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Predictors of mortality in hospitalized patients with COVID-19

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ABSTRACT

Aim. To determine clinical and laboratory factors associated with a severe course and lethality in hospitalized patients with COVID-19.

Materials and methods. A retrospective comparative study included data of 745 adult patients hospitalized with COVID-19 from 16.05.2020 to 30.09.2020 (Tomsk, Russia). The intergroup comparison of indices, ROC analysis, and determination of odds ratio to assess the association between risk factors and the outcome were performed.

Results. Age > 62 years, pneumonia within a year before COVID-19, and the presence of ≥3 comorbidities were associated with a fatal outcome (FO). Negative predictors of the outcome at the time of hospitalization included dyspnea, diastolic blood pressure ≤ 80 and pulse pressure > 48 mmHg, SpO_2 < 94% (and/or a decrease to ≤ 89% throughout hospitalization). Laboratory predictors of FO at admission were platelets ≤ 183 × 10^9 / l, neutrophils > 4.57 × 10^9 / l, lymphocytes ≤ 1.08 × 10^9 / l, neutrophil-to-lymphocyte ratio > 4.8, aspartate aminotransferase > 39 U / l, urea > 6.75 mmol / l, lactate dehydrogenase > 219 U / l, blood albumin ≤ 38 g / l, C-reactive protein (CRP) > 47 mg / l. When threshold values were reached during any of the hospitalization periods, FO was associated with CRP > 38 mg / l, ferritin > 648.6 μg / l, D-dimer > 731.11 ng / ml, white blood cells > 14.27 × 10^9 / l, lymphocytes ≤ 0.73× 10^9 / l, duration of oxygen therapy > 3 days, need for non-invasive and invasive ventilation ≥ 1 day, need for glucocorticoid administration > 1 day, reaching a total course dose > 6 mg for dexamethasone.

Conclusion. The factors associated with FO in hospitalized patients with COVID-19 were identified.

Keywords: novel coronavirus infection, COVID-19, biomarkers, predictors of severe disease, predictors of mortality

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the Ethics Committee at Siberian State Medical University (Protocol No. 8511 of 21.12.2020).

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Предикторы летального исхода у госпитализированных пациентов с COVID-19

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РЕЗЮМЕ

Цель. Установить клинико-лабораторные факторы, ассоциированные с тяжелым течением и летальностью у госпитализированных пациентов с новой коронавирусной инфекцией (COVID-19).

Материалы и методы. Проведено ретроспективное сравнительное исследование по данным 745 взрослых пациентов, госпитализированных с COVID-19 с 16.05.2020 по 30.09.2020 (Томск, Россия). Выполнено межгрупповое сравнение показателей, ROC-анализ, определение отношения шансов для оценки связи между факторами риска и исходом.

Результаты. С летальным исходом (ЛИ) ассоциированы возраст старше 62 лет, пневмония в течение года до COVID-19, наличие ≥3 сопутствующих патологий. Негативные предикторы исхода на момент госпитализации: одышка, диастолическое давление ≤80 и пульсовое давление более 48 мм рт. ст., SpO_2 менее 94% (и (или) снижение за госпитализацию до ≤89%). Лабораторные предикторы ЛИ при госпитализации: тромбоциты ≤ 183 × 10^9/л, нейтрофилы более 4,57 × 10^9/л, лимфоциты ≤1,08 × 10^9/л, нейтрофильно-лимфоцитарное отношение более 4,8, аспартатаминотрансфераза более 39 ЕД/л, мочевина более 6,75 ммоль/л, лактатдегидрогеназа более 219 ЕД/л, альбумин крови ≤38 г/л, С-реактивный белок (СРБ) более 47 мг/л. При достижении пороговых значений в любой из периодов госпитализации с ЛИ ассоциировались: уровень СРБ в крови более 38 мг/л, ферритина более 648,6 мкг/л, D-димера более 731,11 нг/мл, лейкоцитов более 14,27 × 10^9/л, лимфоцитов ≤0,73 × 10^9/л, продолжительность оксигенотерапии более 3 сут, необходимость неинвазивной и инвазивной вентиляции легких ≥1 сут, потребность назначения глюкокортикостероидов более 1 сут, достижение общей курсовой дозы более 6 г по дексаметазону.

Заключение. Выявлены факторы, ассоциированные с ЛИ у госпитализированных пациентов с COVID-19.

