

3. Merzhina E.A., Myasnikov R.P., Kulikova O.V. [et al.] Nekompaktnaya kardiomiopatiya levogo zheludochka: osobennosti klinicheskogo techeniya i vozmozhnosti diagnostiki [Non-compact left ventricular cardiomyopathy: clinical features and diagnostic possibilities]. Racional'naya farmakoterapiya v kardiologii [Rational Pharmacotherapy in Cardiology. 2015; 11 (6): 638-642 (In Russ.).]
4. Benjamin MM 1, Khetan RA, Koval RC, Schussler JM. Diagnosis of left ventricular non-compaction by computed tomography. Proc (Bayl Univ Med Cent) 2012;25(4):354-6.
5. Chin T.K., Perloff J.K., Williams R.G. Isolated noncompaction of left ventricular myo-

cardium: a study of eight cases. Circulation 1990;82:507-13.

6. Engerding R., Yelbuz T. M., Breithardt G. Isolated noncompaction of the left ventricular myocardium – a review of the literature two decades after the initial case description. Clin. Res. Cardiol. 2007; 96(7):481-8.
7. Ichida F., Tsubata S., Boweis K. Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome. Circulation. 2001;103: 1256-64.
8. Jenni R., Oechslin E., Schneider J. et al. Echocardiographic and pathanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a dis-

trict cardiomyopathy. Heart 2001;86:666-71.

9. Nugent A.W., Daubeney P.F., Chondros P. et al. The epidemiology of childhood cardiomyopathy in Australia. N. Engl. J. Med. 2003; 348: 1639-46.
10. Oechslin E.N., Attenhofer Jost C. H., Rojas J. R. et al. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 2000;36:493-500
11. Stöllberger C, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. Am J Cardiol 2002;90:899-902.

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THROMBOTIC COMPLICATIONS ASSOCIATED WITH THE NOVEL CORONAVIRUS INFECTION COVID-19

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We present a clinical case of a fatal thrombotic complication in a patient with coronavirus disease 2019 (COVID-19) in the recuperative period. A retrospective analysis of the patient's medical records with the chronology of laboratory and instrumental examinations, clinical course and intensive therapy was performed. The algorithm of pulmonary embolism (PE) diagnosis, validity and decision-making concerning thrombolytic therapy and extracorporeal membrane oxygenation are shown. The results of autopsy are also presented, which confirmed the diagnosis of PE and the appropriateness of medical interventions.

Keywords: COVID-19, recuperation period, myocarditis, thrombotic complications, pulmonary embolism, acute respiratory failure, artificial ventilation, extracorporeal membrane oxygenation.

Introduction. Covid-associated severe thrombotic complications develop in 17% of patients with coronavirus disease 2019 (COVID-19) and are one of the main causes of patient's death [1, 2].

Thrombosis is observed more often in people with severe course of the disease, with large area of lung lesions [4], in elderly patients, as well as in patients with severe comorbid conditions [7]. At the

same time, the probability of thrombotic complications persists in patients for several months after COVID-19, which is a serious threat and explains the need to control the hemostasis system and to continue anticoagulant therapy after the patient is discharged from the hospital.

We present a clinical case of COVID-associated pulmonary embolism (PE) in the recuperative period in a young female patient without comorbid conditions, and 16% of lungs affected by COVID-19.

The **aim** of the investigation was to analyze the clinical course of and intensive therapy interventions in severe thrombotic complication in a patient with COVID-19.

Clinical observation. Patient M., female, 36 years old. On February 24, 2022 at 18:40 she was delivered by the ambulance to the Republican Hospital №1-National Center of Medicine (RHN №1-NCM) with the referral diagnosis: "Viral myocarditis? Opulent pericarditis. Bilateral polysegmental pneumonia. COVID-19 reconvalescent since February 19, 2022."

The patient complained of generalized weakness and palpitations up to 112 beats/min, elevated blood pressure (BP) up to 150/80 mmHg, dyspnea on minimal physical exertion, bilateral lower legs

edema. On physical examination: height 164 cm, weight 74 kg (body mass index 27.5). General condition of the patient was severe. Patient was alert (15 points on the Glasgow Coma Scale (GCS)) and oriented. The skin was of normal color, normal moisture, turgor was preserved. Visible mucous membranes of normal color and moisture. Body temperature was 36.1°C. Breathing unlabored, without the involvement of auxiliary muscles. On auscultation – breathing was conducted in all pulmonary fields, with increased intensity, symmetrical on both sides, no rales. Respiratory rate (RR) 18-20 breaths/min, SpO₂ - 89% on room air and 94% when insufflating 5 L/min of humidified oxygen. Cardiac tones muffled, rhythmic. BP -121/69 mmHg, heart rate (HR) 101/min. The tongue was clean and moist. The abdomen was not swollen, symmetrical, soft and painless on palpation. The liver and spleen were not enlarged. Intestinal peristalsis was active, uniform. No meteorism. No peripheral edemas. Diuresis, according to the patient, was sufficient.

