UDC 616.15+577.112.82]-07:616.98:578.834]-06:616.14-005.6
DOI: 10.14739/2310-1237.2023.1.274921

The clinical and prognostic role of changes in parameters of the hemostasis system and C-reactive protein in the development of thrombotic complications in oxygen-dependent patients with coronavirus disease (COVID-19)

V. V. Cherkaskyi [B,C,D], **O. V. Riabokon** [*A,E,F], **Yu. Yu. Riabokon** [C,D]

Zaporizhzhia State Medical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Aim. The purpose of our work was to find out the clinical and prognostic role of changes in hemostasis parameters and C-reactive protein (CRP) in the development of thrombotic complications in oxygen-dependent patients with coronavirus disease (COVID-19).

Materials and methods. 211 oxygen-dependent patients with COVID-19 were examined. To assess the prognostic role of changes in hemostasis parameters and CRP, patients were divided into groups: I group – 94 patients who recovered, II group – 117 patients who died. Subgroups: II-A subgroup – 35 patients with thrombotic complications and II-B subgroup – 82 patients without these complications. All patients were examined and received treatment according to the normative documents in force at the relevant time.

Results. The frequency of thrombotic complications in oxygen-dependent patients with COVID-19 was 16.6 %, among which the most common were pulmonary embolism (6.6 %), myocardial infarction (6.2 %), and ischemic stroke (3.2 %). Lifetime diagnosis of thrombotic complications took place on the 18th [16.0; 24.0] day of illness in 45.9 % of cases. Deathtime diagnosis of thrombotic complications took place on the 24th [20.0; 28.0] day of illness in 54.1 % of cases. Lifetime pulmonary artery thromboembolism was diagnosed less frequently than ischemic stroke ($p = 0.002$) and myocardial infarction ($p = 0.02$).

With the development of oxygen dependence and admission to the intensive care unit on the 9th [8.0; 11.0] day of illness, changes in the hemostasis system were characterized as prothrombotic with an increase above the reference values of fibrinogen and D-dimer in patients of all groups. CRP in patients with fatal outcomes of the disease, regardless of the development of thrombotic complications, was higher ($p < 0.05$) than in patients who subsequently recovered, and was accordingly in patients of the I group – 67.65 [41.20; 139.95] mg/l, in the II-A group – 122.2 [61.2; 178.0] mg/l, and in patients of the II-B group – 109.8 [56.3; 180.0] mg/l.

In the dynamics of complex treatment after 5–7 days, the level of fibrinogen, D-dimer and CRP had a diagnostic value in predicting the further development of thrombotic complications. With an increase in the level of fibrinogen >4.6 g/l (AUC = 0.600, $p = 0.042$), D-dimer >2.1 μg/ml (AUC = 0.704, $p = 0.001$) and CRP >89.3 mg/l (AUC = 0.720, $p < 0.001$) the probability of developing thrombotic complications was significant.

Conclusions. In dynamics of complex treatment of oxygen-dependent patients after 5–7 days, the levels of fibrinogen, D-dimer and C-reactive protein had consistent diagnostic value in predicting further development of thrombotic complications. Increased fibrinogen >4.6 g/l, D-dimer >2.1 μg/ml, and CRP >89.3 mg/l were important for predicting the risk of developing thrombotic complications.

Key words: COVID-19, viral infection, thrombotic complications, diagnosis, hemostasis, C-reactive protein, risk factors, prognosis.

Pathologia 2023; 20 (1), 27-35

***E-mail:** ryabokonzsmu@ukr.net

Клініко-прогностична роль змін параметрів системи гемостазу та С-реактивного протеїну в розвитку тромботичних ускладнень у кисневозалежних хворих на коронавірусну хворобу (COVID-19)

В. В. Черкаський, О. В. Рябоконь, Ю. Ю. Рябоконь

Мета роботи – з'ясувати клініко-прогностичну роль змін параметрів гемостазу та С-реактивного протеїну (СРП) в розвитку тромботичних ускладнень у кисневозалежних хворих на коронавірусну хворобу (COVID-19).

Матеріали та методи. Обстежено 211 кисневозалежних хворих на COVID-19. Для оцінювання прогностичної ролі змін параметрів гемостазу та СРП пацієнтів поділили на групи: I – 94 хворих, які одужали; II – 117 осіб, які померли. Підгрупи пацієнтів: II-A – 35 хворих із тромботичними ускладненнями; II-B підгрупа – 82 особи без таких ускладнень. Усіх хворих обстежили, призначили лікування згідно з чинними на той час нормативними документами.

Результати. Частота виникнення тромботичних ускладнень у кисневозалежних хворих на COVID-19 становила 16,6 %. Найчастіші з-поміж них – тромбоемболія легеневої артерії (6,6 %), інфаркт міокарда (6,2 %), ішемічний інсульт (3,2 %). Прижиттєва діагностика тромботичних ускладнень відбулася на 18 [16,0; 24,0] день хвороби в 45,9 % випадків. Посмертна діагностика тромботичних ускладнень – на 24,0 [20,0; 28,0] день хвороби в 54,1 % випадків. Тромбоемболію легеневої артерії прижиттєво діагностували рідше, ніж ішемічний інсульт ($p = 0,002$) та інфаркт міокарда ($p = 0,02$).

Ключові слова: COVID-19, вірусна інфекція, тромботичні ускладнення, діагностика, гемостаз, С-реактивний протеїн, фактори ризику, прогноз.

Патологія. 2023. Т. 20, № 1(57). С. 27-35

У разі виникнення кисневої залежності та надходження до реанімаційного відділення на 9,0 [8,0; 11,0] добу хвороби зміни в системі гемостазу характеризувалися як протромботичні з перевищенням референтних значень фібриногену та D-димеру в пацієнтів усіх груп. СРП у хворих із летальним наслідком хвороби незалежно від виникнення тромботичних ускладнень був вищим ($p < 0,05$), ніж у хворих, які надалі одужали, та становив у хворих I групи 67,65 [41,20; 139,95] мг/л, II-A групи – 122,2 [61,2; 178,0] мг/л, II-B групи – 109,8 [56,3; 180,0] мг/л.

У динаміці комплексного лікування через 5–7 діб діагностичне значення щодо прогнозування наступного виникнення тромботичних ускладнень мали рівень фібриногену, D-димеру та СРП. При підвищенні рівня фібриногену >4,6 г/л (AUC = 0,600, $p = 0,042$), D-димеру >2,1 мкг/мл (AUC = 0,704, $p = 0,001$) та СРП >89,3 мг/л (AUC = 0,720, $p < 0,001$) імовірність виникнення тромботичних ускладнень значуща.

Висновки. У динаміці комплексного лікування кисневозалежних хворих через 5–7 діб діагностичне значення щодо прогнозування наступного виникнення тромботичних ускладнень мають рівень фібриногену, D-димеру та С-реактивного протеїну. Для прогнозування ризику виникнення тромботичних ускладнень мають значення підвищення фібриногену >4,6 г/л, D-димеру >2,1 мкг/мл та СРП >89,3 мг/л.

