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Prognostic role of demographic indicators and Charlson comorbidity index in oxygen-dependent patients with coronavirus disease (COVID-19)

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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; E – critical revision of the article; F – final approval of the article

Key words: coronavirus disease COVID-19, viral infection, comorbidity, risk factors, prognosis.

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Aim. The aim of our work is to establish the prognostic significance of demographic indicators and the Charlson comorbidity index (CCI) in oxygen-dependent patients with coronavirus disease (COVID-19).

Material and methods. The research included 211 oxygen-dependent patients with COVID-19: I group – 94 patients who recovered; II group – 117 patients, the disease ended fatally. We used the WHO age classification when analyzing the age structure of patients. The Charlson comorbidity index was calculated for each patient. The patients were divided into groups Statistical data processing was carried out in the program Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J).

Results. It was established that the median age of the II group patients was higher ($P < 0.001$) than patients the I in group. Elderly patients were more often registered in the II group than among patients in group I (25.6 % vs. 8.5 %, $P = 0.001$). Middle-aged patients were more often registered in the I group than among patients in the II group (34.0 % vs. 19.4 %, $P = 0.02$). According to the result of the ROC analysis, the prognostic value of the age of the patients was established, namely, under conditions of age >66 years (AUC = 0.636, $P = 0.002$), the probability of a fatal outcome of COVID-19 was significant.

Analysis of the influence of comorbid conditions on the risk of COVID-19 fatal outcome in oxygen-dependent patients according to the CCI showed that the absence of comorbid pathology was more common among patients of group I than among patients of group II (12.8 % vs. 2.6 %, $P = 0.004$). The level of CCI in patients of the II group significantly exceeded the corresponding indicator of the patients of the I group ($P < 0.01$), who recovered. According to the obtained result of the ROC analysis, the prognostic value of this indicator was established, namely under the conditions of the CCI index >5 in oxygen-dependent patients with COVID-19 (AUC = 0.652, $P < 0.001$) the probability of fatal outcome of the disease was significant.

Conclusions. In oxygen-dependent patients with COVID-19, patient age and comorbidity are associated with disease outcome. Under conditions of age >66 years (AUC = 0.636, $P = 0.002$) and the Charlson comorbidity index >5, the probability of a fatal outcome of the disease is significant (AUC = 0.652, $P < 0.001$).

Ключові слова: коронавірусна хвороба COVID-19, вірусна інфекція, коморбідність, фактори ризику, прогноз.

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Прогностична роль демографічних показників та індексу коморбідності Charlson у кисневозалежних хворих на коронавірусну хворобу (COVID-19)

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Мета роботи – встановити прогностичну значущість демографічних показників та індексу коморбідності Charlson у кисневозалежних хворих на коронавірусну хворобу (COVID-19).

Матеріали та методи. У дослідження залучили 211 кисневозалежних хворих на COVID-19: I група – 94 пацієнти, які одужали; II група – 117 осіб, у котрих захворювання завершилося летально. Під час аналізу вікової структури хворих користувалися класифікацією віку ВООЗ (2015). У кожного пацієнта розраховували індекс коморбідності Charlson (CCI). Статистичне опрацювання здійснили в програмі Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Результати. Встановлено, що у хворих II групи медіана віку вища ($p < 0,001$), ніж у хворих I групи. У II групі було більше пацієнтів старечого віку, ніж у I (25,6 % проти 8,5 %, $p = 0,001$), а пацієнтів середнього віку було більше у I групі, ніж у II (34,0 % проти 19,4 %, $p = 0,02$). За результатами ROC-аналізу встановлена прогностична цінність віку пацієнтів. Так, якщо вік хворого становив >66 років (AUC = 0,636, $p = 0,002$), імовірність летального результату COVID-19 значуща.

Аналіз впливу коморбідних станів на ризик летального наслідку COVID-19 у кисневозалежних хворих за CCI показав, що коморбідні патології частіше не діагностували в хворих I групи, ніж у пацієнтів із II (12,8 % проти 2,6 %, $p = 0,004$). Рівень CCI у хворих II групи перевищував відповідний показник пацієнтів I групи ($p < 0,01$), які одужали. У результаті ROC-аналізу визначили прогностичну цінність цього показника. Так, якщо CCI становив >5 у кисневозалежних хворих на COVID-19 (AUC = 0,652, $p < 0,001$), імовірність летального наслідку хвороби значуща.

