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Morphofunctional characteristics of the vessels of the small circle of blood circulation in those who died from severe and extremely severe forms of new coronavirus infection

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ABSTRACT

BACKGROUND: An important feature of COVID-19 is the development of pronounced hypercoagulation with an increased risk of thrombotic damage to the pulmonary vascular bed, mainly the pulmonary arteries. Thrombosis of the pulmonary blood vessels causes a local violation of hemodynamics with the development of hyperemia, edema, which leads to a decrease in ventilation of the lung tissue area and serves as one of the causes of respiratory failure.

AIM: This study aimed to conduct a morphological and morphometric analysis of the vascular bed of lung tissues in deceased with severe and extremely severe forms of new coronavirus infection who were on inpatient treatment in the period 2020–2022.

MATERIALS AND METHODS: A pathomorphologic study of 129 autopsy cases with a confirmed diagnosis of a new coronavirus infection COVID-19 was performed. Morphometric analysis and statistical data processing of the pulmonary vascular system in histologic preparations stained with hematoxylin and eosin stain, orcein stain and Martius Scarlet Blue (MSB) stain was performed. The control group consisted of 14 patients who died of cardiovascular disease with bilateral focal confluent pneumonia.

RESULTS: It was found that the proportion of thrombosed vessels in the lung tissues of the deceased was 27.6%. In 87.2% of cases, thrombosis develops in small arteries (lumen diameter 30–500 microns) and small veins (lumen diameter 40–500 microns). The vascular-functional indices of Kernogan and Vogenworth were statistically significantly increased in small arteries and small veins of the 4th order (p=0.001), small arteries (p=0.001) and small veins of the 5th order (p=0.014) compared with the control group.

CONCLUSIONS: Diffuse involvement of small caliber blood vessels in the pathological process reflects the severity of specific hemocoagulopathic disorders in the lung tissue. Such disorders lead to the development of ventilation-perfusion disorders and entail an increase in right ventricular failure.

Keywords: COVID-19; thrombosis; thromboembolism; pulmonary circulation.

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Морфофункциональная характеристика сосудов малого круга кровообращения у умерших от тяжёлых и крайне тяжёлых форм новой коронавирусной инфекции

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АННОТАЦИЯ

Обоснование. Важной особенностью COVID-19 является развитие выраженной гиперкоагуляции с повышенным риском тромботического поражения сосудистого русла лёгких. Тромбозы лёгочных кровеносных сосудов обусловливают локальное нарушение гемодинамики с развитием полнокровия и отёка, что приводит к снижению вентиляции участка ткани лёгкого и служит одной из причин развития дыхательной недостаточности.

Цель исследования — выполнить морфологический и морфометрический анализ сосудистого русла лёгких у умерших с тяжёлыми и крайне тяжёлыми формами новой коронавирусной инфекции, находившихся на стационарном лечении в 2020–2022 гг.

Материалы и методы. Выполнено патоморфологическое исследование 129 секционных случаев с подтверждённым (ПЦР) диагнозом «новая коронавирусная инфекция COVID-19». Гистологические препараты лёгких окрашивали гематоксилином и эозином, орсеином и Martius Scarlet Blue (MSB) по Лендруму с последующей гистоморфометрией и статистической обработкой данных. В качестве контроля использовали архивный аутопсийный материал 14 умерших до 2020 года от сердечно-сосудистых заболеваний с двусторонней очаговой пневмонией.

Результаты. Установлено, что у умерших в тканях лёгких доля тромбированных сосудов составила 27,6%. В 87,2% случаев тромбоз развивался в мелких артериях (диаметр просвета — 30–500 мкм) и мелких венах (диаметр просвета — 40–500 мкм). Сосудисто-функциональные индексы Керногана и Вогенворта статистически значимо увеличены в мелких артериях и мелких венах 4-го порядка (p=0,001), мелких артериях (p=0,001) и мелких венах 5-го порядка (p=0,014) по сравнению с контрольной группой.

Заключение. Диффузное вовлечение в патологический процесс кровеносных сосудов малого круга отражает выраженность гемокоагулопатических нарушений в лёгочной ткани, приводящих к несоответствию вентиляционно-перфузионных отношений и влекущих за собой нарастание правожелудочковой недостаточности, что может быть значимо в декомпенсации сердечной недостаточности и развитии летального исхода.

Ключевые слова: COVID-19; тромбоз; тромбоэмболия; малый круг кровообращения.

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BACKGROUND

One of the first sectional observations of coronavirus disease-2019 (COVID-19) showed that histological examinations of lung tissues revealed signs of diffuse alveolar damage, namely, interstitial and alveolar edema, death and desquamation of alveolocytes, formation of hyaline membranes, and lymphohistiocytic infiltration [1]. Among the causes of death, cardiopulmonary and heart failure rank second in addition to increasing rates of respiratory failure and intoxication [2–4]. An important feature of COVID-19 is the development of severe hypercoagulation with an increased risk of thrombotic damage to the vascular bed of the lungs, mainly the pulmonary arteries [5–9]. This condition should be distinguished from thromboembolism of the pulmonary artery and its branches, which may be also found in a small number of deceased patients. Among the causes of thrombosis of the pulmonary circulation in COVID-19, recent studies have highlighted direct damage to the vascular wall, which causes its impaired permeability and edema. The "cytokine storm" is considered significant in triggering the hemocoagulation cascade; as a result, it received the figurative name "immunotrombosis" [10, 11]. Thrombosis of pulmonary blood vessels causes local impairment of hemodynamics accompanied by organ plethora, edema, and consequently decreased lung ventilation. They serve as one of the causes of respiratory failure. Thrombotic lesions in the vascular bed of the lung tissue without thrombosis of the deep veins of the legs and pelvic tissue determine the unique pathomorphogenesis of COVID-19 [12–18].

