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Clinical Characteristics and Factors Associated with Poor Outcomes in Hospitalized Patients with Novel Coronavirus Infection COVID-19

Aim To evaluate the clinical picture and factors associated with unfavorable outcomes in admitted patients with COVID-19.

Material and methods This study included all patients admitted to the COVID Center of the National Research Center of Cardiology of the Russian Ministry of Health Care from May 1 through May 31, 2020. Clinical demographic, laboratory, and instrumental indexes and associated factors were studied with one-way and multivariate logistic regression analysis.

Results This study included 402 patients aged 18 to 95 years (mean age, 62.9±14.6 years); 43.0% of them were older than 65 years. COVID-19 was frequently associated with chronic comorbidities, including arterial hypertension (74.4%), obesity (41.6%), history of ischemic heart disease (12.9%), atrial fibrillation (18.9%), type 2 diabetes mellitus (DM) (13.0%), and oncological diseases (9.2%). 13.0% of patients were smokers; less than 10% had chronic lung diseases. 3.9% of patients had a combination of COVID-19 and acute coronary pathology, including acute myocardial infarction (MI) in 3.2% (13) and unstable angina in 0.7% (3). The most frequent clinical manifestation of COVID-19 were four symptoms: cough (81.1%), weakness (80.3%), shortness of breath (71.6%), and fever (62.7%). 46.5% of patients had shortage of breath and chest pain/compression, 40.3% had headache, 31.1% had myalgia, 28.8% had anosmia, and 25.5% had ageusia. Arterial oxygen saturation was <93.0% in 55.7% of cases. According to laboratory blood tests the patients had anemia (58.2%), lymphopenia (34.8%), neutropenia (19.2%), thrombocytopenia (11.9%), and increased levels of high-sensitivity C-reactive protein (hsCRP, 87.3%), interleukin-6 (89.3%), ferritin (62.1%), and D-dimer (49.2%). 56.2% of patients required various regimens of oxygen support. 83 (20.6%) patients were admitted to intensive care and resuscitation units; invasive artificial ventilation was performed only for 34 (8.5%) patients. In-hospital mortality was 7.7% (31/402). One-way regression analysis identified major factors associated with death during the stay in the hospital: age >55 years, NEWS scale score >4.0, oxygen saturation <92.0%, blood glucose >5.4 mmol/l, hs-CRP >25.7 mg/l, and creatinine clearance <72.0 ml/min. Furthermore, the risk increased with increasing degree of changes in each factor. According to results of the multivariate regression analysis, three most significant predictors of the hard endpoint, all-cause death during the stay in the hospital, were more than 5-fold increases in aspartate aminotransferase and/or alanine aminotransferase compared to normal levels (relative risk (RR) 16.8 at 95% confidence interval (CI) 5.0–56.3, p<0.001), pronounced changes in the lungs consistent with a CT-4 picture as shown by computed tomography (CT) (RR 13.4; 95% CI 3.9–45.5, p<0.001), and MI/unstable angina during the stay in the hospital (RR 11.3; 95% CI 1.4–90.6, p=0.023). The probability of death was also considerably increased by chronic obstructive pulmonary disease, impaired kidney function (creatinine clearance estimated by Cockcroft-Gault <60.0 ml/min), type 2 DM, oncological diseases, and dementia.

Conclusion This study established factors associated with unfavorable outcomes in admitted patients with COVID-19. This will allow identifying in advance patients with a high risk of complications that require increased attention to take more active diagnostic and therapeutic measures at prehospital and hospital stages.

Keywords COVID-19; clinical characteristics; comorbidities; outcomes; death

For citation Boytsov S. A., Pogosova N. V., Paleev F. N., Ezhov M. V., Komarov A. L., Pevzner D. V. et al. Clinical Characteristics and Factors Associated with Poor Outcomes in Hospitalized Patients with Novel Coronavirus Infection COVID-19. Kardiologiia. 2021;61(2):4–14. [Russian: Бойцов С. А., Погосова Н. В., Палеев Ф. Н., Ежов М. В., Комаров А. Л., Певзнер Д. В. и др. Клиническая картина и факторы, ассоциированные с неблагоприятными исходами у госпитализированных пациентов с новой коронавирусной инфекцией COVID-19. Кардиология. 2021;61(2):4–14]

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ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1532

Introduction

In December 2019, the World Health Organization (WHO) was notified of an outbreak of pneumonia of unknown origin in Wuhan, the People's Republic of China (PRC) [1]. The new disease, which is currently known as the novel coronavirus disease (COVID-19), rapidly spread across countries, becoming a pandemic that threatens the world. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes the disease, is highly contagious and able to cause complications such as bilateral COVID-19 associated pneumonia with the development in some cases of acute respiratory distress syndrome (ARDS), thrombosis, acute respiratory failure, multiple-organ-system failure, and death [2]. The COVID-19 attack rate is very high. Thus, within six months from the first reports of the outbreak in Wuhan, more than 10 million people had become infected and 500 thousand had died [3]. As of December 1, 2020, the WHO reported more than 61.8 million confirmed cases of COVID-19 and more than 1.4 million deaths worldwide, covering 220 countries. By this date, more than 2.2 million cases of COVID-19 had been confirmed and almost 40 thousand deaths registered in the Russian Federation [4].

Huang et al. [5] were the first to report on 41 laboratory-confirmed cases of infection by the novel coronavirus with COVID-19-associated pneumonia. Typical clinical manifestations of the disease were fever, low-productive cough, myalgia or weakness, dyspnea; routine blood tests showed normal or low lymphocyte count; computed tomography (CT) of the lungs had signs of pneumonia (bilateral in 98% of cases); almost a third (30.0%) of patients developed a severe complication in the form of ARDS.