Висновки. У кисневозалежних хворих на COVID-19 вік пацієнта та коморбідність мають зв'язок із наслідком хвороби. Якщо вік пацієнтів становив >66 років (AUC = 0,636, $p = 0,002$), а індекс коморбідності Charlson – >5, імовірність летального наслідку хвороби значуща (AUC = 0,652, $p < 0,001$).

The new coronavirus disease (COVID-19), the etiological factor of which is SARS-CoV-2, has a wide range of clinical manifestations, ranging from almost asymptomatic to extremely severe with a significant risk of death. Already one of the first meta-analyses, which included 61 research from 11 countries of the world (59 254 patients), showed that 81.4 % cases of this disease were mild, 13.9 % were severe, and 4.7 % were critical [1]. However, the mortality rate from COVID-19 in different countries of the world had significant differences. In the first year of the pandemic, before the advent of vaccination, the mortality rate in Italy was 7.2–8.0 %, compared to 2.3–3.8 % in China and about 0.6 % in the South Korea [2,3]. At the same time, attention was drawn to the role of demographic indicators and comorbid pathology as risk factors for the development of a severe course of this infection and fatal consequences.

Increasing the age of patients with COVID-19 is clearly associated with a worse prognosis, but statistical data from different countries of the world have certain discrepancies. Thus, 80 % of patients died over the age of 65 years old in China, and in the USA, the mortality rate among patients over 70 years old was 15 % [4]. According to the American study [5], which included 4226 patients, the highest mortality rate (10–27 %) was observed among people over 85 years old. At the same time, among patients with COVID-19 aged from 20 to 54 years, the mortality rate was less than 1.0 %, and among patients under the age of 19, no deaths were registered [5]. A certain amount of research is devoted to determining the role of gender differences in the course of COVID-19. Thus, the first Chinese studies showed that the mortality rate among men was 2.8 % against 1.7 % among women [6]. However, data on the level of infection with the SARS-CoV-2 virus of different sexes people have certain contradictions. Thus, according to some authors [3], COVID-19 affects both genders equally. According to other researchers [1], among those infected with SARS-CoV-2, women predominate, and the infection rate among men is lower and is 45.8 %. However, according to the results of research by other authors [7], the opposite pattern was established, which indicates the predominance of men among those infected with SARS-CoV-2.

Today, it is clearly understood that the presence of comorbid conditions has a negative influence on the course of COVID-19 and it's consequences. A retrospective analysis of the new coronavirus disease course showed that in the presence of a comorbid pathology in patients older than 60 years, the disease on COVID-19 had a more aggressive character with the development of critical complications with a rapid increase in the mortality rate [4,5,8,9]. In Chinese study, attention was paid to the risk of COVID-19 adverse outcome in patients who had 2 or more comorbidities. At the same time, the highest probability of developing severe acute respiratory distress syndrome occurred with the combination of arterial hypertension and diabetes [10]. During the same period, American researchers, analyzed 5700 patients from 12 New York clinics who required hospitalization due to COVID-19, determined that the most common concomitant diseases were hypertension (56.6 %), obesity (41.7 %) and diabetes (33.8 %) [11]. Data from two meta-analyses proved that cancer, chronic kidney disease, cardiovascular disease, diabetes, and hypertension are independently associated with a significantly higher risk of death from COVID-19 [12,13].

Today, the search for informative ways to assess demographic indicators in relation to comorbid conditions in predicting the course of COVID-19 continues. In this manner, the Charlson comorbidity index attracts attention, which considers both the patient's age and certain pathological conditions [14]. Recently, individual studies appear [15,16] that consider the Charlson comorbidity index (CCI) in the assessment of the prognosis when using different treatment options for patients with COVID-19. Therefore, in our opinion, it is important to find out its prognostic significance in oxygen-dependent patients with COVID-19.

Aim

The aim of our work is to establish the prognostic significance of demographic indicators and the Charlson comorbidity index in oxygen-dependent patients with coronavirus disease (COVID-19).

