

Pulmonary Vascular Thrombosis in COVID-19: Clinical and Morphological Parallels

Porembskaya O.Ya.^{1*}, Kravchuk V.N.¹, Galchenko M.I.², Deev R.V.¹, Chesnokov M.Sh.¹, Avanesyan A.V.¹, Lobastov K.V.^{3,4}, Tsaplin S.N.^{3,4}, Laberko L.A.³, Ermakov V.S.¹, Pashovkina O.V.⁴, Schastlivtsev I.V.³, Sayganov S.A.¹

¹ Mechnikov's North-Western State Medical University, St-Petersburg, Russia

² State Agrarian University, St-Petersburg, Russia

³ Pirogov Russian National Research Medical University, Moscow, Russia

⁴ Clinical hospital no.1 of the Presidents Administration of Russian Federation, Moscow, Russia

Aim. We aimed to study the histological and thrombotic changes in lung vessels in patients who died with COVID-19, to assess the correlation between anticoagulation therapy (ACT) and thrombotic events (TE), treatment results, clinical and laboratory patients' characteristics.

Material and Methods. We retrospectively analyzed treatment results of patients hospitalized with COVID-19 and lung vessel samples of the deceased patients. Dynamic changes and highest levels of D-dimer and fibrinogen were studied in its correlation with the disease severity according to SOFA score, computer tomographic (CT) results, lung, renal and hepatic dysfunction. The association between different doses of ACT and treatment results, laboratory indicators and thrombotic events was assessed. The histological lung vessels examination was performed using Martius Scarlet Blue (MSB) staining.

Results. 313 patients were included in the study (61 patients died). The median age of hospitalized patients was 60 years (IQR 51-66 years). The frequency of the intravitaly confirmed TE was 4,8%. The strong statistical association was revealed between D-dimer level and 3-4 points SOFA score, patients' mortality, oxygen support requirement, CT3-CT4 pneumonia, glomerular filtration rate and TE. There was no mortality in patients with D-dimer normal references, but in cases with three times elevation reached 13%, 48,5% - in cases with 3-6 times elevation and 64,6% - in cases with more than 6 times elevation. The strong statistical association was registered between fibrinogen and SOFA score, CT 3-4 pneumonia, patients' mortality. D-dimer and fibrinogen levels demonstrated weak correlation. There was no statistical correlation between prophylactic, intermediate and therapeutic ACT and D-dimer and fibrinogen levels, CT results, patients' mortality. MSB staining was used in 36 deceased patients tissue samples. 1394 lung vessels were analyzed. Lung vessels thrombi persisted in samples of all 36 patients (100%). Vessels with the diameter 3,5-30 mm were thrombosed in 7%, with the diameter 0,034-0,84 mm - in 48%, with the diameter 0,85-3,4 mm - in 45%. The frequency of thrombi persisted 0-6 hours, 6-12 hours, 12-18 hours, 18-24 hours and more than 24 hours was 12%, 14%, 62%, 5% and 7% respectively.

Conclusion. Thrombi of different ages from fresh to organized were observed in one third of lung vessels in all deceased patients. Lung vessels thrombosis plays an important role in pathogenesis and thanatogenesis of COVID-19. The D-dimer level correlates with lung, renal dysfunction, patients' mortality and doesn't show any correlation with ACT and can be accepted as a criterion of lung vessel thrombotic progression.

Key words: pulmonary artery thrombosis, COVID-19, D-dimer, hypercoagulation

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*Corresponding Author: porembskaya@yandex.ru

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Introduction

Features of the clinical picture of the disease with a high incidence of thrombotic complications, changes in the coagulation system, and ambiguous effects of anticoagulant therapy became apparent from the first months of the spread of a new coronavirus infection (COVID-19) in the world. The conducted meta-analyses indicated a high incidence of venous thromboembolic complications (VTEC), reaching 17-33.1%, of which up to 20% were due to deep vein thrombosis (DVT), and up to 13% were due to pulmonary embolism (PE) [1, 2]. An important feature of the course of COVID-19 is thrombotic lesion of the pulmonary vascular bed, often occurring without simultaneous DVT (up to 58%), which determines the uniqueness of the disease phenotype [3, 4].