The study aimed to conduct clinical and morphological analyses of the status of the pulmonary vessels in patients who were hospitalized in 2020–2022 and died from severe and extremely severe COVID-19.

MATERIALS AND METHODS

The study analyzed data from 129 patients diagnosed with COVID-19. SARS-CoV-2 was confirmed post-mortem through polymerase chain reaction in all deceased individuals included in the study. Clinical data of the deceased patients were collected. During the post-mortem autopsy, lung fragments with macroscopically most pronounced signs of diffuse alveolar damage were taken for histological examination.

Archival autopsy materials from 14 age-matched patients who died from cardiovascular diseases in 2018–2019 were used as controls. In the control group, bilateral focal confluent pneumonia was confirmed, which was indicated in the diagnosis "complications of the underlying disease."

Lung fragments were fixed in a 10% neutral formalin solution for 24 h. Histological examination was performed according to a standard protocol. Moreover, 3–4 μm thick sections were prepared from paraffin blocks on a rotary microtome, and they were stained with hematoxylin and eosin, as well as orcein to identify elastic fibers.

All blood vessels revealed in histological lung preparations were ranked according to their outer diameter by 17 orders of magnitude following the classification proposed by S. Singhal et al. in 1973 [19]. The blood vessels were categorized according to their internal diameter based on the classification of N.C. Staub and E.L. Schultz in 1968 [20].

To assess the age of thrombogenesis in the blood vessels in the lungs, triple staining with Martius Scarlet Blue (MSB) according to Lendrum (BioVitrum, Russia) was used. The method is used to determine the age of the fibrin formation by the color of its staining: "young" fibrin, formed within 6 h before death, stained yellow–orange; "mature" fibrin, formed <24 h before death, has bright red colors of orange, scarlet, and violet shades; and "old" organizing fibrin and collagen fibers formed >24 h before death stained dark purple and blue gray.

Morphometric analysis was performed using ImageJ (National Institutes of Health, USA). In each histological specimen of the lung, the number of completely thrombosed blood vessels was counted. In the case of parietal thrombosis, its severity was determined, namely, with obstruction of <50% of the lumen or with obstruction of >50% of the lumen. Vessel wall thickness (mm), blood vessel lumen area (mm^2), blood vessel area (mm^2), internal blood vessel lumen diameter (mm), and blood vessel outer diameter (mm) were measured. The Kernohan (the ratio of the thickness of the vascular wall to the lumen diameter) and Wogenworth (the ratio of the area of the vascular wall to the area of the vessel lumen) vascular functional indices were determined to assess the perfusion status of the lung tissue.

Statistical processing of the research results was performed using SPSS (USA), compliance of the distributions of quantitative indicators with normality was assessed, and the average values and standard deviations were determined.

The Mann–Whitney *U* test was used to compare the quantitative indicators of two independent samples ($p \leqslant 0.05$). Indicators were presented as M±σ, where M was the average value and σ was the standard deviation, and min–max.

RESULTS

The average age of the patients at the time of death was 71±14 years. Among the deceased patients, 60% were men and 40% were women. Vital and laboratory parameters recorded on the first day and the last day of hospitalization are presented in Tables 1 and 2. The average hospital stay until the death of patients with severe and extremely severe COVID-19 was 8±6 days.

The comorbid background of patients with COVID-19 was characterized by the presence of widespread atherosclerosis

Table 1. Vital signs of patients who died from a new coronavirus infection on the first and last days of hospitalization; *n* — number of analyzed observations

Таблица 1. Витальные показатели пациентов, умерших от новой коронавирусной инфекции, в первые и последние сутки госпитализации; *n* — число проанализированных наблюдений

Indicator	*n*	First day of hospitalization, M±σ, min–max	Last day of hospitalization, M±σ, min–max	Reference values	*p*
Heart rate per minute	127	86±19 53–150	83±6 50–123	60–90	0.758
Respiratory rate per minute*	13	23±6 16–35	21±2 20–25	16–18	0.521
Blood pressure, mm Hg	127	124/72±12/9 50/40–174/100	119/72±4/6 44/15–145/90	<139/<89	0.512
spO_2, %:					
without O_2 insufflation	11	88±11, 60–98	88±4, 78–96	95–100	0.885
with O_2 insufflation+	125	94±9, 70–99	92±1, 80–98	95–100	0.001
Temperature, °C	126	36.7±0.6 36.1–38.5	36.7±1.0 33–38.5	36.6±0.7	0.225

* cases of using artificial ventilation with an induced respiratory rate were excluded from observations; + cases of high-flow oxygenation, noninvasive mechanical ventilation, and artificial ventilation were included.