The new coronavirus disease (COVID-19), which started it's journey in December 2019 from the Chinese province of Wuhan, turned into a pandemic in a fairly short period of time and created an irrevocable challenge to the global health care system [1]. Despite the polymorphism of clinical manifestations, the calling card of COVID-19 there were rapidly progressive lesions of the lungs, which led to the development of acute respiratory distress syndrome, severe respiratory insufficiency and high mortality [2,3]. The SARS-CoV-2 virus, due to its binding to the receptor of angiotensin-converting enzyme type 2, penetrates into the goblet cells of the nasal mucosa and alveolar pneumocytes of type II, where it replicates [3,4]. It is believed that excessive inflammatory response that arises as a result of this is the main reason for the complicated course and the fatal outcome of COVID-19 [5,6]. An excessive inflammatory response during the progression of the disease is accompanied by a significant increase in C-reactive protein (CRP) level, which is a known marker of systemic inflammation. Already at the beginning of the study of this new disease, it was found that the level of CRP can exceed the upper limits of the norm by more than ten times and correlates with severity of the course of COVID-19 and the frequency of fatal consequences [7–9].

Today, the elucidation of the pathogenetic mechanisms of the progression of the new coronavirus disease continues, while attention is paid to the interrelationships of immunoinflammatory reactions with changes in the hemostasis system, which is the basis of the formation of acute respiratory distress syndrome, multiple organ insufficiency, and fatal thrombotic complications. It is believed that a cascade of complex interrelated inflammatory reactions occurs through the activation of complement, the release of cytokines, which leads to the development of endothelial dysfunction, thrombotic microangiopathy, and pathological angiogenesis [10–12]. The currently known model of the pathogenesis of this infection is being refined and supplemented. In particular, the role of certain signs of antiphospholipid syndrome and disseminated intravascular coagulation syndrome is discussed [12–14].

As the main clinical manifestations of this disease were studied, it became obvious that a unique tendency to thrombus formation without further development of the processes of generalized fibrinolysis is typical for its complicated course [15–17]. Literature data show significant discrepancies in the frequency of diagnosis of thrombotic complications in patients with the new coronavirus disease, even when taking into account the severity of the course. Thus, among patients with COVID-19 of light and medium severity, venous thrombotic events are registered with a frequency from 0.09 % to 8.00 %. Among intensive care unit patients, the frequency of thrombotic events are increasing, but the frequency of their diagnosis ranges from 24 % to 85 % [18–20] even despite anticoagulant therapy [10,21].

If according to most researchers, the spectrum of thrombotic complications of COVID-19 includes pulmonary embolism and deep vein thrombosis of the lower extremities as dominant [22,23], then statistical data on the frequency of ischemic strokes and arterial thrombosis vary from 0.9 % to 5.6 % [24,25]. During research of the pathogenetic mechanisms of the development of thrombosis in COVID-19, the attention of researchers is drawn to the abnormality of changes in the hemostasis system at the progression of this disease. Changes in the hemostasis system are characterized by high levels of D-dimer, fibrinogen and fibrin breakdown products, longer prothrombin time and activated partial thromboplastin time, the development of thrombocytosis or thrombocytopenia [26–28].

In April 2020, the International Society of Thrombosis and Hemostasis (ISTH) published interim guidelines for the diagnosis and treatment of COVID-19-associated coagulopathy [29]. This document focused on the strong association between D-dimer levels >2.0 μg/ml and hospital mortality [29]. In fact, according to literary sources, high values fibrinogen and D-dimer have a direct relationship with a significant risk of developing systemic thrombosis and death [30–32]. At the same time, the predictors of the development of venous thrombotic complications still remain insufficiently defined. A few researches draw attention to the fact that only in the case of a combined increase of CRP, as a marker of systemic inflammation, and D-dimer, as a product of fibrin degradation, there is a significantly increased risk of developing venous thrombosis [33].

Therefore, significant discrepancies in the frequency of registration of thrombotic complications in patients with COVID-19 and in the spectrum of these events, insufficient clarity of the features of changes in the hemostasis system in relation to the expressiveness of the inflammatory reaction require further research in this direction in order to determine early predictors of the risk of developing thrombotic complications.

Aim

The purpose of our work was to find out the clinical and prognostic role of changes in hemostasis parameters and C-reactive protein in the development of thrombotic complications in oxygen-dependent patients with coronavirus disease (COVID-19).

Materials and methods

The research included 211 oxygen-dependent patients with coronavirus disease (COVID-19), who during 2020–2021 were being treated in the intensive care unit of the Municipal Non-Profit Enterprise "Regional infectious clinical hospital" Zaporizhzhia Regional Council. The diagnosis in all patients was confirmed by the detection of RNA-SARS-CoV-2 by the polymerase chain reaction method. All patients were examined and received treatment according to the normative documents in force at the relevant time [34–36].

To assess the clinical and prognostic role of changes in hemostasis parameters and CRP, patients were divided into groups: I group – 94 patients who recovered, II group – 117 patients whose disease ended fatally. For analyze the characteristics of changes in laboratory indicators, patients of the II group were additionally divided into subgroups: II-A subgroup – 35 patients who developed thrombotic complications and II-B subgroup – 82 patients without thrombotic complications. The presence of comorbid pathology in the stage of decompensation was a criterion for exclusion from the research. During monitoring of patients for the diagnosis of thrombotic complications were carried out comprehensive assessment of clinical data, laboratory indicators of hemostasis (coagulogram, platelets, D-dimer), electrocardiographic examination, consultations of related specialists (neurologist, cardiologist)

Statistical data processing was carried out using the created patient database in the program Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J). The χ^2 test was used to determine the differences between qualitative features, and the Mann–Whitney test was used between quantitative features. To establish the diagnostic significance of the investigated parameters in predicting outcomes regarding the development of thrombotic complications in oxygen-dependent patients with COVID-19, ROC-analysis was performed with determination of the cut-off point. Spearman's correlation was used to establish relationships between quantitative traits.

Results

Analysis of demographic parameters of oxygen-dependent patients of the investigated groups showed the absence of a statistically significant difference in the median age of patients ($p > 0.05$). Thus, the median age of patients of the I group was 63.0 [56.0; 70.0] years, II-A subgroup – 67.0 [57.0; 79.0] years, II-B subgroup – 67.5 [61.0; 74.0] years old. Patients of the investigated groups also did not statistically differ by gender ($p > 0.05$). Thus, among patients of the I group there were 54 (57.4 %) men, 40 (42.6 %) women; among patients of the II-A subgroup, men – 21 (60.0 %), women – 14 (40.0 %); among patients of II-B subgroup, men – 43 (52.4 %), women – 39 (47.6 %).

Table 1. Frequency of development and spectrum of thrombotic complications in oxygen-dependent patients with COVID-19 depending on the consequences of the disease, abs. (%)

Group	Patients (n = 211)	Patients	
		I group (n = 94)	II group (n = 117)
Presence of thrombotic complications	37 (16.6 %)	2 (2.1 %)	35 (29.9 %)*
Ischemic stroke	7 (3.2 %)	1 (1.1 %)	6 (5.1 %)
Transient ischemic attack	1 (0.5 %)	1 (1.1 %)	–
Thromboembolism of the pulmonary artery	14 (6.6 %)	–	14 (12.0 %)
Myocardial infarction	13 (6.2 %)	–	13 (11.1 %)
Acute coronary syndrome	1 (0.5 %)	–	1 (0.9 %)
Thrombosis of upper extremity veins	2 (0.9 %)	–	2 (1.7 %)
Catheter associated venous thrombosis	1 (0.5 %)	–	1 (0.9 %)
Thrombosis of lower limb arteries	2 (0.9 %)	–	2 (1.7 %)
A combination of several thrombotic complications	3 (1.4 %)	–	3 (2.6 %)

*: the difference is significant, compared to the I group ($p<0.05$).