It is known from the anamnesis that she considers herself sick since January 29, 2022, when she began to feel generalized weakness, vomiting, liquid stools up to 5 times a day. The patient

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called a doctor, PCR result was negative for COVID-19. Taking into account the epidemiological situation, antiviral medications (umifenovir, grippferon) were prescribed, which was a recommended treatment plan according to the 14th version (relevant at the time of presentation) of the Provisional Guidelines of Prevention, Diagnosis and Treatment of Novel Coronavirus Infection (COVID-19) released by Ministry of Health of Russian Federation [1]. The patient's condition remained without improvement. On 31.01.2022, a PCR test returned negative for COVID-19. At the same time, an enzyme immunoassay for COVID-19 showed the presence of IgG 3.0 BAU/ml, with no IgM. All this time the patient's body temperature remained up to 37.2°C. On February 7, 2022, computed tomography (CT) of the chest revealed multiple foci of ground glass opacities in both lungs with up to 10% affected on the right and up to 3% on the left and a high probability of bilateral COVID-19-associated interstitial pneumonia (CT-1). The patient was admitted to the infectious disease unit on February 08, 2022, where she was treated until February 18, 2022. According to the patient, after her discharge she had palpitations, shortness of breath, BP increase to 160/80 mmHg. The patient is known to have had several episodes of syncope on 20 February 2022, and did not seek medical help. On February 24, 22, the patient consulted her general practitioner with the above complaints. Echocardiography revealed 3.0 cm dilated right ventricle (RV), pressure in RV was 42 mmHg, 1st degree regurgitation on mitral valve (MV), 1st degree on tricuspid valve (TV), 1st degree on pulmonary artery valve. End-diastolic dimension (EDD) 4.0 cm, end-systolic dimension (ESD) 2.4 cm, ejection fraction (EF) 67%. Traces of fluid in the pericardial cavity: along the anterior wall of the RV up to 0.4 cm, in the area of the apex 0.8 cm. No local hypo- and akinesis were detected. Patient was referred to the Republican Hospital №1-National Center of Medicine (RHN №1-NCM) immediately.

Diagnosis was made following initial survey: "Subacute viral diffuse myocarditis. Exudative pericarditis. Chronic heart failure with preserved ejection fraction (66%), Functional class 2 by New York Heart Association (NYHA) classification. Bilateral multisegmental pneumonia, moderate severity, 1st degree respiratory failure. Post-COVID syndrome. COVID-19 reconvalescent since 19th February 2022."

Taking into account the severity of her condition due to respiratory failure, the

need for oxygen therapy, hemodynamic control, the patient was immediately transferred from the Emergency department to the Cardiac Intensive Care Unit (CICU), where treatment for myocarditis and multisegmental pneumonia was initiated. Antibiotic therapy, anticoagulant, anti-inflammatory, cardioprotective therapy and correction of electrolyte disorders were prescribed.

On February 25, 2022, the patient's condition stabilized, clinical improvement was observed: complaints of dyspnea, palpitation, generalized weakness disappeared. Normal mental status. Skin and visible mucous membranes were of natural color, BP – 18-20/min, SpO₂ on room air – 94-96%. Hemodynamic parameters were stable: HR 95/min, BP 110/90 mmHg. Survey didn't reveal active course of coronavirus infection (the virus was not identified). Cardiospecific enzymes and D-dimer did not exceed reference values. By the evening of the same day, the patient's condition was assessed as moderate severity, and she was transferred from the CICU to the Cardiology department. After transfer from the ICU to the general ward, dyspnea at rest did not bother her, the patient noted it only during physical exertion. Visible mucous membranes and skin were normal. On auscultation breathing was conducted in all fields, weakening in the lower regions, no rales. BP 19-21/min, SpO₂ 99% with insufflation of humidified oxygen. Heart tones muffled, rhythmic, HR 88/min, BP 90/60 mmHg (adapted BP, according to the patient).

