DOI: 10.56871/RBR.2024.52.14.004
UDC [578.834.1+616-036.21+616.24-002-089.168.8]-053.9

RISK FACTORS FOR ADVERSE OUTCOMES OF COVID-19 PNEUMONIA IN PATIENTS INTENSIVE CARE UNIT WITH COMORBID DISEASES

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For citation: Soloveychik EYu, Lutfarakhmanov II, Mironov PI, Kakaulin AG, Galimov II. Risk factors for adverse outcomes of COVID-19 pneumonia in patients intensive care unit with comorbid diseases. Russian Biomedical Research. 2024;9(2):31–41. DOI: https://doi.org/10.56871/RBR.2024.52.14.004

Received: 05.02.2024 **Revised: 26.03.2024** **Accepted: 20.05.2024**

Abstract. ***Introduction.*** The main risk factors for adverse outcomes in patients with COVID-19 pneumonia are age and comorbidities. For accurate risk stratification, a comprehensive dynamic assessment of clinical, laboratory, and hemodynamic factors of patients is important. ***The aim of the study*** was to assess the risk factors for the development of a lethal outcome in patients with COVID-19 pneumonia with comorbid diseases based on the analysis of time trends in clinical and laboratory characteristics. ***Materials and methods.*** A retrospective observational, multicenter study of 125 patients aged 18 to 75 years with laboratory-confirmed COVID-19 and/or ICD-10 U07.1 hospitalized with acute respiratory failure was conducted from March 2020 to May 2022. Demographic, clinical, and laboratory data of patients were recorded at the time of hospitalization and during the first 5 days of treatment. ***Results.*** In the analysis of operational characteristics and Kaplan–Meier survival curves, the age of patients >71 years, body mass index >29.8 kg/m^2, and D-dimer levels >1600 ng/mL and procalcitonin >3.4 ng/mL were statistically significantly associated with the risk of death. For two parameters (D-dimer and procalcitonin levels), the prognostic value of the temporal trend was statistically significantly higher compared to their daily values. ***Conclusion.*** The increased risk of death in patients with COVID-19 pneumonia and comorbid diseases is associated with older age and high body mass index, but not with comorbid diseases. Temporal trends in D-dimer and procalcitonin have a greater predictive value compared to their daily values.

Keywords: COVID-19, pneumonia, comorbid diseases, risk of death, temporal trends

ФАКТОРЫ РИСКА НЕБЛАГОПРИЯТНЫХ ИСХОДОВ COVID-19 ПНЕВМОНИИ У ПАЦИЕНТОВ ОТДЕЛЕНИЙ ИНТЕНСИВНОЙ ТЕРАПИИ С КОМОРБИДНЫМИ ЗАБОЛЕВАНИЯМИ

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Для цитирования: Соловейчик Е.Ю., Лутфарахманов И.И., Миронов П.И., Какаулин А.Г., Галимов И.И. Факторы риска неблагоприятных исходов COVID-19 пневмонии у пациентов отделений интенсивной терапии с коморбидными заболеваниями // Российские биомедицинские исследования. 2024. Т. 9. № 2. С. 31–41. DOI: https://doi.org/10.56871/RBR.2024.52.14.004

Поступила: 05.02.2024 **Одобрена: 26.03.2024** **Принята к печати: 20.05.2024**

Резюме. ***Введение.*** Основными факторами риска неблагоприятных исходов у пациентов с COVID-19 пневмонией являются возраст и коморбидные заболевания. Для точной стратификации риска важна комплексная

динамическая оценка клинических, лабораторных и гемодинамических факторов пациентов. ***Цель исследования*** — оценка факторов риска развития летального исхода у пациентов с COVID-пневмонией с коморбидными заболеваниями на основе анализа временных трендов клинико-лабораторных характеристик. ***Материалы и методы.*** Ретроспективное обсервационное мультицентровое исследование 125 пациентов в возрасте от 18 до 75 лет с лабораторно подтвержденным COVID-19 и/или с диагнозом U07.1 по МКБ-10, госпитализированных с острой дыхательной недостаточностью, было проведено с марта 2020 г. по май 2022 г. Критерий невключения — рефрактерный септический шок. Демографические, клинические и лабораторные данные пациентов были записаны на момент госпитализации и в первые 5 суток лечения. ***Результаты***. При анализе операционных характеристик и кривых выживаемости Каплана–Мейера возраст пациентов >71 года, индекс массы тела >29,8 кг/м^2 и уровни D-димера >1600 нг/мл и прокальцитонина >3,4 нг/мл были статистически значимо связаны с риском смерти. Для двух параметров (уровни D-димера и прокальцитонина) прогностическая величина временного тренда была статистически значимо выше в сравнении с их суточными значениями. ***Заключение.*** Увеличение риска смерти пациентов с COVID-19 пневмонией и коморбидными заболеваниями связано с пожилым возрастом и высоким индексом массы тела, но не с коморбидными заболеваниями. Временные тренды D-димера и прокальцитонина обладают большей прогностической ценностью в сравнении с их суточными значениями.