At the time of hospitalization of oxygen-dependent patients to the intensive care unit, the median indicator of oxygen saturation in air was 84.5 [80.0; 88.0] %; in patients of II-A subgroup – 78.0 [70.0; 82.0] %; in II-B subgroup patients – 78.0 [74.0; 84.0] %. Statistically significant differences in this parameter were not found when comparing the studied groups of patients at the time of observation ($p > 0.05$). From the moment of hospitalization to the intensive care unit, 12 (12.8 %) patients of the I group, 7 (20.0 %) patients of the II-A subgroup, and 14 (17.1 %) patients of the II-B subgroup needed non-invasive lung ventilation. The other patients were started on oxygen support using a mask with an accumulation bag and a non-reversible valve in a volume of at least 15 L/min. There were no statistically significant differences in the degree of severity of acute respiratory deficiencies and the need for non-invasive lung ventilation at the start of the observation ($p > 0.05$).

According to the results of the research, it was established that among oxygen-dependent patients, 16.6 % (37 out of 211) were diagnosed with thrombotic complications, among which the most frequent were thromboembolism of the pulmonary artery (6.6 %), myocardial infarction (6.2 %) and ischemic stroke (3.2 %), while a combination of two thrombotic complications was recorded in 3 (1.4 %) cases. Thrombotic complications were significantly more often registered in patients of the II group, in whom the disease ended fatally, compared to patients of the I group, who recovered (29.9 % vs. 2.1 %, respectively, $\chi^2 = 27.83$, $p < 0.0001$). It should be noted that the development of ischemic stroke and transient ischemic attack was diagnosed only in isolated cases among patients of the I group (*Table 1*).

Thrombotic complications in 54.1 % (20 out of 37) of patients were diagnosed only on the basis of pathological examinations with a fatal outcome of COVID-19 at 24.0 [20.0; 28.0] day of illness. Lifetime diagnosis of thrombotic complications occurred in 45.9 % (17 out of 37) of patients at 18 [16.0; 24.0] day of illness. Arterial and venous thrombosis of the extremities in all cases was diagnosed with the development of venous thromboembolism during lifetime.

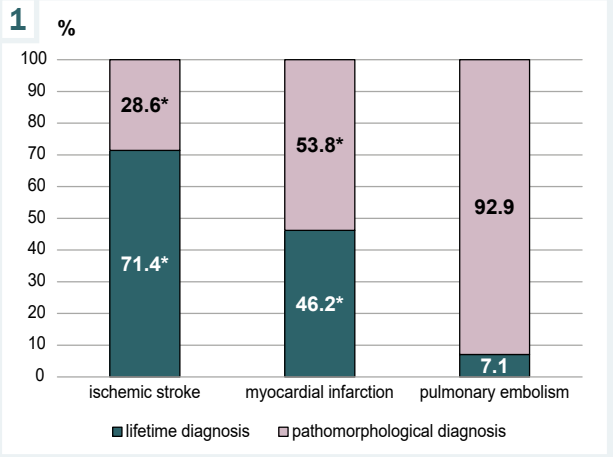
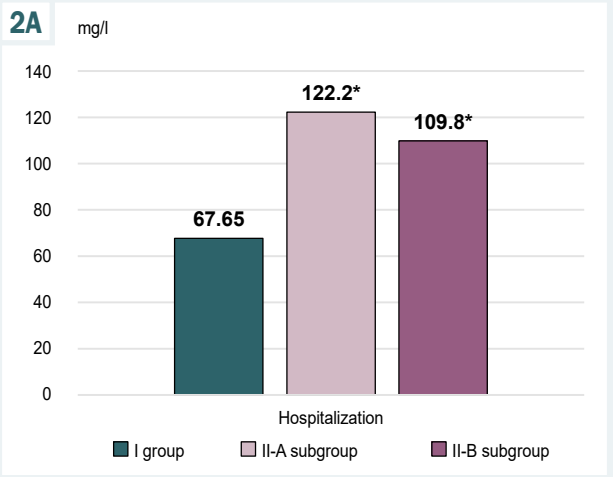


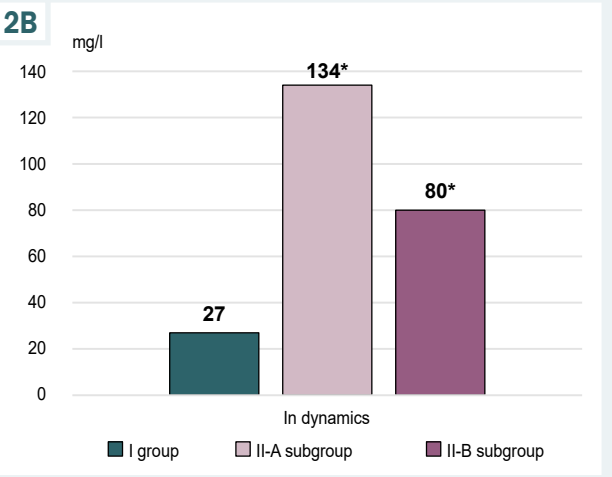
Fig. 1. Comparison of the frequency of intravital and pathological diagnosis of the main thrombotic complications of COVID-19.

*: the difference is significant, compared to the development of pulmonary embolism ($p < 0.05$).

Fig. 2. Comparison of CRP content in patients with COVID-19 depending on the development of thrombotic complications and consequences of the disease during hospitalization (A) and in dynamics after 5–7 days (B).

*: the difference is significant, compared to the I group ($p < 0.05$).





Ischemic stroke in the vast majority of patients (71.4 %) and myocardial infarction in almost half of patients (46.2 %) were also diagnosed during lifetime. However, pulmonary embolism, conversely, was diagnosed during lifetime only in isolated cases (7.1 %). Comparison of the frequency of intravital diagnosis of fatal thrombotic complications showed that pulmonary embolism was diagnosed intravitally statistically significantly less often than ischemic stroke ($\chi^2 = 9.45$, $p = 0.002$) and myocardial infarction ($\chi^2 = 5.34$, $p = 0,02$) (*Fig. 1*).

Analysis of hemostasis parameters at the time of admission to the intensive care unit at 9.0 [8.0; 11.0] day of illness showed that in patients of all investigated groups, changes in hemostasis parameters indicated the development of a prothrombotic state. This was confirmed by an increase in the average prothrombin index (PTI), the level of fibrinogen and D-dimer above the reference values. In the vast majority of patients of all observe groups, the fibrinogen content exceeded upper limits of the norm, namely in 77.7 % of patients of I group, 77.1 % of patients of II-A subgroup and 82.9 % of patients of II-B subgroup. The frequency of increasing the level of D-dimer was similar, namely in 70.2 %, 88.9 % and 95.5 % of patients in the respective groups. At the same time, it should be noted that the level of D-dimer increase was statistically significantly higher in patients with a fatal outcome of the disease of both observe subgroups, compared to patients of the I group ($p < 0.05$). It is worth noting that the median level of the international normalized ratio (INR) in patients of all studied groups was within the reference values. The analysis of the platelet link of hemostasis showed that 29.9 % (63 out of 211) of patients had deviations in level of platelets from normal values, but these changes were multidirectional in nature. Thrombocytopenia was most often registered and the frequency of it did not differ statistically ($p > 0.05$) in the studied groups of patients and amounted to 21.3 %, 14.3 % and 31.7 %, respectively, at the time of hospitalization in the intensive care unit. Thrombocytosis was recorded only in individual patients of all studied groups (*Table 2*).

