УДК 616.14-005.6/.7-02:616.988
DOI: https://doi.org/10.17816/PAVLOVJ110956

Анализ факторов риска венозных тромбоэмболических осложнений и различных вариантов антикоагулянтной терапии у пациентов с новой коронавирусной инфекцией

Р. Е. Калинин[1], И. А. Сучков[1], А. Б. Агапов[2]✉, Н. Д. Мжаванадзе[1, 3], В. О. Поваров[1], А. А. Никифоров[1]

[1] Рязанский государственный медицинский университет имени академика И. П. Павлова, Рязань, Российская Федерация;
[2] Областная клиническая больница, Рязань, Российская Федерация;
[3] Городская клиническая больница скорой медицинской помощи, Рязань, Российская Федерация

АННОТАЦИЯ

Введение. Новая коронавирусная инфекция (НКИ) характеризуется развитием катастрофической коагулопатии с возникновением тромботических и геморрагических осложнений. Выбор оптимального антикоагулянта у данных пациентов остается актуальным вопросом.

Цель. Оценить факторы риска венозных тромбоэмболических осложнений (ВТЭО), эффективность и безопасность различных вариантов антикоагулянтной терапии (АКТ) у пациентов с НКИ.

Материалы и методы. Проведено проспективное исследование, которое включило 370 пациентов с НКИ: 1 группа — больные, получавшие низкомолекулярный гепарин (НМГ) — 190 человек, 2 группа — больные, получавшие нефракционированный гепарин (НФГ) — 123 человека, 3 группа — пациенты, принимавшие прямые оральные антикоагулянты (ПОАК) — 57 человек. Проводилась оценка клинико-анамнестических данных, частоты тромботических и геморрагических осложнений. Исследование одобрено локальным этическим комитетом и зарегистрировано на платформе ClinicalTrials.gov.

Результаты. Наличие хронических заболеваний вен повышает риск развития ВТЭО у пациентов с НКИ в 6,433 (95% доверительный интервал (ДИ) 2,167–19,093) раза (p = 0,001), применение НФГ вместо НМГ или ПОАК — в 3,542 (95% ДИ 1,149–10,916) раза (p = 0,028), применение искусственной вентиляции легких (ИВЛ) — в 5,925 (95% ДИ 2,034–17,26) раза (p = 0,001), высокий уровень Д-димера — в 2,024 (95% ДИ 1,231–3,33) раза (p = 0,005). Уровень С-реактивного белка и ферритина на фоне лечения НКИ снижается у всех пациентов, но их наименьшие показатели зарегистрированы у пациентов, получавших НМГ (С-реактивный белок — 5,8 (1,7–15,0) мг/л, p = 0,004; ферритин — 364 (324–497) мкг/л, p = 0,001). Уровень фибриногена зарегистрирован на более низком уровне у пациентов 1 группы по сравнению со 2 и 3 группами (2,43 (1,9–3,52) г/л против 3,37 (2,8–4,92) г/л и 4,1 (2,8–5,25) г/л соответственно, p = 0,002). Высокая частота тромбоэмболии легочной артерии без установленного источника зарегистрирована у пациентов, получавших НФГ — 11,4% случаев, при этом частота проведения ИВЛ в группе НФГ расценена как высокая — 21% случаев.

Заключение. Факторами риска развития ВТЭО у пациентов с НКИ являются как факторы, типичные для ВТЭО в целом (ожирение, хронические заболевания вен, повышенный уровень Д-димера), так и факторы, специфические для НКИ (ИВЛ, гиповентиляция). Эффективным и безопасным антикоагулянтом в этой группе пациентов являются НМГ, продемонстрировавшие низкую частоту развития ВТЭО и геморрагических осложнений.

Ключевые слова: *новая коронавирусная инфекция; антикоагулянтная терапия; тромбозы; кровотечения; COVID-19*

Для цитирования:
Калинин Р.Е., Сучков И.А., Агапов А.Б., Мжаванадзе Н.Д., Поваров В.О., Никифоров А.А. Анализ факторов риска венозных тромбоэмболических осложнений и различных вариантов антикоагулянтной терапии у пациентов с новой коронавирусной инфекцией // Российский медико-биологический вестник имени академика И. П. Павлова. 2023. Т. 31, № 2. С. 243–250. DOI: https://doi.org/10.17816/PAVLOVJ110956

Рукопись получена: 17.09.2022 **Рукопись одобрена:** 13.01.2023 **Опубликована:** 30.06.2023

ЭКО•ВЕКТОР

DOI: https://doi.org/10.17816/PAVLOVJ110956

Analysis of Risk Factors of Venous Thromboembolic Complications and of Different Variants of Anticoagulant Therapy in Patients with New Coronavirus Infection

Roman E. Kalinin[1], Igor' A. Suchkov[1], Andrey B. Agapov[2]✉, Nina D. Mzhavanadze[1, 3], Vladislav O. Povarov[1], Aleksandr A. Nikiforov[1]

[1] Ryazan State Medical University, Ryazan, Russian Federation;
[2] Ryazan Regional Clinical Hospital, Ryazan, Russian Federation;
[3] Ryazan Region City Clinical Emergency Hospital, Ryazan, Russian Federation

ABSTRACT

INTRODUCTION: A new coronavirus infection (NCI) is characterized by catastrophic coagulopathy with development of thrombotic and hemorrhagic complications. The choice of an optimal anticoagulant in these patients remains an important issue.

AIM: To evaluate risk factors for venous thromboembolic complications (VTEC), effectiveness and safety of different variants of anticoagulant therapy (ACT) in patients with NCI.

MATERIALS AND METHODS: A prospective study was conducted that involved 370 patients with NCI: group 1 — patients who received low molecular weight heparin (LMWH) — 190 people, group 2 — patients who received unfractionated heparin (UFH) — 123 people, group 3 — patients who took direct oral anticoagulants (DOAC) — 57 individuals. Clinical and anamnestic data, frequency of thrombotic and hemorrhagic complications were evaluated. The study was approved by the Local Ethics Committee and was registered on ClinicalTrials.gov. platform.