From February 27 to March 1, 2022, the complaints of moderate dyspnea on physical exertion, dry cough persisted. Hemodynamic parameters were stable, BP within 17-18 /min. SpO₂ 98% against the background of humidified oxygen supply (5-10 l/min). BP within 100/65 mmHg, HR 86 per min.

On 02.03.2022 at 07:45 a.m., the patient got up from bed, after which her condition sharply worsened, the patient had severe dyspnea at rest up to 26-30 breaths/min, SpO₂ on room air was 84%, on oxygen supply (10-15 l/min) 92%, BP 50/00 mmHg, heart rate 120/min. After the consultation of the intensive care physician the patient was urgently transferred to the CICU.

At 08:04 a.m., clinical signs of pulmonary embolism (PE) were revealed: significant increase of D-dimer >5.0 mcg/ml (the norm – 0.046-0.708), signs of right heart overload on ECG, compared with the initial record (Fig.1), as well as on echocardiography (dilated right heart, pressure in the right ventricle 101 mmHg, separation of pericardial sheets 0.3 cm).

General condition was extremely severe, caused by acute cardiovascular and respiratory failure, with signs of obstructive shock due to PE. Skin and visible mucous membranes were sharply pale, acrocyanosis. Body temperature 36.1°C. The patient was lethargic and restless (GCS 13 points), could only answer questions in short phrases. Breathing was unassisted, weakened in the lower portions on both sides, single dry

Laboratory data

Index	Reference	24.02.	25.02.	27.02.	01.03.	02.03.	03.03.
Ph venous blood	7.32 – 7.42	7.43	7.36			7.25	7.16
PaCO ₂ , mmHg	95-110	35				55	43
PaO ₂ , mmHg	42.0-55.0	95				68	205
SvO ₂ , %	94-98	71	70			68	65
Lac, mmol/l	0.2-1.8	3.1	2.1		5	6	10
Glu, mmol/l	3.9-5.3	5.6	4.8	4.5	4.5	13.1	9.8
BE, mmol/l	-2.5 – 2.5	-2	2		-3.5	-4	-6
RBC, 10 ¹² /l	3.74-5.31	4.6	4.4	4.1	4.7	4.1	2.2
Hb, g/l	118-165	146	141	133	147	131	73
PLT 10 ⁹ /l	141-389	136	135	107	118	68	76
WBC, 10 ⁹ /l	3.89-9.23	10.6	10.7	12.2	15.7	18.8	28.5
NT-proBNP, pg/ml	0.0 – 125.0	1201			2303		
Troponine, ng/l	<29.000	0.01			0.1	1.1	2.5
CRP, mg/l	0 - 5	154		91	141	130	199
ESR, mm/h	<15	15	13	10	60	65	66
D-dimer, mkg/ml	0.047-0.7	0.7	0.5	0.5	>5.0	>5.0	>5.0
APTT, sec	25.5-33.5	20.8	39	38	77	79	88
ALT, unit/l	0.0-31.0	76.6	73.4	77.9	69.8	179	1438
AST, unit/l	0.0-31.0	48.2	47.0	40.9	38.4	146	1248
Creatinine, umol/l	53-97	89.3	85.7	75.6	75.4	90.6	309.2
Procalcitonin, ng/ml	0.0-0.05	0.05			0.07	0.5	7.1

rales, BP 34 per min, SpO₂ 60% on 20 L/min with humidified oxygen, auxiliary muscles were noted. Cardiac tones were muffled, rhythmic, heart rate 130 per min, systemic BP 50/00 mmHg, despite intravenous infusion of dopamine 10 mcg/kg/min given by pump. The abdomen was not swollen. Intestinal peristalsis was sluggish. The liver was enlarged by 2 cm at the edge of the right rib arch. Edema of the feet and shins.

At 08:05 a.m. the patient was urgently transferred to artificial lung ventilation (ALV) by Puritan-Bennet 840 machine due to increasing signs of acute respiratory failure and shock with following settings: Control Motion Ventilation (CMV) mode, minute volume (MV) - 7.7 L/min, tidal volume (TV) - 510 ml, FiO₂ - 100%, positive end-expiratory pressure (PEEP) - 5 cm H₂O, pressure airway - 27 cm H₂O. Despite the used "hard" ventilation pattern, peripheral saturation remained below 88%, and at blood gas study, respiratory index (PaO₂/FiO₂) was 84 mmHg with decompensated respiratory acidosis. Due to the patient's critical condition, chest CT with contrast was not possible at the time. Based on the clinical picture of massive PE and the results of survey, it was decided to administer thrombolysis therapy with Urokinase in a starting dose of 4400 units/kg and a maintenance dose of 4400 units/kg/h for 24 h (according to the recommendations of the European Society of Cardiology, 2019) [6].