At the time of hospitalization of patients with COVID-19, the presence of a pronounced inflammatory reaction was confirmed by a high level of CRP in the blood of patients of all investigated groups, the level of which was 67.65 [41.20; 139.95] mg/l in patients of the I group, II-A subgroup – 122.2 [61.2; 178.0] mg/l and in II-B subgroup – 109.8 [56.3; 180.0] mg/l. Comparative analysis showed that the level of CRP in patients with a fatal outcome of both II-A subgroup ($p = 0.027$) and II-B subgroup ($p = 0.029$) was higher than in patients of I group who recovered (*Fig. 2A*).

The conducted ROC analysis did not establish the cut-off level of the investigated parameters of hemostasis such as fibrinogen (AUC = 0.530, $p = 0.578$), D-dimer

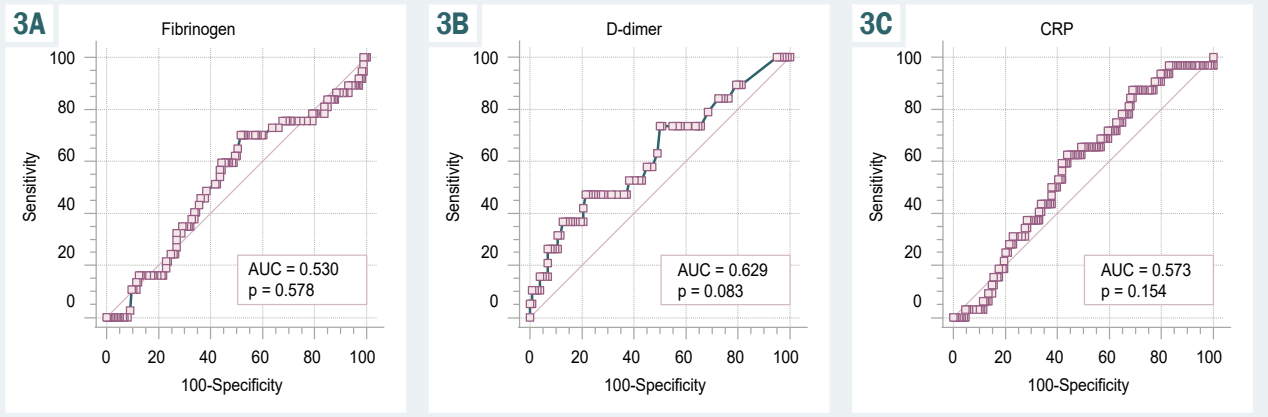


Fig. 3. Prediction of the probability of developing thrombotic complications in oxygen-dependent patients with COVID-19 based on the level of increased fibrinogen (**A**), D-dimer (**B**) and CRP (**C**) at the time of hospitalization.

(AUC = 0.629, p = 0.083) and CRP (AUC = 0.573, p = 0.154) in order to identify their prognostic value of the development of thrombotic complications at the time of the appearance of oxygen dependence and, accordingly, the admission of patients to the intensive care unit (p > 0.05) (*Fig. 3*).

Comparison of hemostasis parameters in patients with COVID-19 in dynamics after 5–7 days of treatment, which was carried out according to the protocol and included the mandatory use of low-molecular-weight heparins, showed that the median level of fibrinogen remained above the upper limit of the reference value in patients of all investigated groups. In particular, the tendency towards a higher frequency of detection of hyperfibrinogenemia in patients of the II-A subgroup, compared to patients of the I group (68.6 % vs. 54.3 %, respectively, p > 0.05) and a significantly higher frequency of hyperfibrinogenemia in patients II-A subgroup, compared with II-B subgroup patients (68.6 % vs. 9.8 %, respectively, χ^2 = 42.71, p = 0.0001). The level of the median D-dimer also remained above the upper limit of the reference value against the background of treatment in patients of all investigated groups, while the median D-dimer of patients of both II-A subgroup and II-B subgroup was statistically significantly higher than in I group patients who recovered (p < 0.05). In addition, the frequency of increased levels of D-dimer in patients of II-A subgroup (100 % vs. 70.3 %, respectively, χ^2 = 6.69, p = 0.009) and II-B subgroup (96.4 % vs. 70.3 %, respectively, χ^2 = 7.24, p = 0.007) turned out to be the highest and significantly exceeded the corresponding indicator of patients of the I group (*Table 3*).

A comparison of the CRP content in blood of patients with COVID-19 after 5–7 days of treatment, depending on the development of thrombotic complications and the consequences of the disease, showed that its highest level remained precisely in patients of II-A subgroup, which developed fatal thrombotic complications and was 134.0 [52.2; 247.9] mg/l. In patients of II-B subgroup, the content of CRP in the blood had a clear tendency to a lower level of increase than in patients of II-A group and amounted to 80.0 [30.5; 172.2] mg/l. The lowest level of CRP is 27.00 [9.80; 59.00] mg/l was recorded in I group patients who recovered. In group I patients, the CRP content during this period of observation was statistically significantly lower, compared to patients of group II-A (p = 0.0001) and compared to patients of group II-B (p = 0.0001) (*Fig. 2B*).

Interrelationship of inflammation parameters according to the level of CRP and indicators of hemostasis confirmed the established direct correlative relationships between the level of CRP and D-dimer (r = 0.40, p < 0.05) and fibrinogen (r = 0.38, p < 0.05).

In the dynamics after 5–7 days of the treatment, according to the ROC analysis, the results regarding the clarification of the role of such indicators as the level of fibrinogen, D-dimer and CRP turned out to be statistically significant.

According to the obtained result of the ROC analysis, the cut-off level of fibrinogen, which indicated a high probability of fatal thrombosis in oxygen-dependent patients with COVID-19, was 4.6 g/l (AUC = 0.600, p = 0.042) (sensitivity – 62.16 %, specificity – 57.65 %) (*Fig. 4*).

Limit level of D-dimer, which indicated a high probability of developing thrombotic complications due to COVID-19, was 2.1 μg/ml (AUC = 0.704, p = 0.001) (sensitivity – 83.33 %, specificity – 53.97 %) (p = 0.001) (*Fig. 5*).

The threshold level of CRP, which indicated a high probability of developing thrombotic complications due to COVID-19, was 89.3 mg/l (AUC = 0.720, p < 0.001) (sensitivity – 69.23 %, specificity – 71.43 %) (*Fig. 6*).

