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The Incidence of Thrombosis and Heparin-Dependent Thrombocytopenia in Patients With COVID-19 and Pneumonia With a Course of the Disease Complicated by Acute Kidney Injury

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Abstract

Relevance. Thrombosis is one of the most dangerous complications of COVID-19, not only at the peak of the disease, but also in the long-term period. During the pandemic, issues of medical prevention of thrombotic complications have been repeatedly reviewed, clarified and supplemented, but the only correct tactics for their diagnosis, prevention and treatment do not yet exist.

Purpose of the study. Determination of the frequency and nature of the development of heparin-dependent thrombocytopenia, accompanied by venous and arterial thrombosis in severe patients with COVID-19 and pneumonia, with a course of the disease complicated by acute kidney injury (AKI), including death, assessment of the effectiveness and safety of their antithrombotic therapy.

Material and methods. Inpatient treatment and diagnostic data 216 patients with COVID-19 with viral pneumonia and signs of acute kidney injury (AKI) according to KDIGO 2012 criteria. Group 1. Deceased patients with severe Covid-19 and pneumonia, with unreliable signs of AKI, 75 (men 19, women 56), ratio 1: 2.9. Age from 29 to 87 years. Mechanical ventilation in 56 (74.7%). Group 2. Died patients with covid-19 and pneumonia with reliable signs of AKI, 77 (men 34, women 43), ratio 1: 1.3. Age from 41 to 88 years. Mechanical ventilation in 53 (70.7%) Group 3. Recovered patients with AKI or CKD, 64 (41 men, 23 women, ratio 1:0.56, age from 43 to 89 years). Mechanical ventilation in 1 (1.6%). Hemostasis study. Activated partial thromboplastin time according to the modified method of plasma recalcification reaction according to Baluda V.P. et al. (1980). The level of fibrinogen in blood plasma studied by the ethanol method according to Breen F., Tullis J. (1982). Determination of the concentration of D-dimer in the blood by microlatex agglutination with photometric registration of the reaction (immunoturbidimetry).

Results. In deceased inpatients with Covid-19 and pneumonia, a high, up to 46-56%, incidence of arterial and venous thrombosis of various localizations was revealed. Thrombotic risk was largely associated with increased levels of D-dimer and the duration of its increase in the blood of patients. Thrombocytopenia was diagnosed in 47-58% of patients

and was a significant risk factor for the development of deaths. In cases where thrombocytopenia was detected in patients below 20 thousand cells per μl, its nature was assessed on the 4Ts scale to identify heparin-dependent thrombocytopenia syndrome. In 92-97% of patients, heparins were prescribed, including fractionated (low molecular weight) ones such as enoxaparin, nadroparin, dalteparin and fundaparinux. Some cases of a combination of thrombosis and thrombocytopenia (about 2.3%) were due to the nature of the drug therapy and the development of confirmed heparin-associated thrombocytopenia syndrome.

Conclusion. The data obtained indicate the possibility of the development of heparin-dependent thrombocytopenia syndrome and the high significance of thrombotic mechanisms with the participation of D-dimer in the pathogenesis and outcomes of the disease in groups of deceased patients with covid-19 and pneumonia, complicated by acute kidney injury and the predominant importance of vascular damage in the activation of thrombotic cascade.

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Key points

- In patients with COVID-19 with pneumonia and symptoms of acute kidney injury, assessment and monitoring of platelet counts in the blood are indicated when treated with heparins.
- This group of patients has a high risk of developing heparin-dependent thrombocytopenia and venous thrombosis.
- The tactics for treating thrombotic complications in them excludes the use of all types of heparins, including fractionated low molecular weight ones, and involves the use of direct oral anticoagulants.
- Antithrombotic therapy with a combination of medium doses of aspirin with heparins negatively affected the life prognosis and survival of severe patients with Covid-19 and pneumonia in acute kidney injury; on the contrary, the use of the LMWH fondaparinux was associated with a reduced risk of developing acute renal failure.

The relevance of research

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection predisposes patients to the development of arterial and venous thrombosis. Studies have noted an increase in thromboembolic complications among hospitalized patients [1][2] and there are anecdotal observations of improved outcomes with the use of systemic anticoagulants (ACs),

but their specific role in the treatment of the disease remains unclear [3][4].