* из наблюдений исключены случаи нахождения на искусственной вентиляции лёгких с индуцированной частотой дыхания; + включены случаи высокопоточной оксигенации, неинвазивной искусственной вентиляции лёгких и искусственной вентиляции лёгких.

in 100% of cases, hypertension in 85.7%, post-infarction cardiosclerosis in 33.3%, and type 2 diabetes mellitus in 38.1% with complications such as microangiopathy, macroangiopathy, and diabetic nephropathy. The concomitant pulmonary pathologies include chronic obstructive pulmonary disease (9.5%), chronic bronchitis (19.0%), and diffuse and peribronchial pneumofibrosis (23.8%). Bilateral total and subtotal pneumonia induced acute respiratory distress syndrome in 47.6% of cases and respiratory failure in 81%, which was combined with acute heart failure in 66.7%.

On the first day and last day of hospitalization, heart rate, respiratory rate, blood pressure, blood oxygen saturation without insufflations, and body temperature were not statistically significant, and the average values of most indicators were within the reference range. Statistically significant differences in the level of blood oxygen saturation (spO_2 during O_2 insufflation) on the first day and last day of hospitalization, before death, should be considered with caution because of the minimal difference in the average values of the indicator.

The results of the blood tests on the first and last days of hospitalization revealed statistically significant changes in indicators, showing an increase in the levels of inflammation markers, namely, leukocyte, neutrophil, and granulocyte counts, C-reactive protein, and procalcitonin; this often coincided with the occurrence of bacterial infection in addition to virus-induced diffuse alveolar damage. Patients also had a statistically significant increase in the neutrophil–lymphocyte ratio from the first day to the last day of hospitalization, which is considered one of the unfavorable diagnostic markers and is associated with a higher mortality risk. Patients admitted to the hospital with COVID-19 presented with laboratory anemia, and no statistically significant differences in red blood cell count and hemoglobin concentration were found from the first day of admission to death. Increased blood concentrations of D-dimer and fibrinogen and mild thrombocytopenia were characteristic laboratory signs of COVID-19-associated coagulopathy.

Histological examination revealed vascular wall changes, such as signs of damage and hydropic degeneration of endothelial cells, edema of the subendothelial connective tissue layer and tunica media, partial fragmentation of the internal and external elastic arterial membranes, and edema and lymphohistiocytic infiltration of the perivascular stroma (Fig. 1).

In the deceased group, blood clots were noted in the pulmonary vessels, which accounted for 27.6%. Obstructive thrombi were found in 53.1% of cases (Fig. 2). "Growing" blood clots (thromboemboli) were found in some cases, in which the previous central part (more than a day old) was covered with blood with newly formed fibrin (Fig. 2).

In blood vessels of the 14th order with a diameter of 4000–6500 microns, blood clots form less frequently (0.7%). Most often, thrombosis occurred in blood vessels of the 5th order with a diameter of 86–120 μm and those of the 6th order with a diameter of 120–250 μm (18.6% and 21.7%, respectively) (Table 3). Moreover, thrombogenesis was most often recorded in small arteries with a diameter of 30–500 μm and small veins with a diameter of 40–500 μm (33.7% and 38.0%, respectively). Less commonly, thrombi were located in large arteries with a diameter of 2800–3000 μm

Table 2. Data from clinical, biochemical blood tests and coagulograms in patients who died from a new coronavirus infection on the first and last days of hospitalization
Таблица 2. Данные клинического, биохимического анализов крови и коагулограммы у пациентов, умерших от новой коронавирусной инфекции, в первые и последние сутки госпитализации

Indicator	*n*	First day of hospitalization, M±σ, min–max	Last day of hospitalization, M±σ, min–max	Reference values	*p*
Leukocytes, 10^9/L	126	10.5±6.0 2.2–41.5	15.0±7.9 2.2–51.9	4–9	0.001
Neutrophils, 10^9/L	123	8.6±5.3 1.1–38.5	13.2±7.5 1.9–47.0	2.0–4.8	0.001
Lymphocytes, 10^9/L	124	1.1±1.3 0.2–14.6	1.0±0.8 0.2–5.6	1.3–2.9	0.097
Monocytes, 10^9/L	124	0.7±0.5 0.1–3.3	0.7±0.5 0.0–3.1	0.3–0.8	0.839
Neutrophil–lymphocyte ratio	123	10.88±8.92 0.0–48.60	18.12±11.26 0.60–56.40	0.78–3.53	0.001
Red blood cells, 10^{12}/L	11	3.89±0.83 2.66–5.17	3.75±0.55 2.70–5.50	4–5	0.660
Hemoglobin, g/L	13	115±22 82–150	114±18 85–175	130–160	0.467
Platelets, 109/L	13	216±154 71–538	149±46 66–243	150–450	0.416
Creatinine, μmol/L	11	153±73 82–288	228±97 93–384	62–115	0.122
Urea, mmol/L	11	15.3±8.5 6.4–27.1	28.9±20.2 7.2–66.1	1.8–8.3	0.098
C-reactive protein, mg/L	113	112.82±45.09 2.10–428.50	144.23±76.55 2.70–433.30	0–5	0.050
D-dimer, μg/mL	5	3.98±3.44 0.34–7.49	1.95±0.37 1.68–2.38	0–0.44	0.786
Troponin T, pg/mL	4	1376.36±2489.80 21.0–5109.0	2419.31±3786.86 94.0–6789.0	⩽14.0*	0.629
Procalcitonin, ng/mL	4	0.562±0.216 0.330–0.760	1.256±0.769 0.710–1.800	<0.500	0.533
Fibrinogen, g/l	9	5.74±2.08 0.74–7.74	3.53±2.10 1.77–5.85	2–4	0.100

* the clinical threshold value for diagnosing myocardial infarction is 100.0 pg/mL.
* клиническое пороговое значение для диагностики инфаркта миокарда — 100,0 пг/мл.

and large veins with a diameter of 12,000–30,000 μm (0.3% and 0.1%, respectively) (Table 4).