RESULTS: The existence of chronic venous diseases increases the risk of development of venous thromboembolism (VTE) in patients with NCI 6.433 times (95% confidence interval (CI) 2.167–19.093)) (p = 0.001), use of UFH instead of LMWH or DOAC — 3.542 times (95% CI 1.149–10.916) (p = 0.028), use of artificial lung ventilation (ALV) — 5.925 times (95% CI 2.034–17.26) (p = 0.001), high D-dimer level — 2.024 times (95% CI 1.231–3.33) (p = 0.005). The level of C-reactive protein and ferritin decreased in all patients in the course of treatment for NCI, with the lowest levels in patients receiving LMWH (C-reactive protein — 5.8 (1.7–15.0) mg/l, p = 0.004; ferritin — 364 (324–497) μg/l, p = 0.001). Lower fibrinogen levels were recorded in patients of group 1 compared to groups 2 and 3 (2.43 (1.9–3.52) g/l versus 3.37 (2.8–4.92) g/l and 4.1 (2.8–5.25) g/l, respectively, p = 0.002). A high frequency of pulmonary embolism with unspecified source was recorded in patients receiving UFH — 11.4% of cases, with this, the frequency of using ALV in the group with UFH was evaluated as high — 21% of cases.

CONCLUSION: Risk factors of VTEC in patients with NCI are both factors typical of VTEC in general (obesity, chronic vein diseases, elevated D-dimer level), and factors specific of NCI (ALV, hypoventilation). Effective and safe anticoagulants in this group of patients are LMWH that demonstrated low frequency of development of VTEC and of hemorrhagic complications.

Keywords: *new coronavirus infection; anticoagulant therapy; thrombosis; bleedings; COVID-19*

For citation:
Kalinin RE, Suchkov IA, Agapov AB, Mzhavanadze ND, Povarov VO, Nikiforov AA. Analysis of Risk Factors of Venous Thromboembolic Complications and of Different Variants of Anticoagulant Therapy in Patients with New Coronavirus Infection. *I. P. Pavlov Russian Medical Biological Herald*. 2023;31(2):243–250. DOI: https://doi.org/10.17816/PAVLOVJ110956

Received: 17.09.2022 **Accepted:** 13.01.2023 **Published:** 30.06.2023

ECO•VECTOR

LIST OF ABBREVIATIONS

ACT — anticoagulant therapy
ALV — artificial lung ventilation
APTT — activated partial thromboplastin time
CI — confidence interval
COVID-19 — infection induced by SARS-CoV-2
CRP — C-reactive protein
CT– computed tomography
DVT — deep vein thrombosis
DOACs — direct oral anticoagulants
ESR — erythrocyte sedimentation rate
ICU — intensive care unit
INR — international normalized ratio
LMWH — low-molecular-weight heparin
NCI — new coronavirus infection
NILV — non-invasive lung ventilation
OR — odds ratio
PE — pulmonary embolism
PT — prothrombin time
RCCECH — Ryazan City Clinical Emergency Care Hospital
RRCH — Ryazan Regional Clinical Hospital
UFH — unfractionated heparin
VTEC — venous thromboembolic complications

INTRODUCTION

One of the main components of treatment of new coronavirus infection (NCI; syn.: infection induced by new coronavirus SARS-CoV-2, COVID-19) is anticoagulant therapy (ACT) which has proven effective in treatment and prevention of thrombotic complications [1–3]. The choice of an anticoagulant is an important issue since it is necessary to take into account not only the usual anamnestic data: concomitant pathology, patient's weight, risk factors for thrombotic complications, but also new pathophysiological processes in NCI [4, 5]. The customary Virchow triad is supplemented with a 'cytokine storm', macrophage activation syndrome, endothelial dysfunction [6, 7]. In management of patients with NCI, not only coagulogram parameters are evaluated, but also inflammation markers that previously were not routinely considered in ACT [8, 9]. The temporary methodical recommendations of the Ministry of Health of the Russian Federation 'Prevention, Diagnostics and Treatment of NCI' classify variants of ACT to low-molecular-weight heparins (LMWH), unfractionated heparin (UFH) and direct oral anticoagulants (DOACs) [6]. The question of choice of the optimal anticoagulant in patients with NCI remains debatable. Thus, consideration of different variants of ACT in patients with NCI is an important question for optimization of effectiveness and safety of complex treatment.

The **aim** of this study to evaluation of risk factors for venous thromboembolic complications (VTEC), of effectiveness and safety of different variants of anticoagulant therapy in patients with new coronavirus infections in conditions of real clinical practice.

MATERIAS AND METHODS

A prospective study was conducted on the base of two 'COVID' hospitals: Ryazan Regional Clinical Hospital (RRCH) and Ryazan City Clinical Emergency Care Hospital (RCCECH). The study was approved by the Local Ethics Committee of Ryazan State Medical University (Protocol No. 3 of 2021, October 11) and registered on ClinicalTrials.gov platform (ID NCT05143567). On admission, all the patients signed Informed consent.

The study included 370 patients with NCI who suffered the disease from June 2021 to January 2022.

Inclusion criteria:

- men and women above 18 with a positive polymerase chain reaction for COVID-19;
- existence of viral pneumonia by the data of computed tomography (KT) of lungs.

Non-inclusion criteria:

- age below 18;
- in women: pregnancy or lactation;
- extremely severe, agonizing patients;
- existence of initial thrombocytopenia;
- impossibility to administer ACT.

Treatment of patients was conducted according to the Temporary Methodical Recommendations of the Ministry of Health of the Russian Federation 'Prevention, Diagnostics and Treatment of NCI' [6]. Besides ACT, on admission all patients received pathogenetic treatment (glucocorticosteroids), etiotropic treatment (antiviral drugs), symptomatic treatment (antipyretic, mucoactive drugs, bronchodilators), oxygen therapy.

All the patients were taken clinical and anamnestic data (concomitant pathology, scope of lung damage, severity of NCI), laboratory parameters, data of initial duplex ultrasound (on admission of the patient with NCI to the intensive care unit (ICU), and also in all patients with NCI at the end of treatment for screening for VTEC).

Depending on ACT variant, patients were divided to 3 groups:

Group 1 — patients receiving LMWH — 190 people;

DOI: https://doi.org/10.17816/PAVLOVJ110956

Group 2 — patients receiving UFH — 123 people;
Group 3 — patients receiving DOACs — 57 people.

The groups were comparable in age, in analysis of gender there were more women in all groups than men (Table 1). In analysis of the ACT variants, LMWH was often used in the COVID hospital of RCCECH (97.4% of cases), and UFH in the COVID hospital of RRCH (70.2% of cases), while DOACs with the same frequency in both hospitals (58.9% and 41.1% of cases, respectively). To note, in the COVID hospitals participating in the study, patients received etiotropic, pathogenetic, symptomatic treatment with a comparable frequency ($p > 0.05$) according to the recommendations. Despite the revealed differences in ACT in the two COVID hospitals, the patients were comparable in the scope of viral damage of lungs and the severity of NCI, which is considered as an integral clinical characteristics, that collectively characterizes saturation, hemodynamics, and CT data of the lungs.