There is evidence that the elderly and patients with chronic conditions such as cardiovascular diseases (CVDs) and diabetes mellitus (DM) are most vulnerable to the development of COVID-19 and associated adverse outcomes. For example, an analysis of more than 72 Chinese cases of COVID-19 showed that mortality in hospitalized patients with CVDs and DM was 10–15% and 7.3%, respectively, compared to the overall mortality of 2.3% [6].

Familiarity with COVID-19 on the part of the medical community has had less than two years to develop. As new information about the disease is accumulated, changes in approaches to treatment are embodied in national and international guidelines [7–10]. However, it must be acknowledged that, since neither the nature of the disease nor its peculiarities as concerning different populations and patients with comorbid and concomitant diseases are yet fully understood, consistent approaches to the treatment of COVID-19 are in the process of development. In this regard, it is essential to analyze the experience of different countries and individual healthcare facilities in the struggle against the 21st-century version of the plague. In April 2020, the Russian National Cardiology Research Center was converted into a temporary COVID care center. The center had all the necessary facilities to provide medical care to such patients, including enough intensive care beds, mechanical ventilators and a complete complement of medicines following then-existing guidelines [8].

Objective

Assess the clinical picture and factors associated with adverse outcomes in COVID-19 inpatients.

Material and methods

A register of inpatients of the COVID care center was created under the Russian National Cardiology Research Center. Patients were delivered by first aid professionals working at the A. S. Puchkov City Ambulance and Emergency Care Station. The register includes all patients without exception admitted from May 1, 2020 to May 31, 2020, i.e., during the peak of incidence of the novel coronavirus disease in Moscow that took place in the spring of 2020 [10].

A total of 402 patients COVID-19 were included in the study. COVID-19 was diagnosed based on virus (causative agent) verification using the qualitative determination of the SARS-CoV-2 RNA in the oropharyngeal swab by a real-time polymerase chain reaction (before or after admission to the center) in 64.2% of patients. COVID-19-associated lung injury was detected using CT in other patients having a typical clinical pattern using the standard protocol with no intravenous contrast enhancement. All patients underwent CT examination, the majority in the COVID-19 care center, while a smaller percentage of patients were examined within a 24-hour period prior to hospitalization.

Physical examination, laboratory tests, and clinical investigations, classification of bilateral COVID-19-associated pneumonia based on CT findings (from CT-1 to CT- 4), assessment of COVID-19 severity using the NEWS (National Early Warning Score) score, and treatment were carried out following the Interim Guidelines of the Russian Ministry of Health «Prevention, Diagnosis, and Treatment of the Novel Coronavirus Disease (COVID-19)» version 6 dated 28/04/2020 [8]. CT-1 was established with no more

than 3 ground-glass opacities (GGO, <3 mm in the maximum diameter) and <25% lung parenchyma involvement; CT-2 with more than 3 such lesions (<5 mm in the maximum diameter) and 25–50% lung parenchyma involvement; CT-3 with multiple GGOs and consolidation lesions, 50–75% lung parenchyma involvement; the presence of diffuse ground glass and consolidation opacities in combination with reticular opacities and >75% lung parenchyma involvement corresponded to CT-4.

The present article presents demographic and clinical characteristics of COVID-19 patients (including complaints, clinical and laboratory findings), analysis of concomitant pathologies, including CVDs and cardiovascular risk factors, major treatment approaches, and outcomes of the disease.

Factors associated with adverse outcomes (endpoints 1–4) were studied. Endpoint 1 is the need for invasive and non-invasive ventilation (nasal oxygenation, high-flow oxygenation, CPAP, mask ventilation, helmet-based ventilation) in surviving patients. Endpoint 2 (hard) is all-cause death. Endpoint 3 (secondary composite) included all-cause death and non-fatal atherothrombotic complications, such as acute myocardial infarction (MI), unstable angina, and cerebral strokes. Endpoint 4 (secondary composite) included all-cause death and venous thrombosis, such as pulmonary embolism (PE) and lower-extremity deep vein thrombosis.

Statistical processing of all obtained data was performed using the Python programming language v^3.8. The distribution pattern of the quantitative variables was assessed using the Shapiro–Wilk test. If the distribution was normal, the mean and standard deviation were determined, while if the distribution was non-normal, median, 25th and 75th percentiles were calculated. The percentage and absolute numbers were determined for the categorical and qualitative variables. The comparative analysis for the normally distributed quantitative variables was performed using the Welch's t-test; for non-normal distribution, the Mann-Whitney U-test was used. The comparative analysis of categorical and qualitative indicators was carried out using a two-tailed Fisher's exact test.

Differences observed between the groups of patients with or without endpoints during the hospital stay in terms of several indicators were included in a univariate logistic regression analysis. Cox regression analysis was used to assess the effects of factors on in-hospital mortality. Relative risk (RR) and 95% confidence intervals (CI) were calculated following adjustment for sex and age. The effects of factors on other endpoints were assessed using logistic regression with an odds ratio (OR) and 95% CI. Multivariate logistic regression analysis was performed after sex and age adjustment using the step-by-step inclusion of variables. In the comparison and regression analyses, differences were considered to be statistically significant at $p<0.05$.

Results

The register comprises 402 patients with COVID-19 at ages ranging from 18 to 95 years (mean age 62.9±14.6 years; median age 63.0 [54.0; 73.0] years), of whom 173 (43%) of patients were older than 65; there were a roughly equal number of male and female patients, i.e., 212 (53%) and 190 (47%), respectively. The median hospital stay of COVID-19 patients was 14.0 days (minimum 1 day, maximum 34 days).