Thrombosis is one of the most dangerous complications of the new coronavirus infection (COVID-19), not only at the peak of the disease, but also in the long-term period [4][5]. At least 15% of adult patients with severe disease develop complications in the form of arterial and venous thrombosis [6]. In children with COVID-19, thrombotic complications have also been reported, but are much less common (from 1% to 2% among patients with severe COVID-19), [7].

The severity of the patient's condition and gas exchange disorders is combined with a high prevalence of deep vein thrombosis (DVT), up to 46%, including a proportion of potentially life-threatening proximal DVT in mechanically ventilated patients with SARS-CoV-2, despite standard prophylactic treatment with anticoagulants. Therefore, there is a need to carefully monitor DVT and evaluate the risk/benefit of more intensive anticoagulation regimens in this patient population [8].

The observed risk of venous thromboembolism (VTE) in COVID-19 is high, particularly high in intensive care unit patients, which should be accompanied by increased clinical suspicion and a low threshold for diagnostic imaging of DVT or pulmonary embolism (PE), [9].

Various types of bleeding disorders can be detected in up to 50% of patients with severe manifestations of COVID-19, and the prevalence of deep vein thrombosis and pulmonary embolism exceeds 40%, despite the use of a standard dose of low molecular weight heparin (LMWH) in most cases. Based on these statistics, the International Society of Thrombosis and Hemostasis (ISTH) and the American Society of Hematology (ASH) recommend prophylactic use of LMWH, but the best effective dosage for COVID-19 is not yet known [10].

It is generally accepted that heparins can improve the complex pattern of coagulopathy in patients with COVID-19. Taking into account individual risk of thrombosis and D -dimer values, higher doses of these drugs may be considered, especially since bleeding is rare in COVID-19 [11].

In the few evidence-based studies on the prevention and treatment of thromboembolic complications in hospitalized patients with COVID-19 available signs of improved results with the use of systemic anticoagulants, however, the statistics of deaths in them changed little and the specific role of AK in the treatment of the disease remains unclear [12].

There is an assumption that treatment with anticoagulants can be effective in terms of a positive effect on mortality and life prognosis in patients with COVID-19 in cases with markedly increased levels of D-dimer (6 times or more), as well as in the development of coagulopathy in patients with sepsis [13].

During the pandemic, issues of medical prevention of thrombotic complications in COVID-19 have been repeatedly reviewed, clarified and supplemented, but generally accepted, unified tactics for their diagnosis, prevention and treatment do not yet exist [14][15][16].

The increased use of heparin during the current COVID-19 pandemic, according to the Division of Haematology, Department of Pathology, has increased the risk of a potentially serious complication of heparin therapy, namely. heparin-dependent thrombocytopenia with phlebitis and thrombosis (HIT syndrome). International guidelines on laboratory testing and clinical management of HIT highlight that there are important similarities and differences between HIT and the novel

form of immune thrombotic thrombocytopenia associated with COVID-19 vaccination, also known as thrombosis with thrombocytopenia syndrome (VITT), [17].

Form of drug-induced thrombocytopenia caused by the use of heparins for antithrombotic prophylaxis or therapy is called heparin-induced thrombocytopenia (HIT) syndrome. It is a rare disease with a high incidence of venous thrombosis, high mortality rates, and is associated with the accumulation of heparin-dependent antibodies to platelet-activating factor 4 (PF4)/heparin [18].

According to a summary of the literature, HIT syndrome is detected in approximately 3% of patients receiving heparinoids. Approximately 30-75% of patients who develop its type 2 variant simultaneously develop thrombosis as a result of platelet activation. Patients with severe COVID-19 are among those receiving heparinoids and are therefore at increased risk of developing the syndrome [19].

Only isolated clinical cases of the development of severe syndrome have been described in the literature. HIT during the Covid-19 pandemic, including with employees of the Italian hospital in Bologna and the Swiss Department of Angiology and Blood Coagulation in Bern [20][21]. At the same time, despite the frequent use of drugs of the heparin group, which are included in the standards and recommendations for antithrombotic therapy for COVID-19, there are practically no specific descriptions of cases of the development of HIT syndrome in patients in the domestic literature during the COVID-19 period.

Based on the above, the purpose of this study was to determine the frequency and nature of the development of blood coagulation disorders, thrombosis and embolism, including heparin-dependent thrombocytopenia in severe patients with COVID-19 and pneumonia, with a course of the disease complicated by acute kidney injury, including ended in death, as well as assessing the effectiveness of their anticoagulant therapy and the frequency of hemorrhagic complications.