The age of fibrin formation in the lumen of blood vessels revealed a heterochronic process. The proportion of "young" thrombi formed within 0–6 h was 29.1%, that of "mature" thrombi (aged 6–24 h) was 48.8%, and that of "old" thrombi (aged >24 h) was 22.1% (Fig. 2). Therefore, at least 2/3 of blood clots in the pulmonary vessels were formed in the last day of life.

The functional state of the pulmonary circulation was characterized by the Kernohan and Wogenworth indices, which in most cases were used to establish a significant decrease in lung perfusion compared with the control. Thus, a comparison depending on the order of blood vessels demonstrated that the Kernohan index was statistically significantly higher in arteries of the 3rd, 4th, and 7th orders (p=0.023, p=0.001, and p=0.010, respectively) and veins of the 4th order (p=0.001) in the COVID-19 group than in the control group and lower in arteries of the 10th order (p=0.003) in the COVID-19 group than in the control group (Table 5, Fig. 3). When comparing the Wogenworth perfusion index of the deceased group with the control group, a statistically significant difference was obtained in many comparison pairs (Table 6, Fig. 4).

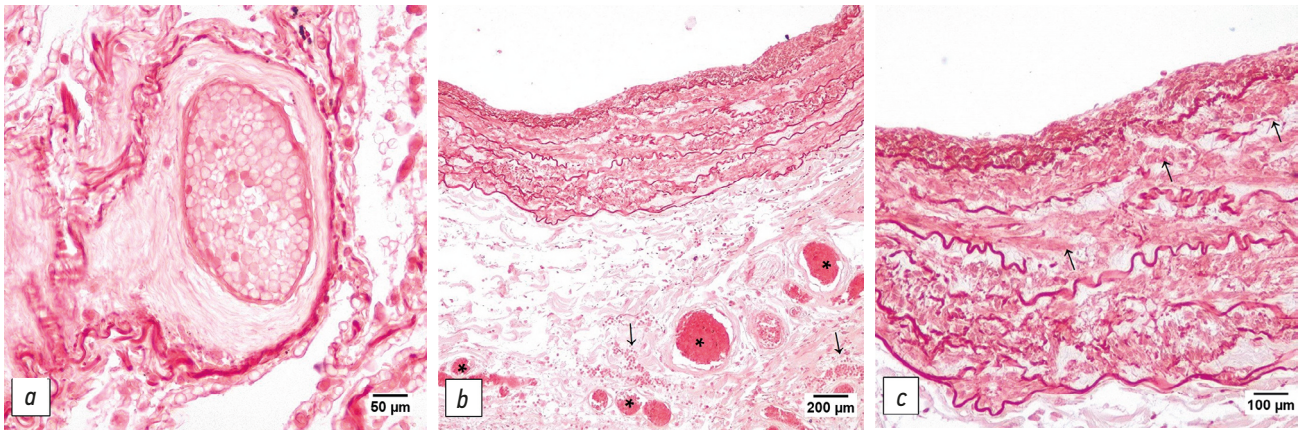

Fig. 1. A cross section of the arteries of the small circulatory circle: *a* — edema and dilution of the t. media of the small artery with displacement of the outer elastic membrane; *b* — edema and destruction of the elastic framework of the t. media major artery (arrows), stasis in the vasa vasorum adventitia (asterisks), with foci of hemorrhage around them (arrows), pronounced perivascular edema with dissociation of connective tissue fibers; *c* — edema of the t. media major artery. Orcein stain; *a* — ×400; *b* — ×100; *c* — ×200.

Рис. 1. Поперечный срез артерий малого круга кровообращения: *a* — отёк и разволокнение tunica media мелкой артерии с оттеснением наружной эластической мембраны; *b* — отёк и разрушение эластического каркаса tunica media крупной артерии (стрелки), стаз в vasa vasorum адвентиции (звёздочки), выраженный периваскулярный отёк с диссоциацией соединительнотканных волокон; *c* — отёк tunica media крупной артерии с очагами кровоизлияний (стрелки). Окраска орсеином; *a* — ×400; *b* — ×100; *c* — ×200.