Ключевые слова: COVID-19, пневмония, коморбидные заболевания, риск смерти, временные тренды

INTRODUCTION

Main factors that contribute to risks of severe morbidity and mortality in patients with COVID-19 and COVID-19-induced pneumonia, in addition to age, are comorbid diseases such as arterial hypertension, diabetes mellitus, overweight and others [1–3, 6–9, 20].

Several large multicenter trials have examined clinical and laboratory characteristics of patients when they were admitted to an intensive care unit (ICU), where several serum biomarkers predicted adverse outcome, including elevated levels of interleukin-6, ferritin, C-reactive protein, lactate dehydrogenase, D-dimer, and fibrinogen, as well as reduced levels of antithrombin and lymphopenia [1, 5, 10, 12, 20]. A comprehensive dynamic assessment of patients' clinical, laboratory, and hemodynamic factors is important for risk stratification when implementing COVID-19 pneumonia treatment protocols. Since patients with COVID-19 pneumonia and comorbid diseases require prolonged respiratory support in ICU, the use of time trends of clinical and laboratory characteristics has been proposed to estimate survival prognosis more accurately [14].

AIM

The aim of was to evaluate risk factors for lethal outcome in ICU patients with COVID-19 pneumonia with comorbid diseases based on time trend analysis of clinical and laboratory characteristics.

MATERIALS AND METHODS

Design — a retrospective observational multicenter research was conducted on the basis of the Republican Clinical Infectious Diseases Hospital and Clinical Emergency Hospital (Ufa, Republic of Bashkortostan) from March 2020 to May 2022. The trial consecutively enrolled 130 patients aged 18 to 75 years with laboratory-confirmed COVID-19 and/or a diagnosis of U07.1 (ICD-10 (highly suspected on clinical grounds and/or confirmed by a positive real-time polymerase chain reaction with reverse transcriptase (PCR test) in nasal and pharyngeal swabs or lower respiratory tract aspirate), hospitalized in ICU with acute respiratory failure (blood oxygen saturation (SpO_2) <90% with room air or <95% with inhalation of 2 L of oxygen through nasal cannulas) for respiratory support. Criteria for non-inclusion were refractory septic shock, defined as requiring a dose of norepinephrine or equivalent above >0.1 mcg/kg per minute or the use of two or more vasopressors.

Patients' clinical data (respiratory support parameters: high-flow oxygen therapy, non-invasive and artificial lung ventilation (NIV and ALV); respiratory parameters: fraction of inhaled oxygen (FiO_2), SpO_2/FiO_2 ratio; medications: antiviral, immunomodulatory and vasoactive drugs, antibiotics, corticosteroids) were recorded in the ProMed medical information system at the time of hospitalization and then daily during the first 5 days of treatment. Patients were treated according to temporary methodological recommendations of the Russian Ministry of Health that were relevant for the period of hospitalization.

Patients who died in the first 24 hours after admission were excluded (n=5), thus 125 patients were included in the final analysis. 110 (88.0%) patients had positive PCR test results. Comorbid disease characteristics of patients with COVID-19 pneumonia are summarized in Table 1. At least 1 disease was reported in 29 patients, most commonly obesity (44.8%) or arterial hypertension (24.1%). The remaining patients had 2 to 7 (total 217) diseases, with an average of 2.26 diseases per patient. Arterial hypertension was the most common comorbid disease (54.4%), followed by heart disease (34.4%), obesity (35.2%), and diabetes mellitus (21.6%). Arterial hypertension was associated with the highest number of comorbid conditions, most commonly heart disease (33.6%), obesity, and diabetes mellitus (equally 18.1% each). Heart disease was legitimately most often accompanied by obesity (15.5%) and cardiac arrhythmia (14.6%). Obesity and diabetes mellitus were found in 9.5% of cases of comorbid diseases.

Statistical data processing was performed by using MedCalc software package (v 11.3.1.0, Belgium) in accordance with recommendations for processing results of biomedical studies. Continuous variables were presented as median and 25–75% interquartile range, categorized variables were presented as absolute values and relative frequency. Comparison of results between patient groups was performed using the Mann-Whitney U-test for nonparametric variables and Pearson's χ^2 test or Fisher's exact test for corresponding categorized variables. Kaplan-Meier survival estimates were calculated and a log-rank test was used to compare groups by survival.