Ключевые слова: новая коронавирусная инфекция, COVID-19, биомаркеры, предикторы тяжелого течения, предикторы летального исхода

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом СибГМУ (протокол № 8511 от 21.12.2020).

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INTRODUCTION

The outbreak of novel coronavirus infection (COVID-19) in late 2019 in the People's Republic of China triggered the pandemic that caused enormous socioeconomic damage and lasted for more than three years. The first waves of the pandemic were characterized by a lack of preparedness and unprecedented collapse of healthcare systems worldwide, as well as by the use of drugs with insufficient evidence-based efficacy.

As of December 2023, there were more than 772 million confirmed cases and more than 6.9 million deaths worldwide. According to the 2022 meta-

analysis, the highest rates of excess mortality from COVID-19 were registered in India (4.07 million deaths), USA (1.13 million deaths), and Russia (1.07 million deaths) [1].

Despite the existing vaccination programs, the emergence of modified variants of the virus with a less dangerous course of the disease and the spread of new strains around the world make the problem of COVID-19 control relevant. As more data become available, an analysis is being conducted to identify unique biomarkers that may correlate with COVID-19 severity and adverse outcomes in order to provide appropriate medical care and reduce the burden on healthcare.

The aim of this study was to determine clinical and laboratory factors associated with a severe course and lethality in hospitalized patients with COVID-19.

MATERIALS AND METHODS

A retrospective comparative study was carried out using a continuous sampling method. The study included medical records of 745 adult patients (343 men (46.0%) and 402 women (54.0%)) with COVID-19 confirmed by polymerase chain reaction (PCR), who were treated at the respiratory hospital (RH) in Siberian State Medical University clinics (Tomsk) from 16.05.2020 to 30.09.2020 (period of circulation of the wild-type SARS-CoV-2 strain in Russia). The study protocol was approved by the local Ethics Committee at Siberian State Medical University (Protocol No.8511 of 21.12.2020).

For all patients of the RH, anamnestic data and results of objective examination and laboratory and instrumental investigations were collected according to the approved algorithm in the first 48 hours from the moment of hospitalization for a dynamic assessment and determination of the relationship with the outcome of hospitalization. Two comparison groups were formed retrospectively, depending on the outcome of hospitalization. The main group consisted of patients whose hospitalization ended in discharge from hospital (survivors, $n = 683$), the comparison group consisted of patients with a fatal outcome (FO, deceased, $n = 62$).

Statistical analysis of the obtained data was performed using the Statistica 12 (StatSoft.Inc, USA), MedCalc 22.009 (Copy©MedCalc SoftWare Ltd., Belgium), and Microsoft® Excel® 2016 MSO (version 2309 16.0.16827.20166, USA) software packages. Quantitative variables were described as the median and the interquartile range Me (Q_{25}; Q_{75}). Qualitative variables were described as absolute and relative frequencies (n (%)). Intergroup comparison of quantitative variables was performed using the nonparametric Mann – Whitney U-test. Qualitative variables were compared using the Pearson's $\chi 2$ test.

The quantitative assessment of the association between the disease outcome and the presence of a risk factor in the sample was performed using odds ratio (OR). Results were presented using the odds ratio and 95% confidence interval (CI). The results were considered statistically significant if CI did not contain 1. In addition, the impact of factors on the odds of FO was assessed using the ROC analysis. The area under the curve (AUC) with 95% CI, the cut-off point according to the Youden index, and sensitivity and specificity for this point were evaluated. The results were considered significant at $p < 0.05$.

RESULTS

Demographic and anamnestic characteristics of the patients. Age of the patients in the group of survivors was 57 (43; 67) years, in the group of the deceased patients – 73 (66; 81) years ($p < 0.001$). Age of more than 62 years (AUC 0.804 (0.774; 0.832), $p < 0.001$) was a risk factor for an adverse outcome with sensitivity of 85.5% and specificity of 65.6%.

The compared patient groups did not differ significantly in gender distribution: the main group consisted of 316 men (46.3%) and 367 women (53.7%), the comparison group consisted of 27 men (43.5%) and 35 women (56.5%), $p = 0.681$. Patients' gender also did not significantly affect the outcome of hospitalization (OR 1.1 (0.7;1.9)). The duration of illness before hospitalization was 6 (3; 9) days in the main group and 5 (1.5; 7.0) days in the comparison group ($p = 0.011$). The analysis showed that pneumonia experienced by patients in the year preceding COVID-19 increased the odds of FO by almost 15 times (OR 14.9 (3.6; 61.6)).