Materials and methods

The research included 211 oxygen-dependent patients with coronavirus disease (COVID-19), who were treated in the intensive care unit of the Municipal Non-Profit Enterprise "Regional infectious clinical hospital" Zaporizhzhia Regional Council for the period from September 2020 to December 2021. The age of the patients ranged from 28 to 89 years; the median age was 66.0 [58.0; 73.0] years old. 118 men and 93 women were included in the research. The diagnosis of COVID-19 in all patients was confirmed by the isolation of RNA-SARS-CoV-2 in the nasopharyngeal mucus by the polymerase chain reaction method at the "Zaporizhzhia Regional Laboratory Center of the Ministry of Health of Ukraine". All patients were not vaccinated against COVID-19. The exclusion criteria were patients with somatic and oncological pathology in the stage of decompensation.

All patients were examined and treated in accordance with the regulations in force at the relevant time. Order of the Ministry of Health of Ukraine dated 28.03.2020 No. 722 "Organization of medical care for patients with coronavirus disease (COVID-19)" (as amended by the order of the Ministry of Health of Ukraine dated 17.09.2020 No. 2122 "On amendments to the Standards of medical care "Coronavirus disease (COVID-19)". Order of the Ministry of Health of Ukraine No. 10 dated 07.01.2021 "On approval of amendments to the Standards of medical care "Coronavirus disease (COVID-19)". Order of the Ministry of Health of Ukraine dated April 6, 2021 No. 638 "Protocol for the provision of medical assistance for the treatment of the coronavirus disease (COVID-19)".

When analyzing the age structure of patients, the age classification of WHO (2015) was used. The CCI was calculated for each patient, which was determined by considering a certain concomitant pathology and the age of the patient [14]. Oxygen-dependent patients

Table 1. Demographic indicators of oxygen-dependent patients with coronavirus disease (COVID-19) depending on the consequences of the disease

Indicator, units of measurement	Patients, n = 221	Patients	
		I group, n = 94	II group, n = 117
Men, abs. (%)	118 (55.9 %)	54 (57.4 %)	64 (54.7 %)
Women, abs. (%)	93 (44.1 %)	40 (42.6 %)	53 (45.3 %)
Age, Me [Q_{25}; Q_{75}] years old	66.0 [58.0; 73.0]	63.0 [56.0; 70.0]	67.0 [60.0; 75.0]*
Young age, abs. (%)	7 (3.3 %)	3 (3.2 %)	4 (3.4 %)
Average age, abs. (%)	55 (26.1 %)	32 (34.0 %)	23 (19.4 %)*
Old age, abs. (%)	111 (52.6 %)	51 (54.3 %)	60 (51.3 %)
Senile age, abs. (%)	38 (18.0 %)	8 (8.5 %)	30 (25.6 %)*

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

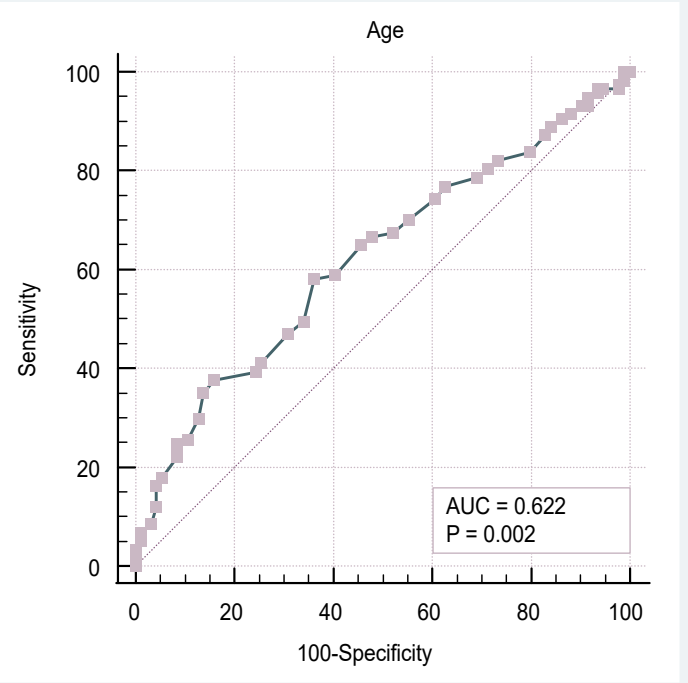

Fig. 1. Prediction of the probability of a fatal outcome in oxygen-dependent patients with COVID-19 by age.

with a severe course of the disease were divided into groups: I group – 94 patients who recovered; II group – 117 patients, the disease ended fatally. All patients were included in the study on a random basis and informed written consent.