RESULTS

Main vital signs and treatment modalities were monitored at the onset of the disease (Table 2).

Median duration of fever in surviving patients was 12.6 (7.8–14.5) days, and cough persisted for 17.9 (13.0–25.6) days (Figure 1). The median time from disease onset to onset of dyspnea was similar in surviving and deceased patients, with a median duration of 14.2 (8.6–17.6) days in surviving patients. Median time from onset to tracheal intubation and ventilator was 17.5 (11.9–21.0) days. Median time from dyspnea to ventilator was 7.0 (3.0–9.5) days. Median duration of respiratory support was 5 (3–19) days ranging from 1 to 70 days. Median duration of hospitalization in ICU was 7.5 (3.5–15.6) days for deceased patients and 9.4 (4.7–24.0) days for surviving patients, ranging from 3 to 73 days. Median length of hospitalization was 19.5 (10.8–44.5) days with a range of 1 to 96 days. Median time from onset to hospital discharge was 25.6 (15.2–36.0) days, and median time to death was 19.6 (9.1–30.1) days. Cumulative follow-up time from hospitalization to transfer from ICU or death was 2655 days with a median of 22.1 (11.3–32.9 days) patient-days with a range of 4 to 50 days.

A comparative analysis of main symptoms of the disease course and treatment tactics in surviving and deceased patients is presented in Figure 1.

At the time of admission to ICU, the SpO_2/FiO_2 ratio was 118.0% (63.1–172.8), and all patients required respiratory support. 65.6% of patients required high-flow oxygen therapy or NILV. Among 46 patients who required ventilator support, 38 patients eventually died. Patients initially

Table 1

Comorbid diseases of patients with COVID-19 pneumonia

Таблица 1

Коморбидные заболевания пациентов с COVID-19 пневмонией

Характеристики / Characteristics	Значения / Values
Артериальная гипертензия / Arterial hypertension, n (%)	68 (54,4)
Сахарный диабет / Diabetes mellitus, n (%)	27 (21,6)
Ожирение / Obesity, n (%)	44 (35,2)
Сердечная аритмия / Cardiac arrhythmia, n (%)	18 (14,4)
Заболевания сердца / Heart diseases, n (%)	43 (34,4)
Заболевания легких / Lung diseases, n (%)	20 (16,0)
Заболевания почек / Kidney diseases, n (%)/	9 (7,2)
Заболевания печени / Liver diseases, n (%)	12 (9,6)
Злокачественные новообразования / Malignant neoplasms, n (%)	8 (6,4)
Индекс Чарльсона, баллы / Charleson Index, points	3,1 (1,6–4,8)
Индекс Чарльсона >3 баллов / Charleson Index >3 points, n (%)	45 (36,0)

Table 2

Demographic and clinical characteristics of stratified groups of patients with COVID-19 pneumonia

Таблица 2

Демографические и клинические характеристики стратифицированных групп пациентов с COVID-19 пневмонией

Характеристики / Characteristics	Выжившие / Survival (n=55)	Умершие / Dead (n=70)	p
Пациенты / Patients, n	55	70	–
Возраст, лет / Age, years	63,0 (48,7–76,4)	72,1 (57,7–81,4)	0,001
Мужчины / Men, n (%)	27 (49,1)	37 (52,9)	Нд / Ud
ИМТ кг/м^2 / BMI, kg/m^2	29,1 (23,4–34,8)	27,1 (22,2–32,0)	0,037
Одышка / Dyspnea, n (%)	52 (94,5)	65 (92,8)	Нд / Ud
Кашель / Cough, n (%)	52 (94,5)	67 (95,7)	Нд / Ud
Лихорадка / Fever, n (%)	50 (90,9)	67 (95,7)	Нд / Ud
Площадь поражения легких начальная / Initial area of lung damage, %	39,3 (19,3–59,3)	46,8 (21,8–71,8)	Нд / Ud
Площадь поражения легких / Final area of lung damage, %	64,9 (47,1–82,7)	62,0 (41,7–82,3)	Нд / Ud
Положительный ПЦР-тест / Positive PCR test, n (%)	52 (94,5)	58 (82,9)	0,048
Медикаменты / Medicines, n (%)			
Противовирусные / Antiviral	47 (85,5)	54 (77,1)	Нд / Ud
Моноклональные антитела / Monoclonal antibodies	13 (23,6)	20 (26,7)	Нд / Ud
Глюкокортикостероиды / Glucocorticosteroids	55 (100,0)	62 (88,6)	0,010
Мочегонные / Diuretics	31 (56,4)	40 (57,1)	Нд / Ud
Антикоагулянты / Anticoagulants	51 (92,7)	67 (89,3)	Нд / Ud
Гипотензивные / Hypotensive	32 (58,2)	45 (64,3)	Нд / Ud
Антибиотики / Antibiotics	55 (100,0)	61 (87,1)	0,006
Лечебные мероприятия, n (%)			
Респираторная поддержка / Respiratory support	47 (85,4)	35 (50,0)	0,001
ИВЛ / MV	8 (14,5)	35 (50,0)	0,001
Вазопрессорная поддержка / Vasopressor support	19 (34,5)	21 (28,0)	Нд / Ud
Нутритивная поддержка / Nutritional support	31 (56,4)	52 (69,3)	Нд / Ud