Table 1. Initial Clinical and Demographic Characteristics of Patients with New Coronavirus Infection in Study Groups

Parameters	Group of LMWH	Group of UFH	Group of DOACs	p
n	190	123	57	–
Age, Me (Q1–Q3), years	63 (56–70)	61 (51–68)	63 (53–71)	0.213
Male gender, n (%)	85 (4.7)	35 (28.2)	15 (26.8)	***0.003***
Medical Institution, n (%) - RRCH - RCCECH	 5 (2.6) 185 (97.4)	 87 (70.2) 37 (29.8)	 33 (58.9) 23 (41.1)	***< 0.001***
Degree of lung damage according to CT results, n (%) - 0 - 1 - 2 - 3 - 4	 11 (5.8) 43 (22.6) 81 (42.6) 45 (23.7) 10 (5.3)	 0 (0) 23 (18.5) 53 (42.7) 37 (29.8) 11 (8.9)	 2 (3.6) 11 (19.6) 17 (30.4) 24 (42.9) 2 (3.6)	***0.025***
Degree of severity of NCI, n (%) - Mild - Moderate - Severe - Extremely severe	 21 (11.1) 94 (49.5) 58 (30.5) 17 (8.9)	 6 (4.8) 50 (40.3) 48 (38.7) 20 (16.1)	 7 (12.5) 19 (33.9) 26 (46.4) 4 (7.1)	***0.021***

Notes: RCCECH — Ryazan City Clinical Emergency Care Hospital, RRCH — Ryazan Regional Clinical Hospital, CT –computed tomography, NCI — new coronavirus infection, LMWH — low molecular weight heparin, UFH — unfractionated heparin, DOACs — direct oral anticoagulants

In the analysis of the anamnestic data, a triad of the most common concomitant diseases is observed in the study groups: essential hypertension, obesity and diabetes mellitus (Table 2). Statistically significant differences in the groups were recorded in obesity and atrial fibrillation: there were significantly fewer obese patients among those taking DOACs than among those receiving parenteral anticoagulants, and the opposite tendency was observed for atrial fibrillation. Patients admitted to the hospital with a previously known rhythm disorder, continued to receive DOACs in the hospital.

Frequency of thrombolytic complications and of bleedings, mortality were evaluated in dynamics.

Statistical analysis of the basic results of the clinical trial was carried out in the IBM SPSS Statistics program ver. 26 (SPSS: An IBM Company, USA). The analysis of qualitative parameters was performed using Pearson and Fisher criteria $\chi 2$. The distribution of quantitative parameters was evaluated using Kolmogorov–Smirnov and Shapiro–Wilk tests ($p > 0.05$). Due to the distribution of parameters different from normal, the average values were represented by the median (Me) and the interquartile interval (Q1–Q3), and the analysis was carried out using Wilcoxon, Mann–Whitney, Kruskal–Wallis tests ($p < 0.05$). To determine risk factors for the development of VTE, a univariate and multivariate analysis were carried out. Its results are presented in the form of odds ratio (OR) with 95% confidence interval (CI).

RESULTS

Despite the conducted treatment, the condition of some patients worsened, and they were transferred to the ICU for enhancement of oxygen support (Figure 1). In the ICU, the number of patients on noninvasive lung ventilation (NILV) was fewer in group 2, but

Table 2. Concomitant Pathology in Patients with New Coronavirus Infection in Study Groups

Parameters	Group of LMWH	Group of UFH	Group of DOACs	p
n	190	123	57	–
Obesity, n (%)	***76 (40)***	***66 (53.2)***	***9 (16.1)***	***< 0.001***
Essential hypertension, n (%)	151 (79.5)	96 (77.4)	44 (78.6)	0.91
Diabetes mellitus, n (%)	59 (31.1)	43 (35)	15 (26.8)	0.531
Coronary heart disease, n (%)	48 (25.3)	26 (21)	19 (33.9)	0.178
Atrial fibrillation, n (%)	***30 (15.8)***	***17 (13.7)***	***57 (100)***	***< 0.001***
Oncology, n (%)	22 (11.6)	9 (7.3)	5 (8.9)	0.431
Bronchial asthma, n (%)	6 (3.2)	9 (7.3)	3 (5.4)	0.252
Chronic obstructive pulmonary disease, n (%)	***15 (7.9)***	***2 (1.6)***	***0***	***0.007***
Gastric ulcer, n (%)	11 (5.8)	13 (10.5)	3 (5.4)	0.245
Postinfarction cardiosclerosis, n (%)	16 (8.5)	9 (7.3)	5 (8.9)	0.904
Chronic kidney disease, n (%)	***39 (20.5)***	***7 (5.6)***	***6 (10.7)***	***0.001***
Chronic venous disorder, n (%)	***16 (8.4)***	***19 (15.3)***	***2 (3.6)***	***0.030***
Venous thromboembolic complications, n (%)	***4 (2.1)***	***12 (9.7)***	***0***	***0.001***

Notes: LMWH — low-molecular-weight heparin, UFH — unfractionated heparin, DOACs — direct oral anticoagulants

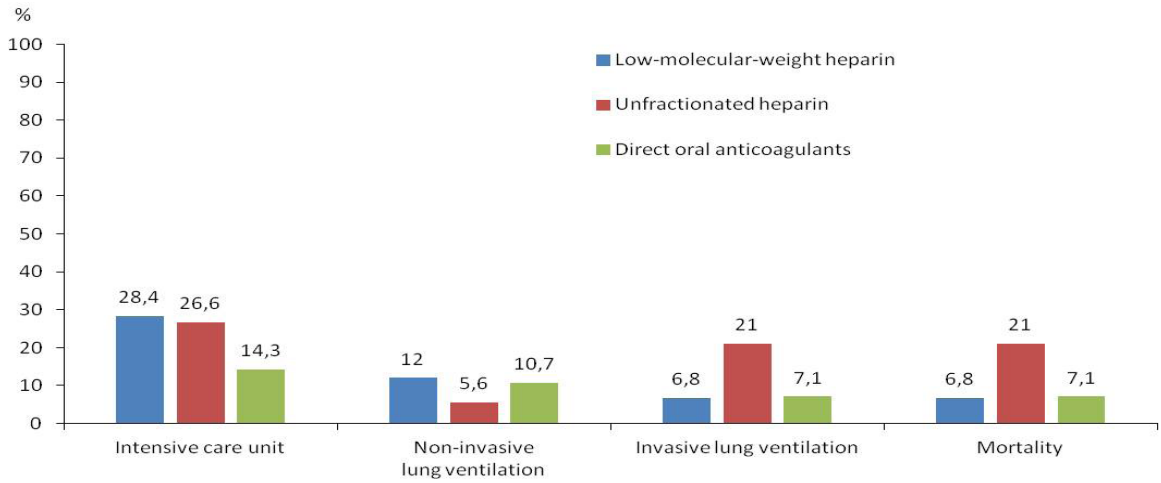

Fig. 1. Frequency of hospitalization to intensive care unit, use of noninvasive lung ventilation and invasive lung ventilation, mortality of patients with new coronavirus infection in the study groups.