In the outpatient setting, patients with COVID-19 were treated by a variety of medication groups. The analysis included only records of the patients whose data on pre-hospital drug intake could be clarified. Thus, antibacterial drugs (ABD) were taken in the outpatient setting by 117 (17.1% of 683) patients of the main group and 10 (16.1% of 62) patients of the deceased group ($p = 0.840$). Antiviral drugs were taken by 8 (36.4% of 22) patients from the deceased group and 146 (90.1% of 162) patients from the main group ($p < 0.001$). Non-steroidal anti-inflammatory drugs (NSAIDs) were received by 8 (34.8% of 23)

patients from the deceased group and 82 (82% of 100) survivors. Administration of antiviral drugs (umifenovir, interferon alfa-2b, interferon beta-1b, imidazolyl ethanamide pentandioic acid, ritonavir + lopinavir, tilorone, rimantadine, oseltamivir, meglumine acridone acetate, and kagocel) and NSAIDs at the prehospital stage was associated with a reduction of the odds for mortality by approximately 16 (OR 0.06 (0.02; 0.17)) and 9 (OR 0.11 (0.04; 0.32)) times, respectively ($p < 0.050$).

Following the analysis of patients' comorbidities, we formed groups of diseases that increased the odds of FO and did not affect it. Thus, the diseases that increased the risk of FO included coronary heart disease (by 8 times), essential hypertension (by 5 times), diabetes mellitus (by 2 times), chronic heart failure (by 5 times), anemia (by 4 times), liver cirrhosis (by 11 times), decreased glomerular filtration rate (GFR) of less than 60 ml / min / 1.73 m² according to the CKD-EPI equation (by 11 times), previous stroke (by 9 times), alcoholism (by 9 times), bedsores (by 9 times), cooccurring cancer (by 6 times), and neurological disorders (by 5 times). Group 2 encompassed diseases that did not increase the odds of FO: bronchial asthma, chronic obstructive pulmonary disease, liver diseases, except for cirrhosis, kidney diseases without decreased GFR, drug addiction (Table 1).

The presence of at least three comorbidities was associated with FO (AUC 0.821 (0.792; 0.848), $p < 0.001$) with sensitivity of 83.9% and specificity of 64.3%.

Table 1

Characteristics of comorbidities in the patients

Parameter	Main group (survivors), *n* (%)	Comparison group (deceased), *n* (%)	*p*	OR (95% CI), *Me* (Q_{25}; Q_{75})
CHD	160 (23.4%)	44 (71.0%)	<0.001	7.99 (4.49; 14.28)
Hypertension	386 (56.5%)	54 (87.1%)	<0.001	5.19 (2.43; 11.08)
Diabetes mellitus	107 (15.7%)	16 (25.8%)	0.039	1.87 (1.02; 3.43)
Chronic heart failure	147 (21.5%)	36 (58.1%)	<0.001	5.05 (2.95; 8.63)
Bronchial asthma	29 (4.3%)	3 (4.8%)	0.830	1.15 (0.34; 3.88)
COPD	27 (4.0%)	5 (8.1%)	0.127	2.13 (0.79; 5.74)
Anemia	37 (5.4%)	11 (17.8%)	0.001	3.76 (1.81; 7.81)
Liver cirrhosis	2 (0.3%)	2 (3.2%)	0.003	11.35 (1.57; 82.02)
Other liver diseases	30 (4.4%)	5 (8.1%)	0.191	1.91 (0.71; 5.11)
HIV infection	5 (0.7%)	2 (3.2%)	0.051	4.52 (0.86; 23.80)
Kidney diseases	223 (32.7%)	26 (41.9%)	0.138	1.49 (0.88; 2.53)
GFR < 60 ml / min / 1.73 m²	50 (7.3%)	29 (46.8%)	<0.001	11.13 (6.25; 19.79)
Injection drug abuse	1 (0.2%)	1 (1.6%)	0.328	11.16 (0.70; 180.71)
Previous stroke	20 (2.9%)	13 (21.0%)	<0.001	8.78 (4.12; 18.71)
Alcoholism	4 (0.6%)	3 (4.8%)	0.001	8.61(1.88; 39.37)
Bedsores	5 (0.7%)	4 (6.5%)	0.001	9.34 (2.44; 35.73)
Cancer	30 (4.4%)	14 (22.6%)	<0.001	6.34 (3.15; 12.75)
Neurological disorders	132 (19.3%)	35 (56.5%)	<0.001	5.41 (3.16; 9.26)