Note: Ud — unreliable differences; BMI — body mass index; MV — mechanical ventilation; PCR — polymerase chain reaction.
Примечание: ИВЛ — искусственная вентиляция легких; ИМТ — индекс массы тела; нд — недостоверные отличия; ПЦР — полимеразная цепная реакция.

receiving respiratory support in the form of non-invasive lung ventilation had a statistically significant lower risk of death than patients initially receiving ventilator support: relative risk (RR) 0.82; 95% CI 0.72–0.95; p=0.010. Patients who initially received respiratory support by NILV followed by a switch to ventilator had a statistically significant higher risk of death compared to patients whose respiratory support was limited to NILV: OR 1.49; 95% CI 1.23–1.78; p=0.010. The mortality of patients with subsequent ventilator support was similar to patients who received ventilator support from the beginning of hospitalization: OR 1.18; 95% CI 0.75–1.33; p=0.120. 80.8% of patients received antiviral drugs, 92.8% of patients received antibiotic therapy, 26.4% of patients received monoclonal antibodies, and 93.6% of patients received corticosteroids. Time median from onset of illness to treatment was 9.9 (82–17.4) days for surviving patients receiving antiviral drugs.

Table 3 presents time trends consisting of 23 parameters over the course of hospitalization in stratified patient groups.

Baseline lymphocyte levels were roughly equal in surviving and deceased patients at onset; surviving patients had the lowest lymphocyte levels on day 7–8 after onset and returned to normal during hospitalization, whereas