At 08:07 a.m. asystole was registered on the monitor. A complex of cardiopulmonary resuscitation (CPR) was performed, including external cardiac massage and ALV in the ratio of 30:2, intravenous injection of adrenaline hydrochloride solution 0.1%-1.0 ml with successful recovery of cardiac activity after 3 min of resuscitation, ECG showed sinus tachycardia of 130 per min. Cardiotonic and vasopressor drugs with stepwise titration of norepinephrine at a dose of 0.5 µg/kg/min, dobutamine at a dose of 5 µg/kg/min were started, and arterial pressure of 115/75 mmHg and central venous pressure (CVP) of 9 mmHg were achieved. A low saturation level of below 82% remained.

At 4:50 p.m. her condition was evaluated as critical with dramatically negative course: SOFA - 19 points (80% probability of death), LIS (Lung Injury Score) - 2.25, RESP (Respiratory ECMO Survival Prediction) - 6 points with a survival rate of 36%. Decision to use veno-venous extracorporeal membrane oxygenation (VV-ECMO) was made after failure of standard therapy to improve hypoxemia despite AVL, the increase of decompensated respiratory acidosis, increasing blood lactate - 4 mmol/l, increasing PaCO₂ >55 mmHg, respiratory index (PaO₂/FiO₂) <85, SvO₂ <65%. VV-ECMO was performed on a Maquet Rotaflow device using a Medtronic Bio - Medicus 21 Fr cannula. V. femoralis dextra was used for blood sampling, the Medtronic

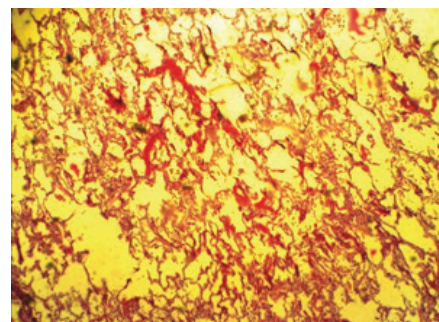
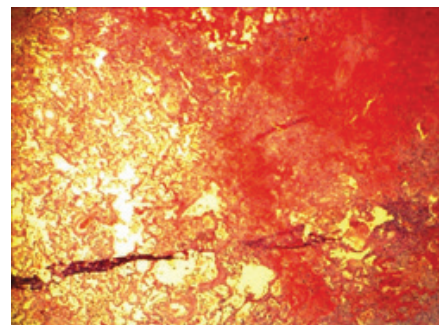


Fig. 2. Fragment of the right lung: thickened interalveolar septa due to fibrosis. Erythrocytes, single- and double-nucleated macrophages, lymphocytes, leukocytes, traces of protein fluid are observed in lumens of alveoli. Desquamated respiratory epithelium can be seen in some alveoli. (Fig.2-4 preparations stained with hematoxylin and eosin, x100)

a



b

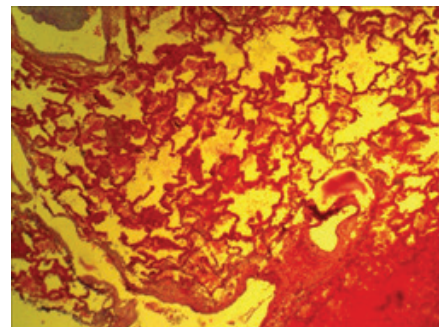


Fig. 3. Fragments of the right lung, infarction zone: a) in fragments from the lower lobe of the lung there are extensive hemorrhage fields with foci of necrosis of the underlying tissue, b) the border of the lung tissue and the infarction zone displayed in the sample