this group appeared to have the largest number of patients on artificial lung ventilation (ALV) in general than groups 1 and 3 (21% cases vs. 7% of cases, $p < 0.001$). Switching a patient to ALV worsened the prognosis for recovery, in group 2 high mortality was observed — 21% of cases.

By the results of clinical blood analysis, coagulogram and biochemical blood analysis, the study groups were comparable. With this, all patients had high concentrations of proinflammatory markers (C-reactive protein (CRP), ferritin)) and coagulation parameters (fibrinogen and D-dimer, Table 3).

At the end of inpatient treatment for NCI using complex therapy, a decrease in the concentration of CRP and ferritin was noted in all the patients, but the lowest concentration was achieved in patients of group 1 receiving LMWH (CRP

Table 3. Laboratory Parameters of Patients with New Coronavirus Infection in Study Groups on Admission (Me(Q1–Q3))

Parameters	Norm	Group of LMWH	Group of UFH	Group of DOACs	p
n	–	190	123	57	–
Red blood cells, x 10^{12}/l	3.5–5.5	4.8 (4.4–5.1)	4.7 (4.3–5.0)	4.5 (4.2–4.8)	0.103
Hemoglobin, g/l	110–160	135 (122–145)	138 (129–147)	132 (125–140)	0.325
White blood cells, x 10^9/l	4.0–10.0	6.7 (4.7–9.2)	6.8 (4.9–9.0)	7.6 (5.4–11.7)	0.194
Platelets, x 10^9/l	***100–400***	***189 (144-260)***	***195 (167-257)***	***236 (174–322)***	***0.016***
ESR, mm/hour	2–18	23 (11–33)	19 (8–34)	27 (15–43)	0.082
CRP, mg/l	≤ 5	57.8 (24.0–101.3)	66.3 (38.0–126.9)	47.7 (17.2–104.4)	0.412
Ferritin, μg/l	10–200	738 (210–967)	848 (596–953)	432.5 (278–884)	0.371
APTT, sec	12.6–28.7	34.3 (25.9–36.8)	33.75 (27.8–40.5)	30.9 (27.8–36.8)	0.541
Prothrombin time, sec	9.8–12.2	13.2 (12.2–14.2)	12.4 (11.2–13.4)	11.85 (11.0–13.0)	0.251
Fibrinogen, g/l	1.8–3.5	6.2 (5.4–6.8)	5.5 (3.28–5.55)	4.4 (3–5.66)	0.061
INR	0.81–1.25	1.11 (1.03–1.2)	1.06 (0.98–1.14)	1.06 (0.98–1.14)	0.301
D-dimer, mg/l	≤ 0.5	0.68 (0.4–0.75)	0.62 (0.37–1.01)	0.54 (0.39–0.84)	0.214

Notes: APTT — activated partial thromboplastin time, INR — international normalized ratio, LMWH — low-molecular-weight heparin, UFH — unfractionated heparin, DOACs — direct oral anticoagulants, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein

Table 4. Laboratory Parameters of Patients with New Coronavirus Infection in Study Groups at the End of Hospital Treatment (Me (Q1–Q3))

Parameters	Norm	Group of LMWH	Group of UFH	Group of DOACs	p
n	–	190	123	57	–
Red blood cells , x 10^{12}/l	3.5–5.5	4.5 (4.1–4.9)	4.5 (4.1–4.8)	4.3 (4.0–4.6)	0.064
Hemoglobin, g/l	110–160	127 (115–137)	130 (120–142)	127 (120–135)	0.156
White blood cells, x 10^9/l	4.0–10.0	10.2 (8.3–12.7)	10.5 (8.1–13.6)	9.9 (7.6–11.8)	0.313
Platelets, x 10^9/l	100–400	219 (176–303)	258 (184–323)	235 (178–308)	0.372
ESR, mm/hour	2–18	14 (6–20)	10 (2–22)	13 (3–24)	0.159
CRP, mg/l	≤ 5	***5.8 (1.7–15.0)***	***10.6 (4.1–13.4)***	***9.1 (4.6–19.7)***	***0.004***
Ferritin, μg/l	10–200	***364 (324–497)***	***578 (367–986)***	***579 (402–952)***	***0.001***
APTT, sec	12.6–28.7	34.5 (26.3–37.0)	29.6 (25.9–36.9)	27.3 (24.8–32.8)	0.081
Prothrombin time, sec	9.8–12.2	12.0 (11.1–13.0)	11.6 (10.9–12.7)	11.7 (10.9–12.6)	0.160
Fibrinogen, g/l	1.8–3.5	***2.4 (1.9–3.5)***	***3.4 (2.8–4.9)***	***4.1 (2.8–5.3)***	***0.002***
INR	0.81–1.25	1.01 (0.95–1.09)	1.00 (0.93–1.08)	1.05 (0.98–1.14)	0.471
D-dimer, mg/l	≤ 0.5	0.52 (0.36–0.65)	0.58 (0.27–0.83)	0.70 (0.45–0.90)	0.388

Notes: APTT — activated partial thromboplastin time, INR — international normalized ratio, LMWH — low-molecular-weight heparin, UFH — unfractionated heparin, DOACs — direct oral anticoagulants, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein

— 5.8 (1.7–15) mg/l, p = 0.004), ferritin — 364 (324–497) μg/l, p = 0.001). Besides, fibrinogen had statistically lower level in patients receiving LMWH (group 1) than in patients receiving UFH and DOACs (2.43 (1.9–3.52) g/l vs. 3.37 (2.8–4.92) g/l and 4.1 (2.8–5.25) g/l, respectively, p = 0.002). D-dimer remained elevated in all study groups, which indicates the state of hypercoagulation after treatment for NCI and the need to continue ACT in the outpatient period.