The combination of COVID-19 with comorbid chronic diseases, including CVDs and cardiovascular risk factors, was typical (Table 1). The most common comorbidities were arterial hypertension (AH) (74.4% of patients) and obesity (41.6%). The most frequent heart rhythm disorder was atrial fibrillation (AF) in almost every fifth patient. The percentage of smokers was 13.0%, which was the same proportion of patients who had type 2 DM. One in ten patients had a history of exertional/rest angina; 12.9% – of MI. 10.0% had undergone myocardial revascularization, 8.4% had peripheral atherosclerosis, while 14.9% had a history of heart failure. Cerebrovascular pathologies such as a history of MI or transient ischemic attacks were registered in 7.7% of cases. It should be noted that 16 (3.9%) patients had a combination of COVID-19 and acute coronary pathology – specifically, a history of MI and unstable angina experienced in 13 (3.2%) and 3 (0.7%) patients, respectively. Most patients were admitted for suspected acute MI or acute coronary syndrome, as was confirmed later. Ten (2.5%) patients underwent emergency percutaneous coronary revascularization with stenting.

Chronic bronchopulmonary pathology (bronchial asthma (n=3.2%), chronic obstructive pulmonary disease (COPD, n=7.0%)) was not as frequent in patients with COVID-19 as expected. At the same time, a relatively high (9.2%) prevalence of cancers was, to a certain extent, due to organizational reasons, such as the transfer of 12 patients with recurrent cancers from other hospitals due to the detection of COVID-19. Of the 37 cancer patients, 17 (45.9%) individuals had recurrences.

Clinical manifestations and severity of COVID-19 are described in Table 2.

ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1532

Table 1. Clinical and demographic characteristics, cardiovascular risk factors, and concomitant diseases in COVID-19 inpatients (n=402)

Indicator	Value
Male/female	53% (212)/47% (190)
Age, years	63.0 [54.0; 73.0]
Age>65 years old	43.0% (173)
Cardiovascular risk factors, history of cardiovascular and other diseases/conditions	
Smoking	13.0% (47/362)
Obesity (BMI ≥ 30.0 kg/m^2)	41.6% (160/385)
Arterial hypertension	74.4% (299)
Diabetes mellitus type 2	13.0% (53)
Angina pectoris	10.2% (41)
Myocardial infarction	12.9% (52)
History of PCI/CABG	8.0% (32)/2.0% (8)
Atrial fibrillation	18.9% (76)
Heart failure	14.9% (60)
Peripheral atherosclerosis	8.4% (32)
History of brain stroke/TIA	7.2% (29)/0.5% (2)
Deep vein thrombosis, history of PE	2.7% (11)
Chronic kidney disease	9.7% (39)
Gout	2.0% (8)
Dementia	4.7% (19)
Chronic obstructive pulmonary disease	7.0% (28)
Bronchial asthma	3.2% (13)
Cancers,	9.2% (37)
including relapses	4.2% (17)
Comorbid diseases/conditions during the hospital stay	
Acute myocardial infarction	3.2% (13)
Unstable angina	0.7% (3)
PCI during the hospital stay	2.5% (10)
Brain stroke (ischemic)	0.2% (1)
Deep vein thrombosis, PE	1.2% (5)

Data are presented as % (n) or the median [25th percentile; 75th percentile]. BMI – body mass index; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; TIA – transient ischemic attack; PE – pulmonary embolism.

The vast majority (more than 60.0%) of patients with symptomatic COVID-19 had the following four symptoms: cough (most often dry, nonproductive), weakness, dyspnea, and fever. About half of patients complained of air hunger and chest pain/tightness. Headache (40.3%) and myalgia (31.1%) were also relatively frequent complaints. Anosmia (impairment or loss of smell) and ageusia (loss of taste) were less frequent, occurring in 28.8% and 25.5% of cases, respectively. Other symptoms often associated with COVID-19, such as nasal congestion or mild rhinorrhea, nausea, vomiting, stomach pains, skin rash, were observed in a minority of patients.

Some patients had severe hypoxemia (down to 45.0%), while median oxygen saturation was 91.5 [87.0, 95.0%]; in more than half (55.7%) of inpatients, oxygen saturation was below 93.0%. The total clinical severity (NEWS) was 5.0 [3.0; 7.0], with 184 (45.8%) patients having an individual severity score of more than 5.0. The maximum pulmonary tissue injury on CT was 95.0%, median 50.0 [27.5; 70.0] %, while the maximum pulmonary tissue injury due to COVID-19 associated pneumonia (ground glass±consolidation opacities) corresponding to the CT-1, CT-2, CT-3 and CT-4 grades were detected in 16.5, 31.7, 34.7 and 10.0% of patients, respectively. Decreased kidney function was frequent: almost half of patients had creatinine clearance (Cockroft – Gault) <80 L/min, while 28.1% had <60.0 mL/min. Significantly increased levels of lactic dehydrogenase (LDH), aspartate transaminase (AST) and alanine transaminase (ALT) turned out to be typical of COVID-19 (> 60.0% of patients).

Attention should be paid to the very high (58.2%) incidence of anemia in the hospitalized COVID-19 patients. Lymphocytopenia was observed in more than a third of patients (34.8%), while every fifth (19.2%) patient had neutropenia and every tenth (11.9%) – thrombocytopenia. The hs-CRP levels, which reflect inflammatory activity, were significantly increased in the absolute majority (87.3%) of in-patients; the median was 53.2 [25.8; 133.0] mg/L, while the maximum was 437.3 mg/L. The increased levels of other markers of acute inflammation were also common, e.g., interleukin-6 (IL-6) (maximum level 324,400.0 pg/mL) and ferritin (maximum 40,000 μg/L) were elevated in 89.3% and 62.1% of the 149 patients included in the analysis, respectively. Every other (49.2%) patient with COVID-19 had increased D-dimer levels (maximum of 12,846.0 ng/mL), indicating thrombotic activation typical of this disease.