Clinical manifestations of VTEC are accompanied by changes in laboratory parameters, which are considered as prognostic factors. The D-dimer level is significant with high sensitivity (91%) in relation to the detection of VTEC in patients with COVID-19 [3]. An increase in D-dimer >2000 ng/mL is associated with the risk of severe COVID-19 (66%), thrombotic events (37.8%), kidney damage (58.3%), and death (47%) [5]. The predictive value of D-dimer is emphasized by its use in the Caprini and Improve DD scales, validated to assess the risk of developing VTEC in patients with COVID-19 [6, 7].

The course of the disease with a high incidence of VTEC gave rise to the concept of thromboprophylaxis in the treatment of patients with COVID-19 and was reflected in the recommendations of various communities for the appointment of anticoagulant therapy (ACT) as a basic component of therapy for patients hospitalized with COVID-19 [8, 9]. Controversy arose regarding the need to escalate ACT dosages. A meta-analysis has shown a reduction in the risk of arterial and venous thrombotic events with the use of higher doses of anticoagulants [10]. There was no correlation between therapeutic doses of ACT and the survival of severe patients, and the probability of discharge from the hospital without organ support increased only in patients with a moderate course of the disease [11-13].

A feature of ongoing studies to determine the effectiveness of ACT in COVID-19 is the assessment of the combined endpoint, where VTEC is considered as one of the criteria for the effectiveness of therapy [11-13]. This indicates a complex pathogenesis and thanatogenesis of COVID-19, in which thrombotic processes are integrated with specific features of the

course and with a limited response to the administration of anticoagulants [14, 15].

The aim of the study was to study the histological changes and features of thrombotic lesions of the pulmonary vascular bed in patients who died with COVID-19, to access the relationship between different doses of anticoagulant drugs and thrombosis processes, treatment outcomes and laboratory patients' characteristics.

Material and Methods

The study is a combination of a retrospective analysis of the results of inpatient treatment of patients with confirmed COVID-19 and a morphological study of lung tissue samples obtained from deceased patients.

The study included 313 patients who were treated with a confirmed diagnosis of COVID-19 in May, October 2020 and July 2021 in two hospitals repurposed as infectious diseases hospitals during the pandemic: Federal State Autonomous Educational Institution of Higher Education «North-Western State Medical University named after I.I. Mechnikov» The Clinic named after Peter the Great and the Federal State Autonomous Educational Institution «Clinical Hospital No. 1» of the Administration of the President of the Russian Federation (Volynskaya Hospital) in Moscow.

Clinical study. The analysis of clinical and laboratory data and the results of instrumental studies was carried out on the basis of the content of the case histories of hospitalized patients with COVID-19 for the studied period of time. The analysis of laboratory parameters was carried out according to the peak values of the deviation from the normal values. The levels of D-dimer and fibrinogen in dynamics during monitoring during the treatment period were also assessed in several patients. DIC was diagnosed according to the ISTH criteria (>5 points) [16].

Patients were treated in accordance with the current interim Clinical Guidelines of the Ministry of Health of the Russian Federation. Prevention of VTEC was carried out using low molecular weight heparins (LMWH), or in more rare cases, unfractionated heparin (UFH), in standard prophylactic and intermediate or therapeutic dosages. The choice of the dose of the drug was determined by the severity of the patients' condition, the presence of risk factors for venous thromboembolic complications and the likelihood of bleeding, taking into account current recommendations for the use of anticoagulant drugs.

We switched to escalation of ACT dosages in case of aggravation of the severity of the patient's condition. Prophylactic and therapeutic doses of LMWH when administered subcutaneously corresponded to the official instructions for preparations, and the intermediate dose meant the introduction of 50% or 75% of the therapeutic dose.

All patients underwent computed tomography (CT) of the chest. Dynamic CT results over the period of hospital stay were available for analysis in individual cases. We performed contrast CT angiopulmonography for suspected thromboembolism of the pulmonary artery branches. Ultrasound angioscanning of the veins of the lower extremities was performed when symptoms of DVT appeared, or when searching for the source of PE, if such a diagnosis was made or suspected.