Note. CHD – coronary heart disease, COPD – chronic obstructive pulmonary disease, GFR – glomerular filtration rate. OR – odds ratio
p – statistical significance of intergroup differences. 95% CI –95% confidence interval.

Patient complaints and objective examination data on admission to the RH. Symptoms of patients on admission to the RH that affected the odds of FO were identified. Thus, dyspnea, which was present in 28.4% of survivors and 62.0% of the deceased ($p < 0.001$), was associated with higher odds of mortality. In contrast, the presence of anosmia and headache was associated with lower odds of mortality – OR 4.11 (2.30;7.50), OR 0.08 (0.01;0.57), and OR 0.51 (0.26;0.99), respectively. The proportion of patients with headache was 37.6 and 23.5% among survivors and deceased patients, respectively ($p = 0.044$). Anosmia was almost 10.5 times less common in the group of deceased patients (2%) compared to survivors (20.5%, $p = 0.001$). Such symptoms as cough, purulent sputum production, fever, chest pain, general weakness, chills, myalgia, and diarrhea were not significantly associated with mortality in the compared groups ($p > 0.05$).

Among the objective examination findings at admission to the RH, FO was also associated with diastolic blood pressure ≤ 80 mm Hg (AUC

0.603 (0.567; 0.639), p = 0.005, sensitivity 78.7%, specificity 38.3%), pulse pressure value > 48 mm Hg (AUC 0.581 (0.544; 0.616), p = 0.048, sensitivity 64.5%, specificity 56.4%), respiratory rate >19 breaths per minute (AUC 0.704 (0.670; 0.737), p < 0.001, sensitivity 44.3%, specificity 91.9%), blood oxygen saturation (SpO_2) measured by pulse oximetry < 94% (AUC 0.751 (0.718; 0.782), p < 0.001, sensitivity 64.5%, specificity 73.0%). A decrease in SpO_2 to ≤ 89% during hospital stay was also associated with FO (AUC 0.859 (0.831; 0.884), p < 0.0001, sensitivity 77.8%, specificity 84.6%). The odds of FO were increased if auscultatory signs, such as diminished breath sounds (OR 2.06 (1.15; 3.70)) and moist rales (OR 3.96 (1.51; 10.37)), were registered on admission in patients with COVID-19.

Laboratory parameters during hospital stay. Among hemogram parameters on admission to the RH, statistically significant predictors associated with FO included:

1) platelet count ≤ 183 × 10^9 / l (AUC 0.673 (0.638; 0.708), p = 0.001, sensitivity 61.7%, specificity 71.8%);

2) neutrophil count > 4.57 × 10^9 / l (AUC 0.696 (0.660; 0.730), p < 0.001, sensitivity 63.8%, specificity 72.4%);

3) lymphocyte count ≤ 1.08 × 10^9 / l (AUC 0.768 (0.735; 0.798), p < 0.001, sensitivity 70.2%, specificity 70.3%);

4) neutrophil-to-lymphocyte ratio > 4.8 (AUC 0.774 (0.741; 0.804), p < 0.001, sensitivity 66.0%, specificity 80.7%).

The analysis of changes in the hematologic parameters throughout hospitalization showed that increased leukocyte count > 14.27 × 10^9 (AUC 0.855 (0.827; 0.880), p < 0.001, sensitivity 70.0%, specificity 90.0%) and decreased lymphocyte count ≤ 0.73 × 10^9 / l (AUC 0.878 (0.852; 0.901), p < 0.001, sensitivity 85.0%, specificity 82.3%) were also predictors of FO of the disease (Table 2).

