НИРКИ KIDNEYS

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Analysis of risk factors for severe COVID-19

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Abstract. *Global aging has accompanied the worldwide increase in average life expectancy over the past century. The coronavirus disease (COVID-19) pandemic has increased morbidity among all groups of the population, but it poses a particular threat to people of older age groups. Multiple concomitant pathologies form an unfavorable background for the course of COVID-19. It was found that the level of in-hospital mortality in the care of older age groups was high, including in countries with high-income levels and expenditures on health care. We have identified predictors of the severe course of COVID-19. In our opinion, such predictors should be considered when identifying risk groups and applying anticipatory strategies to them, in particular, timely hospitalization, the administration of antiviral therapy, and treatment of concomitant pathology (chronic kidney disease, hypertension, diabetes mellitus, etc.). The question of testing elderly patients for the presence of SARS-CoV-2 is especially relevant when weakness increases, the state of consciousness worsens, and/or dyspnea appears or worsens. Postponement of hospitalization can negatively affect the results of treatment. Thus, interleukin-6, C-reactive protein, the absolute level of lymphocytes, albumin, and ferritin can be used when evaluating the criteria for hospitalization in this group of patients. Interleukin-6 and C-reactive protein are positively associated with body mass index. The excess of adipose tissue is considered an independent predictor of severe COVID-19 and, unlike age, can be modified. We suggested that a hospital mortality risk calculator based on the personalized lethality risk index on admission should be used in practice. Adequate therapy of concomitant pathology is also important in the prevention of COVID-19 complications. Protection of susceptible groups at high risk of severe COVID-19 has strategic importance in preventing high mortality rates in population regardless of age.*

Keywords: *COVID-19; diabetes mellitus; risk factor; obesity; mortality; body mass index; acute kidney injury; risk management*

Introduction

Globally, as of October 2022, there have been reported 632.8 million confirmed cases of coronavirus disease (COVID-19) causing 6.6 million deaths as a direct result of this disease [5]. The presence of obesity, diabetes mellitus, cardiovascular disease, male sex and old age significantly worsened the course of COVID-19 (Cinti, 2022 [2]; Halushko, 2021 [11]; Holman, 2020 [12]; Huang, 2020 [13]; Ivanov, 2022 [14], Khalangot, 2022 [17], Lim, 2020 [19]; Morys, 2021 [21]; Saito, 2022 [25]).

The study of the international and domestic experiences on the national and global response to the COVID-19 pandemic challenges and the organization of healthcare to the population, especially high-risk groups, requires analysis and systematization. The fundamental strategy to overcome the coronavirus pandemic was to respond rapidly to public health challenges and to prevent the exponential growth of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) morbidity. There was a high rate of outpatient encounters, and hospital admissions, including to the intensive care units. There was a need for rapid triage and decision-making on the management of each individual patient in a situation of limited resources.

One of the signs of a worsening demographic situation in Ukraine is population aging caused by the falling crude birth rates and slow growth of average life expectancy, lea-

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ding to the increased demographic burden [10]. The medical consequences of population aging are an increase in the prevalence of multiple chronic pathologies, peculiar to older people, and, consequently, an increase in morbidity, disability, and mortality rates in the general population, as well as in the need for health and social care services to meet the specific needs of older people [9]. Against the background of the COVID-19 pandemic, the situation dramatically exacerbated: on the one hand, the elderly was more likely to have severe COVID-19, frequently accompanied by complications and deaths. This was mainly due to the layering of the infection with chronic pathology, late encounters of elderly patients to general practitioners (family doctors), and correspondingly, late hospitalization. Moreover, in Ukraine, this patient population was the least vaccinated. On the other hand, during the COVID-19 pandemic, the priorities of healthcare delivery had to be changed: the efforts of healthcare professionals were predominantly concentrated on treating a significant number of patients with infectious pathology, and a considerable proportion of beds were repurposed to contagious diseases, leaving a part of the elderly population with multiple chronic pathologies with less medical attention and delayed elective treatment for many patients. Therefore, the achieved sustained remission of chronic diseases over time turned into exacerbations and complications, and the long-term pathology was diagnosed later in a more severe stage.

Inpatient care is the most expensive type of medical service. There has been a downward trend in the bed capacity in Europe in recent decades [7].

Given the current and predicted trends, public policy priorities, and the WHO recommendations, organisational optimisation of the primary healthcare delivery for high-risk individuals during the COVID-19 pandemic is of relevance, which determined the study objective and tasks.

