
3–4 балла (*n*=108)	69	63.9	
Более 5 баллов (*n*=291)	215	73.9	

Notes: p-value — statistical significance, * — differences are statistically significant, Pearson's chi-squared test

The relationship between mortality and comorbidity is more clearly demonstrated by the Kaplan-Meier survival plot, which shows that with an increase in the Charlson Comorbidity Index, the mortality of patients increases linearly. At the same time, the overall median time of onset of death of patients is 9.0±0.4 (IQR 6.0–15.0) bed-days (Fig. 3).

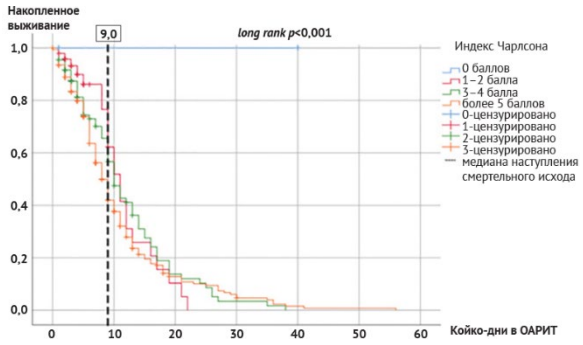


Fig. 3. Impact of comorbidity on mortality

Note: ОАРИТ — Department of Anesthesia, Resuscitation and Intensive Care

During treatment in the DARIC, patients experienced severe complications that should be considered as complicated comorbidity, when, as a result of the progression of the underlying disease, failure of the damaged organ is added, and in the future, multiple organ dysfunction syndrome (MODS) may develop. An example of complicated comorbidity is the development of acute kidney injury (AKI) against the background of CKD due to diabetic nephropathy in patients with type 2 diabetes. Thus, in our study, signs of AKI (oliguria with uremia, hyperkalemia and hypervolemia) developed in 306 patients (68.0%) with a mortality rate of 76.5%. Among these patients, CKD occurred in 183 patients (59.8%).

The development of severe complications significantly increased the probability of a fatal outcome. Thus, the risk of death increased in acute cerebral failure by 2.73 times (95% CI: [1.66–4.48]; p<0.001; Cramer's V 0.191), in AKI — by 1.83 times (95% CI: [1.19–2.82], p=0.005; Cramer's V 0.131), in MODS — by 4.13 times (95% CI: [2.61–6.55]; p<0.001; Cramer's V 0.295) (Table 4).

DISCUSSION

The results of this study indicate a statistically significant effect of the patient's comorbid status on the course and outcome of NCVI COVID-19. In our study, chronic diseases of the cardiovascular system, kidneys and lungs were the leading comorbidities, which does not contradict the data of other studies. A high incidence of chronic CVD in patients with COVID-19 has been reported by Russian authors [7]. Foreign meta-analyses devoted to the study of comorbidity in patients with COVID-19 also confirm the role of these diseases on the course and outcome of the disease. Thus, according to Y. Khairy et al.,

Table 4

Impact of complications on fatality rates

Complication	Fatality rate, n (%)		*p-value*	OR (95% CI)	Cramer's V
	Absence of factor	Presence of factor			
Acute cerebral insufficiency	198 (62.3)	108 (81.8)	<0.001*	2.73 (1.66–4.48)	0.191
Acute kidney injury	92 (63.9)	306 (76.5)	0.005*	1.83 (1.19–2.82)	0.131
Acute liver failure	226 (65.7)	80 (75.5)	0.059	–	–
Multiple organ dysfunction syndrome	44 (42.7)	262 (75.5)	<0.001*	4.13 (2.61–6.55)	0.295

Notes: p-value – statistical significance (Pearson's chi-squared test), *– differences are statistically significant, CI – confidence interval; OR – odds ratio

hypertension is the most common disease among CVD, and significantly increases the likelihood of severe complicated course of the infectious process, hospitalization of the patient in the intensive care unit, and the risk of death [8]. The study by X. Fang et al. showed that CKD was an independent factor influencing mortality (OR=7.10; 95% CI: [3.14–16.02]); COPD influenced the severity of the disease (OR=4.20; 95% CI: [2.82–6.25]), hospitalization in the intensive care unit (OR=5.61; 95% CI: 2.68–11.76), and the need for invasive mechanical ventilation (OR=6.53; 95% CI: [2.70–15.84]); and chronic cardiovascular diseases contributed to the development of ARDS (OR=3.15; 95% CI: [1.23–8.04]) and acute cardiovascular failure (OR=5.37; 95% CI: [1.74–16.54]) [9]. In addition, data has emerged that COVID-19 not only leads to the progression of existing CKD, but can also initiate its development [10].