Table 2

Hematologic parameters					
Parameter	AUC, *Me* (Q_{25}; Q_{75})	p	Cut-off point	Sensitivity, %	Specificity, %
Thrombocytes, thousands / μl	0.673 (0.638; 0.708)	0.001	≤183	61.7	71.8
Leukocytes, ×10^9 / l	0.615 (0.578; 0.650)	0.028	>7.71	48.0	81.1
Neutrophils, ×10^9 / l	0.696 (0.660; 0.730)	<0.001	>4.57	63.8	72.4
Lymphocytes, ×10^9 / l	0.768 (0.735; 0.798)	<0.001	≤1.08	70.2	70.3
Neutrophil-to-lymphocyte ratio	0..774 (0.741; 0.804)	<0.001	>4.80	66.0	80.7
Leukocytes (maximum level)	0.855 (0.827; 0.880)	<0.001	>14.27	70.0	90.0
Lymphocytes (minimum level)	0.878 (0.852; 0.901)	<0.001	≤0.73	85.0	82.3

Note. Here and in Table 3, AUC – area under the curve.

p – significance of differences

Among the blood biochemistry parameters on admission, statistically significant predictors associated with FO were registered:

1) aspartate aminotransferase level > 39 U / l (AUC 0.647 (0.610; 0.682), p = 0.001, sensitivity 68.5%, specificity 58.8%);

2) urea level > 6.75 mmol / l (AUC 0.796 (0.764; 0.824), p < 0.001, sensitivity 75.9%, specificity 74.1%);

3) lactate dehydrogenase level > 219 U / l (AUC 0.777 (0.718; 0.828), p < 0.001, sensitivity 95.2%, specificity 51.8%);

4) blood albumin level ≤ 38 g / l (AUC 0.792 (0.731; 0.844), p < 0.001, sensitivity 89.5%, specificity 62%);

5) C-reactive protein (CRP) level > 47 mg / l (AUC 0.782 (0.744; 0.816), p < 0.001, sensitivity 66.7%, specificity 81%).

The analysis of blood biochemistry parameters demonstrated that CRP concentration > 38 mg / l (AUC 0.862 (0.833; 0.887), p < 0.001, sensitivity 89.4%, specificity 71.0%), ferritin level > 648.6 μg / l (AUC 0.715 (0.666; 0.761), p = 0.001, sensitivity 52.4%, specificity 86.0%), and serum D-dimer level > 731.11 ng / ml (AUC 0.792 (0.723; 0.850), p < 0.001, sensitivity 90.0%, specificity 61.%), registered as the highest at any of the hospitalization periods, were significantly associated with FO in COVID-19 (Table 3).

Table 3

Blood biochemistry parameters					
Parameter	AUC, *Me* (Q_{25}; Q_{75})	p	Cut-off point	Sensitivity, %	Specificity, %
Total protein, g / l	0.687 (0.650; 0.722)	<0.001	≤60	51.0	78.6
Glucose, mmol / l	0.637 (0.599; 0.674)	0.003	>6.13	55.0	76.3
Aspartate aminotransferase, U / l	0.647 (0.610; 0.682)	0.001	>39	68.5	58.8
Urea, mmol / l	0.796 (0.764; 0.824)	<0.001	>6.75	76.0	74.1
Creatinine, μmol / l	0.592 (0.555; 0.629)	0.057	>116	31.5	94.1
Sodium, mmol / l	0.637 (0.599; 0.674)	0.005	≤139.5	56.0	73.9
C-reactive protein, mg / l	0.782 (0.744; 0.816)	<0.001	>47	66.7	81.0
Lactate dehydrogenase, U / l	0.777 (0.718; 0.828)	<0.001	>219	95.2	51.8
Albumin, g / l	0.792 (0.731; 0.844)	<0.001	≤38	89.5	62.0
D-dimer, ng / ml	0.746 (0.655; 0.823)	0.002	>731	85.7	61.2
C-reactive protein	0.862 (0.833; 0.887)	<0.001	>38	89.4	71.0
Ferritin (maximum level), μg / l	0.715 (0.666; 0.761)	0.001	>648.6	52.4	86.0
D-dimer (maximum level), ng / ml	0.792 (0.723; 0.850)	<0.001	>731.11	90.0	61.1

Risks associated with therapeutic interventions. According to the ROC analysis, duration of oxygen therapy > 3 days (AUC 0.809 (0.779; 0.837), $p < 0.001$, sensitivity 88.7%, specificity 59.7%), the need for noninvasive ventilation (NIV) for ≥ 1 day (AUC 0.700 (0.666; 0.733), $p < 0.001$, sensitivity 43.6%, specificity 96.5%), and the need for invasive mechanical ventilation (IMV) for at least 1 day (AUC 0.699 (0.665; 0.732), $p < 0.001$, sensitivity 40.3%, specificity 99.6%) were associated with FO in hospitalized patients with COVID-19. It is important to note that the need for oxygen therapy via a face mask (OR 14.97 (5.38; 41.71)), the use of NIV (OR 22.61 (11.86; 43.10)), and the use of IMV (OR 384.35 (110.59; 1335.72), $p < 0.001$) increased the odds of FO.