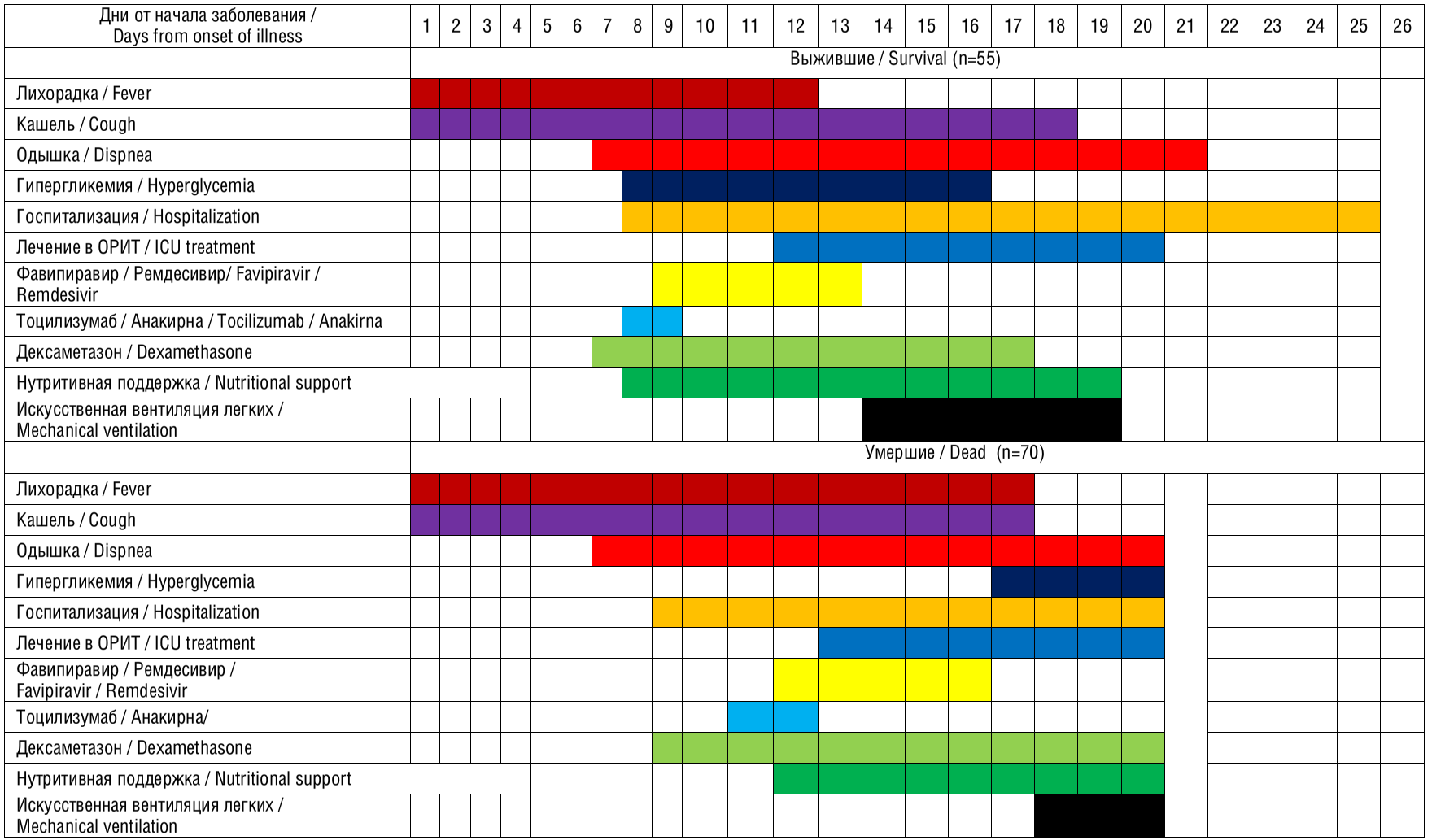

Fig. 1. Clinical course of the main symptoms and treatment tactics of stratified groups of patients with COVID-19 pneumonia and comorbid diseases. ICU — intensive care unit

Рис. 1. Клиническое течение основных симптомов и тактики лечения стратифицированных групп пациентов с COVID-19 пневмонией и коморбидными заболеваниями. ОРИТ — отделение реанимации и интенсивной терапии

eISSN 2658-6576

Table 3

Time trends of the vital characteristics of stratified groups of patients with COVID-19 pneumonia

Таблица 3

Временные тренды жизненно важных характеристик у стратифицированных групп пациентов с COVID-19 пневмонией