Material and Research methods

A total of 216 patients with COVID-19 with viral pneumonia (or acute gas exchange disorders) were included in the study. ICD-10 codes: U07.1 Coronavirus infection caused by the COVID-19 virus, the virus has been identified (confirmed by laboratory testing, regardless of the severity of clinical signs or symptoms); J12.9 Community-acquired pneumonia. U07.2 Coronavirus infection caused by the COVID-19 virus, virus not identified (COVID-19 is diagnosed clinically or epidemiologically, but laboratory tests are inconclusive or unavailable. B.34.2. Coronavirus infection, unspecified. All patients had signs of acute kidney pathology, including 75 patients (group 1) without significant signs of acute kidney injury (AKI) according to the KDIGO classification (2012), but with signs of acute nitrogen metabolite disturbance and an increase in serum concentrations of creatinine and (or) urea in blood serum by 1.3-4.9 times or more, but only in the last day of life, who died in hospital, including 19 men and 56 women aged from 29 to 87 years (average age 65.8±5.9 of the year). The second group consisted of 77 patients with reliable signs of acute kidney injury, with an increase in serum creatinine levels by 1.56-6.64 times and disturbances in the dynamics of urinary excretion, including 34 men (age 41-85 years, average 70.1±7.8 years) and 43 women (age from 47 to 88 years, average 72.5±7.4 years), with deaths in the

hospital (Table 1). The comparison group (group 3) included 64 patients, including 41 men (age from 43 to 84 years, on average 66.2±5.4 and 23 women aged from 53 to 89 years, on average 69.9± 6.8 years) with COVID-19 and viral pneumonia (or acute gas exchange disorders), with signs of kidney pathology and an increase in serum concentrations of creatinine and (or) urea by 1.20-2.95 times, but without reliable signs of acute kidney injury. All patients were tested for SARS-CoV-2 using reverse transcriptase polymerase chain reaction (RT-PCR). The reaction was positive in 92-94.8% of patients in the three groups; the frequency of diagnosis confirmation did not differ significantly and statistically between the groups (Table 1).

Table 1. Number, gender and age of examined patients in three groups

Indicators	Group 1. Deceased patients with COVID-19 without AKI	Group 2. Deceased patients with COVID-19 with AKI	Group 3. Discharged COVID-19 patients with AKI and CKD	Significance of differences
Number of patients, men, women	n = 75 (men 19, women 56), ratio 1: 2.9	n=77 (men 34, women 43), ratio 1:1.3	n=64 (men 41, women 23), ratio 1:0.56	-
Age of men, limits of fluctuations, number of men	65.8+5.9 From 33 to 87 years. n=19 (25.3%)	70.1+7.8 From 41 to 85 years n=34 (44.1%)	66.2+5.4 From 43 to 84 years n=41 (64.1%)	Nd p1-2 <0.0 5 p1-3 <0.0 1 p2-3 <0.0 5
Age of women, limits of fluctuations, number of women	66.5±6.2 From 29 to 87 years old n=56 (74.7%)	72.5±7.4 From 47 to 88 years n=43 (55.9%)	69.9+6.8 From 53-89 years n=23 (35.9%)	Nd p1-2 <0.0 5 p1-3 <0.0 1 p2-3 <0.0 5
ICD-X diagnosis: U07.1, number of patients	n=70 out of 75 (93.3%)	n=73 out of 77 (94.8%)	n= 46 out of 50 (92%)	Nd
ICD-X diagnosis: U07.2, number of patients	n=5 out of 75 (6.7%)	n=4 out of 77 (5.2%)	n=4 out of 50 (8%)	Nd

Designations: Nd - unreliable difference in indicators in 3 groups; nd - unreliable difference between the indicators in the two groups; "-" - there is no data to compare the reliability of the indicators.