Morphological study. Autopsy was performed in all patients included in the study. At autopsy, we took lung fragments with typical macroscopic signs of diffuse alveolar damage. The fragments didn't include the vessels of the lung root and large branches of the pulmonary artery. Histological preparations of autopsy material were stained with hematoxylin and eosin and by Mallory. We used a triple stain to detect fibrin age based on the Martius Scarlet Blue (MSB) method according to Lendrum (BioVitrum, article 07-014, ErgoProduction) to assess the age of thrombosis in lung preparations. With this technique, «young» fibrin up to 6 hours old is characterized by yellow-orange staining, and «mature» fibrin up to 24 hours old is characterized by bright red. Blue and gray-blue colors were typical for fibrin older than 24 h and organizing fibrin with collagen fibers [17]. All vessels found in histological preparations of the lungs were ranked according to their diameter into 17 classes according to S. Singhal [18]. Additional informed consent for histological studies was not signed from relatives, because all studies met the ethical standards adopted in the Russian Federation.

Statistical analysis. Data processing was performed using the statistical programming language R (R Language version 4.1, jamovi). All numbers were presented as mean with standard deviation ($M \pm SD$) or median (Me) with interquartile range (25%; 75%), relative values with 95% confidence interval (CI) calculated by Wilson's method. Mann-Whitney-Wilcoxon's and Kruskal-Wallis's tests were used to assess differences between groups, and a chi-square test for cross-tabulations was used to assess association in the case of nominal traits. The Spearman's and

Kendall's correlation was used to estimate correlations. The interpretation is in line with the levels reported in Dong Kyu Leo's paper for estimating effect sizes in the case of nominal Cramer's V features [19]. D-dimer levels could be used when using the chi-square test due to the small number of patients in some of the groups. The indicator $p < 0.05$ was taken as statistically significant.

Results

General characteristics of patients. The median age of hospitalized patients ($n=313$) was 60 (51; 66) years, with higher mortality among patients older than 70 years ($p < 0.001$). The proportion of men was 52.4% and the proportion of women was 47.6%, the median duration of hospitalization was 13 (11; 16) days. The median body mass index was 29 (26; 32) kg/m² without its correlation with the outcome of the disease ($p=0.064$). Lethal outcome was observed in 61 cases (19.5%). Hypertension and coronary heart disease were diagnosed in 62.0% of patients, chronic obstructive pulmonary disease or bronchial asthma was diagnosed in 28 (8.9%), diabetes mellitus was diagnosed in 50 (16.0%), cerebrovascular disease was diagnosed in 13 (4.2%), oncological diseases were diagnosed in 13 (4.2%), other chronic diseases (chronic kidney disease, diseases of the gastrointestinal tract, autoimmune diseases) were diagnosed in 13 (4.2%). Thrombotic events were registered in 15 (4.8%) cases and were represented by: PE ($n=6$; 40.0% of the total number of VTECs), DVT ($n=3$; 20.0%), a combination of DVT and PE ($n=1$; 6.7%), thrombosis of the superficial veins of the lower extremities ($n=2$; 13.3%), post-injection thrombosis of the veins of the upper extremities ($n=1$; 6.7%), acute coronary syndrome ($n=2$; 13.3%).

Assessment of laboratory parameters

D-dimer. An increase in D-dimer up to 3 times (≤ 1500 µg/l) was observed in 37.1% of patients, an increase of 3-6 times (> 1500 and ≤ 3000 µg/l) was observed in 11.3%, an increase of more than 6 times (> 3000 mcg/l) was observed in 16.5% of cases. We observed an increase in the proportion of patients with high D-dimer levels as the severity of the disease on the SOFA scale increased (Cramer's $V=0.346$, $p < 0.001$) (Fig. 1). In the group of patients with a disease severity of 3-4 points on the SOFA scale, the proportion of persons without an increase in the D-dimer level was 8.7%, and the proportion

of persons with an increase of $>3000 \mu\text{g/l}$ in the D-dimer level was 43.5%. The same values of the indicator were determined in 37.7% and 3.3% of patients, respectively, in cases of mild course of the disease, corresponding to 0 points according to SOFA.