Показатели / Indicators	Выжившие / Survival (n=55)			Умершие / Dead (n=70)			p
	Госпитализация / Hospitalization	Перевод в ОРИТ / ICU transfer	Начало ИВЛ / Start MV	Госпитализация / Hospitalization	Перевод в ОРИТ / ICU transfer	Начало ИВЛ / Start MV	
САД, мм рт.ст. / MAP, mm Hg	95,0 (83,7–106,3)	93,8 (74,8–112,8)	87,8 (72,1–103,5)	95,1 (85,1–105,1)	96,2 (83,6–108,8)	89,6 (71,8–107,4)	Нд / Ud
ЧСС, мин / RR, min	89,7 (75,2–104,2)	86,2 (72,8–99,6)	92,6 (72,5–112,7)	87,4 (76,0–98,8)	84,4 (70,3–98,5)	85,9 (69,7–102,1)	Нд / Ud
ЧДД, мин / HR, min	23,4 (20,9–25,9)	25,2 (22,6–27,8)	28,1 (23,0–33,2)	23,3 (20,3–26,3)	23,8 (20,6–27,0)	25,4 (20,8–30,0)	Нд / Ud
Температура тела / Body temperature, °C	37,4 (36,7–38,1)	36,9 (36,3–37,5)	36,9 (36,2–37,6)	37,3 (36,6–38,0)	36,9 (36,5–37,3)	36,6 (35,9–37,3)	Нд / Ud
SpO_2/FiO_2	177,4 (164,1–190,4)	115,2 (67,6–162,8)	90,4 (76,3–104,5)	174,8 (158,4–191,2)	120,8 (58,7–182,9)	90,0 (76,7–103,3)	Нд / Ud
Гемоглобин, г/л / Hemoglobin, g/l	125,8 (100,4–151,2)	119,8 (93,7–145,9)	115,0 (89,5–140,5)	124,2 (96,8–151,2)	123,4 (99,9–157,0)	114,1 (87,9–140,3)	Нд / Ud
Эритроциты, × 10^6/мкл / Erythrocyte, ×10^6/vcl	4,2 (3,3–5,1)	3,9 (3,1–4,7)	3,9 (3,0–4,7)	4,2 (3,4–5,0)	4,1 (3,3–4,9)	3,9 (3,0–4,8)	Нд / Ud
Лейкоциты, ×10^3/мкл / Leukocyte, ×10^3/vcl	8,4 (4,2–12,6)	11,6 (5,6–17,6)	14,7 (6,1–23,3)	8,9 (3,3–14,5)	12,5 (5,1–19,9)	15,5 (4,2–26,8)	Нд / Ud
Лимфоциты, ×10^3/мкл / Lymphocyte, ×10^3/mcl	1,15 (0,35–1,95)	0,83 (0,20–1,46)	0,90 (0,15–1,65)	1,03 (0,37–1,69)	0,66 (0,06–1,24)	0,68 (0,14–1,22)	Нд / Ud
Нейтрофилы, ×10^3/мкл / Neutrophils, ×10^3/mcl	8,4 (7,4–9,3)	8,8 (7,9–9,7)	8,5 (7,3–9,7)	8,1 (6,8–9,4)	8,4 (7,5–9,4)	8,6 (7,6–9,6)	Нд / Ud
Тромбоциты, ×10^3/мкл / Platelets, ×10^3/mcl	194,1 (100,5–187,7)	216,2 (103,1–329,3)	193,6 (78,5–308,7)	202,4 (112,2–292,6)	214,7 (111,2–318,2)	206,0 (94,5–317,5)	Нд / Ud
СОЭ, мм/час / ESR, /mm/h	37,8 (21,9–53,7)	42,6 (11,4–73,8)	31,9 (9,9–53,9)	33,4 (14,2–52,6)	31,9 (15,7–48,1)	27,4 (9,3–45,5)	Нд / Ud
Глюкоза, ммоль/л / Glucose, mmol/l	9,1 (3,7–14,5)	9,3 (4,6–14,0)	10,2 (6,7–15,7)	8,4 (4,8–12,0)	8,2 (4,4–12,0)	10,2 (2,1–18,3)	Нд / Ud
Натрий, ммоль/л / Sodium, mmol/l	139,2 (131,4–147,0)	139,8 (132,4–209,6)	143,2 (132,7–153,7)	138,1 (131,7–144,5)	138,5 (133,1–143,9)	141,6 (133,5–149,7)	Нд / Ud
Калий, ммоль/л / Potassium, mmol/l	4,4 (3,3–5,5)	4,3 (3,6–5,0)	4,7 (3,4–6,0)	4,6 (3,4–5,8)	4,2 (3,3–5,1)	4,7 (3,2–6,2)	Нд / Ud
Креатинин, мкмоль/л / Creatinine, mcmol/l	107,5 (29,7–185,3)	101,1 (32,6–209,6)	118,5 (60,7–220,2)	87,9 (42,6–133,2)	82,7 (32,7–147,6)	101,0 (58,0–198,0)	Нд / Ud
Билирубин, мкмоль/л / Bilirubin, mcmol/l	8,9 (3,2–15,0)	10,6 (4,9–26,3)	12,4 (7,0–25,5)	12,5 (3,2–32,2)	10,4 (6,0–24,8)	8,6 (3,9–14,3)	0,004
АЛТ, Ед/л / ALT, un/l	35,3 (16,5–54,1)	39,0 (12,8–65,2)	42,7 (10,3–85,2)	33,4 (17,1–59,7)	39,8 (12,7–66,9)	52,9 (13,8–102,0)	Нд / Ud
АСТ, Ед/л / AST, un/l	53,6 (17,8–89,4)	54,1 (12,5–105,7)	64,1 (18,5–99,7)	54,7 (10,2–99,2)	63,9 (13,9–150,0)	62,9 (11,7–107,2)	Нд / Ud
МНО / INR	1,1 (0,9–1,3)	1,2 (1,0–1,4)	1,3 (0,9–1,7)	1,2 (0,8–1,6)	1,2 (0,9–1,5)	1,3 (0,7–1,9)	Нд / Ud