Methods for assessing renal dysfunction

Diagnosis and assessment of the severity of AKI was carried out in accordance with data on changes in serum creatinine concentration and the degree of decrease in diuresis, according to the KDIGO 2012 criteria [Classification of acute kidney injury according to KDIGO 2012. Clinical practice guideline for the evaluation and management of Chronic Kidney Disease. 2013]. The classification uses an assessment of serum creatinine levels, dynamics of diuresis volume and the

severity of urodynamic disorders (oliguria, anuria). A comparison of clinical, biochemical, instrumental and pathomorphological data in 3 groups of patients with COVID-19, pneumonia and changes in renal function made it possible to establish that signs of disorders of the nitrogen and water excretion function of the kidneys during hospital treatment and upon admission were diagnosed in the majority of patients, however the nature of these disorders differed significantly in groups, so in the 2nd group, signs of acute kidney injury of stages 1-3 were diagnosed with an increase in creatinine levels by 1.5-6.6 times, an increase in urea concentration and a decrease in daily diuresis in all 77 cases (100 %), and in the 1st group - in 75.4% (the difference is statistically significant - by 24.6%; $p < 0.03$), in another 42.7% of them it was symptoms of AKI - stage 0 (with an increase in serum creatinine levels by 1.30-1.49 times) and without diuresis disturbances. In the first group of patients, disorders of nitrogen excretion function of the kidneys were observed in 57 cases out of 75 (75.4%), and an increase in serum creatinine concentration was diagnosed in deceased patients only in the last day of life. The incidence of AKI on admission was approximately similar in the 3 analyzed groups of patients, ranging from 12.5% in the group of discharged patients to 26% in the 2nd group of deceased patients with reliable clinical and biochemical signs of AKI ($p>0.1$; the difference is unreliable). The majority of cases of AKI in the groups of deceased patients developed during hospital treatment - up to 84% - in the 2nd group, the difference from the indicator of discharged patients of the 3rd group by 82.4% ($p < 0.001$; significant) and by 33.8% from the indicator in the 1st group of deceased patients ($p<0.01$; significant). The severity of developed AKI was maximum in the 2nd group of deceased patients, so in 37.7% of them it met the criteria of stage 3, which was 27% more than in the 1st group ($p <0.02$; significant). There were no cases of AKI stages 2 and 3 in the 3rd group of discharged patients. On the contrary, the number of cases of mild AKI stage 1 was maximum in the 1st group - 46.7%, which was significantly higher than in the 2nd group - by 24.6% ($p <0.03$) and in the 3rd group of discharged patients – by 32.7% ($p<0.01$).

Methods for studying hemostasis indicators

Coagulogram parameters were studied using an automatic analyzer “ACL Elite Top”, USA. The following indicators were assessed: prothrombin time according to Quick, prothrombin index and international normalized ratio by calculation. Activated partial thromboplastin time was determined using a modified plasma recalcification reaction method according to the method of V.P. Baluda. et al. (1980). The level of fibrinogen in blood plasma was determined by the ethanol method according to the method of Breen F., Tullis J. (1982). The concentration of D-dimer in the blood was studied by microlatex agglutination with photometric registration of the reaction (immunoturbidimetry). The following indicators were determined: international normalized ratio (norm 0.9 - 1.15), prothrombin time (norm 10.3 - 16.6 s), prothrombin according to Quick (norm 60 - 130%), thrombin time (norm 18-24 s), fibrinogen concentration (normal 2.00 - 4.00 g/l), activated partial thromboplastin time (normal 25.4 - 36.9 seconds), D-dimer (normal 0-250 ng/ml). The study was carried out in 216 patients over time (376 determinations).

Research results and Discussion

The frequency of thrombosis and embolism in the studied groups of patients with COVID-19 and pneumonia was high,

ranging from 25% in the group of discharged, recovered patients (group 3) to 56% in group 1 of those who died (Table 2).

Table 2. The nature and frequency of venous and arterial thrombosis and identified pathology of the circulatory system according to clinical-biochemical, instrumental and pathomorphological diagnostics in 3 groups of patients