The increase in the number of adverse outcomes is associated with an increase in the number of comorbidities. The most vulnerable is the older age group, which is due to both the increase in the number of comorbidities and the decrease in the body's resistance with age. This thesis is supported by studies investigating the relationship between mortality and age in COVID-19 [11–13].

Of course, when treating patients, one should not take into account the presence of individual concomitant diseases and consider them in isolation, but rather approach them from the position of the general relationship of pathologies, that is, comorbidity or polymorbidity. Thus, the conducted study demonstrates a significant role of CKD in the risk of death and the obviousness of its relationship with obesity, coronary heart disease, hypertensionб and diabetes mellitus. We also noted that in 359 patients studied (79.8%) the body mass index exceeded normal values, and class III obesity (morbid obesity) was observed in 30 (6.7%), of whom 20 (66.7%) died. In this regard, in our opinion, it is necessary to study the course and outcome of COVID-19 in patients with metabolic syndrome, the components of which are abdominal obesity, type 2 diabetes, hypertension and dyslipidemia. This is confirmed by a review of foreign studies conducted by N.V. Zhdankina et al., which indicates a more severe course of COVID-19 in patients with metabolic syndrome [14].

Therefore, in the context of the trend of modern medicine towards standardization of treatment in comorbid patients, a special comprehensive approach is needed that takes into account the pathogenetic relationship of diseases. Understanding the problem of treating comorbid patients prompted the adoption of the National Consensus on the management of patients with concomitant cardiovascular diseases, diabetes, COPD, and gastrointestinal diseases at the beginning of the COVID-19 pandemic. This statement presents the characteristics of therapy for this category of patients, limitations in the selection and correction of drug doses, and also indicates contraindications to the prescription of certain groups of drugs during antiviral therapy [4].

Thus, the importance of assessing the patient's comorbid status in the treatment of the underlying disease is beyond doubt, and indicates the need for further study of this problem. The NCVI COVID-19 has become a significant medical and social problemб and has indicated the need to consolidate the scientific and practical medical community to find ways to improve the effectiveness of treatment. The presented study confirms the need for a targeted study of one of the areas to improve the treatment results for severe pathologies with a high incidence of complications and high mortality - the study of the patient's comorbid status and assessment of its impact on the course and outcome of the disease. The development of scientifically based clinical guidelines for the management of patients with comorbidity will improve treatment outcomes not only for COVID-19, but also for other novel diseases with severe clinical course, the possibility of which in the future cannot be ruled out.

CONCLUSIONS

1. In patients with severe COVID-associated pneumonia, the most common comorbidities were as follows: chronic CVD (94.2% of patients), including arterial hypertension (91.8%) and coronary heart disease (75.1%); chronic kidney disease (48.9%); chronic obstructive pulmonary disease (44.9%), including bronchial asthma (6.2%); type 2 diabetes mellitus (38.2%), and chronic diseases of the central nervous system (32.3% of patients).

2. The majority (99.1%) of patients had one comorbidity, 12.7% of patients had two, and 82% had three or more pathologies. The risk of death was

influenced by the following combinations of comorbidities: chronic diseases of the central nervous system with chronic kidney disease (mortality - 79.3%; OR = 2.04; 95% CI: [1.16-3.58], p = 0.011); arterial hypertension with chronic kidney disease (mortality - 76.4%; OR = 2.11; 95% CI: [1.40-3.19], p = 0.015); ischemic heart disease with chronic kidney disease (mortality - 82.1%; OR = 3.24; 95% CI [2.06-5.09], p < 0.001); class 3 obesity with coronary heart disease and chronic kidney disease (mortality - 82.1%; OR = 2.50; 95% CI [1.38-4.55], p = 0.002); class 3 obesity with coronary heart disease and type 2 diabetes mellitus (mortality - 80.6%; OR = 2.17; 95% CI [1.17-4.04], p = 0.013).

3. The increase in the number of adverse outcomes is statistically significantly associated with the increase in the number of comorbidities and an increase in the Charlson Comorbidity Index: 1–2 points — mortality 46.8%; 3–4 points — mortality 63.9%; more than 5 points — mortality 73.9% of patients (p<0.001).

4. The mortality rate increases with the development of acute cerebral failure by 2.73 times (95% CI: [1.66–4.48]; p<0.001), acute kidney injury by 1.83 times (95% CI: [1.19–2.82], p=0.005), and multiple organ dysfunction syndrome by 4.13 times (95% CI: [2.61–6.55]; p<0.001).

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