Based on the anamnestic data and the conducted treatment for NCI, we performed a univariate and multivariate analysis of risk factors for VTEC (Table 5). A multivariate analysis showed that the presence of

Table 5. Risk Factors of Venous Thromboembolic Complications in Patients with New Coronavirus Infection

Parameters	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.02 (0.982–1.060)	0.296	–	–
Gender - male - female	 0.482 (0.155–1.495) 2.075 (0.669–6.435)	 0.206	 –	 –
NILV	0.533 (0.069–4.125)	0.547	–	–
ALV	***9.353 (3.478–25.153)***	***< 0.001***	***5.925 (2.034–17.260)***	***0.001***
Obesity	***7.137 (2.293–22.208)***	***0.001***	***4.282 (1.230–14.906)***	***0.022***
CVeD	***8.91 (3.264–24.326)***	***< 0.001***	***6.433 (2.167–19.093)***	***0.001***
Kind of ACT: - LMWH - UFH - DOACs	 ***0.255 (0.082–0.790)*** ***5.645 (1.964–16.223)*** 0.318 (0.041–2.436)	 ***0.018*** ***0.001*** 0.27	 0.882 (0.092-8.463) ***3.542 (1.149-10.916)*** –	 0.914 ***0.028*** –
Initial parameters of coagulogram: - APTT - PT - Fibrinogen - INR - D-dimer	 1.025 (0.9999–1.050) 0.913 (0.682–1.224) 0.846 (0.652–1.096) 1.041 (0.586–1.851) ***1.945 (1.304–2.902)***	 0.051 0.543 0.205 0.891 ***0.001***	 1.009 (0.982-1.037) – – – ***2.024 (1.231-3.330)***	 0.503 – – – ***0.005***

Notes: APTT — activated partial thromboplastin time, CI — confidence interval, ALV –artificial lung ventilation, INR — international normalized ratio, NILV — noninvasive lung ventilation, LMWH — low-molecular-weight heparin, UFH — unfractionated heparin, OR — odds ratio, PT — prothrombin time, DOACs — direct oral anticoagulants, CVeD — chronic venous disorder

chronic venous diseases (CVeD) in a patient increases the risk of VTEC 6.433 (95% CI 2.167–19.093) times (p = 0.001), the use of UFH instead of LMWH or DOACs — 3.542 (95% CI 1.149–10.916) times (p = 0.028), the use of ALV — 5.925 (95% CI 2.034–17.260) times (p = 0.001), high level of D-dimer — 2.024 (95% CI 1.231–3.330) times (p = 0.005). The frequency of thrombotic and hemorrhagic complications in the study groups during the period of inpatient treatment is shown in Table 6. The largest number of VTEC was recorded in patients

Table 6. Thrombotic and Hemorrhagic Complications in Patients with New Coronavirus Infection in Study Groups in Period of Inpatient Treatment

Complications	Group of LMWH	Group of UFH	Group of DOACs	p
n	190	123	57	–
Deep vein hrombosis	***3 (1.6%)***	***8 (6.5%)***	***1 (1.8%)***	***0.031***
Pulmonary embolism without source	***2 (1.1%)***	***14 (11.4%)***	***0***	***0.028***
Pulmonary embolism in combination with deep vein hrombosis	***1 (0.5%)***	***8 (6.5%)***	***0***	***0.003***
Large bleedings	***1 (0.5%)***	***6 (4.9%)***	***0***	***0.004***
Significant bleedings	3 (1.6%)	5 (4.06%)	0	0.246
Minor bleeding	***14 (7.4%)***	***22 (17.9%)***	***3 (5.3%)***	***0.025***

Notes: LMWH — low-molecular-weight heparin, UFH — unfractionated heparin, DOACs — direct oral anticoagulants

of group 2. Of attention is the fact that the frequency of isolated pulmonary embolism without a verified source in the lower limbs in patients receiving UFH, was relatively high — 11.4% of cases, which indicates a probable cause of a large number of patients on ALV in this group — 21% of cases. In patients receiving DOACs (group 3), only 1 (1.8%) case of deep vein thrombosis (DVT) was recorded.

In analysis of hemorrhagic complications, the greatest number of bleedings was observed in group 2 (intestinal, bronchial bleedings). Despite the treatment, all large bleedings in group 2 had fatal outcomes. All the groups were comparable in frequency of significant bleedings. The frequency of minor bleedings was higher in patients receiving UFH — 17.9% of cases.

DISCUSSION

The use of ACT in patients with NCI is very important taking into account the pathogenesis of COVID-19 in which *thrombosis and inflammation are closely connected*. To traditional risk factors for VTEC (obesity, immobilization, hormonal therapy, surgical treatment, etc.), new factors add in these patients: infectious diseases, oxygen therapy, hypoventilation, hyperthermia [10].

According to our study, the leading triad of concomitant pathology is represented by *obesity, essential hypertension* and *diabetes mellitus*. Of attention is the fact that patients receiving parenteral anticoagulants (groups 1 and 2) were also diagnosed with CVeD (group 1 — 8.4% of cases, group 2 — 16.3% of cases), which are independent risk factors for VTEC. Multivariate analysis showed that the presence of CVeD in a patient increases the risk of developing VTEC 6.433 (95% CI 2.167–19.093) times ($p = 0.001$).

The transfer of the patient to the ICU, where he receives intensive oxygen therapy, requires his immobilization, and it is there, according to our data, that VTEC most often develops. According to the meta-analysis, which included 42 studies of patients with NCI, the overall incidence of VTEC was 21% of cases, DVT — 20% of cases, PE — 13% of cases. Here, the frequency of these complications in ICU patients increased: 31% — cases of VTE, 28% — cases of DVT and 19% — cases of PE [11]. In our work, the VTEC mostly occurred in patients who received UFH. Moreover, a high frequency of PE without a verified source was recorded in patients receiving a *therapeutic dose* of anticoagulant (11.4% of cases, $p = 0.028$).

In some studies, autopsies of patients who died from severe COVID-19 infection, were performed, and in most of them microthrombi were found in the pulmonary circulation [12, 13]. In one of these studies, small thrombi were 9 times more often present in the pulmonary circulation of patients with COVID-19 than in patients who died from influenza virus ($p < 0.001$). Besides, growth of new vessels in COVID-19 was 2.7 times higher than in influenza ($p < 0.001$) [14]. In addition to *diffuse damage of alveoli*, which is a distinctive feature of COVID-19, *microvascular thrombosis in the pulmonary circulation can derange gas exchange promoting significant hypoxemia observed in patients* [15]. Thus, despite the conducted ACT, isolated microthrombosis of pulmonary arteries can probably develop requiring more enhanced oxygen therapy.