Frequency and nature of pathology	**Group 1. Deceased patients with COVID-19 without AKI.** **n=75**	**Group 2. Deceased patients with COVID-19 with APP.** **n=77**	**Group 3. Patients with COVID-19 discharged from hospital** **n=64**	**Difference in %, reliability (p1-2;p1-3; p1-3)**
Total diseases of the circulatory system and their frequency in %	n=42 out of 75 (56%)	n=36 out of 77 (46.7%)	n=16 out of 64 (25%)	P1-2 <0.05 P2-3 <0.0 3
1. PE	n=14 (18.7%)	n=3 (3.9%)	n=3 (4.7%)	Nd
2. Hemorrhagic pulmonary infarction	n=2 (2.7%)	n= 1 (1.5%)	n=0	P1-2 nd
3. Venous thrombosis of the vessels of the extremities:	n=9 (12%)	n=6 (7.8%)	n=5 (7.8%)	Nd
4. LV thrombosis	n=3 (4%)	n=0	n=0	Nd
5. Acute myocardial infarction	n=3 (4%)	n=9 (11.7%)	n=0	P1-2 nd
6. Coronary stenting and TLAP in acute coronary thrombosis	n=5 (6.7%)	n=6 (7.8%)	n=5 (7.8%)	Nd
7. Thrombosis of the abdominal aorta	n=0	n=2 (2.6%)	n=0	-
8. Transient ischemic attack (TIA)	n=0	n=0	n=3 (4.7%)	-
9. Thrombectomy, aspiration of thrombus from cerebral arteries	n=0	n=2 (2.6%)	n=0	-
10. ACVA	n=6 (8%)	n=3 (3.9%)	n=0	p1-2 nd
11. Acute thrombosis of the arteries of the lower extremities	n=0	n=3 (3.9%)	n=0	-
12. Total diseases with arterial thrombosis	n=17 (22.7%)	n=25 (32.5%)	n=8 (12.5%)	p1-2 nd p1-3 nd p2-3< 0.05
13. Total diseases with venous thrombosis	n=25 (33.3%)	n=11 (14.3%)	n=8 (12.5%)	P1-2< 0.05 p1-3<0.03 p2-3 nd

Designations: Nd - unreliable difference in indicators in 3 groups; nd - unreliable difference between the indicators in the two groups; "-" - there is no data to compare the reliability of the indicators. ACVA - acute cerebrovascular accident; TLAP —translumenal angioplasty; PE—pulmonary embolism; LV - left ventricle of the heart

Arterial thrombosis was diagnosed most often in those who died with AKI in the 2nd group in 32.5% of patients, and venous thrombosis in the 1st group - in 33.3% of patients. The most common cause of venous thrombosis was pulmonary embolism (PE) - in 18.7% of patients in group 1 and thrombosis of the veins of the extremities - in 12% of them. Approximately similar statistics on the incidence of pulmonary embolism in COVID-19 according to pathomorphological studies are provided by domestic researchers from the city hospital of Severodvinsk (Russian Federation), repurposed for the period of the pandemic [21].

The main cause of arterial thrombosis was acute coronary syndrome - which led to the formation of necrosis in 11.7% of patients in group 2 or was relieved by stenting of a thrombosed artery during translumenal angioplasty with revascularization - in 7.8% of patients in groups 2 and 3 groups.

From the comparison, it could be concluded that anticoagulant therapy, prescribed prophylactically for the majority of patients with COVID-19, according to the existing standard of treatment, very often does not achieve its goal and prevent various forms of venous and arterial thrombosis.

In our study, antithrombotic therapy was carried out in the majority of patients in 3 groups; in 92-97% of patients, heparins were prescribed, including fractionated (low molecular weight) heparins such as enoxaparin, nadroparin, dalteparin and fundaparinux, according to the existing Federal standard [Temporary guidelines recommendations: Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Version 15 (22/02/2022). Ministry of Health of the Russian Federation. Moscow, 2022]. Analysis of the use of mainly fractionated heparins for the treatment of patients with COVID-19 and pneumonia allowed us to note a negative relationship between the prescription of both heparin and the low molecular weight drug, enoxaparin, with the survival rates of patients in the group with signs of AKI. Thus, in the 2nd group of deceased patients with AKI, treatment with heparin, both in medium and high dosages, was used significantly more often, on average by 18.2%, than in the 3rd group of discharged patients, the difference is significant ($p2\text{-}3 < 0.05$), table 3.

Table 3. Frequency of heparin therapy in 3 groups of patients with covid-19 and pneumonia