Ending of the table 3 / Окончание табл. 3

Показатели / Indicators	Выжившие / Survival (n=55)			Умершие / Dead (n=70)			p
	Госпитализация / Hospitalization	Перевод в ОРИТ / ICU transfer	Начало ИВЛ / Start MV	Госпитализация / Hospitalization	Перевод в ОРИТ / ICU transfer	Начало ИВЛ / Start MV	
АЧТВ, сек / APTT, sec	33,9 (25,1–42,7)	33,8 (25,3–42,3)	36,5 (19,7–53,3)	32,6 (24,1–41,1)	34,4 (18,6–50,2)	33,7 (20,2–47,2)	Нд / Ud
Фибриноген, г/л / Fibrinogen, g/l	5,2 (4,1–6,3)	4,8 (3,4–6,2)	4,1 (2,8–5,4)	4,7 (3,5–5,9)	4,7 (3,1–6,3)	3,5 (2,2–4,8)	Нд / Ud
D-димер, нг/мл / D-dimer, ng/ml	1409 (365–3154)	1506 (419–2993)	1532 (1249–2782)	2453 (773–4133)	1850 (424–3274)	3031 (1759–4303)	0,001
Белок, г/л / Protein, g/l	62,6 (50,4–74,8)	57,3 (68,4–66,2)	50,9 (43,2–58,6)	66,3 (59,0–73,6)	59,0 (50,4–67,6)	54,0 (45,3–62,7)	Нд / Ud
Альбумин, г/л / Albumen, g/l	32,5 (26,4–38,6)	28,6 (24,0–33,2)	26,2 (20,4–32,0)	32,8 (26,1–39,5)	30,5 (24,4–36,6)	29,4 (24,8–34,0)	Нд / Ud
Прокальцитонин, нг/мл / Procalcitonin, ng/ml	2,7 (0,7–8,1)	1,7 (0,9–5,5)	2,8 (0,8–8,8)	2,8 (0,8–6,7)	5,6 (2,2–17,9)	11,2 (4,5–17,9)	Нд / Ud
СРБ, мг/л / CRP, mg/l	101,7 (15,1–188,3)	98,9 (14,4–193,4)	97,3 (24,3–153,9)	123,5 (23,2–245,9)	106,9 (17,6–196,2)	118,1 (12,2–234,0)	Нд / Ud

Note: ALT — alanine aminotransferase; AST — aspartate aminotransferase; APTT — activated partial thromboplastin time; CRP — C-reactive protein; ESR — erythrocyte sedimentation rate; HR — heart rate; ICU — intensive care unit; INR — international normalized ratio; MAP — mean arterial pressure; MV — Mechanical ventilation; RR — respiratory rate; ud — unreliable differences; FiO_2 — fraction of inspired oxygen; SpO_2 — blood oxygen saturation.
Примечание: АЛТ — аланинаминотрансфераза; АСТ — аспартатаминотрансфераза; АЧТВ — активированное частичное тромбопластиновое время; ИВЛ — искусственная вентиляция легких; МНО — международное нормализованное отношение; нд — недостоверные отличия; ОРИТ — отделение реанимации и интенсивной терапии; САД — среднее артериальное давление; СОЭ — скорость оседания эритроцитов; СРБ — С-реактивный белок; ЧДД — частота дыхательных движений; ЧСС — частота сердечных сокращений; FiO_2 — фракция вдыхаемого кислорода; SpO_2 — сатурация крови кислородом.

lymphopenia without dynamics was observed in deceased patients. D-dimer levels were clearly elevated in deceased compared to surviving patients throughout the clinical course and increased as the course of the disease worsened. In deceased patients, procalcitonin levels increased rapidly from day 7–8 after disease onset, whereas CRP levels decreased from day 12 of illness in surviving patients. Daily values of three parameters (respiratory rate, erythrocyte sedimentation rate, and total bilirubin) were statistically significantly associated with a lower risk of death. The prognostic value of time trend was statistically significantly higher for two parameters (D-dimer and procalcitonin levels) compared with their daily values.

ROC-analysis of multiple clinical and laboratory parameters of heart, lung, kidney, liver and blood coagulation system at the time of hospitalization was performed. Only age >71 years, BMI >29.8 kg/m^2, D-dimer levels >1600 ng/mL and procalcitonin levels >3.4 ng/mL were strongly associated with the risk of death (Table 4). At the same time, the degree of comorbidity severity (Charlson index) almost did not determine the outcome of the disease.

Assessment of Kaplan-Meier survival curves showed statistically significantly lower survival in elderly patients with higher BMI. Moreover, they had higher levels of biomarkers (Table 5).

DISCUSSION

Clinical and laboratory parameters, as well as outcomes of consecutively hospitalized patients with comorbid diseases who had severe acute respiratory failure associated with COVID-19 pneumonia were described in the research. In order to identify risk factors for death, daily values and time trends of 23 clinical and laboratory parameters associated with acute organ dysfunction, blood coagulation disorders, and inflammatory response during the first 5 days of treatment and their relationship with mortality were analyzed. The majority of patients were hospitalized in ICU due to acute hypoxemic respiratory failure, which required respiratory support ranging from high-flow oxygen therapy to ventilator support. Overall mortality amounted to 56.0%, reaching 81.4% in patients on ALV. 34.4% of patients required ALV, which was consistent with previously published data ranging from 15 to 71%. The rate of NIVL use was 65.6% which appeared to be higher than previously cited rates varying from 14 to 62% [8, 12, 15, 18, 20].