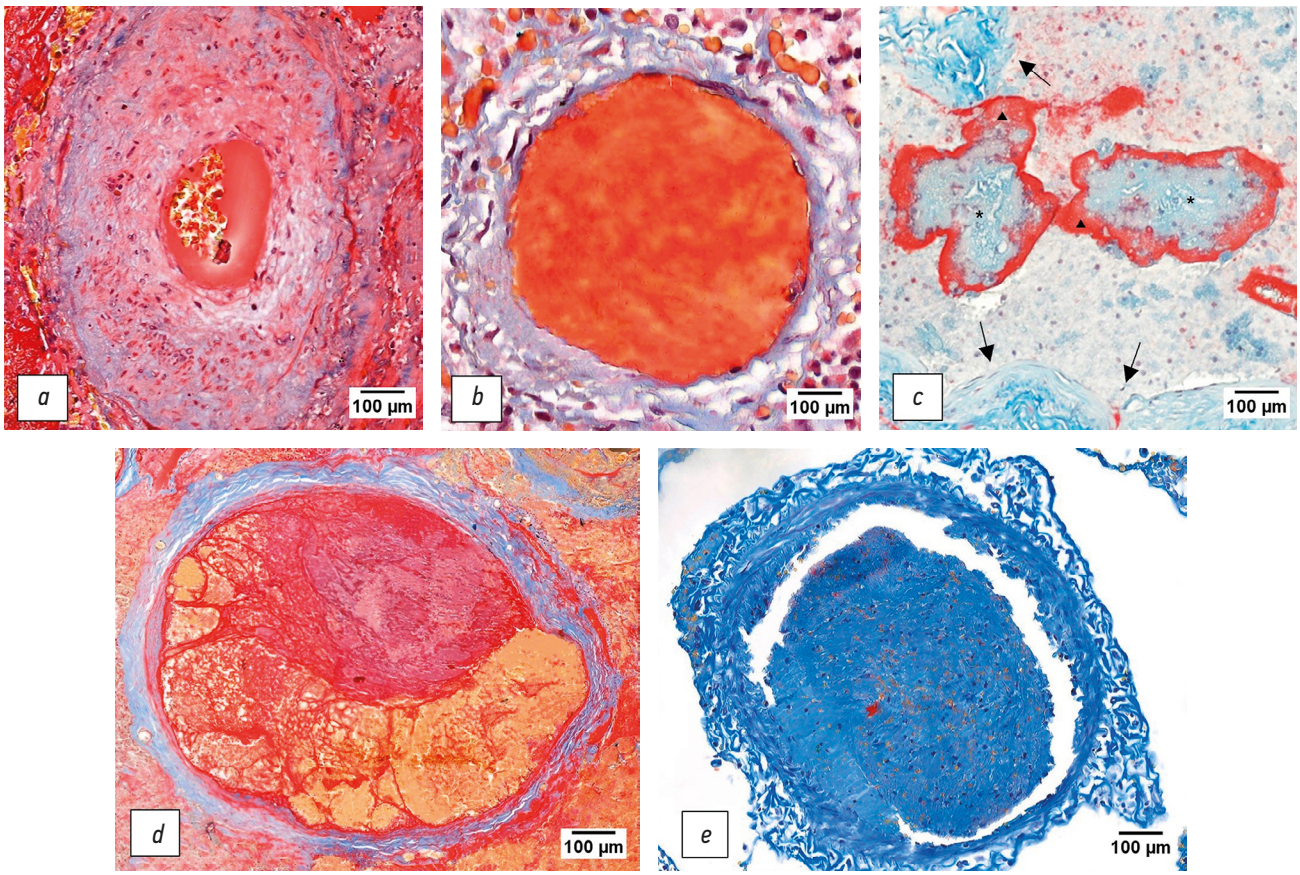

Fig. 2. Blood clots in the lumen of pulmonary vessels in those who died from a new coronavirus infection: *a* — sludge and hyaline thrombus in a vessel with a sharply hypertrophied wall; *b* — a fresh thrombus covering 100% of the vessel lumen; *c* — "growing" thromboembolism in the lumen of the lung vessel, the "old core" of the thrombus (asterisks), on which fresh fibrin is layered (triangles), the walls of the vessel (arrows); *d* — a thrombus consisting of fragments of various prescription; *e* — an "old" thrombus (>24 hours). Fibrin staining using Martius Scarlet Blue (MSB) technology by Lendrum; ×200.

Рис. 2. Тромбы в просвете лёгочных сосудов у умерших от новой коронавирусной инфекции: *a* — сладж эритроцитов и гиалиновый тромб в средней артерии с резко гипертрофированной стенкой; *b* — «молодой» тромб (0–6 ч), полностью обтурирующий просвет сосуда; *c* — «растущий» тромбоэмбол в просвете сосуда лёгкого, «старое ядро» тромба (звёздочки), на которое наслаивается свежий фибрин (треугольники), стенки сосуда (стрелки); *d* — тромб, состоящий из фрагментов различной давности; *e* — «старый» тромб (>24 ч). Окраска на фибрин по методу Martius Scarlet Blue (MSB) по Лендруму; ×200.

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Table 3. Proportion of thrombosed blood vessels of the lungs depending on the order according to S. Singhal et al. (1973) [19])
Таблица 3. Долевое соотношение тромбированных кровеносных сосудов лёгких в зависимости от порядка (по S. Singhal и соавт. (1973) [19])

Vessel order	Vessel size, μm	Proportion of thrombosed vessels, %
1	0–13	0
2	13–21	0
3	21–34	1.4
4	34–86	7.6
5	86–120	18.6
6	120–250	21.7
7	250–370	15.0
8	370–600	13.8
9	600–800	7.0
10	800–1000	3.6
11	1000–1200	3.4
12	1200–2800	6.0
13	2800–4000	0.9
14	4000–6500	0.7
15	6500–10000	0.2
16	10 000–19 000	0.1
17	19 000–30 000	0.1

Table 4. Proportion of the thrombosed blood vessels in the lungs depending on the internal diameter according to N.C. Staub and E.L. Schultz (1968) [20])
Таблица 4. Долевое соотношение тромбированных кровеносных сосудов в лёгких в зависимости от внутреннего диаметра (по N.C. Staub и E.L. Schultz (1968) [20])