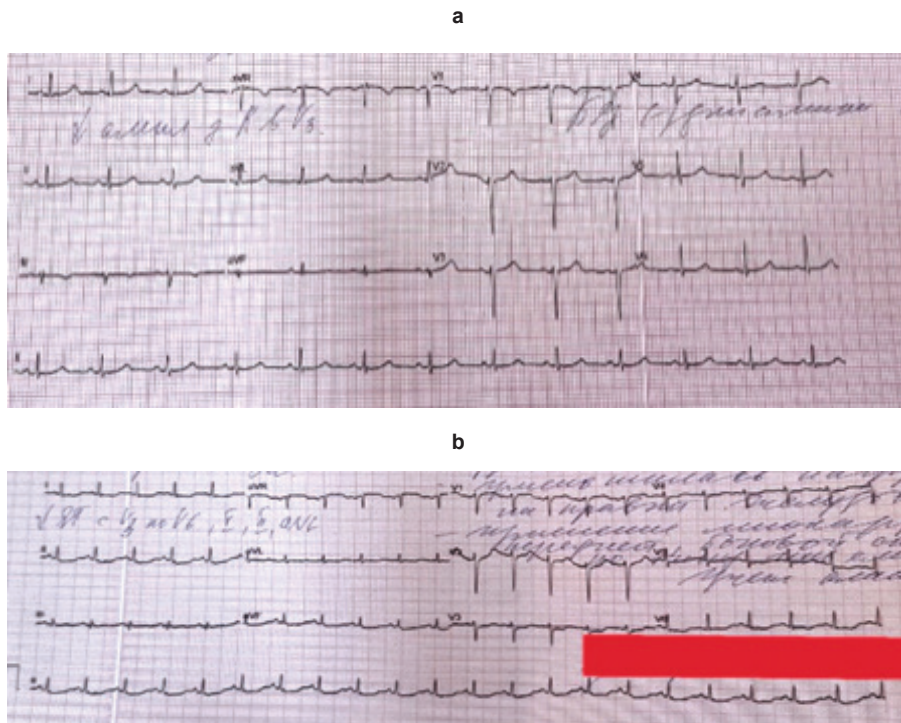


Fig. 1. ECG of patient M.: a - admittance day 24.02.22, b - day of deterioration 02.03.22

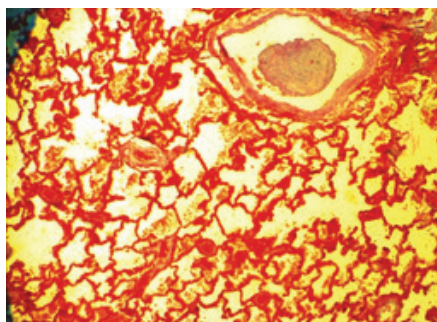


Fig. 4. Fragment of the right lung: there is a mixed thrombus in the vascular lumen.

Bio-Medicus 19 Fr return cannula was placed in v. jugularis interna dextra. Venous catheterization was performed using puncture ultrasound navigation under total intravenous anesthesia. The volume perfusion rate of VV-ECMO was 2.5 l/min, $\text{FiO}_2 = 90\%$, and AVL was continued with saturation at 94% to maintain airiness of the lung tissue. Anticoagulant therapy was performed by titrating the dose of unfractionated heparin under constant laboratory control in order to prevent massive blood loss due to hypocoagulation. Activated clotting time was maintained in the range of 380–420 s. The conducted VV-ECMO allowed to improve the parameters of gas exchange in arterial blood ($\text{PaO}_2 = 125$ mmHg, $\text{PaCO}_2 = 43$ mmHg), while mixed decompensated lactacidosis persisted (ph 7.16) (Table).

On March 3, 2022, at 11:10 a.m., despite the ongoing measures, clinical death happened due to progressive hypoxemia and multiorgan failure. CPR for 30 minutes without effect and at 11:40 min patient was pronounced dead.

Autopsy established the following diagnosis: Main diagnosis: U07.2 Novel coronavirus infection, not laboratory confirmed (virus not identified). Community-acquired bilateral viral pneumonia, in the process of resolution, with organized thrombi in the pulmonary vessels.

Complications of the main diagnosis: Subacute myocarditis, with foci of necrosis. Disseminated and microfocal cardio-sclerosis. Cardiovascular insufficiency (NT-proBNP from 01.03.2022 - 2308 pg/ml). Thromboembolism of small branches of the pulmonary artery. S4, 5, 8 infarctions of the right lung.

The diagnosis was confirmed by the results of pathomorphological study (Fig.2-4).