According to our study, application of ALV increases the risk of VTEC by 5.925 (95% CI 2.034–17.26) times ($p = 0.001$). The number of patients who needed to be switched to ALV was higher in group 2, they received UFH in 21% of cases ($p < 0.001$). Patients who took LMWH showed good survival rate in severe NCI, since ALV was used only in 6% of cases ($p < 0.001$). This phenomenon can probably be explained by resistance to heparin. According to R. Beun, et al., the phenomenon of heparin resistance was observed in almost 80% of patients with COVID-19 who received UFH at high doses (> 35,000 IU /day) to achieve the target APTT, presumably due to an increase in the level of factor VIII [16]. Patients who require high doses of UFH to achieve the target APTT may also develop a life-threatening bleeding in the absence of monitoring of antithrombotic activity using anti-factor Xa analysis. Monitoring of anti-Xa activity in patients receiving UFH is associated with a better achievement of therapeutic anticoagulation compared to monitoring of APTT; it reduces the time to reach the therapeutic range, as well as increases the time of stay within the therapeutic range [17]. Unfortunately, routine determination of anti-factor Xa in a COVID hospital is not always possible due to the small volume of the laboratory and the high cost of the method. However, these techniques are used in the ICU in particularly severe patients with NCI [18–20].

In real clinical practice, examination of the general laboratory parameters gives answers to the important questions concerning treatment tactics and choice of an ACT. In the analysis of parameters of coagulogram, fibrinogen level decreased in all the groups, with the lowest concentration in patients receiving LMWH. According to our analysis, a high level of D-dimer increases the risk of development of VTEC by 2.024 (95% CI 1.231–3.33) times ($p = 0.005$), so there is a need for the extended anticoagulant prophylaxis in the outpatient period.

The peculiarity of patients with NCI is that they receive etiotropic, pathogenetic and symptomatic treatment for a viral infectious disease *together with ACT*. In all patients, a reliable reduction of ferritin and CRP levels was noted, with the lowest concentrations of inflammatory markers in the LMWH group. This

result can be explained by the fact that, in addition to anticoagulation effect, parenteral anticoagulants can also have *antiviral, anti-inflammatory* and *cytoprotective effects*. Only 30% of the UFH components have an anticoagulant effect, and the remaining 70% possess multiple pharmacological properties, including liberation of a tissue factor inhibitor from the endothelium, direct interaction with the vascular surface, cytoprotective effects, interaction with growth factors and modulations of cellular regulatory processes [21, 22]. LMWH also possesses anti-inflammatory properties, including binding of inflammatory cytokines, inhibition of chemotaxis of neutrophils and protection of endothelial cells, as well as a potential antiviral effect; with this; it has a longer half-life and a low potential to induce bleeding and thrombocytopenia compared to UFH [23].

We observed different bleeding variants in patients with NCI with the highest complication rate in the UFH group (group 2): large bleedings 4.9%, minor bleedings — 17.9%. Large and significant bleedings require cessation of ACT and hemotransfusion, which aggravates the condition of patients with NCI and leads to high mortality. So, *use of LMWH is a safer variant for VTEC prevention in patients with NCI with low frequency of development of large and significant bleedings*.

CONCLUSION

According to our study, the main risk factors for development of venous thromboembolism in patients with new coronavirus infection are both the 'traditional' factors (obesity, chronic venous disorders, D-dimer level), and factors specific of the new coronavirus infection (artificial lung ventilation, hypoventilation, hyperthermia).

Analysis of different variants of anticoagulant therapy in this group of patients showed the most effective and safe group being low molecular weight heparins. They are characterized by low frequency of venous thromboembolic and hemorrhagic complications. Direct oral anticoagulants showed effective prevention of the development of venous thromboembolic complications in patients with new coronavirus infection and cardiologic concomitant pathology, but their use requires further study with large comparison groups.

Routine laboratory parameters of hemostasis and inflammation confirm the effectiveness of low-molecular-weight heparins both in terms of anti-inflammatory effect (reduction of the level of C-reactive protein, ferritin), and the coagulation status (reduction of fibrinogen).

ADDITIONALLY

Funding. This article was not supported by any external sources of funding.
Conflict of interests. The authors declare that there is no external funding for the study.

Contribution of authors: *R. E. Kalinin* — research concept, verification of critical intellectual content; *I. A. Suchkov* — development of the concept and design, verification of critical intellectual content, final approval for publication of the manuscript; *N. D. Mzhavanadze* — collection of material, editing; *A. B. Agapov* — carrying out the main stages of work, recruiting material, writing an article; *V. O. Povarov* — statistical analysis and interpretation of data; *A. A. Nikiforov* — carrying out biochemical analyses. The authors confirm the correspondence of their authorship to the ICMJE International Criteria. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Вклад авторов: *Калинин Р. Е.* — концепция исследования, проверка критически важного интеллектуального содержания; *Сучков И. А.* — разработка концепции и дизайна, проверка критически важного интеллектуального содержания, окончательное утверждение для публикации рукописи; *Мжаванадзе Н. Д.* — сбор материала, редактирование; *Агапов А. Б.* — проведение основных этапов работы, набор материала, написание статьи; *Поваров В. О.* — статистический анализ и интерпретация данных; *Никифоров А. А.* — проведение биохимических анализов. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