Statistical data processing was carried out using the created patient database in the program Statistica for Windows 13 (StatSoft Inc., Serial No. JPZ804I382130ARCN10-J). The χ^2 criterion was used to determine the differences between qualitative features. When comparing the age of patients, the Mann–Whitney test was used, and the data were presented accordingly Me [Q_{25}; Q_{75}].

The critical level of significance when testing statistical hypotheses in this research is equal to 0.05. ROC analysis with a cut-off point was performed to determine the effect of age and the degree of reliability of the CCI for predicting mortality outcomes in oxygen-dependent patients with COVID-19.

Results

According to the results of the analysis of the demographic indicators of oxygen-dependent patients with COVID-19, it was established that the median age of patients with a fatal outcome of the disease was statistically significantly higher (P < 0.001) than in group I patients who recovered. Analyzing of the oxygen-dependent patients age structure with COVID-19 shown that every second patient of both group was elderly, and there were only a few cases of young patients among oxygen-dependent patients. Statistically significant differences were established in the frequency of middle-aged and elderly patients registration in research groups. Thus, elderly patients more often registered in the group with COVID-19 fatal outcome than among patients in group I (25.6 % vs. 8.5 %, χ^2 = 10.36, P = 0.001). Middle-aged patients, vice versa, were more often registered in the group of oxygen-dependent patients who recovered than among patients of the II group (34.0 % vs. 19.4 %, χ^2 = 5.57, P = 0.02) (*Table 1*).

Among oxygen-dependent patients with COVID-19, there was a tendency for men to predominate over women (55.9 % vs. 44.1 %, P > 0.05). This ratio was preserved in each researched groups of patients, so, the gender of oxygen-dependent patients with COVID-19 did not have a statistically significant effect on the risk of developing a fatal outcome of the disease (P > 0.05) (*Table 1*).

To establish the influence of age in oxygen-dependent patients with COVID-19 on development of the disease fatal outcome was performed ROC-analysis with determination of the cut-off point. According to the obtained ROC-analysis result, the diagnostic value of this indicator in oxygen-dependent patients with COVID-19 was established the age limit, which indicates a high probability of disease fatal outcome, was 66 years old (AUC = 0.622, P = 0.002). In oxygen-dependent patients with COVID-19 >66 years old (AUC = 0.636; sensitivity – 58.1 %, specificity– 63.8 %), the probability of a fatal outcome of COVID -19 is significant (P = 0.002) (*Fig. 1*).

In the subsequent part of the work, the influence of comorbid conditions on the risk of COVID-19 fatal outcome in oxygen-dependent patients was analyzed according to CCI, which takes into account not only certain comorbid conditions, but also the age of the patient (if age is over 40 years old). It was established that the absence of comorbid pathology was more common among patients of group I than among patients of group II, in which the disease ended fatally (12.8 % vs. 2.6 %, χ^2 = 8.21, P = 0.004). CCI level in patients of the II group significantly exceeded the corresponding indicator of the patients of the I group (P < 0.01), who recovered (*Fig. 2*).

A comparison of comorbid conditions frequency, which are considered when calculating the CCI, in oxygen-dependent patients with COVID-19, depending on the consequences of the disease, showed that the presence of ischemic heart disease and chronic kidney disease of the III–IV stages increases the risk of a fatal outcome. Thus, among patients of the II group more often than among patients of the I group, ischemic heart disease occurred (84,6 % vs. 43.2 %, χ^2 = 39.24, P = 0.0001), the presence of a myocardial infarction in the anamnesis (12.8 % vs. 4.3 %, χ^2 = 4.67, P = 0.03), congestive heart failure (13.7 % vs. 4.3 %, χ^2 = 5.39,