The use of antiviral drugs (favipiravir, umifenovir, interferon alpha-2b, interferon beta-1b, ritonavir + lopinavir) and anticoagulants during hospitalization did not demonstrate a significant effect on the outcome of COVID-19 ($p > 0.05$).

According to the ROC analysis, the need for in-hospital glucocorticoid (GCS) administration for > 1 day (AUC 0.803 (0.772; 0.831), $p < 0.0001$, sensitivity 90.3%, specificity 62.1%) and reaching a total course dose of > 6 mg for dexamethasone (AUC 0.834 (0.806; 0.860), $p < 0.0001$, sensitivity 91.9%, specificity 60.9%) were predictors of mortality. The study also found that the odds of mortality in patients with COVID-19 who required the use of GCS (OR 29 (9.00; 93.45), $p < 0.001$), interleukin-6 inhibitors (OR 7.08 (2.99; 16.78), $p < 0.001$), and Janus kinase inhibitors (OR 7.78 (2.14; 28.36), $p = 0.001$) were significantly higher than in patients who did not receive these drugs.

DISCUSSION

The age of COVID-19 patients is considered as one of the key factors associated with mortality. Thus, according to the data of a multicenter study by F. Zhou et al. [2], increased odds of in-hospital mortality were associated with older age (a median age in the deceased group was 69.0 (63.0; 76.0) years, in the survivor group –52.0 (45.0; 58.0) years ($p < 0.0001$) OR 1.10 (1.03; 1.17), $p = 0.0043$). In a study by L. Kubiliute et al. (2023), older age was an independent predictor of in-hospital mortality, associated with a 4% increase in the odds of FO per year. This has been associated with a large number of comorbidities and immunosenescence characterized by age-related defects in T- and B-cell function, which attenuate the immune response to most viruses, including SARS-CoV-2 [3, 4].

In the performed study, no significant differences were revealed in the incidence of FO in hospitalized patients with COVID-19 depending on gender. It is worth noting that previously published clinical trial data cite different results on the effect of gender on mortality rates in COVID-19. Thus, in the studies by A.C. Jain et al. (2020) and N.Ç. Başaran et al. (2022), the mortality rate in men was higher than in women [5, 6]. In contrast, other studies have found no significant effect of gender on a hospitalization outcome [7–9] and patient survival [10].

According to a systematic review by L.J. Quinton et al. (2018), pneumonia has a significant impact on the physiological processes that maintain pulmonary homeostasis, with the development of long-term negative consequences that impair health and

accelerate mortality after the end of the acute disease phase [11]. In our study, the fact of developing pneumonia in the year preceding COVID-19 increased the odds of mortality almost by 15 times.

According to published data, the risk of FO is associated with the presence of comorbid pathology in the patient [12, 13]. In this study, not only the total number of comorbidities, but also the presence of a certain pathology or groups of diseases in patients, including CHD, essential hypertension, CHF, stroke, diabetes mellitus, anemia, alcoholism, liver cirrhosis, neurological diseases, decreased GFR of < 60 ml / min / 1.73m² according to CKD-EPI, and cancer, at the time of hospitalization or in the medical history had a significant impact on the outcome of COVID-19. Our results on the role of concomitant and comorbid pathology in predicting the severity of the course and outcome of COVID-19 generally correlate with the data of other authors [14–18].

In our study, the use of antiviral drugs at the outpatient stage was associated with decreased odds of mortality from COVID-19, which did not contradict the results of several other studies [19, 20].

The analysis of patient complaints demonstrated that anosmia and headache on admission to the hospital were associated with a favorable disease outcome in patients with COVID-19. Interestingly, similar results were obtained in the study by B. Talavera et al. (2020) [21].