The COVID-19 pandemic in 2020–2022 demonstrated how a novel respiratory infection could affect the public healthcare system worldwide. The high COVID-19 mortality rates were observed in countries with different income levels. According to Vezhnovets et al. [27], there was a reverse correlation between population mortality and health expenditure. During the COVID-19 pandemic, the scientists observed a distribution in terms of disease severity, which was as follows: an asymptomatic course in 30 % of cases, a mild and moderate course in 55 %, 10 % of patients needed hospitalization due to severe and 5 % due to critical course of COVID-19, with increasing mortality in each of these categories (0.7, 2.3, 15, 50 %, respectively) [6].

Age is one of the risk factors, according to researchers (Linda Katharina Karlsson et al.) who studied a population of hospitalized COVID-19 residents in Denmark who had reached the age of 80 [15]. The late diagnosis explained the "serious health consequences for older patients" due to atypical non-specific symptoms of the onset of the disease due to comorbidities. Among 102 patients (mean age 85 years), the most common symptoms were fever (74 %), cough (62 %), and shortness of breath (54 %), followed by mental confusion (29 %), difficulty walking (13 %), and episodes of falling (8 %). The in-hospital and 30-day mortality rates were 31 % (n = 32) and 41 % (n = 42), respectively [15]. According to the literature, hospital mortality in elderly patients was as high as 20 [4], 28.9 [8], 31 [15], and 38 % [1]. The data from the Polish nationwide COVID-19 patient registry (Kanecki et al., 2021 [16]), the American study (Richardson et al., 2020 [24]) were analyzed, and the rates of hospital mortality by age categories are presented below (Table 1).

According to CDC and Polish study (Kompaniyets et al., 2021), comorbid pathology significantly determined the COVID-19 severity [18, 26]:

— Bronchial asthma.
— Oncological diseases:
  – haemoblastosis.
— Cerebrovascular diseases.
— Chronic kidney disease.
— Chronic lung disease:
  – bronchiectasis;
  – chronic obstructive pulmonary disease;
  – interstitial lung diseases;
  – pulmonary embolism;
  – pulmonary hypertension.
— Chronic liver disease:
  – cirrhosis;
  – non-alcoholic fatty liver disease;
  – alcoholic liver disease;
  – autoimmune hepatitis.
— Cystic fibrosis.

Table 1. Hospital mortality rates by age categories, % [16, 24]

Age, years	Polish National Registry data (Kanecki et al., 2021 [16])	American population (male)	American population (female)
20–29	0.2	7.1	1.8
30–39	0.8	4.6	2.5
40–49	2.8	8.2	2.5
50–59	4.6	12.2	6.9
60–69	10.6	18.7	12
70–79	21.3	35.8	27.4
80–89	30.9	60.6	48.1
90–99	34	63.6	46.4
All age categories	11.7	–	–

— Type 1 diabetes mellitus.
— Type 2 diabetes mellitus.
— Gestational diabetes.
— Disability, including Down's syndrome.
— Cardiovascular diseases (such as heart failure, coronary artery disease, cardiomyopathy).
— Human immunodeficiency virus.
— Mental illness.
— Neurological diseases.
— Obesity (body mass index (BMI) > 30 kg/m^2 or > 95th percentile in children).
— Hypodynamia.
— Pregnancy.
— Primary immunodeficiencies.
— Smoking.
— Post-transplantation status.
— Tuberculosis.
— Use of glucocorticoids.

The **purpose** of the study was to examine the relationship between clinical and laboratory findings and the COVID-19 severity for preventing hospital mortality in the elderly.

Materials and methods

The research methods included medical and statistical, content analysis, structural-logical analysis, modelling, clinical, laboratory, and instrumental techniques.

The data was processed using EZR [15], MedStat software (Liakh, Hurianov, 2003–2019) [20]. When performing the analysis for quantitative indicators, the mean value (M), standard error (± m) and 95% confidence interval (95% CI) were calculated for the normal distribution; the median value (Me) and interquartile range (QI-QIII) were calculated for the non-normal distribution. For qualitative indicators, prevalence (%) and 95% CI were calculated. The Mann-Whitney test was used to compare mean values in two groups for quantitative measures, and the chi-square test (with Yates' correction) was used to compare qualitative measures. Methods of constructing and analysing logistic regression models were used to evaluate the association of factorial features with the mortality risk. The impact of the factorial features was assessed by the odds ratio (OR), for which 95% CI was calculated. The model adequacy was assessed by area under the receiver operating characteristic (ROC) curve of the model and its 95% CI; the model sensitivity and specificity, positive and negative predictive values were calculated. All calculations were performed for a critical significance level of 0.05.