We found a moderate statistically significant relationship between D-dimer values and the need for oxygen support (with non-invasive and invasive ventilation; Cramer's $V=0.44$, $p<0.001$) and with death (Cramer's $V=0.6$, $p<0.001$) (Fig. 2). The association of D-dimer level $>1500 \mu\text{g/L}$ with glomerular filtration rate $<60 \text{ ml/min}$ (average association, Cramer's $V=0.258$, $p=0.002$) and high creatinine level (average association, Cramer's $V=0.314$, $p<0.001$) was significant. There was no correlation with the level of liver enzymes (AST, ALT). Widespread changes in the lung parenchyma at CT3 and CT4 severity of pneumonia were accompanied by a steady increase in the D-dimer level: an increase in the range >500 and $\leq 1500 \mu\text{g/l}$ up to 8%, $>3000 \mu\text{g/l}$ up to 48% (Cramer's $V=0.413$, $p<0.001$) (see Fig. 1). We found a moderate statistically significant association between thrombotic events and D-dimer levels (Cramer's $V=0.321$, $p<0.001$). The proportion of patients with thrombosis increases from 0% in patients with D-dimer $<500 \mu\text{g/l}$ to 38% with a value of $>3000 \mu\text{g/l}$.

A lethal outcome was not observed in any of the patients with a normal D-dimer value ($<500 \mu\text{g/l}$), but occurred in 13% of cases with its increase up to 3 times, in 48.5% with its increase by 3-6 times and in 64.6% with an increase of more than 6 times. D-dimer exceeded 3000 mcg/l in deceased patients in 50.8% of cases; D-dimer was in the range of >1500 and $\leq 3000 \text{ mcg/l}$ in 26.2%; and it was in the range of >500 and $\leq 1500 \text{ mcg/l}$ in 23% of cases.

Fibrinogen. The fibrinogen level exceeding 5 g/l was associated with the severity of the disease according to the SOFA scale of 3-4 points (Cramer's $V=0.224$, $p=0.02$), with the severity of pneumonia (CT3 and CT4 of the severity of pneumonia; Cramer's $V=0.241$, $p<0.001$). An increase in the fibrinogen level above 9 g/l was statistically significantly associated with the outcome of the disease: an increase in the proportion of deaths, especially at rates >4 and $\leq 5 \text{ g/l}$ and $>9 \text{ g/l}$ relative to normal values (Cramer's $V=0.226$, $p=0.002$). There was no statistically significant association with oxygen demand, glomerular filtration rate, creatinine levels, and ALT and AST activity. The fibrinogen level was within normal limits in deceased patients in 26.2% of cases, varied from >4 to $\leq 9 \text{ g/l}$ in 55.7%, exceeded 9 g/l in 16.4% of cases, and one patient had less than 1 g/l .