The development of respiratory failure and its severity in COVID-19 reflects the severity of pulmonary parenchyma damage and is associated with a disease outcome according to studies [22]. Our study demonstrated that a decrease in SpO_2 to < 94% on admission and / or to ≤ 89% throughout hospital stay was associated with FO.

To date, multiple studies have been published that consider various laboratory values as predictors of an adverse outcome. At the same time, there is a noticeable variation in the threshold values of the studied parameters. According to the results of the study by B. Cheng et al. (2019), NLR value > 3.19 (AUC 0.810 (0.732; 0.878), $p < 0.001$) and CRP > 33.4 mg / l (AUC 0.890 (0.825; 0.946), $p < 0.001$) on admission were associated with FO [23]. In the performed study neutrophil-to-lymphocyte ratio > 4.8 (AUC 0.774 (0.741; 0.804), $p < 0.0001$, sensitivity 66%, specificity 80.7%) and CRP level > 47 mg / l (AUC 0.782 (0.744; 0.816), $p < 0.001$, sensitivity 66.7%, specificity 81.0%) measured early during hospital stay were associated with an adverse outcome in COVID-19.

According to H. Ghobadi et al. (2022), who studied the role of systemic inflammatory markers, leukocyte levels > 9.05×10^9/ l (AUC 0.969 (0.960; 0.977), $p < 0.0001$, sensitivity 89.0%, specificity 95.9%), neutrophil count > 8.79×10^9 / l (AUC 0.971 (0.962; 0.978), $p < 0.0001$, sensitivity 89.8%, specificity 94.3%), and lymphocyte count < 0.91×10^9 / l (AUC 0.566 (0.543; 0.589), $p < 0.0001$, sensitivity 50.4%, specificity 61.2%) were threshold values in predicting FO in patients with COVID-19 [24]. In our study, neutrophil level > 4.57×10^9 / l (AUC 0.696 (0.660; 0.730), $p < 0.001$, sensitivity 63.8%, specificity 72.4%), lymphocyte level ≤ 1.08×10^9 / l (AUC 0.768 (0.735; 0.798), $p < 0.001$, sensitivity 70.2%, specificity 70.3%), an increase in the leukocyte count > 14.27×10^9 / l (AUC 0.855 (0.827; 0.880), $p < 0.001$, sensitivity 70.0%, specificity 90.0%), and a decrease in the lymphocyte count ≤ 0.73×10^9 / l (AUC 0.878 (0.852; 0.901), $p < 0.001$, sensitivity 85.0%, specificity 82.3%) throughout hospital stay were associated with an adverse disease outcome.

Many researchers have considered platelet count as an available biomarker associated with disease severity and a risk of mortality in COVID-19. Thus, in a study by J. Duan et al. (2020), platelet level ≤ 174×10^9 / l (AUC 0.810 (0.760; 0.850, sensitivity 100.0%, specificity 56.0%) allowed to predict progression to severe disease [25]. In our study, the platelet count ≤ 183×10^9 / l (AUC 0.673 (0.638; 0.708), $p = 0.001$, sensitivity 61.7%, specificity 71.8%) was associated with an adverse outcome.

In a study by Z. Mohammadi et al. (2022), AST elevation > than 36.5 U / l (AUC 0.374 (0.328; 0.403, sensitivity 61.9%, specificity 57.6%) was a significant predictor of in-hospital COVID-19 mortality [26]. According to A. Pitamberwale et al (2022), a serum urea concentration of ≥ 52 mg / dl (sensitivity 73.6%, specificity 60.5%) was associated with FO. Maintaining a serum albumin concentration ≥ 3.25 g / dl demonstrated significance as a predictor of survival with 76.7% sensitivity and 59.3% specificity [27]. In our study, AST level > 39 U / l (AUC 0.647 (0.610; 0.682), $p = 0.001$, sensitivity 68.5%, specificity 58.8%), blood albumin ≤ 38 g / l (AUC 0.792 (0.731; 0.844), $p < 0.001$, sensitivity 89.5%, specificity 62.0%), and urea level > 6.75 mmol / l (AUC 0.796 (0.764; 0.824), $p < 0.001$, sensitivity 76.0%, specificity 74.1%) were predictors of FO in COVID-19 patients. It is worth noting that creatinine level did not significantly affect the outcome of the disease ($p = 0.057$) according to the performed study.