Results and discussion

In accordance with the study objective, we conducted a retrospective analysis of the medical reports of the COVID-19 patients who were treated at the KAPITAL Ltd. (Medical Centre Universal Clinic "Oberig"). The analyzed COVID-19 hospitalizations (n = 129) were divided into 2 groups: group I (n = 88) consisted of patients with a moderate to severe course discharged from hospital, group II (n = 41) included cases of hospitalization with severe to critical COVID-19 courses with poor outcomes. There was no statistically significant difference in sex distribution between the groups (p = 0.161). In both groups, the distribution differed from normal at the level of significance (p < 0.001 and p = 0.022, respectively); Me and QI-QIII were used to represent the data in the groups (Table 2).

The inclusion criterion was a verified COVID-19 diagnosis based on clinical-anamnestic, laboratory and instrumental tests, including a positive test for SARS-CoV-2 RNA (by polymerase chain reaction) or a rapid test for SARS-CoV-2 antigen.

The treatment outcomes of patients hospitalised for COVID-19 (n = 129) were analysed. Table 3 shows the clinical and laboratory data.

A comprehensive statistical analysis of hospital admissions for COVID-19 (median age 81 and 79 years), considering clinical, laboratory and instrumental findings of patients, revealed the following trends.

Almost all patients complained of weakness (97.9 and 92.7 % in groups I and II, respectively). The next most common were fever (76.4 and 70.7 %), dyspnoea (30.3 and 53.7 %) and cough (49.4 and 39 %). Moreover, in group II, the prevalence of dyspnoea exceeded the prevalence of cough. Notably, a larger proportion of pulmonary parenchymal involvement was observed in patients with severe COVID-19 at baseline (62 % in group II vs 25 % in group I, p < 0.001), which generally corresponded to the prevalence of dyspnoea complaints in this population (up to 53.7 % in group II vs 30.3 % in group I). Upon admission, they had more severe respiratory failure, most commonly complained of dyspnoea on exertion as well as at rest. Patients in group II more often required continuous oxygen support.

There was no statistically significant difference in the prevalence of diarrhoeal syndrome in either group (9 vs 7.3 %, respectively).

There was a statistically significant difference in the duration of hospital stay between the groups (p < 0.001): 9 bed days in group I and 14 in group II, so in group II, the average length of hospital stay was five bed-days longer (+ 35.7 %).

The mean BMI of patients in group I was 27.57 ± ± 1.20 kg/m^2 (95% CI 25.09–30.06) and in group II — 31.2 ± 2.2 kg/m^2 (95% CI 26.01–36.39), but no statistically significant difference was found (p = 0.122).

All patients with respiratory failure and decreased blood saturation (SpO_2) below 92 % were administered anti-inflammatory therapy with glucocorticoids (methylprednisolone or dexamethasone) and oxygen support (using oxygen

Table 2. Sex-age structure of hospitalized patients, abs./%

Groups	Females (n = 73)	Males (n = 56)
Group I (n = 88)	54/61.4	34/38.6
Group II (n = 41)	19/46.3	22/53.7

concentrator and a continuous positive airway pressure machine, or non-invasive ventilation, or invasive ventilation) depending on the severity of the respiratory failure.

Lymphopenia progressed against the background of the coronavirus disease progression and the use of glucocorticoids. Notably, in blood tests, more severe lymphopenia was shown in patients with poor outcomes of COVID-19. Thus, the minimum absolute lymphocyte count in group II was $0.2 \cdot 10^9$/L, while in group I it was $0.56 \cdot 10^9$/L ($p < 0.001$).

There was a statistically significant difference in the median value of the highest CRP level in group II, which was 118.02 mg/L compared to 36.68 mg/L in group I ($p < 0.001$). Group II patients had twice the ferritin level at baseline compared to those in group I (753 vs 328 μg/L respectively, $p < 0.001$).

There was a difference between IL-6 content in the groups: 23.65 pg/mL in group I and 34.4 pg/mL in group II ($p = 0.009$).

There was no statistically significant difference ($p = 0.083$) in HbA1c levels between the groups.