Discussion

According to the data of various research [18–20], the frequency of detected venous thrombosis among oxygen-dependent patients who were treated in intensive care units varied in a fairly wide range from 24 % to 85 %. According to the results of our research, the frequency of thrombotic complications in oxygen-dependent patients was 16.6 % at the same time, the development of pulmonary embolism (7.1 %), myocardial infarction (6.2 %) and ischemic stroke (3.2 %) was most often recorded. It should be noted that arterial and catheter-associated thrombosis were diagnosed during lifetime in all cases, ischemic stroke – in most patients (71.4 %). It was the identified clear clinical symptoms that allowed us to establish the development of

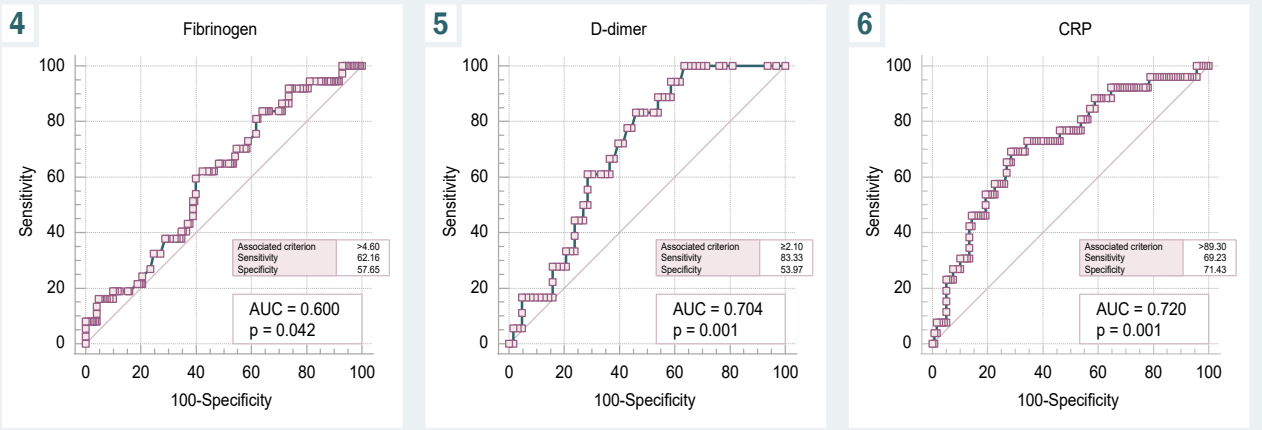


Fig. 4. Prediction of the probability of developing thrombotic complications in oxygen-dependent patients with COVID-19 by the level of increased fibrinogen.

Fig. 5. Prediction of the probability of developing thrombotic complications in oxygen-dependent patients with COVID-19 based on the level of D-dimer elevation.

Fig. 6. Prediction of the probability of the development of fatal thrombotic complications in oxygen-dependent patients with COVID-19 according to the level of CRP increase.

Table 3. Parameters of hemostasis and CRP in oxygen-dependent patients with COVID-19 depending on the development of thrombotic complications and consequences of the disease in dynamics after 5–7 days against the background of treatment

Indicator, units of measurement	Reference values	I group (n = 94)	II group (n = 117)	
			II-A subgroup (n = 35)	II-B subgroup (n = 82)
PTI, %	80–100	102.0 [90.0; 115.5]	88.6 [64.5; 102.0]*	84.7 [64.8; 99.0]*
INR	0.80–1.24	0.98 [0.90; 1.06]	1.08 [0.98; 1.33]	1.14 [1.00; 1.41]
Fibrinogen, g/l	2–4	4.15 [3.29; 5.10]	4.86 [3.90; 5.80]	5.00 [2.94; 6.06]
Fibrinogen increase, abs (%)	–	51 (54.3 %)	24 (68.6 %)	8 (9.8 %)*,**
Platelets, $\times 10^9$/l	180–390	283.0 [218.0; 345.0]	239.0 [159.0; 315.0]	189.5 [136.0; 273.5]
Thrombocytosis, abs (%)	–	19 (20.2 %)	4 (11.4 %)	7 (8.5 %)*
Thrombocytopenia, abs (%)	–	5 (5.3 %)	10 (28.6 %)*	38 (46.3 %)*
D-dimer, μg/ml	<0.1	1.01 [0.50; 2.03]	6.80 [3.68; 23.30]*	12.00 [4.15; 21.90]*
Increase in D-dimer, abs (%)	–	70.3 % (26 of 37)	100 % (18 of 18)*	96.4 % (27 of 28)*

*: the difference is significant compared to patients of the I group ($p < 0.05$); **: compared with II-A subgroup patients ($p < 0.05$).

these thrombotic complications during lifetime. Less than half of the patients managed to diagnose a myocardial infarction during lifetime (46.2 %), at the same time, the basis of the diagnosis was the detection of changes on the electrocardiogram in combination with an increase in the level of troponin.

In contrast to the above, pulmonary embolism was suspected during lifetime in only one patient, and in 92.9 % of cases this diagnosis was established only on the basis of pathomorphological examination of the lungs of the deceased. In our previous publication [37], we analyzed the results of pathomorphological examinations of 41 deceased persons and also demonstrated that thrombotic complications were detected in 22.0 % of deceased persons as a result of COVID-19, and pulmonary embolism occurred in every third deceased person in the absence of its diagnosis during lifetime in any case.

The results obtained in our research to a certain extent coincide with the data of the literature, and the discrepancies in the frequency of lifetime diagnosis of pulmonary embolism have an explanation. On the one hand, it is known that rapidly progressing acute respiratory distress syndrome and thromboembolism of the pulmonary artery have a certain similarity in clinical symptoms, which in the conditions of a severe and critical course of COVID-19 most often prompts the doctor to intensively treat acute respiratory distress syndrome, and the diagnosis of probable pulmonary embolism artery on the background of severe acute respiratory distress syndrome is not considered accordingly. On the other hand, the absence in the vast majority of cases of the possibility of conducting computed tomography of the lungs in oxygen-dependent patients treated in intensive care units led to the fact that the only reliable tool for in situ diagnosis of pulmonary thrombotic lesions was not used [31,38,39]. Precisely because of these and other similar moments, the question of the impact of thrombotic complications on the overall mortality rate and on the progression of disorders of the external respiratory system among patients with COVID-19 still remains open and continues to be studied [39,40].

A number of researchers believe that one of the ways to increase the effectiveness of lifetime diagnosis of thrombotic complications can be ultrasound screening of the venous system of the extremities of patients with a severe course of COVID-19 [41,42]. The hypothesis proposed by researchers [32] regarding the stage course of COVID-19-associated coagulopathy indicates that there are no thromboembolic complications at the initial stage of its development. With systemic activation of the processes of thrombus formation, which is clearly evidenced by a

rapid increase in the level of D-dimer, signs of deep vein thrombosis of the extremities can already be detected, but only with the help of ultrasound examination, since these thrombotic complications are asymptomatic in the vast majority of patients [41–43]. The above is confirmed by the results of a research in which, during a full autopsy with the use of postmortem computed tomography, deep vein thrombosis was detected in 58 % of the deceased, in whom there was no suspicion of the development of venous thromboembolism during lifetime [44].

Significant discrepancies in literature data regarding the frequency of thrombotic complications in patients with COVID-19 can also be explained by the polymorphism of genetic factors that have an impact on the features of the immune response to SARS-CoV-2 antigens, which determines the features of the course of the disease, in particular, the risk of developing coagulopathy and related thrombotic complications [45,46].

Abnormal changes in the hemostasis system during COVID-19 in patients with a critical course reach their maximum expression and are able to persist for a long time, despite anticoagulant therapy [21]. Already at the initial stages of studying the pathogenetic mechanisms of the progression of COVID-19, attention was paid to the increase in the level of D-dimer in the blood of patients. At the same time, in clinically significant cases, this indicator was increased in patients at the time of hospitalization and subsequently, during the first five days of treatment, it continued to increase, reaching its maximum [47]. According to the results of many research, precisely the level of D-dimer in blood that is one of the informative prognostic indicators regarding the risk of an adverse outcome of the disease. Among patients with a critical course of COVID-19, level of D-dimer is significantly higher, compared to patients with a medium and light degree of severity, and a high level of this indicator is closely related to the development of thrombotic complications and hospital mortality [36,37,39].