СПИСОК ИСТОЧНИКОВ

1. Официальная информация о коронавирусе в России [Интернет]. Доступно по: https://стопкоронавирус.рф/. Ссылка активна на 17.09.2022.
2. Gil–Sala D., Riera C., García–Reyes M., et al. Mortality and bleeding complications of COVID-19 critically ill patients with venous thromboembolism // International Angiology. 2022. Vol. 41, No. 1. P. 1–8. doi: 10.23736/s0392-9590.21.04704-0
3. Калинин Р.Е., Сучков И.А., Филимонов В.Б., и др. Венозные тромбоэмболические осложнения у пациентов с COVID-19 во время первой и второй волн пандемии: данные реальной клинической практики // Флебология. 2022. Т. 16, № 2. С. 122–129. doi: 10.17116/flebo202216021122
4. Российские клинические рекомендации по диагностике, лечению и профилактике венозных тромбоэмболических осложнений (ВТЭО) // Флебология. 2015. Т. 9, № 4, Вып. 2. С. 3–52.
5. Калинин Р.Е., Сучков И.А., Агапов А.Б. Эффективность различных вариантов антикоагулянтной терапии у пациентов с тромбозом глубоких вен нижних конечностей в условиях реальной клинической практики // Флебология. 2017. Т. 11, № 1. С. 21–27. doi: 10.17116/flebo201711121-27
6. Временные методические рекомендации Министерства здравоохранения РФ. Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19). Версия 17 (14.12.2022). Доступно по: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/061/254/original/%D0%92%D0%9C%D0%A0_COVID-19_V17.pdf?1671088207. Ссылка активна на 13.01.2023.
7. Верткин А.Л., Авдеев С.Н., Ройтман Е.В., и др. Вопросы лечения COVID-19 с позиции коррекции эндотелиопатии и профилактики тромботических осложнений. Согласованная позиция экспертов // Профилактическая медицина. 2021. Т. 24, № 4. С. 45–51. doi: 10.17116/profmed20212404145
8. Bellmunt–Montoya S., Riera C., Gil D., et al. COVID-19 Infection in Critically Ill Patients Carries a High Risk of Venous Thrombo-embolism // European Journal of Vascular and Endovascular Surgery. 2021. Vol. 61, No. 4. P. 628–634. doi: 10.1016/j.ejvs.2020.12.015
9. Čelovska D., Wawruch M., Stvrtinová V. COVID-19-associated coagulopathy and immuno-thrombosis // Acta Phlebologica. 2021. Vol. 22, No. 2. P. 55–60. doi: 10.23736/S1593-232X.21.00510-5
10. Malas M.B., Naazie I.N., Elsayed N., et al. Thromboembolism Risk of COVID-19 Is High and Associated with a Higher Risk of Mortality: A Systematic Review and Meta-Analysis // EClinicalMedicine. 2020. Vol. 29. P. 100639. doi: 10.1016/j.eclinm.2020.100639
11. Dolhnikoff M., Duarte–Neto A.N., de Almeida Monteiro R.A., et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19 // Journal of Thrombosis and Haemostasis. 2020. Vol. 18, No. 6. P. 1517–1519. doi: 10.1111/jth.14844
12. Ackermann M., Verleden S.E., Kuehnel M., et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19 // The New England Journal of Medicine. 2020. Vol. 383, No. 2. P. 120–128. doi: 10.1056/NEJMoa2015432
13. Fox S.E., Akmatbekov A., Harbert J.L., et al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans // The Lancet. Respiratory Medicine. 2020. Vol. 8, No. 7. P. 681–686. doi: 10.1016/S2213-2600(20)30243-5
14. Carsana L., Sonzogni A., Nasr A., et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study // The Lancet. Infectious Diseases. 2020. Vol. 20, No. 10. P. 1135–1140. doi: 10.1016/S1473-3099(20)30434-5
15. Bertolidi Lemos A.C., do Espírito Santo D.A., Salvetti M.C., et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID) // Thrombosis Research. 2020. Vol. 196. P. 359–366. doi: 10.1016/j.thromres.2020.09.026
16. Beun R., Kusadasi N., Sikma M., et al. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2 // International Journal of Laboratory Hematology. 2020. Vol. 42, Suppl. 1. P. 19–20, doi: 10.1111/ijlh.13230
17. Panigada M., Bottino N., Tagliabue P., et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis // Journal of Thrombosis and Haemostasis. 2020. Vol. 18, No. 7. P. 1738–1742. doi: 10.1111/jth.14850
18. Бородина И.А., Селезнева И.А., Борисова О.В., и др. Группы крови и секреторное состояние при COVID-19 // Наука молодых (Eruditio Juvenium). 2021. Т. 9, № 4. С. 589–596. doi: 10.23888/HMJ202194589-596
19. Mortus J.R., Manek S.E., Brubaker L.S., et al. Thromboelastographic Results and Hypercoagulability Syndrome in Patients With Coronavirus Disease 2019 Who Are Critically Ill // JAMA Network Open. 2020. Vol. 3, No. 6. P. e2011192. doi: 10.1001/jamanetworkopen.2020.11192
20. Бицадзе В.О., Бредихин Р.А., Булатов В.Л., и др. Флебит и тромбофлебит поверхностных сосудов // Флебология. 2021. Т. 15, № 3. С. 211–244. doi: 10.17116/flebo202115031211
21. Агапов А.Б., Сучков И.А., Рябков А.Н. Прямые пероральные антикоагулянты в лечении тромбоза глубоких вен нижних конечностей // Наука молодых (Eruditio Juvenium). 2016. № 2. С. 147–157.
22. Петриков А.С., Дудин Д.В., Попкова Л.Н., и др. Течение тромбоза глубоких вен нижних конечностей в остром периоде на фоне антикоагулянтной терапии в зависимости от содержания D-димеров и С-реактивного белка // Наука молодых (Eruditio Juvenium). 2018. Т. 6, № 2. С. 233–241. doi: 10.23888/HMJ201862233-241
23. Калинин Р.Е., Сучков И.А., Нарижный М.В. Диспансеризация больных с венозными тромбоэмболическими осложнениями // Российский медико-биологический вестник имени академика И. П. Павлова. 2011. № 3. С. 104–109.