As mentioned above, patients were treated following the Interim Guidelines of the Russian Ministry of Health «Prevention, Diagnosis and Treatment of the Novel Coronavirus Disease (COVID-19) in force as of May 2020 [8]. Drug treatment included hydroxychloroquine (75.1% of patients), lopinavir/ritonavir (24.1%), azithromycin (65.9%), interferon (interferon beta-1b; 17.2%) (Table 3). IL-6 inhibitors (26.9%), selective JAK-kinase inhibitors (6.5%), and glucocorticoids (21.9%), mainly dexamethasone, were ordered for patients with moderate to severe COVID-19 and high markers of inflammation (hs-CRP, IL-6, ferritin)

Table 2. Clinical manifestations, laboratory findings, and severity of COVID-19 in hospitalized patients (n=402)

Indicator	Value
Clinical symptoms	
Cough	81.1% (319)
Weakness	80.3% (323)
Dyspnea	71.6% (288)
Fever >37.5°C	62.7% (252)
Maximum body temperature,°C	38.1 [37.1; 38.7]
Air hunger	46.5% (187)
Chest pain/compressing pain	46.5% (187)
Headache	40.3% (162)
Myalgias	31.1% (125)
Anosmia	28.1% (113)
Loss of taste	24.9% (100)
Diarrhea	24.1% (97)
Sputum	22.6% (91)
Throat pain/irritation	14.7% (59)
Decreased appetite	10.7% (43)
Rhinorrhea	9.0% (36)
Nausea/vomiting	8.2% (33)
Hemoptysis	2.7% (11)
Stomach pain	2.5% (10)
Skin symptoms	0.5% (2)
Respiratory function. lung injury, and severity	
Respiratory rate. maximum	24.0 [20.0; 28.0]
Breathing rate>23.0 movements per minute	54.5% (219)
SpO_2 minimum, %	91.5 [87.0; 95.0]
SpO_2<93.0%	55.7% (224)
Severity. NEWS score, maximum	5.0 [3.0; 7.0]
NEWS score>5.0	45.8% (184)
CT lung injury, maximum. %	50.0 [27.5; 70.0]
Lung injury degree: • CT-0 • CT-1 • CT-2 • CT-3 • CT-4 (maximum)	 7.2% (29) 16.5% (66) 31.7% (127) 34.7% (139) 10.0% (40)

Indicator	Value
Laboratory values that are most different possible from the references during the hospital stay	
Hemoglobin, g/dL	12.1 [11.0; 13.3]
Anemia (Hb <13.0 g/dL in males. <12.0 g/dL in females)	58.2% (234)
WBC count, 10^9/L	7.5 [5.8; 10.8]
Neutrophil count.,10^9/ L <1.9×10^9/ L	4.0 [2.8; 5.8] 19.2% (77)
Lymphocyte count, 10^9/ L <0.9×10^9/ L	1.1 [0.7; 1.6] 34.8% (140)
Platelet count, 10^9/ L <130.0×10^9/ L	181.0 [139.2; 231.0] 11.9% (48)
Creatinine clearance (Cockcroft-Gault equation) <60.0 mL/min	80.5 [57.0; 111.4] 28.1% (113)
Albumin, g/L <34 g/L	39.0 [36.0; 42.0] 14.2% (57)
LDH, U/L > 220 U/L	295.0 [221.0; 384.0] 64.7% (260)
AST, U/L > 34 U/L	49.0 [32.0; 84.0] 70.6% (284)
ALT, U/L > 40 U/L	54.0 [30.0; 101.0] 62.7% (252)
hs-CRP, mg/L > 5 mg/L	53.2 [25.8; 133.0] 87.3% (351)
IL-6, pg/mL > 7 pg/mL	63.8 [20.5; 350.5] 89.3% (133/149)
Ferritin, μg/L >400.0 μg/L	642.0 [281.4;1023.0] 62.1% (105/169)
D-dimer, ng/mL > 355.0 ng/mL	351.0 [209.0; 835.8] 49.2% (175/356)

Data are presented as % (n) or the median [25th percentile; 75th percentile]. SpO_2, oxygen blood saturation; IL-6, interleukin-6.

with normal levels of procalcitonin (<0.05 ng/mL). Such IL-6 inhibitors as netakimab, tocilizumab and sarilumab that demonstrated the greatest efficacy in stopping the cytokine storm were used. Selective JAK-kinase inhibitors baricitinib, tofacitinib and ruxolitinib were used.

The majority of patients without contraindications, including active bleeding, severe thrombocytopenia, etc., received parenteral anticoagulant low-molecular-weight heparin (most often enoxaparin) or unfractionated heparin. It should be noted that 59.2% and 38.3% of patients received preventive and therapeutic doses of anticoagulants, respectively. If the initial treatment was oral anticoagulant (e.g., in AF), this drug was temporarily replaced in most cases with a parenteral anticoagulant in a therapeutic dose, given the fewer drug interactions with COVID-19 treatments. The use of anticoagulants in different dosage forms and doses and the relevant side effects will be discussed in a separate publication.

For the most severe patients with COVID-19 and signs of cytokine storm, who did not respond to drug therapy, extracorporeal hemocorrection was used, including cytokine adsorption, selective plasma filtration, hemodialysis, hemofiltration and hemodiafiltration. A total of 31 procedures were performed in 23 patients. Most patients underwent extracorporeal hemocorrection combined with a sequential connection of cytokine adsorption and selective plasma filtration columns, which allowed a wider range of inflammation mediators to be eliminated. Selective plasmofiltration was the first-line treatment for patients with sepsis or septic shock.

ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1532

Table 3. Management of COVID-19 inpatients (n=402)

Drug treatment	Value
Hydroxychloroquine	75.1% (302)
Lopinavir/ritonavir	24.1% (72)
Azithromycin Antibiotics, 2 and more	65.9% (265) 41.8% (166)
Interferon	17.3% (69)
IL-inhibitors	26.9% (108)
JAK kinase inhibitors	6.5% (26)
Glucocorticoids	21.9% (88)
Anticoagulants (low-molecular-weight heparin. non-fractionated heparin): • preventive dose • treatment dose	98.5% (396) 59.2% (238) 38.3% (126)
Non-drug treatment	
Oxygen support, any	56.2% (226)
Nasal oxygenation	20.4% (82)
High-flow nasal oxygenation	16.4% (66)
CPAP, mask ventilation, helmet-based ventilation	10.9% (44)
Invasive ventilation	8.5% (34)
Extracorporeal hemocorrection	5.7% (23)

The data are expressed as % (n).
IL, interleukin; CPAP, continuous positive airway pressure.

In hospital, 20.6% (83/402) of patients stayed in intensive care units. The management of patients in the center included the broadest possible use of various non-invasive oxygen support methods, such as nasal oxygenation (up to 20 L/min), high-flow oxygenation (30–60 L/min), CPAP, mask ventilation and helmet-based ventilation in the prone position. Only 34 (8.5%) patients received invasive ventilation. Most patients, including those in intensive care units, performed breathing exercises supervised by physical therapists, which demonstrated positive clinical effects; those in general wards additionally did some therapy training.

Outcomes and relevant factors thereto

The hospital prognosis for COVID-19 patients was relatively serious. The frequency of endpoints 1–4 is shown in Figure 1.

The need for invasive and non-invasive ventilation (nasal oxygenation, high-flow oxygenation, CPAP, mask ventilation, helmet-based ventilation) in survivors (endpoint 1) accounted for 53.0% (197/371) of cases.

The in-hospital mortality rate (endpoint 2) was 7.7% (31/402). The most severe complications were: ARDS 9.5% (38), sepsis 4.5% (18), acute cardiovascular failure 7.0% (28), acute renal failure 4.2% (17), multiple organ system failure 4.2% (17), acute MI 3.2% (13), unstable angina 0.7% (3), ischemic stroke 0.2% (1), PE 0.2% (1), lower extremity deep vein thrombosis 1.0% (4), bleeding 7.0% (28).

Endpoint 3 (composite secondary), which included all-cause death and non-fatal atherothrombotic complications, such as acute MI, unstable angina, stroke, was reported in 11.9% of patients.

Endpoint 4 (composite secondary), which included all-cause death and non-fatal venous thrombotic complications, such as PE and lower extremity deep vein thrombosis, was established in 8.9% of cases.

Univariate regression analysis was used to study many factors that could be associated with the hard endpoint, i.e., in-hospital death. The most significant factors were an age of ≥55 years, a NEWS score of ≥4.0, oxygen saturation <92.0%, glucose level >5.4 mmol/L, hs-CRP >25.7 mg/L and creatinine clearance <72 mL/min. Table 4 clearly demonstrates that the risk of mortality increases as the severity of these factors increases. For example, with a NEWS score of 4.0–6.0, the risk of all-cause death increases 4.7-fold; with NEWS 7.0–8.0, it is 7.8-fold; while with NEWS 9.0–18.0, the risk increase is 10-fold.

Based on the univariate regression analysis results, factors were selected to be included in the multivariate regression models of the endpoints. Age and sex adjustments were made. The results are presented in Table 5.

The need for invasive and non-invasive ventilation (nasal oxygenation, high-flow oxygenation, CPAP, mask ventilation, helmet-based ventilation) in surviving

Figure 1. Percentage of patients who reached endpoints 1–4 during hospital stay

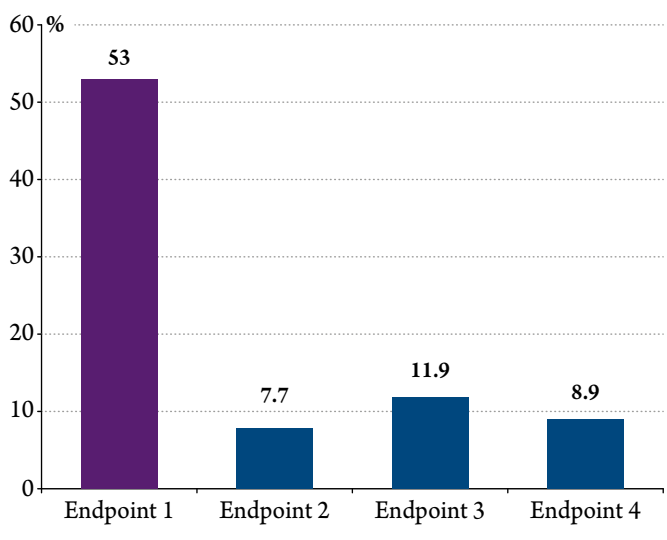

Table 4. Factors associated with fatal outcomes according to the univariate regression analysis (n=402)

Indicator	Quartiles	RR	95% CI	p
Age, years	18; 54*	0.11	0.02–0.83	0.032
	55; 63	8.85	1.20–65.07	0.032
	64; 73	9.84	2.99–32.38	< 0.001
	74; 95	6.44	3.03–13.71	< 0.001
NEWS score	0.0; 3.0*	0.10	0.01–0.76	0.026
	4.0; 6.0	4.66	1.10–19.74	0.036
	7.0; 8.0	7.84	2.36–26.07	0.001
	9.0; 18.0	10.78	4.37–26.61	<0.001
SpO_2, %	45.0; 87.0	8.44	3.41–20.84	<0.001
	88.0; 91.0	1.10	1.04–1.25	<0.001
	92.0; 95.0	0.10	0.02–0.42	0.002
	96.0; 100.0*	0.32	0.04–2.34	0.260
Glucose, mmol/L	3.6; 5.4*	0.20	0.05–0.84	0.028
	5.5; 6.2	5.16	1.23–21.66	0.025
	6.3; 8.1	7.86	2.38–26.00	0.001
	8.2; 24.0	4.57	4.57–27.52	<0.001
hs-CRP, mg/L	0.3; 25.7*	0.15	0.02–1.09	0.061
	25.9; 53.0	7.04	0.95–51.98	0.056
	53.5; 132.6	23.51	3.19–173.25	0.002
	133.0; 437.3	4.74	2.19–10.26	<0.001
Creatinine clearance, mL/min	15.0; 48.9	11.36	5.06–25.53	<0.001
	49.0; 72.7	10.60	3.70–30.31	<0.001
	72.8; 90.8	0.06	0.02–0.16	<0.001
		0.20	0.05–0.84	0.028

RR, relative risk; CI, confidence interval;
*, reference quartiles; SpO_2, oxygen blood saturation;
hs-CRP, highly sensitive C-reactive protein.