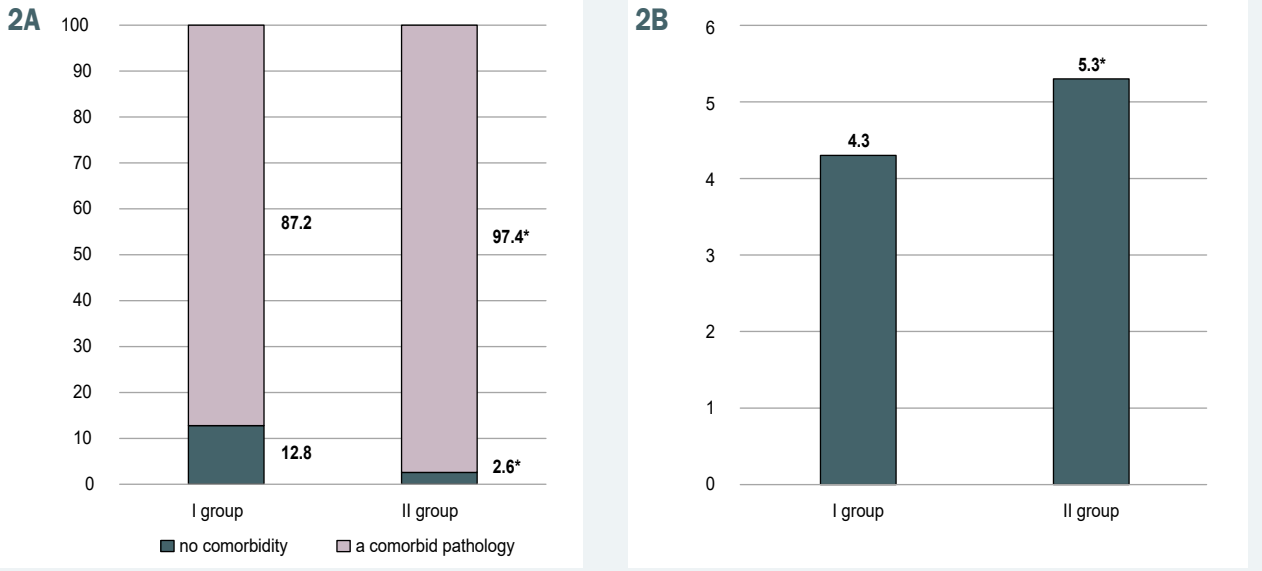

Fig. 2. Comparison of the frequency of presence of comorbid pathology (A) and the level of CCI (B) in oxygen-dependent patients with COVID-19, depending on the outcome of the disease.

P = 0.02) and chronic kidney disease of the III–IV stages (70.1 % vs. 46.8 %, χ^2 = 11.74, P = 0.0006). The analysis of patients age structure that older than 40 years according to the CCI showed that among patients of the II group, there were more patients aged 80–89 years than in the I group (17.9 % vs. 5.3 %, χ^2 = 7.70, P = 0.005) and less often there were patients aged 50–59 years (16.2 % vs. 28.7 %, χ^2 = 4.77, P = 0.03) (*Table 2*).

To establish the influence of comorbidity and age according to CCI on the development of disease fatal outcome in oxygen-dependent patients with COVID-19, ROC analysis was performed with the determination of the cut-off point. According to the obtained result of the ROC-analysis, the diagnostic value of this indicator in oxygen-dependent patients with COVID-19 was established, namely the threshold level of CCI, which indicates a high probability of disease fatal outcome, was >5 (AUC = 0.652, P < 0.001). That is, under the conditions of the CCI >5 in oxygen-dependent patients with COVID-19 (AUC = 0.652; sensitivity – 47.0 %, specificity – 80.9 %) the probability of disease fatal outcome is significant (P < 0.001) (*Fig. 3*).

Table 2. The frequency of comorbid conditions and age categories, which are considered by CCI, in oxygen-dependent patients with COVID-19 depending on the consequences of the disease, abs. (%)