REFERENCES

1. Ofitsial'naya informatsiya o koronaviruse v Rossii [Internet]. Available at: https://стопкоронавирус.рф/. Accessed: 2022 September 17. (In Russ).
2. Gil–Sala D, Riera C, García–Reyes M, et al. Mortality and bleeding complications of COVID-19 critically ill patients with venous thromboembolism. *Int Angiol.* 2022;41(1):1-8. doi: 10.23736/s0392-9590.21.04704-0
3. Kalinin RE, Suchkov IA, Filimonov VB, et al. Venous Thromboembolism in COVID-19 Patients During the First and the Second Waves of the Pandemic: Real-Practice Data. *Flebologiya.* 2022;16(2):122–9. (In Russ). doi: 10.17116/flebo202216021122
4. Rossiyskiye klinicheskiye rekomendatsii po diagnostike, lecheniyu i profilaktike venoznykh tromboembolicheskikh oslozhneniy (VTEO). *Flebologiya.* 2015;9(4-2):3–52. (In Russ).
5. Kalinin RE, Suchkov IA, Agapov AB. The Effectiveness of the Various Options of Anticoagulant Therapy for the Treatment of the Patients with Thrombosis of the Deep Veins of the Lower Extremities in the Routine Clinical Practice. *Flebologiya.* 2017;11(1):21–7. (In Russ). doi: 10.17116/flebo201711121-27
6. Vremennyye metodicheskiye rekomendatsii Ministerstva zdravookhraneniya RF. Profilaktika, diagnostika i lecheniye novoy koronavirusnoy infektsii (COVID-19). Version 17 (14/12/2022). Available at: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/061/254/original/%D0%92%D0%9C% D0%A0_COVID-19_V17.pdf?1671088207. Accessed: 2023 January 13. (In Russ).
7. Vertkin AL, Avdeev SN, Roitman EV, et al. Treatment of COVID-19 from the perspective of endotheliopathy correction and prevention of thrombotic complications. The agreed position of the experts. *Profilakticheskaya Meditsina.* 2021;24(4):45–51. (In Russ). doi: 10.17116/profmed20212404145
8. Bellmunt–Montoya S, Riera C, Gil D, et al. COVID-19 Infection in Critically Ill Patients Carries a High Risk of Venous Thrombo-embolism. *Eur J Vasc Endovasc Surg.* 2021;61(4):628–34. doi: 10.1016/j.ejvs.2020.12.015
9. Čelovska D, Wawruch M, Stvrtinová V. COVID-19-associated coagulopathy and immuno-thrombosis. Acta Phlebologica. 2021;22(2):55–60. doi: 10.23736/S1593-232X.21.00510-5
10. Malas MB, Naazie IN, Elsayed N, et al. Thromboembolism Risk of COVID-19 Is High and Associated with a Higher Risk of Mortality: A Systematic Review and Meta-Analysis. *EClinicalMedicine.* 2020;29:100639. doi: 10.1016/j.eclinm.2020.100639
11. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *J Thromb Haemost.* 2020;18(6):1517–9. doi: 10.1111/jth.14844
12. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med.* 2020;383(2):120–8. doi: 10.1056/NEJMoa2015432
13. Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med.* 2020;8(7):681–6. doi: 10.1016/S2213-2600(20)30243-5
14. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis.* 2020;20(10):1135–40. doi: 10.1016/S1473-3099(20)30434-5
15. Bertolidi Lemos AC, do Espírito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). *Thromb Res.* 2020;196:359–66. doi: 10.1016/j.thromres.2020.09.026
16. Beun R, Kusadasi N, Sikma M, et al. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. *Int J Lab Hematol.* 2020;42(Suppl 1):19–20. doi: 10.1111/ijlh.13230
17. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost.* 2020;18(7):1738–42. doi: 10.1111/jth.14850
18. Borodina IA, Selezneva IA, Borisova OV, et al. Blood groups and secretory state in COVID-19. *Nauka Molodykh (Eruditio Juvenium).* 2021;9(4):589–96. (In Russ). doi: 10.23888/HMJ202194589-596
19. Mortus JR, Manek SE, Brubaker LS, et al. Thromboelastographic results and hypercoagulability syndrome in patients with coronavirus disease 2019 who are critically III. *JAMA Netw Open.* 2020;3(6):e2011192. doi: 10.1001/jamanetworkopen.2020.11192
20. Bitsadze VO, Bredikhin RA, Bulatov VL, et al. Superficial phlebitis and thrombophlebitis. *Flebologiya.* 2021;15(3):211–44. (In Russ). doi: 10.17116/flebo202115031211
21. Agapov AB, Suchkov IA, Ryabkov AN. Direct oral anticoagulants in patients with deep venous thrombosis of lower extremities. *Nauka Molodykh (Eruditio Juvenium).* 2016;(2):147–57. (In Russ).
22. Petrikov AS, Dudin DV, Popkova LN, et al. Clinical course of deep venous thrombosis of lower limbs in acute period with underlying anticoagulant therapy depending on concentration of D-dimers and C-reactive protein. *Nauka Molodykh (Eruditio Juvenium).* 2018;6(2):233–41. (In Russ). doi: 10.23888/HMJ201862233-241
23. Kalinin RE, Suchkov IA, Narizhny MV. Dispensary management of patients with venous thromboembolic complications. *I. P. Pavlov Russian Medical Biological Herald.* 2011;(3):104–9. (In Russ).

ОБ АВТОРАХ

Калинин Роман Евгеньевич, д.м.н., профессор;
ORCID: https://orcid.org/0000-0002-0817-9573;
eLibrary SPIN: 5009-2318; e-mail: kalinin-re@yandex.ru

Сучков Игорь Александрович, д.м.н, профессор;
ORCID: https://orcid.org/0000-0002-1292-5452;
eLibrary SPIN: 6473-8662; e-mail: suchkov_med@mail.ru

***Агапов Андрей Борисович**, к.м.н.;
ORCID: https://orcid.org/0000-0003-0178-1649;
eLibrary SPIN: 2344-5966; e-mail: agapchik2008@yandex.ru

Мжаванадзе Нина Джансуговна, д.м.н., доцент;
ORCID: https://orcid.org/0000-0001-5437-1112;
eLibrary SPIN: 7757-8854; e-mail: nina_mzhavanadze@mail.ru

Поваров Владислав Олегович, к.м.н.;
ORCID: https://orcid.org/0000-0001-8810-9518;
eLibrary SPIN: 2873-1391; e-mail: ecko65@mail.ru

Никифоров Александр Алексеевич, к.м.н., доцент;
ORCID: https://orcid.org/0000-0003-0866-9705;
eLibrary SPIN: 8366-5282; e-mail: a.nikiforov@rzgmu.ru

AUTHOR'S INFO

Roman E. Kalinin, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-0817-9573;
eLibrary SPIN: 5009-2318; e-mail: kalinin-re@yandex.ru

Igor' A. Suchkov, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-1292-5452;
eLibrary SPIN: 6473-8662; e-mail: suchkov_med@mail.ru

***Andrey B. Agapov**, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0003-0178-1649;
eLibrary SPIN: 2344-5966; e-mail: agapchik2008@yandex.ru

Nina D. Mzhavanadze, MD, Dr. Sci. (Med.), Associate Professor;
ORCID: https://orcid.org/0000-0001-5437-1112;
eLibrary SPIN: 7757-8854; e-mail: nina_mzhavanadze@mail.ru

Vladislav O. Povarov, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0001-8810-9518;
eLibrary SPIN: 2873-1391; e-mail: ecko65@mail.ru

Aleksandr A. Nikiforov, MD, Cand. Sci. (Med.), Associate Professor;
ORCID: https://orcid.org/0000-0003-0866-9705;
eLibrary SPIN: 8366-5282; e-mail: a.nikiforov@rzgmu.ru

* Автор, ответственный за переписку / Corresponding author