COVID-19 patients was two times higher in AH and glucose levels >6.1 mmol/L, three times higher in severe lung injury (CT-3) and lymphocytopenia, almost four times higher with the severity corresponding to NEWS >5.0 at admission, 21 times higher with hs-CRP >5 mg/L.

The three most significant predictors of the hard endpoint (all-cause death during hospital stay) were more than 5 fold increase in the levels of AST and/or ALT compared to the normal values (RR 16.8; 95% CI 5.0–56.3; p<0.001), CT-4 lung injury (OR 13.4; 95% CI 3.9–45.5; p<0.001), and MI/unstable angina during hospital stay (RR 11.3; 95% CI 1.4–90.6; p=0.023). The probability of death was also significantly increased by COPD, decreased kidney function (creatinine clearance by Cockroft – Gault <60.0 mL/min), type 2 DM, cancer and dementia.

The main factors predisposing to the onset of endpoint 3 (all-cause death + non-fatal acute MI, unstab-

Table 5. Independent predictors of adverse outcomes in hospitalized patients with COVID-19 according to the multivariate regression analysis

Indicator	OR	95% CI	p
Endpoint 1. **Different oxygen support modes**			
Arterial hypertension	2.0	1.1–3.6	0.025
Glucose >6.1 mmol/L	2.2	1.3–3.7	0.002
Lymphocytopenia<0.9×10⁹/L	2.8	1.6–4.9	<0.001
Lung injury CT-3	2.8	1.4–5.4	0.004
NEWS score at admission >5.0	3.8	1.7–8.2	0.001
hs-CRP>5.0 mg/L	21.1	4.8–92.1	<0.001
Endpoint 2. **All-cause mortality**			
Age>65 years	5.7	1.8–18.1	0.003
Elevated AST and/or ALT >5 norm	16.8	5.0–56.3	<0.001
Lung injury CT-4	13.4	3.9–45.5	<0.001
MI, UA during hospital stay	11.3	1.4–90.6	0.023
COPD	5.4	1.4–20.5	0.014
Creatinine clearance* <60 mL/min	4.5	1.4–14.0	0.010
DM type 2	3.9	1.2–12.3	0.023
Cancers	4.9	1.6–15.5	0.006
Dementia	8.4	1.9–36.5	0.005
Endpoint 3. **All-cause death + MI, unstable angina, stroke**			
History of MI	5.8	2.5–13.7	<0.001
Elevated AST and/or ALT >5 norm	6.9	2.6–18.0	<0.001
AF, persistent	3.9	1.3–11.8	0.018
DM type 2	2.9	1.2–7.1	0.018
Gout	6.9	1.3–36.7	0.024
Dementia	4.1	1.2–13.8	0.023
Lung injury CT-4	2.8	1.1–7.7	0.039
Lymphocytopenia<0.9×10⁹/L	2.3	1.1–4.9	0.030
Endpoint 4. **All-cause death + PE, lower extremity deep vein thrombosis**			
Albumin <34.0 g/L	2.8	1.0–7.7	0.040
Age>65 years	3.5	1.1–10.9	0.034
Creatinine clearance* <80 mL/min	5.3	1.6–17.7	0.006
Lymphocytopenia>11.0×10⁹/L	6.1	2.1–17.2	0.001
Elevated AST/ALT >5 norm	8.1	2.4–27.2	0.001
SpO_2<93.0%	16.7	2.9–141.9	0.010
Gout	82.6	5.9–1162.4	0.001

OR – odds ratio; RR – relative risk; CI – confidence interval;
CT – computed tomography; hs-CRP – high-sensitivity C-reactive protein; AST – aspartate transaminase; ALT – alanine transaminase; UA – unstable angina; COPD – chronic obstructive pulmonary disease; * – Cockropht-Gault equitation; DM – diabetes mellitus; MI – myocardial infarction; AF – atrial fibrillation; SpO_2 – oxygen blood saturation.

ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1532

le angina and MI) were a history of MI with an almost 6-fold risk (OR 5.8, 95% CI 2.5–13.7, p<0.001); persistent AF – a 4-fold risk (OR 3.9; 95% CI 1.3–11.8; p=0.018) and type 2 DM (OR 2.9; 95% CI 1.2–7.1; p=0.018), as well as 5-times higher levels of AST and/or ALT, lymphocytopenia, gout, dementia and lung injury corresponding to CT-4.

Finally, endpoint 4 (all-cause death + nonfatal venous thromboembolic complications) was most likely in patients with COVID-19 older than 65 years with low oxygen saturation <93.0% (OR 16.7; 95% CI 2.9–141.9; p=0.010), impaired renal function (creatinine clearance <80.0 mL/min), leukocytosis (>11.0×109/L), more than 5-times elevated levels of AST and/or ALT, low levels of albumin (<34.0 g/L) and gout.