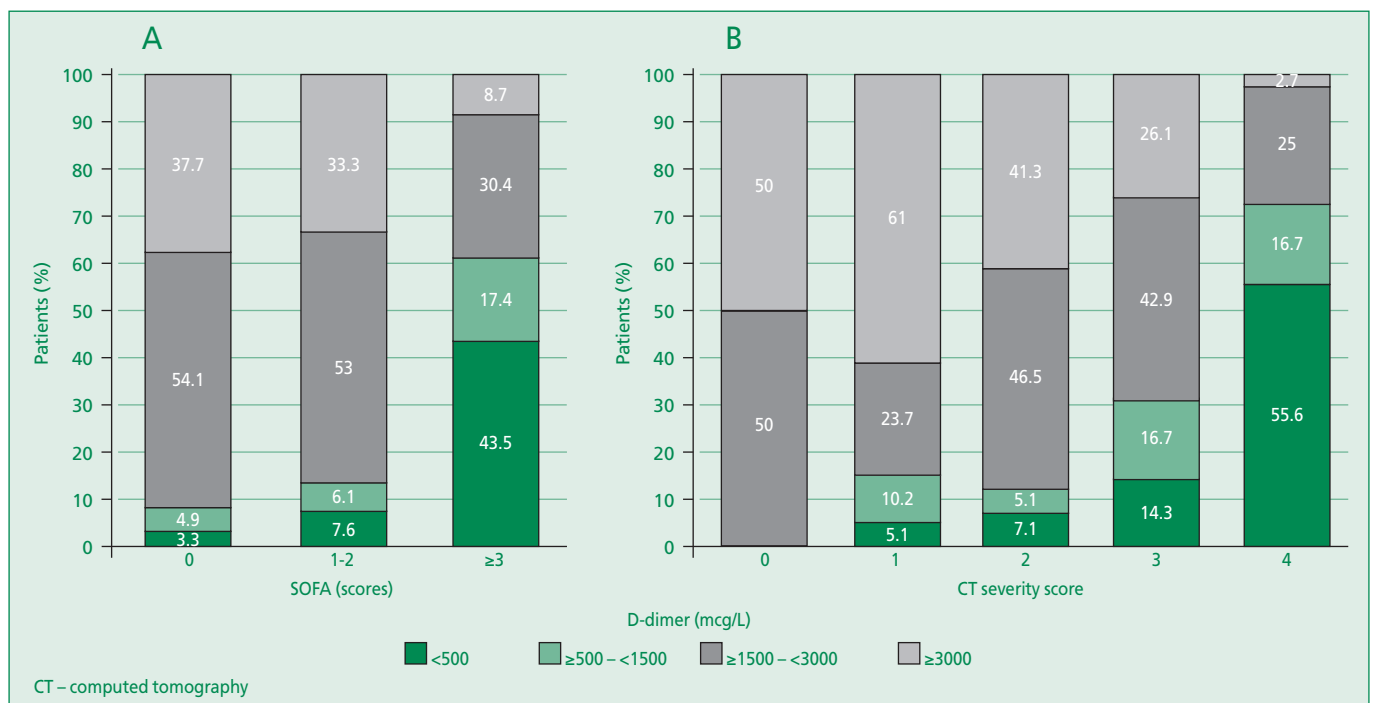


Figure 1. Ratios of D-dimer levels according to SOFA score (A) and CT severity score (B) in patients with COVID-19

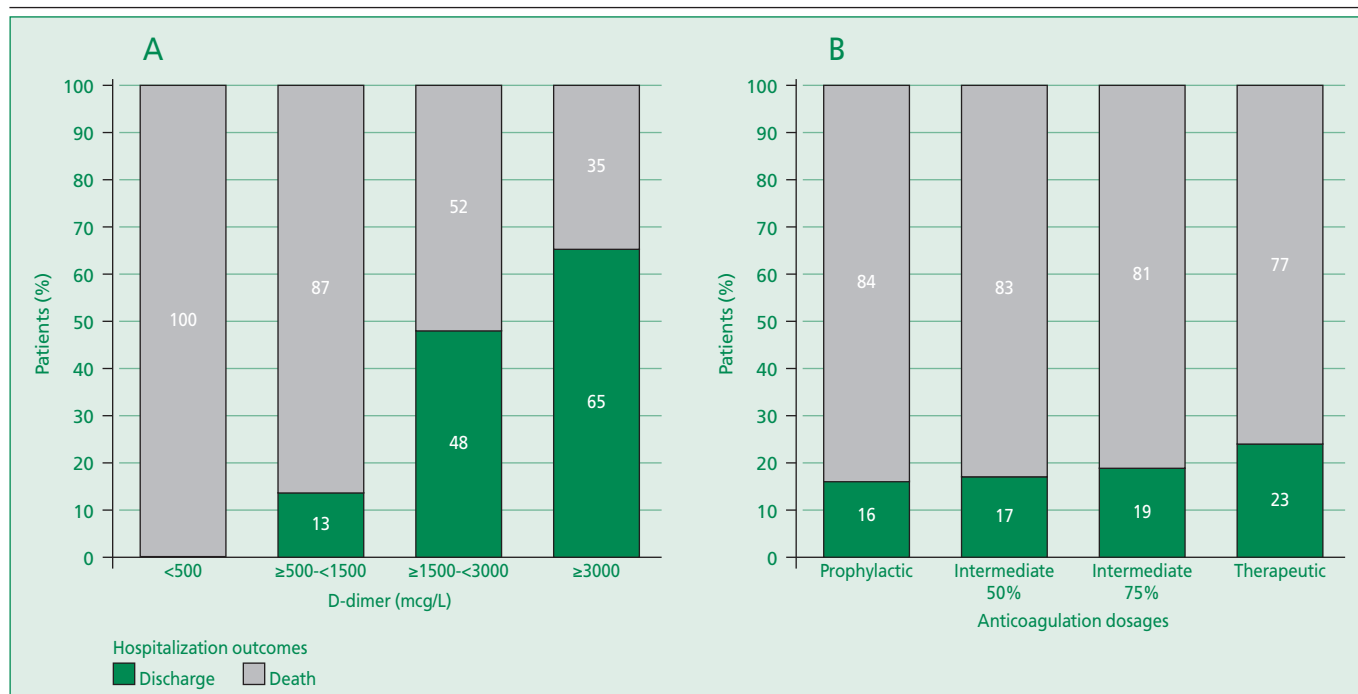


Figure 2. Distribution of hospitalization outcomes with D-dimer levels (A; n=291) and anticoagulant regimens (B; n=307) in patients with COVID-19

D-dimer and fibrinogen showed a weak but significant correlation in peak values and in the dynamics of indicators ($r=0.241$, $p<0.001$; $r=0.204$, $p<0.001$, respectively).