In the study by E. Poggiali et al. (2020), lactate dehydrogenase (LDH) level was considered as a marker of tissue damage and a predictor of severity of acute respiratory failure in patients with fatal acute respiratory distress syndrome (ARDS). In the meantime, LDH level > 450 U / l (AUC 0.760, $p < 0.0001$) with sensitivity of 75.0% and specificity of 70.0% allowed to predict moderate and severe ARDS [28]. In our study, the predictor of an adverse outcome was LDH level on admission > 219 U / l (AUC 0.777 (0.718; 0.828), $p < 0.001$, sensitivity 95.2%, specificity 51.8%).

In the study by A. Bastug et al., D-dimer on admission ≥ 0.565 mg / l (AUC 0.896 (0.810; 0.970), $p < 0.001$, sensitivity 85.7%, specificity 80.6%) allowed to predict an unfavorable course of the disease [8]. In our study, we demonstrated that the D-dimer level (throughout hospitalization) > 731.11 ng / ml (AUC 0.792 (0.723; 0.850), $p < 0.001$, sensitivity 90.0%, specificity 61.1%) was significantly associated with FO.

The analysis of prescribed therapy for COVID-19 during the hospitalization period draws attention to the fact that using GCS > 1 day and reaching a total course dose > 6 mg for dexamethasone were associated with an adverse hospitalization outcome. The odds of FO in patients who required the use of GCS, interleukin-6 inhibitors, and Janus kinase inhibitors were significantly higher than in patients who were not prescribed these drugs. Our findings should be interpreted with caution, as these groups of drugs have been used with a limited evidence base for efficacy and safety in COVID-19 and more often in a more severe progressive course of the disease [23, 29].

In addition, according to our study, duration of oxygen therapy for more than 3 days (AUC 0.809 (0.779; 0.837), $p < 0.001$, sensitivity 88.7%, specificity 59.7%), the need for NIV for ≥ 1 day (AUC 0.700 (0.666; 0.733), $p < 0.001$, sensitivity 43.6%, specificity 96.5%), and the need for IMV for ≥ 1 day (AUC 0.699 (0.665; 0.732), $p < 0.001$, sensitivity 40.3%, specificity 99.6%) were associated with FO in hospitalized patients with COVID-19. The obtained results do not contradict the data of other authors. Thus, in a study by V.N. Gorodin et al. (2022), the duration of oxygen therapy via nasal cannulas or a face mask for more than 4.5 days significantly increased the odds of FO (length between two successive R waves (RR) 1.919 (1.308; 2.817), $p < 0.05$, sensitivity 35.7%, specificity 95.2%). The fact of using NIV as a second step of respiratory support and the duration of its use > 2 days significantly increased the risk of an adverse outcome (RR 2.276 (1.202; 4.311), $p < 0.05$, sensitivity 75.9%, specificity 66.7% and RR 2.0 (1.184; 3.377), $p < 0.05$, sensitivity 68.2%, specificity 100.0%, respectively) [30].

CONCLUSION

The results of the study allowed us to identify a number of factors and their quantitative values that were predictors of FO already at the early stage of hospitalization for COVID-19. Thus, older age, presence of comorbidities, and pneumonia in the year preceding COVID-19 played a key role among anamnestic factors. In contrast, outpatient antiviral medication reduced the risk of an adverse outcome.

When assessing physical status, severe dyspnea, diastolic and pulse pressure levels, decreased oxygen saturation on admission and throughout hospitalization, as well as the presence of moist rales and diminished breathing may be considered as potential risk factors for COVID-19.

Decreased levels of platelets, lymphocytes, and serum albumin, increased levels of leukocytes, neutrophils, neutrophil-to-lymphocyte ratio, AST, urea, LDH, CRP, D-dimer, and ferritin should be identified among the laboratory markers associated with the risk of FO.

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Malinovskiy V.A.– conception and design, collection and processing of the material, drafting of the article. Fedosenko S.V. – conception and design, drafting and editing of the article. Semakin A.V. – collection and processing of the material, drafting of the article. Dirks I.I., Semenova O.L. – collection and processing of the material. Arzhanik M.B., Agaeva S.A. – collection and processing of the material, editing of the manuscript. Vinokurova D.A. – conception and design. Starovoitova E.A., Nesterovich S.V., Kalyuzhin V.V. – conception and design, editing of the manuscript.

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