According to the results of our research, on the day of admission of oxygen-dependent patients to the intensive care unit by the 9th [8.0; 11.0] day of the illness, the analysis of hemostasis parameters revealed development of a prothrombotic state in them. The medians of such parameters as PTI, fibrinogen and D-dimer were higher than the reference values. At the same time, the level of increase in D-dimer was statistically significantly higher in patients with subsequent development of a fatal outcome of the disease ($p < 0.05$). Our results correspond to the interim recommendations of the International Society of Thrombosis and Hemostasis (ISTH) regarding the recognition and treatment of COVID-19-associated coagulopathy, according to which D-dimer level >2.0 μg/ml is a marker of significantly higher hospital mortality [35]. The median of this indicator, among the patients examined by us who later died due to thrombotic complications, was 2.25 [1.20; 8.40] μg/ml. According to the results of our research, more pronounced laboratory signs of a prothrombotic state were combined with a higher level of CRP increase in patients with a fatal outcome of the disease ($p < 0.05$) than in patients who subsequently recovered. When observing the dynamics after 5–7 days in patients with the subsequent development of fatal thrombotic complications, the detected disorders worsened, despite the treatment. It was during these observation periods that we managed to establish the threshold levels of fibrinogen >4.6 g/l (AUC = 0.600, $p = 0.042$), D-dimer >2.1 μg/ml (AUC = 0.704, $p = 0.001$) and CRP >89.3 mg/l (AUC = 0.720, $p < 0.001$), which have diagnostic value in predicting further development of thrombotic complications.

Data from the literature indicate that the excessive inflammatory response that occurs as a result of infection with the SARS-CoV-2 virus is the main cause of the complicated course of the disease and death [5,6,8]. A severe course of COVID-19 is accompanied by an increase more than ten times the level of CRP already in the early stages of the disease. A high level of CRP correlates with the severity of the disease and the risk of death [7–9]. And the risk of developing venous thromboembolic complications among patients with a critical course of the disease is the highest in the case of a combined increase in the levels of CRP and D-dimer [7].

Conclusions

1. The frequency of developing thrombotic complications in oxygen-dependent patients with COVID-19 is 16.6 %, among which the most common are pulmonary embolism (6.6 %), myocardial infarction (6.2 %), ischemic stroke (3.2 %) and in some cases a combination of thrombotic complications (1.4 %). Thrombotic complications are more often registered in oxygen-dependent patients with a fatal outcome of the disease, compared to patients who recovered (29.9 % vs. 2.1 %, respectively, $p < 0.0001$).

2. Lifetime diagnosis of thrombotic complications in oxygen-dependent patients with COVID-19 occurs in 45.9 % of patients on the 18th [16.0; 24.0] day of the illness. Thromboembolism of the pulmonary artery is less often diagnosed during lifetime than ischemic stroke (7.1 % vs. 71.4 %, respectively, $p = 0.002$) and myocardial infarction (7.1% vs. 46.2 %, respectively, $p = 0.02$).

3. With the development of oxygen-dependence and admission to the intensive care unit on the 9th [8.0; 11.0] day of the illness, changes in the hemostasis system are characterized as prothrombotic with increased levels of fibrinogen and D-dimer in patients of all investigated groups, regardless of the risk of further development of thrombotic complications. C-reactive protein in patients with a subsequent fatal outcome of the disease, regardless of the development of thrombotic complications, is higher ($p < 0.05$) than in patients who subsequently recover.

4. In dynamics of complex treatment of oxygen-dependent patients after 5–7 days, the level of fibrinogen, D-dimer and C-reactive protein have a diagnostic value in predicting the further development of thrombotic complications. When the level of fibrinogen increases >4.6 g/l (AUC = 0.600, $p = 0.042$), D-dimer >2.1 μg/ml (AUC = 0.704, $p = 0.001$) and C-reactive protein >89.3 mg/l (AUC = 0.720, $p < 0.001$), the probability of developing thrombotic complications is significant.

Prospects for further research. In our opinion, a promising direction of research is to find out the risk of developing thrombotic complications depending on the presence of various comorbid pathologies.

Конфлікт інтересів: відсутній.
Conflicts of interest: authors have no conflict of interest to declare.

Надійшла до редакції / Received: 06.02.2023
Після доопрацювання / Revised: 03.03.2023
Прийнято до друку / Accepted: 13.03.2023

Information about authors:
Cherkaskyi V. V., MD, Assistant of the Department of Infectious Diseases, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0003-2959-8803
Riabokon O. V., MD, PhD, DSc, Professor, Head of the Department of Infectious Diseases, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0002-7394-4649
Riabokon Yu. Yu., MD, PhD, DSc, Professor of the Department of Children Infectious Diseases, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0002-2273-8511

Відомості про авторів:
Черкаський В. В., асистент каф. інфекційних хвороб, Запорізький державний медичний університет, Україна.
Рябоконь О. В., д-р мед. наук, професор, зав. каф. інфекційних хвороб, Запорізький державний медичний університет, Україна.
Рябоконь Ю. Ю., д-р мед. наук, професор каф. дитячих інфекційних хвороб, Запорізький державний медичний університет, Україна.

References

[1] Muralidar, S., Ambi, S. V., Sekaran, S., & Krishnan, U. M. (2020). The emergence of COVID-19 as a global pandemic: Understanding the epidemiology, immune response and potential therapeutic targets of SARS-CoV-2. *Biochimie*, *179*, 85-100. https://doi.org/10.1016/j.biochi.2020.09.018

[2] Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, *395*(10223), 497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

[3] Synowiec, A., Szczepański, A., Barreto-Duran, E., Lie, L. K., & Pyrc, K. (2021). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection. *Clinical microbiology reviews*, *34*(2), e00133-20. https://doi.org/10.1128/CMR.00133-20

[4] Zhang, S., Liu, Y., Wang, X., Yang, L., Li, H., Wang, Y., Liu, M., Zhao, X., Xie, Y., Yang, Y., Zhang, S., Fan, Z., Dong, J., Yuan, Z., Ding, Z., Zhang, Y., & Hu, L. (2020). SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *Journal of hematology & oncology*, *13*(1), 120. https://doi.org/10.1186/s13045-020-00954-7

[5] Merad, M., & Martin, J. C. (2020). Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nature reviews. Immunology*, *20*(6), 355-362. https://doi.org/10.1038/s41577-020-0331-4

[6] Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., Manson, J. J., & HLH Across Speciality Collaboration, UK (2020). COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*, *395*(10229), 1033-1034. https://doi.org/10.1016/S0140-6736(20)30628-0

[7] Petrilli, C. M., Jones, S. A., Yang, J., Rajagopalan, H., O'Donnell, L., Chernyak, Y., Tobin, K. A., Cerfolio, R. J., Francois, F., & Horwitz, L. I. (2020). Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ (Clinical research ed.)*, *369*, m1966. https://doi.org/10.1136/bmj.m1966

[8] Liu, F., Li, L., Xu, M., Wu, J., Luo, D., Zhu, Y., Li, B., Song, X., & Zhou, X. (2020). Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *Journal of clinical virology*, *127*, 104370. https://doi.org/10.1016/j.jcv.2020.104370

[9] Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive care medicine*, *46*(5), 846-848. https://doi.org/10.1007/s00134-020-05991-x