Indicator, units of measurement	Patients, n = 211	Patients	
		I group, n = 94	II group, n = 117
Ischemic heart disease, in particular:	140 (66.4 %)	41 (43.2 %)	99 (84.6 %)*
– myocardial infarction	19 (9.0 %)	4 (4.3 %)	15 (12.8 %)*
– congestive heart failure	20 (9.5 %)	4 (4.3 %)	16 (13.7 %)*
Diseases of peripheral arteries	6 (2.8 %)	0 (0%)	6 (5.1 %)
Cerebrovascular diseases	14 (6.6 %)	4 (4.3 %)	10 (8.5 %)
Chronic obstructive lung diseases	24 (11.4 %)	13 (13.8 %)	11 (9.4 %)
Diabetes, in particular:	64 (30.3 %)	23 (24.5 %)	41 (35.0 %)
– compensated	51 (24.2 %)	20 (21.3 %)	31 (26.5 %)
– with organ damage	13 (6.1 %)	3 (3.2 %)	10 (8.5 %)
Diseases of connective tissue	8 (3.8 %)	5 (5.3 %)	3 (2.6 %)
Liver disease, in particular:	17 (8.1 %)	9 (9.6 %)	8 (6.8 %)
– mild or moderate severity	16 (7.6 %)	9 (9.6 %)	7 (5.9 %)
– heavy	1 (0.5 %)	–	1 (0.9 %)
Chronic kidney disease of the III–IV stages	126 (59.7 %)	44 (46.8 %)	82 (70.1 %)*
Dementia	29 (13.7 %)	10 (10.6 %)	19 (16.2 %)
Ulcer disease	3 (1.4 %)	2 (2.1 %)	1 (0.9 %)
40–49 years old	10 (4.7 %)	6 (6.4 %)	4 (3.4 %)
50–59 years old	46 (21.8 %)	27 (28.7 %)	19 (16.2 %)*
60–69 years old	77 (36.5 %)	35 (37.2 %)	42 (35.9 %)
70–79 years old	46 (21.8 %)	19 (20.2 %)	27 (23.1 %)
80–89 years old	26 (12.3 %)	5 (5.3 %)	21 (17.9 %)*

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

Discussion

The data of modern research demonstrate the connection of COVID-19 fatal outcome risk with increasing age of patients and the presence of comorbid pathology. Researchers [8] believe that age over 50 years is one of COVID-19 adverse course predictor, which directly affects the 28-day patients mortality hospitalized in the intensive care unit for artificial lung ventilation. However, patients over 60 years old have a higher risk of fatal COVID-19, especially when combined with such diseases as chronic cardiovascular diseases, diabetes and obesity [4,8,9,17]. At the same time, researchers [18] considered age over 70 to be a risk factor for mortality, regardless of comorbid pathology. According to the results of our research, in oxygen-dependent patients with COVID-19 who were treated in the intensive care unit, age over 66 indicated a high probability of a fatal outcome of the disease (AUC = 0.636, P = 0.002). At the same time, elderly patients were more often registered in the group with a fatal outcome of COVID-19 than among patients who recovered (25.6 % vs. 8.5 %, P = 0.001).

Today, these patterns are explained by certain pathogenetic mechanisms. On the one hand, these age-related features of the expression of receptors for angiotensin-con-

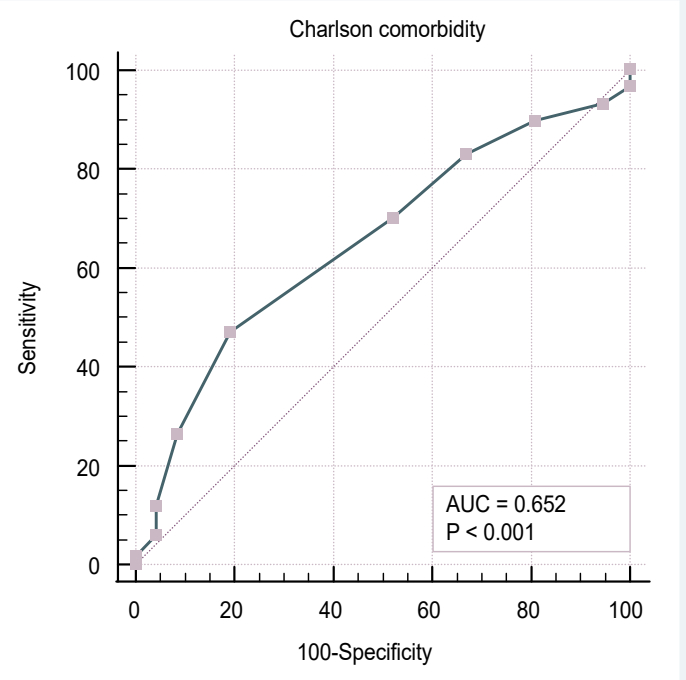

Fig. 3. Prediction of the probability of a fatal outcome in oxygen-dependent patients with COVID-19 according to the Charlson comorbidity index.