Coagulation system changes. DIC was not diagnosed in any of the patients who were hospitalized. An increase in prothrombin time (PT) was significantly associated with the risk of death (Cramer's $V=0.437$, $p<0.001$) and was observed in 17.9% of patients. Thrombocytopenia was not typical for patients. The number of platelets $<100 \times 10^9/l$ and $>50 \times 10^9/l$ was determined in 24 patients (7.7%), $<50 \times 10^9/l$ was determined in 3 cases (1%). The association between thrombocytopenia and death was relatively strong (Cramer's $V=0.456$, $p<0.001$).

Anticoagulant therapy. Carrying out anticoagulant therapy in different modes (prophylactic, intermediate and therapeutic) didn't show a statistically significant relationship with the D-dimer levels ($p=0.122$), fibrinogen ($p=0.97$), with the dynamics of changes during CT ($p=0.12$), and with overall mortality (Cramer's $V=0.116$, $p=0.368$) (see Fig. 2). In the group of patients with a lethal outcome, we didn't D-dimer reveal the predominance of any of the used ACT modes ($p=0.39$). Major bleeding according to ISTH against the background of ACT was not registered in any of the patients.

Data of histological studies. We noted a number of changes in the wall of pulmonary vessels: dystrophy

and focal death of the endothelium, edema of the subendothelial connective tissue layer and tunica media, lymphohistiocytic infiltration.

Histological examination using MSB staining was performed in 36 of 61 patients (59%). Thrombi of different age were found in the vessels of the lungs in all 36 patients (100%) (Fig. 3). «Mature» thrombi older than 24 hours in the studied sections of preparations were not detected in 10 of them (27.8%). In all micropreparations of 36 patients, we analyzed 1,394 vessels in the lung tissue, of which $29.8 \pm 4.48\%$ were thrombosed with lumen occlusion or contained parietal thrombi. In vessels of large caliber of 13-17 orders (3.5-30 mm), thrombi were the least common (7%). On the contrary, in vessels of small caliber of 4-7 orders (0.034-0.84 mm), thrombi were found most often (48%). Vessels of medium caliber of 8-12 orders (0.85-3.4 mm) were thrombosed in 45% of cases.

Analysis of the statute of limitations for the formation of thrombi shows that the proportion of «young» and «mature» thrombi aged 0-6 hours, 6-12 hours, 12-18 hours, 18-24 hours is 12%, 14%, 62% and 5%, respectively. Thrombi with a duration of formation of more than a day amounted to only 7%, which suggests a gradual increase in thrombus formation, reaching the greatest severity in the terminal period.