[10] Smadja, D. M., Mentzer, S. J., Fontenay, M., Laffan, M. A., Ackermann, M., Helms, J., Jonigk, D., Chocron, R., Pier, G. B., Gendron, N., Pons, S., Diehl, J. L., Margadant, C., Guerin, C., Huijbers, E. J. M., Philippe, A., Chapuis, N., Nowak-Sliwinska, P., Karagiannidis, C., Sanchez, O., … Griffioen, A. W. (2021). COVID-19 is a systemic vascular hemopathy: insight for mechanistic and clinical aspects. *Angiogenesis*, *24*(4), 755-788. https://doi.org/10.1007/s10456-021-09805-6

[11] Connors, J. M., & Levy, J. H. (2020). COVID-19 and its implications for thrombosis and anticoagulation. *Blood*, *135*(23), 2033-2040. https://doi.org/10.1182/blood.2020006000

[12] Singhania, N., Bansal, S., Nimmatoori, D. P., Ejaz, A. A., McCullough, P. A., & Singhania, G. (2020). Current Overview on Hypercoagulability in COVID-19. *American journal of cardiovascular drugs : drugs, devices, and other interventions*, *20*(5), 393-403. https://doi.org/10.1007/s40256-020-00431-z

[13] Levi, M., & Iba, T. (2021). COVID-19 coagulopathy: is it disseminated intravascular coagulation?. *Internal and emergency medicine*, *16*(2), 309-312. https://doi.org/10.1007/s11739-020-02601-y

[14] van der Linden, J., Almskog, L., Liliequist, A., Grip, J., Fux, T., Rysz, S., Ågren, A., Oldner, A., & Ståhlberg, M. (2020). Thromboembolism, Hypercoagulopathy, and Antiphospholipid Antibodies in Critically Ill Coronavirus Disease 2019 Patients: A Before and After Study of Enhanced Anticoagulation. *Critical care explorations*, *2*(12), e0308. https://doi.org/10.1097/CCE.0000000000000308

[15] Becker, R. C. (2020). COVID-19 update: Covid-19-associated coagulopathy. *Journal of thrombosis and thrombolysis*, *50*(1), 54-67. https://doi.org/10.1007/s11239-020-02134-3

[16] Colling, M. E., & Kanthi, Y. (2020). COVID-19-associated coagulopathy: An exploration of mechanisms. *Vascular medicine*, *25*(5), 471-478. https://doi.org/10.1177/1358863X20932640

[17] Peyvandi, F., Artoni, A., Novembrino, C., Aliberti, S., Panigada, M., Boscarino, M., Gualtierotti, R., Rossi, F., Palla, R., Martinelli, I., Grasselli, G., Blasi, F., & Tripodi, A. (2021). Hemostatic alterations in COVID-19. *Haematologica*, *106*(5), 1472-1475. https://doi.org/10.3324/haematol.2020.262634

[18] Ribes, A., Vardon-Bounes, F., Mémier, V., Poette, M., Au-Duong, J., Garcia, C., Minville, V., Sié, P., Bura-Rivière, A., Voisin, S., & Payrastre, B. (2020). Thromboembolic events and Covid-19. *Advances in biological regulation*, *77*, 100735. https://doi.org/10.1016/j.jbior.2020.100735

[19] Middeldorp, S., Coppens, M., van Haaps, T. F., Foppen, M., Vlaar, A. P., Müller, M. C. A., Bouman, C. C. S., Beenen, L. F. M., Kootte, R. S., Heijmans, J., Smits, L. P., Bonta, P. I., & van Es, N. (2020). Incidence of venous thromboembolism in hospitalized patients with COVID-19. *Journal of thrombosis and haemostasis : JTH*, *18*(8), 1995-2002. https://doi.org/10.1111/jth.14888

[20] Malas, M. B., Naazie, I. N., Elsayed, N., Mathlouthi, A., Marmor, R., & Clary, B. (2020). Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine*, *29*, 100639. https://doi.org/10.1016/j.eclinm.2020.100639

[21] Lopes, R. D., de Barros E Silva, P. G. M., Furtado, R. H. M., Macedo, A. V. S., Bronhara, B., Damiani, L. P., Barbosa, L. M., de Aveiro Morata, J., Ramacciotti, E., de Aquino Martins, P., de Oliveira, A. L., Nunes, V. S., Ritt, L. E. F., Rocha, A. T., Tramujas, L., Santos, S. V., Diaz, D. R. A., Viana, L. S., Melro, L. M. G., de Alcântara Chaud, M. S., … ACTION Coalition COVID-19 Brazil IV Investigators (2021). Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*, *397*(10291), 2253-2263. https://doi.org/10.1016/S0140-6736(21)01203-4

[22] Jenner, W. J., Kanji, R., Mirsadraee, S., Gue, Y. X., Price, S., Prasad, S., & Gorog, D. A. (2021). Thrombotic complications in 2928 patients with COVID-19 treated in intensive care: a systematic review. *Journal of thrombosis and thrombolysis*, *51*(3), 595-607. https://doi.org/10.1007/s11239-021-02394-7

[23] Nahum, J., Morichau-Beauchant, T., Daviaud, F., Echegut, P., Fichet, J., Maillet, J. M., & Thierry, S. (2020). Venous Thrombosis Among Critically Ill Patients With Coronavirus Disease 2019 (COVID-19). *JAMA network open*, *3*(5), e2010478. https://doi.org/10.1001/jamanetworkopen.2020.10478

[24] Rey, J. R., Caro-Codón, J., Poveda Pineda, D., Merino, J. L., Iniesta, Á. M., López-Sendón, J. L., & investigadores CARD-COVID (2020). Complicaciones arteriales trombóticas en pacientes hospitalizados con COVID-19 [Arterial thrombotic complications in hospitalized patients with COVID-19]. *Revista espanola de cardiologia*, *73*(9), 769-771. https://doi.org/10.1016/j.recesp.2020.05.013

[25] Tan, Y. K., Goh, C., Leow, A. S. T., Tambyah, P. A., Ang, A., Yap, E. S., Tu, T. M., Sharma, V. K., Yeo, L. L. L., Chan, B. P. L., & Tan, B. Y. Q. (2020). COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. *Journal of thrombosis and thrombolysis*, *50*(3), 587-595. https://doi.org/10.1007/s11239-020-02228-y

[26] Levi, M., Thachil, J., Iba, T., & Levy, J. H. (2020). Coagulation abnormalities and thrombosis in patients with COVID-19. *The Lancet. Haematology*, *7*(6), e438-e440. https://doi.org/10.1016/S2352-3026(20)30145-9

[27] Thachil, J., Cushman, M., & Srivastava, A. (2020). A proposal for staging COVID-19 coagulopathy. Research and practice in thrombosis and haemostasis, 4(5), 731-736. https://doi.org/10.1002/rth2.12372

[28] Helms, J., Severac, F., Merdji, H., Anglés-Cano, E., & Meziani, F. (2020). Prothrombotic phenotype in COVID-19 severe patients. *Intensive care medicine*, *46*(7), 1502-1503. https://doi.org/10.1007/s00134-020-06082-7

[29] Thachil, J., Tang, N., Gando, S., Falanga, A., Cattaneo, M., Levi, M., Clark, C., & Iba, T. (2020). ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *Journal of thrombosis and haemostasis : JTH*, *18*(5), 1023-1026. https://doi.org/10.1111/jth.14810