Vessel type	Vessel size, μm	Proportion of thrombosed vessels, %
Large arteries	2800–3000	0.3
Middle arteries	500–2800	6.8
Small arteries	30–500	33.7
Arterioles	20–30	2.6
Capillaries	<20	0.3
Venules	20–40	7.9
Small veins	40–500	38.0
Middle veins	50–12 000	10.4
Large veins	12 000–30 000	0.1

DISCUSSION

The vasopathic and hemostatic effects of SARS-CoV-2 were already described at the beginning of the pandemic [9, 13]. The cytopathic effect of SARS-CoV-2 against endothelial cells is implemented through the interaction of the virus S protein with angiotensin-converting enzyme 2, which can lead to pyroptosis (proinflammatory apoptosis) and the release of damage-associated molecular fragment patterns or pathogen-associated molecular patterns. These fragments are recognized by receptors, such as Toll-like receptors and C-type lectin receptors, which trigger intracellular signaling cascades and thus stimulate the production of proinflammatory cytokines and chemokines that can potentiate coagulation by nearby epithelial cells, endothelial cells, and alveolar macrophages, namely interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α [21], which in turn have damaging effects on endothelial cells. As a result, the procoagulant potential increases, fibrinolysis decreases, and platelet adhesion and aggregation are disrupted. In addition, inflammatory factors promote additional migration of inflammatory and immune system cells to the damaged site, namely, neutrophil granulocytes, monocytes, macrophages, dendritic cells, T lymphocytes, natural killer cells, and mast cells [22–24]. Pathomorphological manifestations of pyroptosis and damage to the endothelium of the blood vessels of the pulmonary bed, hydropic degeneration and foci of death and desquamation of endothelial cells, and edema of the subendothelial connective tissue layer were described in the scientific literature and revealed in this study.

When the tunica intima of blood vessels is damaged, the basement membrane is exposed, which has prothrombogenic potential because of the production of von Willebrand factor and P-selectin contained in Weibel–Palade bodies [25].

The interaction of the SARS-CoV-2 S protein with the α5β1 integrin located on the platelet membrane leads to changes in their functional activity and is manifested by impaired platelet hemostasis. The internalization of SARS-CoV-2 viral particles into platelets was assumed to lead to the activation of Toll-like receptors 7 located in the lysosomes, which is accompanied by the release of the contents of α-granules and consequently the interaction of platelets with neutrophil granulocytes. In addition, the stimulation of Toll-like receptors 7 can enhance the production of the C3 component of complement by platelets, which promotes the formation of neutrophil extracellular traps, which further stimulate local thrombogenesis [26].

The results of pathomorphological and morphometric analyses confirm literature data that anti-inflammatory and anticoagulant therapy exert suboptimal effects on patients with severe and extremely severe COVID-19 [27]. This is evidenced by the proportion of thrombosed blood vessels in the lungs (27.6%) and more than half of all blood clots completely obstruct the lumen. The predominant damage to small- and medium-sized blood vessels (87.2% and 11.6%, respectively)

Table 5. Comparison of the Kernogan index depending on their order and inner diameter
Таблица 5. Сравнение индекса Керногана в зависимости от порядка кровеносных сосудов и их внутреннего диаметра

Order of the vessel and its dimensions, μm (according to S. Singhal et al. (1973) [19])	Type of vessel and its dimensions, μm (according to N.C. Staub and E.L. Schultz (1968) [20])	COVID-19, M±σ, min–max	Control, M±σ, min–max	*p*
Arterioles, 3rd order (21–34)	Arterioles (20–30)	0.23±0.05 0.18–0.30	0.17±0.08 0.08–0.45	0.023
Arteries and arterioles, 4th order (34–86)	Arterioles (20–30)	0.46±0.23 0.12–1.19	0.29±0.16 0.08–1.07	0.001
	Small arteries (30–50)	0.24±0.11 0.05–0.76	0.20±0.15 0.03–0.68	0.001
Arteries, 7th order (250–370)	Small arteries (30–50)	0.18±0.13 0.00–1.03	0.12±0.07 0.03–0.26	0.010
Arteries, 10th order (800–1000)	Middle arteries (500–2800)	0.11±0.08 0.01–0.40	0.19±0.03 0.15–0.23	0.003
Veins, 4th order (34–86)	Small veins (40–500)	0.17±0.07 0.02–0.55	0.15±0.07 0.05–0.55	0.001

Note. Only data with significant differences $p \leqslant 0.05$ are given.
Примечание. Приведены только данные со статистической значимостью различий $p \leqslant 0,05$.