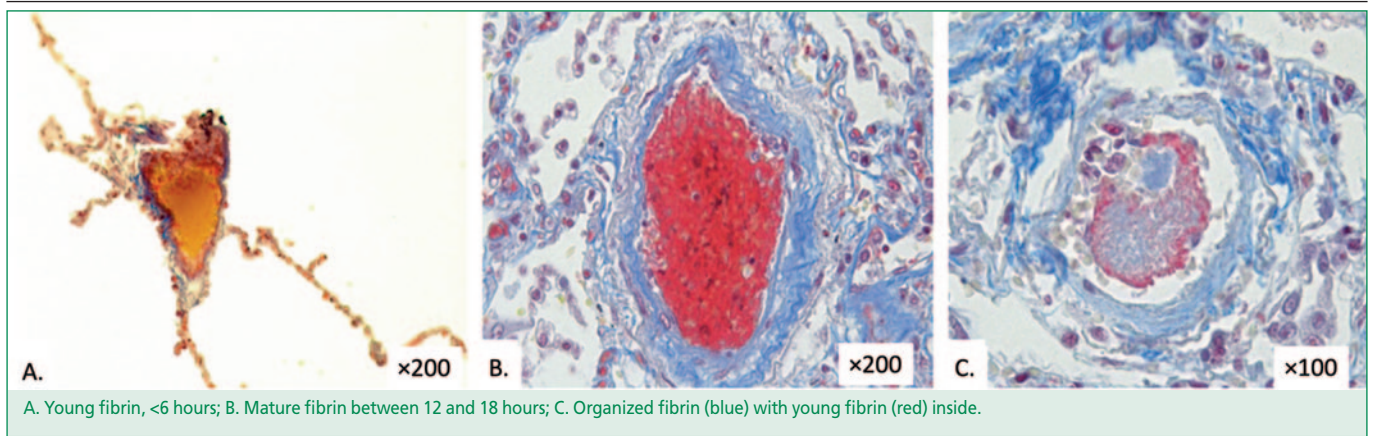


Figure 3. Thrombi of different ages in pulmonary artery branches (MSB staining)

Discussion

From the first months of the COVID-19 pandemic, clinicians encountered the features of the disease, which manifested themselves in significant shifts in the parameters of the coagulation system with lengthening of PT, activated partial thromboplastin time (APTT), and an increase in the D-dimer level associated with an unfavorable prognosis of the disease [21]. But if the levels of PT and APTT remain within normal values in a number of cases, including in patients in intensive care units, then D-dimer demonstrates the properties of a reliable predictor of the severity of COVID-19 [22]. The data obtained in the study confirm the correlation of this indicator with the severity of organ dysfunction according to the SOFA scale, the severity of pneumonia according to CT data, the need for oxygen support, and impaired renal function. We can't rule out that such a correlation between D-dimer and an increase in lung damage is due to progressive thrombus formation in the pulmonary vascular bed [23]. Fibrinogen, which showed a weak correlation with D-dimer, was associated only with the severity of the patients' condition, but not with morphological and functional changes in the lungs, kidneys, liver, or with thrombosis of the pulmonary artery. These results are consistent with the opinion that in COVID-19, fibrinogen exhibits the properties of an acute phase protein to a greater extent than a participant in thrombotic processes [24].

The development of hypercoagulability in COVID-19 is based on excessive activation of the hemostasis system under conditions of progressive immunothrombosis in the vessels of various beds, which can be an extrapulmonary cause of death in patients [25]. The trigger mechanism for the process is the formation

of a prothrombotic phenotype of the vascular wall, as well as the activation of platelets and neutrophils [26]. As COVID-19 progresses, platelets and neutrophils show excessive activation and retain thrombogenic potential despite the depletion of many functions, and are also repeatedly recruited to participate in the process of thrombosis [27, 28].

Histological manifestations of activation of the endothelium of the vessels of the pulmonary bed, up to its damage, are endothelial vacuolization, its desquamation, fibrinoid necrosis of the layers of the vessel wall, and leukocyte infiltration, which is confirmed by the data of this study [29, 30]. Changes are observed both in thrombosed vessels and in those vessels where a thrombus has not yet formed [14]. The composition of formed thrombi is characteristic of immunothrombosis and includes platelets, neutrophilic platelet aggregates, neutrophilic extracellular traps (NETs), and fibrin [29, 31].

The procoagulant effect of the immune component of thrombosis, underlying hypercoagulability, is so pronounced that it distorts the properties of the hemostasis system and largely levels out the effects of anticoagulant therapy [23, 32]. Preservation of normal thrombin generation in vitro, accompanied by hypercoagulability in vivo with high concentrations of thrombin-antithrombin (TAT) and plasmin-antiplasmin complexes, has been shown in patients with COVID-19 against the background of LMWH administration [23]. At the same time, anti-Xa activity, which reflects the response to the administration of LMWH, doesn't correlate with markers of hemostasis activation, in particular, D-dimer and TAT [23]. In this work, we also did not find a correlation between the level and dynamics of changes in D-dimer and doses of anticoagulants.

The consequence of immunothrombosis is a thrombotic lesion of the vessels of the pulmonary bed, resistant to anticoagulant therapy due to uncontrolled hypercoagulation [3, 14, 15, 33, 34]. Thrombotic lesions of the pulmonary artery bed, including isolated ones, cover large and small branches of the pulmonary artery (lobar, segmental, and subsegmental), as well as vessels of the microvasculature [35, 36]. The results of a systematic review show damage to the main pulmonary artery in 13.5% of patients, damage to small and medium-caliber branches in 100% [29]. Based on the results of this work, we can state that in each case, about half of the pulmonary vessels with a diameter of less than 3.4 mm are thrombosed. At the same time, thrombus formation continues against the background of ongoing therapy, as evidenced by the presence of both «mature» thrombi more than 24 hours old, and «fresh» thrombi formed less than 6 hours before the death of the patient. The detection of parietal thrombi in the preparations allows us to assume that in one vascular segment there may be thrombi with fragments of varying degrees of maturity due to ongoing thrombus formation.