Discussion. The presented clinical case shows that in the patient during

the recuperative period of COVID-19 the symptoms of myocarditis prevailed, which were successfully managed at the initial stage of treatment. However, another complication in the form of thromboembolism of small branches of the pulmonary artery led to acute respiratory and cardiovascular failure with the development of clinical death. Due to the severity of the condition, PE was not verified by computed tomography with pulmonary artery contrast. The diagnosis and decision to perform systemic thrombolysis were justified by the specific presentation and laboratory data (D-dimer >5.0 $\mu\text{g/mL}$, NT-proBNP - 2303 pg/mL). The results of pathological examination confirmed PE and indicated that the patient had multiple "old" intravascular thrombi of small branches, which probably began to form in the acute period of the disease and had few symptoms. That is why the thrombi were lysed only partially and thrombolytic therapy was not effective.

At present, the mechanism of hypercoagulation triggering and thrombosis development after COVID-19 is not fully understood and requires further investigation. The main theory remains the development of endothelial dysfunction due to SARS-CoV-2 lesion and inflammatory reaction at the contact site [10]. The target of the virus is angiotensin-converting enzyme-2 (ACE-2), which is expressed in endothelial cells of arterial, venous and cardiomyocyte smooth muscle and alveolar lung epithelial cells [3, 5, 8]. The SARS-CoV-2 virus also contacts cells with the major protease Mpro with high affinity, binding to the receptor (ACE-2) and transmembrane serine protease-2 (TMPRSS-2) [9]. The active site of Mpro in SARS-CoV-2 has structural similarities to the coagulation factors Xa and thrombin and can therefore activate the clotting system, triggering a reaction cascade with thrombosis.

This case demonstrates that the process of intravascular thrombosis can develop in cases of mild to moderate COVID-19, in the recuperative period of the disease, in the absence of obvious risks of venous thromboembolic complications and up to a certain point proceed without evident laboratory and clinical manifestations.

Conclusion. Thus, high suspicion for thromboembolic complications should remain in any patient who has had COVID-19. The presented clinical case demonstrates that the risk of fatal throm-

boembolic complications during the convalescent period persists not only in the severe form of the COVID-19 course, but also in patients who have undergone this disease in mild and moderate severity. If the prophylactic use of low molecular weight or unfractionated heparin is mandatory during the entire inpatient period of treatment of patients with COVID-19, then the issues of choosing anticoagulant drugs, their dose and timing of administration after discharge remain unresolved. Early stratification of patients according to the risk of thrombotic complications, the correct choice of anticoagulant therapy at all stages of treatment of patients with COVID-19 will help to avoid or reduce the development of severe thrombotic complications.

Reference

1. Vremennye metodicheskie rekomendacii. «Profilaktika, diagnostika i lechenie novoj koronavirusnoj infekcii COVID-19» [Temporary guidelines. Prevention, diagnosis and treatment of the COVID-19. Version 14. M. 2021 (In Russ.).]
2. Galstyan G.M. Koagulopatiya pri COVID-19 [Coagulopathy in COVID-19]. *Pul'monologiya* [Pulmonology. 2020; 30 (5): 645 – 657 (In Russ.).]
3. Zagidullin N.SH., Gareeva D.F., Ishmetov V.S. [et al.] Renin-angiotenzinovaya sistema pri novoj koronavirusnoj infekcii COVID - 2019 [Renin-angiotensin-aldosterone system in new coronavirus infection 2019]. *Arterial'naya gipertenziya* [Arterial Hypertension. 2020; 26(3): 240-247 (In Russ.).]
4. Yavelov I.S., Drapkina O.M. COVID-19: state of hemostasis system and features of antithrombotic therapy. *Cardiovascular therapy and prevention*. 2020; 19 (3): 310 – 318 (In Russ.).]
5. Aimes R.T., Zijlstra A., Hooper J.D. Endothelial cell serine proteases expressed during vascular morphogenesis and angiogenesis. *Thromb. Haemost.* 2003; 89 (3): 561-572.
6. Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *European Heart Journal*. 2020; 41: 543-603.
7. Guo T, Fan Y, Chen M, Wu X, Zhang L, and He T. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020; 5: 811-818. <http://dx.doi.org/10.1001/jamacardio.2020.1017>.
8. Hamming I, Timens W, Bulthuis M.L. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* 2004; 203 (2): 631-637. doi:10.1002/path.1570.
9. Lu R, Zhao X, Li J. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020; 395: 565-574. doi:10.1016/S0140-6736(20)30251-8.
10. Varga Z, Flammer A.J., Steiger P. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* 2020; 395:1417-1418. doi:10.1016/S0140-6736(20)30937-5.