Thus, several factors proved to be very significant predictors of multiple endpoints in hospitalized patients with COVID-19. Those included a more than 5-fold increase in AST and/or ALT levels, type 2 DM, hyperglycemia and lung injury (CT-3/CT-4). Gout was also a significant factor. Although there were only 8 patients with gout, which explains an extended 95% CI, the predictive value of this factor was very high due to the development of adverse outcomes in most patients with this disease (high-flow oxygen support was required in 2 cases and 4 patients died).

Discussion

In this study, we analyzed clinical characteristics, findings of laboratory tests and clinical investigations, drug treatment and other treatment approaches, outcomes and other relevant factors, in 402 inpatients with COVID-19.

Our register included a roughly equal number of male and female patients, which is consistent with the work by Zhang et al. [11] and differs from findings of some Chinese [5] and US colleagues [12] who reported a predominance of males among hospitalized patients. A significant percentage (43.0%) of our patients were older 65 years, and the median age was 63.0 [54.0; 73.0] years. According to the US authors, 199 patients with COVID-19 hospitalized between February 27, 2020 and April 2, 2020 in 12 hospitals in New York City had a similar mean age of 65, and the mean age of the deceased patients was 75 years [13]. Older patients are likely to be more vulnerable to COVID-19, both due to having more comorbidities and possible aging of immunity [14]. A study conducted in the UK [15] with more than 10 thousand patients showed a nearly linear correlation between age and the risk of death following COVID-19. Our findings (Table 4) also clearly show an increasing risk of death with older age of inpatients with COVID-19, starting at 55.

In their systematic review and meta-analysis of 7 studies and 1,576 patients, Yang et al. showed that AH, DM, CVDs of atherosclerotic origin, as well as respiratory diseases, were the most common concomitant pathologies in COVID-19 [16]. A high prevalence of AH (56.6%), obesity (41.7%) and DM (33.8%) was also established in a large, multicenter US hospital register [13]. According to our data, 74.4% of patients with COVID-19 had AH, 41.6% had obesity; both type 2 DM and smoking were reported in 13.0% of patients. One in ten patients had a history of exertional/rest angina, MI and myocardial revascularization, while almost every fifth patent had AF and 14.9% of patients had heart failure. In some of our patients, COVID-19 was combined with acute coronary pathology: acute MI was diseased in 13 (3.2%) patients during the hospital stay; 3 (0.7%) patients had unstable angina. AH and atherosclerosis are believed to interfere with the vessel structure, thus increasing the probability of complications in COVID-19 [7]. The frequent combination of COVID-19 and metabolic disorders (DM, obesity) has been shown in many studies [12, 17, 18]. Metabolic disorders are likely to be accompanied by a weakening of immune response due to malfunction of macrophages and lymphocytes, which can cause complications in COVID-19 [17].

The vast majority (more than 60.0%) of patients with symptomatic COVID-19 had the following four symptoms: cough (most often nonproductive), weakness, dyspnea, and fever. About half of patients complained of air hunger air and chest pain/tightness. Anosmia and ageusia were less frequent (28.8% and 25.5% of cases, respectively). This data is consistent with the reports of other clinics [15, 19]. Other symptoms associated with COVID-19, such as nasal congestion or mild rhinorrhea, nausea, vomiting, stomach pains and skin rash, were observed in a minority of our patients. According to Li et al. [17], headache, dizziness, nausea and vomiting were reported in 4–12% of cases, while some Chinese authors [11] reported a much higher incidence (39.6%) of intestinal symptoms.

A significant percentage of patients in our study experienced severe hypoxemia during hospital stay: oxygen saturation was less than 93.0% in more than half (55.7%) of patients. Italian authors described similar symptoms: median oxygen saturation of 93.0 [60; 99%], fever >37.5°C in 67.5% of patients [20]. The total clinical severity (NEWS) was 5.0 [3.0; 7.0], while 184 (45.8%) patients had an individual severity score of more than 5.0. It should be noted that COVID-19

is often insidious. Some patients presented with minor pulmonary tissue injury experienced sudden dramatic clinical deterioration with lung injury progression on CT despite proactive treatment. The maximum pulmonary tissue injury to CT findings during hospital stay was 95.0%; CT-3 and CT-4 grades were established in 34.7% and 10.0% of patients, respectively. Typical signs of COVID-19 associated pneumonia were observed in most patients (92.9%). Similar results were found in other studies. For example, Zhang et al. [11] reported that 89.6% of patients had ground-glass opacities on CT.

According to the literature, COVID-19 is characterized by the following laboratory signs: lymphocytopenia, increased levels of D-dimer, hs-CRP, and other markers of inflammation, decreased albumin, as well as deviations in various indicators of renal function (increased creatinine, decreased creatinine clearance) and liver function (increased levels of AST, ALT, LDH) [13, 21], which is consistent with our findings. For example, the levels of hs-CRP that reflect the inflammatory activity were significantly increased in most of our patients (87.3%). An increase in other markers of acute inflammation, e.g., IL-6 (89.3%) and ferritin (62.1%), was also common. We observed increased D-dimer levels that indicate thrombotic activation typical of COVID-19 in almost half of the patients (49.2%). Renal (Cockcroft-Gault creatinine clearance less than 60.0 mL/min in 28.1% of cases) and liver malfunction, such as marked increases in LDH, AST and ALT in more than 60.0% of patients, were also typical.

According to the New York Register [13], 14.2% of patients required intensive care; in our center, the corresponding figure was 20.6%. At the same time, we used invasive ventilation less frequently in patients with COVID-19 than our US colleagues (8.5% vs. 12.2%, respectively).