Table 4

Operational characteristics of ROC-analysis

Таблица 4

Операционные характеристики ROC-анализа

Характеристики / Characteristics	Точка разделения / Cut of point	Площадь под ROC-кривой / AUG ROC	95% ДИ / CI	p
Возраст, лет / Age, year	71	0,69	0,61–0,78	0,001
ИМТ, кг/м^2 / BMI, kg/m^2	29,8	0,61	0,51–0,69	0,047
Индекс Чарльсона, баллы / Charleson Index, points	3	0,57	0,48–0,66	0,154
Кортикостероиды, сутки назначения / Corticosteroids, daily prescription	8	0,80	0,69–0,85	0,001
D-димер, нг/мл / D-dimer, ng/ml	1600	0,62	0,53–0,70	0,023
Прокальцитонин, нг/мл / procalcitonin, ng/ml	3,4	0,57	0,48–0,66	0,099

Note: CI — confidence interval; IBM — body mass index.
Примечание: ДИ — доверительный интервал; ИМТ — индекс массы тела.

Table 5

Comparison of Kaplan–Meier survival curves

Таблица 5

Сравнение кривых выживаемости Каплана–Мейера

Характеристики / Characteristics	OP / OR	95% ДИ / CI	Величина p / Magnitude p
Возраст >71 года / Age >71 years	2,83	1,75–4,58	0,001
ИМТ >29,8 кг/м^2 / BMI >29.8 kg/m^2	1,60	1,07–2,66	0,044
Индекс Чарльстона >3 баллов / Charleson Index >3 points	1,35	0,69–2,64	0,310
Кортикостероиды >8 суток назначения / Corticosteroids >8 days of prescription	3,67	2,24–6,00	0,001
Д-димер >1600 нг/мл / D-dimer >1600 ng/ml	2,09	1,16–3,78	0,010
Прокальцитонин >3,4 нг/мл / Procalcitonin >3.4 ng/ml	2,19	1,24–3,89	0,003

Note: CI — confidence interval; IBM — body mass index; OR — odds ratio.
Примечание: ДИ — доверительный интервал; ИМТ — индекс массы тела; ОР — отношение рисков.

Our cohort trial identified several clear adverse outcome factors in patients with COVID-19 pneumonia and comorbid conditions. Among them there were age older than 71 years, BMI greater than 29.8 kg/m^2, levels of D-dimer greater than 1600 ng/mL and procalcitonin greater than 3.4 ng/mL. These factors were associated with higher risks of in-hospital mortality. It has been previously reported that older age is an important independent predictor of mortality in SARS and MERS [4, 11]. Our findings confirm that patient mortality was particularly high among elderly males. The median age of patients hospitalized in ICU was 69.0 (59.7–79.2) years, indicating that older age is a risk factor.

Two parameters of risk factors for death showed a statistically significant greater difference in time trends between surviving and deceased patients than their daily value. Thus, it confirms the data that changes in clinical parameters during the first days of treatment differ between surviving and deceased patients and that the dynamics of variables during treatment are more relevant than their daily value at the time of patient hospitalization [13, 16, 17, 19]. A strong association between the risk of death and a biomarker of coagulation system dysfunction was found.

The influence of D-dimer time trend levels in relation to the risk of death exceeded the daily value of this parameter on any day of measurement. Many clinical and laboratory parameters of organ failure and inflammatory response, which were recorded at the time of hospitalization of patients, were greater in deceased patients, and these differences increased in the course of treatment. Thus, early and timely detection of the time trend of the most threatening parameters at the time of hospitalization may help to reduce organ damage and optimize treatment. At the same time, there was no relationship between the degree of comorbidity severity and the risk of developing lethal

outcome. There are several limitations in the study. Data on pre-existing comorbid conditions were obtained from the medical information system, hence their severity was not assessed. Considering a difficult study period, not all laboratory tests were performed in all patients, including lactate dehydrogenase and serum ferritin, so their role in predicting unfavorable outcome may be underestimated. Interpretation of results may be limited by a small sample of patients. A larger sample may help to determine prognostic values of predictors of adverse outcomes such as hospitalization in ICU, ALV or death.

CONCLUSION

1. Increased risk of death in patients with COVID-19 pneumonia and comorbid diseases was associated with older age (OR 2.83; 95% CI 1.75–4.58; p=0.001) and high BMI (OR 1.60; 95% CI 1.07–2.66; p=0.044), but not with comorbid diseases.

2. Time trends of clinical and laboratory parameters associated with acute organ dysfunction or systemic inflammation such as high levels of D-dimer (OR 2.09; 95% CI 1.16–3.78; p=0.010) and procalcitonin (OR 2.19; 95% CI 1.24–3.89; p=0.003), have greater prognostic value compared to their daily single rates.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

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

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

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