Against the background of progressing respiratory failure and hypoxemia, an increase in creatinine levels and a decrease in the eGFR were observed in some patients. In group II, the incidence of AKI reached up to 46.3 % (CI 95% 31–62 %), $p < 0.001$. According to the results of BIRCOV study, reported by Ivanov D.D. et al., 2022 [14], effect of COVID-19 on kidney function in people with

Table 3. Clinical and laboratory results of patients in both groups

Parameter	Group I (n = 88)	Group II (n = 41)	p
Age, years, Me (QI-QIII)	81 (79–84)	79 (70–80)	< 0.001*
BMI, kg/m^2, M ± m (95% CI)	27.57 ± 1.20 (25.09–30.06)	31.2 ± 2.2 (26.01–36.39)	0.122
Duration of hospital stay, bed days, Me (QI-QIII)	9 (7–12)	14 (10–22)	< 0.001*
Prevalence of cough on admission, % (95% CI)	49.4 (39–59.9)	39 (24.4–54.7)	0.359
Prevalence of dyspnoea on admission, % (95% CI)	30.3 (21.2–40.4)	53.7 (38–69)	0.021*
Reported fever before admission, % (95% CI)	76.4 (66.9–84.7)	70.7 (55.6–83.8)	0.639
Prevalence of weakness on admission, % (95% CI)	97.7 (93.5–99.8)	92.7 (82.5–98.7)	0.397
Diarrhoeal syndrome before admission, % (95% CI)	9 (3.9–15.9)	7.3 (1.3–17.5)	0.984
Severity of lung damage on MSCT (pulmonary parenchymal involvement), % (95% CI)	25 (10–45)	61 (40–75)	< 0.001*
Minimum absolute lymphocyte count, $\times 10^9$/L, Me (QI-QIII)	0.56 (0.41–0.9)	0.2 (0.11–0.28)	
Maximum CRP level, mg/L, Me (QI-QIII)	36.68 (16.78–75.41)	118.02 (75.21–178.94)	
Ferritin, μg/L, Me (QI-QIII)	328 (156–558)	753 (442–1176)	
IL-6, pg/mL, Me (QI-QIII)	23.65 (9.2–43.6)	34.4 (17.7–74.9)	0.009*
HbA1c, % (95% CI)	5.28 (4.79–5.87)	5.54 (5.04–6.56)	0.083
ALT, U/L, Me (QI-QIII)	26.9 (16.3–40.3)	29 (20.3–42.6)	0.404
AST, U/L, Me (QI-QIII)	33.15 (25.8–47.5)	37.3 (26.8–53.5)	0.191
AST/ALT, Me (QI-QIII)	1.31 (1.01–1.77)	1.32 (1.07–1.51)	0.906
Baseline albumin, g/L, Me (QI-QIII)	35.7 (34.33–40.53)	32.33 (29.56–35.44)	0.015*
Minimum albumin, g/L, Me (QI-QIII)	35.71 (32.24–37.02)	27.66 (25.6–29.95)	< 0.001*
eGFR on admission, mL/min, Me (QI-QIII)	59.95 ± 2.10 (55.9–64.02)	60.32 ± 3.80 (52.62–68.03)	0.929
Minimum eGFR, mL/min, Me (QI-QIII)	59.80 ± 2.55 (43.7–76)	33.70 ± 5.06 (15–55.8)	< 0.001*
Incidence of AKI during hospitalization, per 100 patients, Me (QI-QIII)	0 (0–2.2)	46.3 (31–62)	

Notes: * — a statistically significant test result ($p \leq 0.05$); MSCT — multislice spiral computed tomography; IL-6 — interleukin-6; CRP — C-reactive protein; ALT — alanine aminotransferase; HbA1c — glycated hemoglobin; AST — aspartate aminotransferase; eGFR — estimated glomerular filtration rate; AKI — acute kidney injury.

grade 1–2 hypertension and chronic kidney functions was explained "as effect of decrease in blood pressure with a gradual return to baseline values in COVID patients" and also could be caused by the use of dexamethasone with an accompanied decrease in the eGFR in chronic kidney disease stages 3b-4 [14].

Notably, patients in group II showed a progressive decrease in albumin levels, whereas in group I, the median value of this indicator did not change significantly. Group II was found to have a minimum albumin level of 27.66 mg/L, even though correction was carried out, in contrast to the group I with a corresponding indicator of 35.71 mg/L ($p < 0.001$), indicating a deterioration of the protein-synthesizing liver function. There was no statistically significant difference between ALT, AST levels, and AST/ALT ratio between the groups.

A higher prevalence of comorbidities was observed in group II — 2.31 ± 0.14 in contrast to group I, 1.91 ± 0.12 ($p = 0.022$) (Table 4). However, no advantage in the prevalence of pathologies in the structure of comorbidities between the groups was detected. The prevalence of diabetes mellitus differed between groups I and II, 18 and 31.7 %, respectively, but no statistically significant difference was found ($p = 0.141$).