The combination of thrombosed pulmonary segments with high D-dimer levels in patients with moderate and severe COVID-19 in the absence of thrombosis in other vascular beds allows us to speak of D-dimer as a laboratory sign of progression of thrombus formation in the lungs. This fact can be confirmed by the lack of dependence of the D-dimer level on anticoagulant therapy, and its correlation with the severity of changes on CT scan, the severity of the patient's condition, which contributes to thrombotic damage to the pulmonary vessels [25].

Thrombus formation resistant to anticoagulant therapy can also be caused by other processes besides the activation of the immune component. A decrease in lung perfusion due to lung tissue destruction and thickening of vessel walls as a result of edema and inflammation lead to the formation of dead spaces in the lungs, shunting of blood flow, which limits the effect of systemic antithrombotic and fibrinolytic drugs in these foci [14, 37]. In addition, hypoxia due to reduced perfusion is a condition that enhances

endothelial and platelet activation, including through the secretion of hypoxia-induced factor (HIF), EGR-1 (early growth response-1) [38]. An important role in local activation and disruption of the integrity of the endothelium is also played by the effect of cytokines secreted by damaged lung epithelium, which is stronger than the systemic effects of counteracting drugs [39].

Study limitations. The study limitations are a retrospective analysis of the data obtained, the lack of a single examination protocol for all patients, a sectional protocol that would allow obtaining more diverse material for the histological study of the vascular bed of the lungs. But thanks to the array of data collected, the study results give us a clear idea of the patterns of development of the thrombotic process in the branches of the pulmonary artery and the microvasculature of the lungs. Overcoming the limitations will allow us to conduct a more detailed study of this process and, through understanding the pathogenesis, will lead to the search for effective treatments for thrombosis in COVID-19.

Conclusion

Thrombotic changes in the pulmonary artery system are found in all deceased patients, affect about a third of the vessels of the pulmonary bed, predominantly of small caliber, and represent thrombi of varying degrees of maturity, with a predominance of those aged 12-18 hours. Thrombotic processes in the vascular bed of the lungs develop according to atypical venous thromboembolic events patterns that play a significant role in pathogenesis and thanatogenesis in COVID-19. The criterion for the progression of thrombosis in the pulmonary artery system in COVID-19 may be the D-dimer level, the increase of which correlates with the severity of organ dysfunction, morphological changes in the lungs, the risk of death and doesn't depend on the nature of anticoagulant therapy.

Relationships and Activities. None.

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About the Authors:

Olga Ya. Porembskaya

eLibrary SPIN 9775-1057, ORCID 0000-0003-3537-7409

Viacheslav N. Kravchuk

eLibrary SPIN 4227-2846, ORCID 0000-0002-6337-104X

Maxim I. Galchenko

eLibrary SPIN 8858-2916, ORCID 0000-0002-5476-6058

Roman V. Deev

eLibrary SPIN 2957-1687, ORCID 0000-0001-8389-3841

Mikhail S. Chesnokov

ORCID 0000-0002-9171-8338

Albert V. Avanesyan

eLibrary SPIN 5704-3320, ORCID 0000-0002-2751-5587

Kirill V. Lobastov

eLibrary SPIN 2313-0691, ORCID 0000-0002-5358-7218

Sergey N. Tsaplin

eLibrary SPIN 8827-1385, ORCID 0000-0003-1567-1328

Leonid A. Laberko

eLibrary SPIN 8941-5729, ORCID 0000-0002-5542-1502

Valerii S. Ermakov

eLibrary SPIN 9095-3330, ORCID 0000-0003-3008-5124

Olga V. Pashovkina

eLibrary SPIN 3448-9764, ORCID 0000-0001-6955-4595

Ilya V. Schastlivtsev

eLibrary SPIN 7329-6994, ORCID 0000-0002-1306-1502

Sergey A. Sayganov

eLibrary SPIN 2174-6400, ORCID 0000-0002-9880-516X