verting enzyme 2 (ACE 2). In the lungs of elderly people, there is a higher expression of ACE2, compared to young people and children, which explains the more aggressive viral load at the stage of entry the SARS-CoV-2 virus into the body of an elderly person [19,20]. On the other hand, one of the explanations for the relationship between the degree of COVID-19 course severity in elderly people and the development of complications is acquired immune dysfunction, that is an integral part of the natural aging process and is closely related to the presence of chronic concomitant diseases [4,8,9,17]. The aging process is accompanied not only by the loss of all body cells ability to regenerate, but also cells acquiring a pro-inflammatory secretory phenotype. This phenotype is characterized by excessive synthesis of acute phase proteins, proinflammatory cytokines, chemokines and oxidative stress factors, etc. All this creates favorable conditions for the development of a "cytokine storm" and exacerbation of chronic diseases, which closes the vicious circle of immune changes [21,22]. In addition, the natural involution of the thymus, which is accompanied by the accumulation of senescent CD4+ lymphocytes with the loss of the ability to adequately control the replication of SARS-CoV-2, as well as the accumulation of senescent CD8+ lymphocytes and B-lymphocytes with a distinct secretory phenotype, leads to the inability to develop effective controlled antiviral immunity in people over 65 years old [23,24].

The majority of research show a more severe course of COVID-19 and a higher risk of death in men than in women. Thus, already in 2020, data analysis of 59,254 patients from 11 different countries of the world showed a close connection between the male gender and a higher mortality rate [1]. Later, an Italian analysis of 239,709 patients showed that the mortality rate among men was 17.7 % against 10.8 % among women [25]. Our research also proved a certain predominance among sick men (55.9 % vs. 44.1 %), however, the gender of these patients did not have a statistically significant effect on the risk of disease fatal outcome in oxygen-dependent patients.

Data from the literature regarding comorbid pathology, which has the greatest impact on the formation of COVID-19 adverse course, has certain discrepancies according to researchers in different countries of the world. At the same time, according to the meta-analysis [26], which included the results of 6 Chinese researches (1527 patients), it was proved that the most common concomitant pathology in patients with COVID-19 was arterial hypertension, cardiovascular diseases, and diabetes, with a frequency of 17.1 %, 16.4 % and 9.7 %, respectively. However, according to the results of an American research (5700 patients), the most common concomitant diseases were hypertension (56.6 %), obesity (41.7 %) and diabetes (33.8 %) [11]. According to the results of our research, the most common comorbid condition in oxygen-dependent patients with COVID-19 was coronary heart disease (66.4 %), the presence of which had a statistically significant effect on the risk of disease fatal outcome in this category of patients (84.6 % vs. 43.2 %, P = 0.03). Besides, in our previous research [27] we demonstrated that morphological signs of chronic ischemic heart disease and hypertension were determined in majority of those who died as a result of COVID-19. Our results agree with the statistical data that came from China and Italy regarding the detection of chronic cardiovascular pathology in half of the hospitalized patients [18]. In addition, in our research we determined that comorbidity of oxygen-dependent patients with COVID-19 according to CCI had a connection with the risk of fatal outcome (P < 0.05). A threshold level (>5) was determined, which makes it possible to predict the probability of a fatal outcome of the disease in these patients. It should be noted that a number of research works presented in the literature also used the definition of the CCI in patients with COVID-19, however, with the aim of clarifying the comparison of groups of patients when evaluating different treatment methods [15,16].

Conclusions

1. In oxygen-dependent patients with COVID-19, the age of the patient is related to the outcome of the disease. Elderly patients more often registered in the group with COVID-19 fatal outcome than among patients who have recovered (25.6 % vs. 8.5 %, $\chi^2 = 10.36$, P = 0.001). Given the age of oxygen-dependent patients with COVID-19 >66 years, the probability of COVID-19 fatal outcome is significant (AUC = 0.636, P = 0.002). The gender of oxygen-dependent patients with COVID-19 does not have a statistically significant effect on the risk of an adverse course of the disease (P > 0.05).

2. Comorbidity of oxygen-dependent patients with COVID-19 according to the CCI is associated with the risk of an adverse outcome of the disease (P < 0.05). Under the conditions of the Charlson comorbidity index >5 in oxygen-dependent patients with COVID-19, the probability of disease fatal outcome is significant (AUC = 0.652, P < 0.001).

Prospects for further research. In our opinion, determination in further studies of the impact of various comorbid conditions in relation to demographic indicators on the effectiveness of various options of immunotropic treatment is promising.

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