We suggested using the PLRI, which was calculated based on the following parameters:

1) presence of comorbidities (arithmetic sum of the number of organ systems affected by a chronic pathology according to ICD-10);

2) age over 70 years;

3) presence of obesity (BMI more than 30 kg/m^2);

4) presence of cardiovascular disease;

5) neurological pathology (cerebrovascular events) in the past;

6) respiratory failure with decreased blood saturation ($SpO_2 < 92$ %), requiring the oxygen therapy and glucocorticoid administration;

7) pulmonary parenchymal involvement over than 50 %.

The presence of one of the above criteria resulted in a score of 1. The personalized lethality risk index was calculated as the sum of these scores.

Based on the PLRI obtained, a logistic regression model was developed (Table 5, Fig. 1). The one-factor model for predicting mortality risk in COVID-19 patients was built on the selected feature set; the model is adequate (chi-square = 20.13 at 1 degree of freedom, $p < 0.001$).

When the optimal threshold of Ycrit ≥ 5.0 was chosen (high risk of lethal outcome), the model sensitivity was 75.6 % (95% CI 59.7–87.6 %), the model specificity was 70.5 % (95% CI 59.8–79.7 %), the positive predictive value was 54.4 % (95% CI 40.7–67.6 %), and the negative predictive value was 86.1 % (95% CI 75.9–93.1 %).

Table 4. Prevalence of comorbidities in the groups

Disease	Group I (n = 88)	Group II (n = 41)	p
Cardiovascular pathology, % (95% CI)	75.3 (65.7–83.7)	87.8 (75.8–96.1)	0.144
Endocrine pathology, % (95% CI)	47.2 (36.8–57.7)	51.2 (35.6–66.7)	0.811
Diabetes mellitus, % (95% CI)	18 (10.7–26.7)	31.7 (18.2–47.1)	0.141
Newly diagnosed diabetes, % (95% CI)	9 (3.9–15.9)	9.8 (2.5–21)	0.850
Chronic respiratory disease, % (95% CI)	5.6 (1.8–11.4)	2.4 (0–9.6)	0.719
Chronic kidney disease, % (95% CI)	10.1 (4.7–17.3)	17.1 (7–30.4)	0.419
Gastroenterological pathology, % (95% CI)	13.5 (7.1–21.4)	29.3 (16.2–44.4)	0.068
Neurological pathology, % (95% CI)	9 (3.9–15.9)	17.1 (7–30.4)	0.314
Cancer, % (95% CI)	13.5 (7.1–21.4)	17.1 (7–30.4)	0.788
Anaemia, % (95% CI)	14.6 (8–22.8)	9.8 (2.5–21)	0.625
Average number of comorbidities, M ± m (95% CI)	1.91 ± 0.12 (1.67–2.14)	2.31 ± 0.14 (2.03–2.6)	0.022*
PLRI, M ± m (95% CI)	4.09 ± 0.17 (3.75–4.44)	5.09 ± 0.23 (5.09–6.04)	0.001*
Padua score, M ± m (95% CI)	3.18 ± 0.08 (3.03–3.33)	5.60 ± 0.23 (3.63–4.13)	

Notes: * — a statistically significant test result (p ≤ 0.05); PLRI — personalized lethality risk index.

Table 5. Coefficients of the one-factor logistic regression model predicting the risk of lethal outcome (Y) for COVID-19 patients according to the personalized lethality risk index

Factorial feature	Model coefficient value, $b \pm m_b$	Significance level of coefficient difference from 0, p	OR (95% CI)
	–3.40 ± 0.71	0.001*	
PLRI (X1)	0.57 ± 0.14		1.77 (1.34–2.34)

Notes: * — difference of the model parameter from 0 is statistically significant, p < 0.05; ln(Y/(1 – Y)) = –3.4 + + 0.57 × X1.