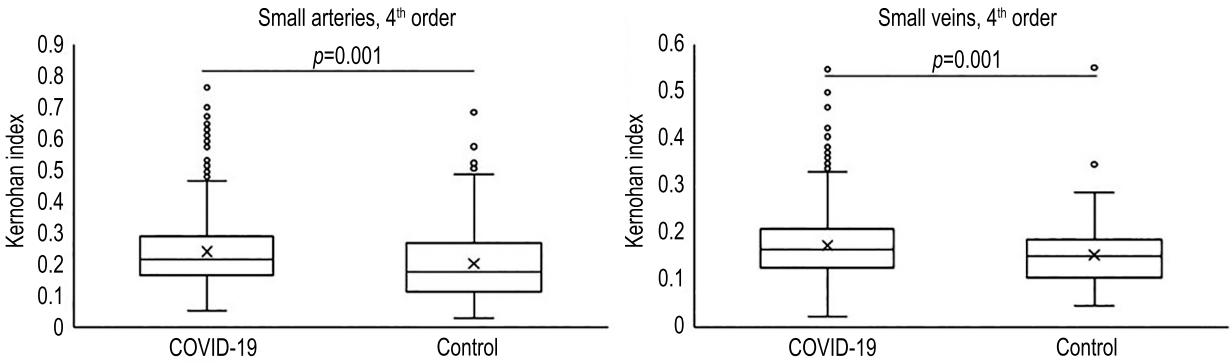

Fig. 3. Kernogan index in small arteries and veins of the 4th order in patients who died from a new coronavirus infection and the control group according to the size of the vessels, depending on their order and internal diameter.
Рис. 3. Индекс Керногана в мелких артериях и венах 4-го порядка у умерших от новой коронавирусной инфекции и группы контроля по размерам сосудов в зависимости от их порядка и внутреннего диаметра.

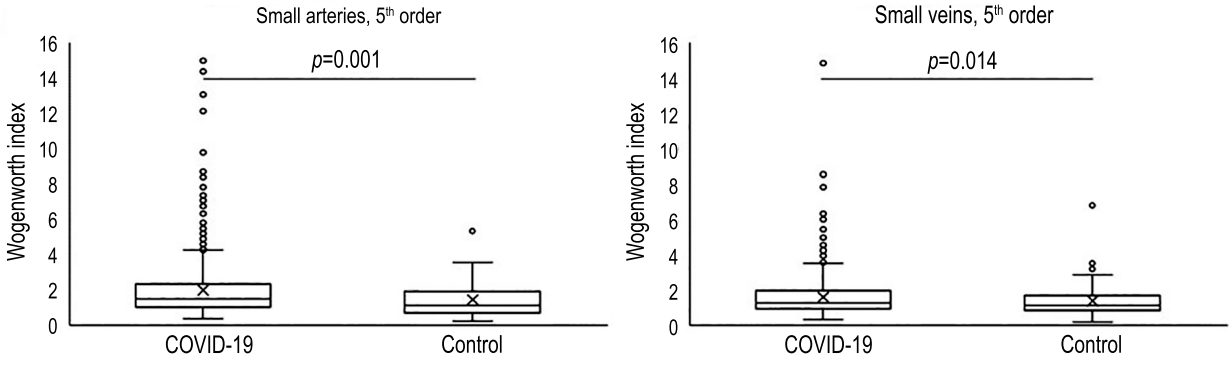

Fig. 4. The Vogenworth index in small arteries and veins of the 5th order in those who died from a new coronavirus infection and the control group according to the size of the vessels, depending on their order and internal diameter.
Рис. 4. Индекс Вогенворта в мелких артериях и венах 5-го порядка у умерших от новой коронавирусной инфекции и группы контроля по размерам сосудов в зависимости от их порядка и внутреннего диаметра.

in COVID-19 reflects the systemic nature of endothelial dysfunction and immunothrombosis in the lung tissue. In 2021, a systematic review indicated that small vessels in the lung tissue were predominantly affected. According to L.P. Hariri et al., in 57% of the deceased patients with COVID-19, histological examination revealed microthrombi in the lung tissue. This percentage is significantly higher than that in patients with influenza A/H1N1 (≈24%) [28]. The causes of blood clots in predominantly small-sized blood vessels are currently unknown and require further investigations.

The use of triple staining to detect the age of fibrin by MSB technology according to Lendrum helped establish that the majority of blood clots (up to 77.9%) were formed in the last day of life of the patients. This finding helps us draw conclusions about the influence of thrombotic lesions in the blood vessels in the lung tissues on the development of a terminal pulmonary condition, which is characterized by ventilation–perfusion disorders and ends in death due to the pulmonary disease.

The results indicated that the vascular link in the pathomorphogenesis of COVID-19 is important in the development of severe diseases. The evaluation of the Kernohan and Wogenworth indices allows for the characterization of the decreased capacity of pulmonary blood vessels, which is associated with changes in the lumen diameter and vascular wall thickness (Kernohan index) and/or its area (Wogenworth index), including in patients with comorbidities and chronic hypertension; these cases account for 66%–88% in the deceased group [2, 3]. The statistically significant increase in the Kernohan and Wogenworth indices in small- and medium-sized blood vessels indicates more pronounced vasoconstriction and/or thickening of the wall or an increase in its area compared with the control group, which is generally consistent with previous reports [29]. The patho- and thanatogenetic significance of increased Kernohan and Wogenworth indices indicate that a decrease in the capacity of pulmonary blood vessels is accompanied by an increase in pulmonary vascular resistance and pressure in the pulmonary artery.

Thus, massive thrombotic damage to small- and medium-sized blood vessels of the lungs, vasoconstriction, and thickening of blood vessel walls (including due to edema) overload the right ventricle, leading to dilatation and dysfunction of the right ventricle [30].

CONCLUSIONS

The results of the morphological and morphometric studies of blood vessels demonstrate the systemic nature of thrombogenesis in the lung tissue. Lesions were predominantly found in small- and medium-sized blood vessels, and blood clots most commonly formed on the last day of life and completely obturate the lumen. The pathogenetic and thanatogenetic significance of diffuse microthrombosis in the lungs is associated with the development of ventilation–perfusion disorders and overload of the right heart compartments, which leads to right ventricular dysfunction. In some cases, this is a significant factor in thanatogenesis in patients with comorbidities, which account for the majority of patients who died from COVID-19.