[30] Shah, S., Shah, K., Patel, S. B., Patel, F. S., Osman, M., Velagapudi, P., Turagam, M. K., Lakkireddy, D., & Garg, J. (2020). Elevated D-Dimer Levels Are Associated With Increased Risk of Mortality in Coronavirus Disease 2019: A Systematic Review and Meta-Analysis. *Cardiology in review*, *28*(6), 295-302. https://doi.org/10.1097/CRD.0000000000000330

[31] Kwee, R. M., Adams, H. J. A., & Kwee, T. C. (2021). Pulmonary embolism in patients with COVID-19 and value of D-dimer assessment: a meta-analysis. *European radiology*, *31*(11), 8168-8186. https://doi.org/10.1007/s00330-021-08003-8

[32] Chocron, R., Duceau, B., Gendron, N., Ezzouhairi, N., Khider, L., Trimaille, A., Goudot, G., Weizman, O., Alsac, J. M., Pommier, T., Bory, O., Cellier, J., Philippe, A., Geneste, L., Ben Abdallah, I., Panagides, V., El Batti, S., Marsou, W., Juvin, P., Deney, A., … Critical COVID-19 France investigators (2021). D-dimer at hospital admission for COVID-19 are associated with in-hospital mortality, independent of venous thromboembolism: Insights from a French multicenter cohort study. *Archives of cardiovascular diseases*, *114*(5), 381-393. https://doi.org/10.1016/j.acvd.2021.02.003

[33] Smilowitz, N. R., Kunichoff, D., Garshick, M., Shah, B., Pillinger, M., Hochman, J. S., & Berger, J. S. (2021). C-reactive protein and clinical outcomes in patients with COVID-19. *European heart journal*, *42*(23), 2270-2279. https://doi.org/10.1093/eurheartj/ehaa1103

[34] Ministry of Health of Ukraine. (2021, January 7). *Pro zatverdzhennia Zmin do Standartiv medychnoi dopomohy "Koronavirusna khvoroba (COVID-19)".* Nakaz MOZ Ukrainy No. 10 [On the approval of the Amendments to the Medical Care Standards "Coronavirus Disease (COVID-19)" (No. 10)]. URL: https://zakon.rada.gov.ua/rada/show/v0010282-21?lang=en#Text

[35] Ministry of Health of Ukraine. (2020, April 2). *Protokol nadannia medychnoi dopomohy dlia likuvannia koronavirusnoi khvoroby (COVID-19)*. Nakaz MOZ Ukrainy No. 762 [Protocol for the provision of medical assistance for the treatment of the coronavirus disease (COVID-19) (No. 762)]. https://zakon.rada.gov.ua/rada/show/v0762282-20#Text

[36] Ministry of Health of Ukraine. (2020, March 28). *Orhanizatsiia nadannia medychnoi dopomohy khvorym na koronavirusnu khvorobu (COVID-19)*. Nakaz MOZ Ukrainy No. 722 [Organization of medical care for patients with coronavirus disease (COVID-19) (No. 722)]. https://zakon.rada.gov.ua/rada/show/v0722282-20?lang=en#Text

[37] Riabokon, O. V., Tumanska, L. M., Cherkaskyi, V. V., & Riabokon, Yu. Yu. (2021). Clinical and pathomorphological analysis of deaths from COVID-19 in 2020. *Pathologia*, *18*(3), 269-277. https://doi.org/10.14739/2310-1237.2021.3.242247

[38] Longchamp, A., Longchamp, J., Manzocchi-Besson, S., Whiting, L., Haller, C., Jeanneret, S., Godio, M., Garcia Martinez, J. J., Bonjour, T., Caillat, M., Maitre, G., Thaler, J. M., Pantet, R., Donner, V., Dumoulin, A., Emonet, S., Greub, G., Friolet, R., Robert-Ebadi, H., Righini, M., … Delaloye, J. (2020). Venous thromboembolism in critically Ill patients with COVID-19: Results of a screening study for deep vein thrombosis. *Research and practice in thrombosis and haemostasis*, *4*(5), 842-847. https://doi.org/10.1002/rth2.12376

[39] Lodigiani, C., Iapichino, G., Carenzo, L., Cecconi, M., Ferrazzi, P., Sebastian, T., Kucher, N., Studt, J. D., Sacco, C., Bertuzzi, A., Sandri, M. T., Barco, S., & Humanitas COVID-19 Task Force (2020). Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thrombosis research*, *191*, 9-14. https://doi.org/10.1016/j.thromres.2020.04.024

[40] Kollias, A., Kyriakoulis, K. G., Lagou, S., Kontopantelis, E., Stergiou, G. S., & Syrigos, K. (2021). Venous thromboembolism in COVID-19: A systematic review and meta-analysis. *Vascular medicine*, *26*(4), 415-425. https://doi.org/10.1177/1358863X21995566

[41] Mansory, E. M., Srigunapalan, S., & Lazo-Langner, A. (2021). Venous Thromboembolism in Hospitalized Critical and Noncritical COVID-19 Patients: A Systematic Review and Meta-analysis. *TH open : companion journal to thrombosis and haemostasis*, *5*(3), e286-e294. https://doi.org/10.1055/s-0041-1730967

[42] Nopp, S., Moik, F., Jilma, B., Pabinger, I., & Ay, C. (2020). Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. *Research and practice in thrombosis and haemostasis*, *4*(7), 1178-1191. https://doi.org/10.1002/rth2.12439

[43] Voicu, S., Bonnin, P., Stépanian, A., Chousterman, B. G., Le Gall, A., Malissin, I., Deye, N., Siguret, V., Mebazaa, A., & Mégarbane, B. (2020). High Prevalence of Deep Vein Thrombosis in Mechanically Ventilated COVID-19 Patients. *Journal of the American College of Cardiology*, *76*(4), 480-482. https://doi.org/10.1016/j.jacc.2020.05.053

[44] Wichmann, D., Sperhake, J. P., Lütgehetmann, M., Steurer, S., Edler, C., Heinemann, A., Heinrich, F., Mushumba, H., Kniep, I., Schröder, A. S., Burdelski, C., de Heer, G., Nierhaus, A., Frings, D., Pfefferle, S., Becker, H., Bredereke-Wiedling, H., de Weerth, A., Paschen, H. R., Sheikhzadeh-Eggers, S., … Kluge, S. (2020). Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Annals of internal medicine*, *173*(4), 268-277. https://doi.org/10.7326/M20-2003

[45] Deng, H., Yan, X., & Yuan, L. (2021). Human genetic basis of coronavirus disease 2019. *Signal transduction and targeted therapy*, *6*(1), 344. https://doi.org/10.1038/s41392-021-00736-8

[46] Carter-Timofte, M. E., Jørgensen, S. E., Freytag, M. R., Thomsen, M. M., Brinck Andersen, N. S., Al-Mousawi, A., Hait, A. S., & Mogensen, T. H. (2020). Deciphering the Role of Host Genetics in Susceptibility to Severe COVID-19. *Frontiers in immunology*, *11*, 1606. https://doi.org/10.3389/fimmu.2020.01606

[47] Berger, J. S., Kunichoff, D., Adhikari, S., Ahuja, T., Amoroso, N., Aphinyanaphongs, Y., Cao, M., Goldenberg, R., Hindenburg, A., Horowitz, J., Parnia, S., Petrilli, C., Reynolds, H., Simon, E., Slater, J., Yaghi, S., Yuriditsky, E., Hochman, J., & Horwitz, L. I. (2020). Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. *Arteriosclerosis, thrombosis, and vascular biology*, *40*(10), 2539-2547. https://doi.org/10.1161/ATVBAHA.120.314872