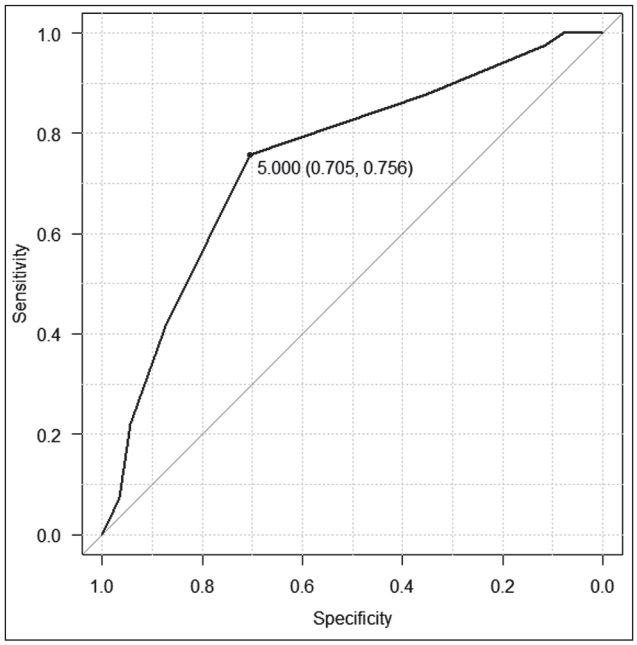

Figure 1. ROC-curve of a logistic regression model of the hospital-based lethal outcome risk prediction for patients with COVID-19 (area under curve = 0.748; 95% CI 0.658–0.839)

Conclusions

The aging of the world population has accompanied the global rise in average life expectancy over the past century. The COVID-19 pandemic has led to increased morbidity in all segments of the population, but it is particularly threatening for the elderly. Comorbid pathology forms an unfavorable background for the course of COVID-19.

We have identified predictors of severe coronavirus disease, which, in our opinion, should be taken into account, when identifying risk groups and applying a feedforward approach to such groups, particularly early hospitalization, antiviral therapy administration, and treatment of comorbidities. Testing elderly patients for SARS-CoV-2 when there is increasing weakness, altered consciousness, and/or dyspnoea appears/worsens is especially relevant. Delayed hospital admission may affect treatment outcomes.

IL-6, CRP, absolute lymphocyte count, albumin, and ferritin can be used additionally in assessing hospitalization criteria in this group of patients. IL-6 and CRP are positively associated with BMI. Excess adipose tissue is considered an independent predictor of severe COVID-19 and can be modified in contrast to age or comorbidities.

We suggested that a hospital mortality risk calculator based on the personalized lethality risk index on admission should be used in practice.

Adequate treatment of comorbidities is also essential for the prevention of COVID-19 complications. Protecting high-risk groups has a strategic impact on preventing high mortality rates irrespective of age.

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Аналіз факторів ризику тяжкого перебігу COVID-19

Резюме. Глобальне зростання середньої очікуваної тривалості життя протягом останнього століття супроводжувалося постарінням населення світу. Пандемія коронавірусної хвороби (COVID-19) призвела до зростання рівня захворюваності серед усіх верств населення, але особливу загрозу вона становить для людей старших вікових груп. Супутня поліморбідна патологія формує несприятливий фон для перебігу COVID-19. Виявлено, що рівень госпітальної летальності в пацієнтів старших вікових груп був високим, у тому числі в державах із високими рівнями доходів та витратами на охорону здоров'я. Визначено предиктори тяжкого перебігу коронавірусного захворювання, які, на наш погляд, слід враховувати при визначенні груп ризику і застосовувати щодо них випереджальну тактику, зокрема визначення показань до госпіталізації, призначення противірусної терапії, лікування супутньої патології. Особливо актуалізується питання тестування літніх пацієнтів на наявність SARS-CoV-2 при наростанні слабкості, погіршенні стану свідомості та/або появі чи погіршенні задишки. Відстрочення госпіталізації може негативно позначитися на результатах лікування. Показники інтерлейкіну-6, С-реактивного білка, абсолютний рівень лімфоцитів, альбуміну, феритину можна додатково застосовувати при оцінці критеріїв госпіталізації цієї групи пацієнтів. Рівні інтерлейкіну-6 та С-реактивного білка позитивно пов'язані з індексом маси тіла. Надлишок жирової тканини розглядається як незалежний предиктор тяжкого перебігу COVID-19 і на відміну від віку може бути модифікований. Для підрахунку ризику госпітальної летальності пропонується використовувати персоніфікований індекс ризику летальності як додатковий інструмент для прийняття рішення на користь госпіталізації з приводу COVID-19. Адекватна терапія супутньої патології відіграє важливу роль у профілактиці ускладнень COVID-19. Захист груп ризику має стратегічне значення в запобіганні високим рівням смертності населення незалежно від віку.

Ключові слова: COVID-19; цукровий діабет; фактори ризику; ожиріння; смертність; індекс маси тіла; гостре пошкодження нирок; ризик-менеджмент