ADDITIONAL INFORMATION

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Authors' contribution. 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. A.M. Emelin — collection and processing of material, writing the text; I.P. Sorochanu — literature review, collection and processing of material, writing the text; Z.P. Asaulenko — literature review, collection and processing of material, writing the text; V.A. Rogovoy — collection and processing of material, writing the text; O.S. Popov — concept and design research, collection and processing of material; S.V. Mosenko — concept and design research, collection and processing of material; S.V. Apalko — concept and design of research, collection and processing of material; A.S. Buchaka — collection and processing of material; S.V. Gladchenko — concept and design of research; A.Yu. Anisenkova — concept and design of research; S.G. Shcherbak — the concept and design of the study; R.V. Deev — the concept and design of the study, writing and editing the text.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Источник финансирования. Исследование выполнено в рамках проекта Федерального государственного бюджетного образовательного учреждения высшего образования «Санкт-Петербургский государственный университет», ID 94029859.

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Вклад авторов. 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). Наибольший вклад распределён следующим образом: А.М. Емелин — сбор и обработка материала, написание текста; И.П. Сорочану — обзор литературы, сбор и обработка материала, написание текста; З.П. Асауленко — обзор литературы, сбор и обработка материала, написание текста; В.А. Роговой — сбор и обработка материала, написание текста; О.С. Попов — концепция и дизайн исследования, сбор и обработка материала; С.В. Мосенко — концепция и дизайн исследования, сбор и обработка материала; С.В. Апалько — концепция и дизайн исследования, сбор и обработка материала; А.С. Бучака — сбор и обработка материала; С.В. Гладченко — концепция и дизайн исследования; А.Ю. Анисенкова — концепция и дизайн исследования; С.Г. Щербак — концепция и дизайн исследования; Р.В. Деев — концепция и дизайн исследования, написание и редактирование текста.

Appendix 1.
Приложение 1.

Table 6. Comparison of the Vogenworth index depending on their order and inner diameter
Таблица 6. Сравнение индекса Вогенворта в зависимости от порядка кровеносных сосудов и их внутреннего диаметра

Order of the vessel and its dimensions, μm (according to S. Singhal et al. (1973) [19])	Type of vessel and its dimensions, μm (according to N.C. Staub and E.L. Schultz (1968) [20])	COVID-19, M±σ, min–max	Control, M±σ, min–max	*p*
Arteries and arterioles, 4th order (34–86)	Arterioles (20–30)	3.53±3.03 0.63–20.48	1.65±0.87 0.47–5.04	0.001
	Small arteries (30–500)	1.66±0.98 0.43–7.09	1.21±0.84 0.12–7.83	0.001
Arteries, 5th order (86–120)	Small arteries (30–500)	1.98±1.60 0.39–14.97	1.46±1.00 0.24–5.33	0.001
Arteries, 6th order (120–250)	Small arteries (30–500)	2.38±2.35 0.19–24.57	1.41±1.17 0.04–6.83	0.001
Arteries, 7th order (250–370)	Small arteries (30–500)	3.12±3.71 0.12–35.74	0.66±0.46 0.13–1.76	0.001
Arteries, 8th order (370–600)	Small arteries (30–500)	2.96±3.89 0.09–39.08	0.83±0.67 0.14–3.38	0.001
Arteries, 9th order (600–800)	Middle arteries (500–2800)	3.38±4.37 0.17–23.49	0.49±0.25 0.1–0.79	0.001
Arteries, 10th order (800–1000)	Middle arteries (500–2800)	3.69±4.84 0.14–23.69	0.90±0.18 0.67–1.15	0.028
Arteries, 12th order (1200–2800)	Middle arteries (500–2800)	2.82±3.07 0.11–20.5	0.45±0.13 0.36–0.60	0.002
Veins, 4th order (34–86)	Venules (20–40)	1.74±1.06 0.41–9.89	1.91±0.9 0.55–4.75	0.038
Veins, 5th order (86–120)	Small veins (40–500)	1.6±1.12 0.32–15.01	1.37±0.88 0.19–6.79	0.014
Veins, 6th order (120–250)	Small veins (40–500)	2.17±1.54 0.19–13.56	1.28±0.83 0.27–5.01	0.001
Veins, 7th order (250–370)	Small veins (40–500)	2.72±2.09 0.21–21.82	0.97±0.65 0.12–2.39	0.001
Veins, 8th order (370–600)	Small veins (40–500)	2.73±2.36 0.12–17.04	0.51±0.43 0.09–1.95	0.001
	Middle veins (500–12 000)	3.31±2.62 0.16–11.94	0.25±0.10 0.14–0.33	0.009
Veins, 9th order (600–800)	Middle veins (500–12 000)	2.67±3.16 0.15–18.68	0.42±0.22 0.05–1.01	0.001
Veins, 10th order (800–1000)	Middle veins (500–12 000)	3.25±5.56 0.19–36.81	0.61±0.35 0.24–1.06	0.035

Note. Only data with significant differences $p \leqslant 0.05$ are given.
Примечание. Приведены только данные со статистической значимостью различий $p \leqslant 0{,}05$.

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