However, it should be noted that the in-hospital prognosis for COVID-19 patients was relatively serious. Invasive and non-invasive ventilation (nasal oxygenation, high-flow oxygenation, CPAP, mask ventilation, helmet-based ventilation) was required by a significant percentage (56.2%) of our patients. In-hospital mortality (hard endpoint) was 7.7%. The cumulative rate of fatal outcomes and non-fatal atherothrombotic complications (acute MI, unstable angina, stroke) was 11.9%, while the cumulative rate of fatal outcomes and non-fatal PE involving lower extremity deep vein thrombosis was 8.9%. This demonstrates the important role of coagulation disorders and cardiovascular pathologies in the development of possible complications of COVID-19.

According to our univariate regression analysis, which covered many factors potentially associated with the hard endpoint (in-hospital death), the following are the main predictors: age ≥55 years, NEWS score ≥4.0, oxygen saturation <92.0%, glucose >5.4 mmol/L, hs-CRP >25.7 mg/L, and creatinine clearance <72.0 mL/min. Table 4 clearly demonstrates that the risk of death increases as the severity of these factors increases.

By means of multivariate logistic regression, a comprehensive assessment the likelihood of the hard endpoint was carried out. The three most significant predictors of all-cause death during hospital stay were a more than 5 fold increase in the levels of AST and/or ALT compared to the normal values (RR 16.8; 95% CI 5.0–56.3; p<0.001), CT-4 lung injury (OR 13.4; 95% CI 3.9–45.5; p<0.001) and acute MI/unstable angina during hospital stay (RR 11.3; 95% CI 1.4–90.6; p=0.023). The probability of death was also significantly increased by COPD, decreased kidney function (creatinine clearance by Cockroft–Gault <60.0 mL/min), type 2 DM, cancer and dementia.

Similar conclusions were reached by Ciceri et al. [20]. The main predictors of death in COVID-19 patients are age, the presence of severe lung injury according to CT, coronary artery disease, cancer and lymphocytopenia.

Chinese researchers developed an original risk assessment score for COVID-19 inpatients, which included the most significant predictors of life-threatening complications, including age, severe changes in lung CT, dyspnea, number of comorbidities and a history of cancer [22].

Meanwhile, a recent study by Petrilli et al. [23], including 5,279 patients with severe COVID-19, identified low oxygen saturation (<88.0%) and high levels of hs-CRP and D-dimer to be the main factors increasing the risk of life-threatening complications and death. According to a large multicenter Spanish study of 4,034 patients with COVID-19 with 28.0% in-hospital mortality, 17 factors were identified as independent predictors of death, the most significant factors being age, low oxygen saturation and glomerular filtration rate, elevated hs-CRP, and cirrhosis [24]. Data of a retrospective analysis of 3,987 patients in 33 US and European hospitals (28.6% mortality) used to create a COVID-19 mortality stratification score showed that age, low oxygen saturation (≤93.0%), as well as elevated levels of hs-CRP, urea and creatinine were the most significant predictors of death [25].

ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1532

According to the systematic analysis of 14 studies and 4,569 patients carried out by Tian et al. [26], the likelihood of death in COVID-19 patients increases significantly in the presence of AH (OR 2.5, 95% CI 2.1–3.1, p<0.00001), coronary artery disease (OR 3.8, 95% CI 2.1–6.9, p<0.00001) and DM (OR 2.0, 95% CI 1.7–2.3; p<0.00001), elevated levels of hs-CRP, IL-6, troponin, D-dimer, creatinine, ALT, and low albumin levels. We found that AH, hyperglycemia, elevated hs-CRP, marked changes in lung CT (CT-3), NEWS >5.0 at admission and lymphocytopenia were independent predictors of the need for various forms of oxygen support (invasive and non-invasive ventilation) in COVID-19 patients. At the same time, a history of MI, persistent AF, type 2 DM, lung injury (CT-4), significantly increased levels of ALT and AST, lymphocytopenia, dementia and gout increase the risk of composite endpoint, including all-cause death, acute MI, unstable angina and stroke. Interestingly, our study gout established as an independent predictor. This may attract other researchers' attention and require further studies in this direction.

Conclusion

In conclusion, the presented analysis is important from both scientific and clinical points of view. Identifying factors closely associated with the adverse course and outcomes of COVID-19 will allow physicians to proactively identify patients at a high risk of developing complications that require increased attention, including more proactive diagnostic and treatment interventions. Treatment approaches briefly described in this article were applied in the Russian National Cardiology Research Center, including the administration of glucocorticoids, IL-6 inhibitors, JAK-kinase inhibitors, low-molecular-weight- and non-fractionated heparin in combination with different non-invasive oxygen support (nasal oxygenation, high-flow oxygenation, CPAP, mask ventilation, helmet-based ventilation). In the most severe patients, extracorporeal hemocorrection and early intensive care activities resulted in low rates of in-hospital mortality (compared to the European and US rates). Despite the significant burden of comorbidities, including acute coronary artery diseases and recurrent cancers, most COVID-19 patients recovered leading to their discharge. Long-term follow-up of the discharged patients is underway, with results to be presented at a later date.

Acknowledgements

The authors thank for the assistance in organization of the registry the National Medical Research Center of Cardiology, especially M.A. Matveeva, E.S. Kropacheva, Yu.A. Fedotkina, O.N. Svirida, N.M. Abduzhamalova, A.M. Aleevskaya, G.K. Arutyunyan, O.S. Bulkina, N.S. Zhukova, M.V. Kostyukevich, T.S. Sukhinina, D.V. Ognerubov, O.A. Fomicheva, A.M. Shariya, O.O. Shakhmatova, P.S. Novikov, V.V. Lopukhova, E.V. Smolyakova, A.B. Popova, D.R. Mindzaev, A.R. Denisova, T.V. Fofanova, T.E. Kolmakova, N.S. Kurochkina, R.A. Zhetisheva, T.A. Teteryan, A.A. Safiullina.

No conflict of interest is reported.

The article was received on 19/01/2021

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ISSN 0022-9040. Kardiologiia. 2021;61(2). DOI: 10.18087/cardio.2021.2.n1532