Types of drugs, frequency of prescription and doses used. No drugs	Group 1. Deceased patients with COVID-19 without AKI. n=73 out of 75 (97.3%) n=2 (2.7%)	Group 2. Deceased patients with COVID -19 with APP. n=75 out of 77 (97.4%) n=2 (2.6%)	Group 3. Patients with COVID-19 with AKI and CKD discharged. n=59 out of 64 (92.2%) n=5 (7.8%%)	Difference in %, reliability (p1-2;p1-3;p1-3) Nd Nd
1. Heparin Dose 5-20 thousand units/day Dose 25-100 thousand units/day	n=13 out of 73 (17.8%) n=3(23.1%) n=10(76.9%)	n=20 out of 75 (26.7%) n=9(45%) n=11(55%)	n=5 out of 59 (8.5%) n=3 n=2	p1-2 nd p1-3 nd p2-3 <0.05 p1-2 <0.03 p 1-2<0.0 3
2. Nadroparin (2850 IU) Dose 2850-3800 IU/day Dose 5700 IU/day	n=1(1.4%) n=0 n=1	n=1(1.3%) n=1 n=0	n=11(17.2%) n=9(81.8%) n=2(18.2%)	p1-2 nd p1-3 >0.1 p 2-3>0.1 - -
3. Fondaparinux (2.5 mg/0.5 ml) Dose 2.5 mg/day Dose 5 mg/day	n=24 (32.9%) n=19(79.2%) n=5(20.8%)	n=6 (8%) n=3 n=3	n=0 n=0 n=0	p1-2 < 0.03 - -
4. Enoxaparin Dose 4-12 units/day Dose 16-24 units/day	n=67 (91.8%) n=49 (73.1%) n=18 (26.9%)	n=73 (97.3%) n=56 (76.7%) n=17 (23.3%)	n=48 (75%) n=26 (72.2%) n=13 (27.1%)	p1-2 nd p1-3 >0.05 p2-3 <0.03 Nd Nd
5. Dalteparin Dose 2.5-5 units Dose 10-16 units	n=0 n=0 n=0	n=0 n=0 n=0	n=7 (10.9%) n=4 n=3	- - -

The same pattern was noted when prescribing fractionated heparin - enoxaparin, which was more often used in prophylactic dosages of 4-12 units / day. The drug was significantly more often prescribed to patients in group 2 compared to the group of discharged patients, on average by 22.3% (significant, p<0.03). In contrast, use of fractionated genarin

fondaparinux was associated with a reduced risk of AKI. Thus, in the 1st group of deceased patients, the frequency of taking fondaparinux was significantly higher than in the 2nd group of deceased patients with AKI, on average by 24.9% (the difference is significant; p1-2<0.03).

The connection revealed in the study between the worsening life prognosis and the nature of heparin therapy in some COVID-19 patients with pneumonia, as well as the frequent development of thrombocytopenia, was the basis for assessing the criteria for HIT syndrome. According to the literature, it is an immune-mediated side effect of the use of unfractionated or low molecular weight heparin, which leads to thrombocytopenia and potentially catastrophic thrombosis [18][22]. Given the severity of thrombocytopenia that develops and the type of heparin used in hospitalized patients, it is recommended that a 4Ts score be calculated to identify patients at increased risk of developing the syndrome and to guide further evaluation. In patients with an intermediate or high likelihood of 4Ts evaluation, immunoassays are recommended to confirm or refute the diagnosis of HIT. Withdrawal of heparin and initiation of non-heparin anticoagulant therapy are the mainstays of treatment for acute HIT syndrome [18]. The 4Ts scoring system for diagnosing HIT consists of four criteria, each scoring 0, 1, or 2 points. The first criterion for thrombocytopenia is a decrease in platelet count by 30-50% or a lower platelet value of 10-19x10 9 /l. A number of studies have noted that the incidence of HIT is relatively lower with the use of low molecular weight heparins. Thrombosis is more often diagnosed in the venous system than in the arterial circulatory system, and multivessel coronary artery thrombosis is rare, but can develop [23].

In our study, 5 patients (2.3%) met the HIT criteria according to the 4Ts grading system out of 216 patients. Their minimum platelet count ranged from 7 to 18 thousand per µl, and the average score was 4.7 on the 4Ts scale. All 5 were diagnosed with signs of thrombosis: one patient developed coronary thrombosis, and 4 had symptoms of venous thrombosis: including PE (1 patient) and phlebitis of the deep veins of the leg, 3 had acute phlebitis with thrombosis of the veins of the lower (2) and upper (1) extremities. The development of HIT syndrome and worsening thrombocytopenia was observed during therapy with unfractionated heparin (2 cases), enoxaparin (2 cases) and nadroparin (1 case). All cases belonged only to patients of group 2 who had signs of AKI (Table 4).

Table 4. The number of platelets in the peripheral blood in 3 groups of hospitalized patients with covid-19 and pneumonia and their changes during the period of hospital treatment

The number of platelets in the blood. ***The norm is 150-450 thousand in µl.*** ***Indicators***	**Group 1.** **Patients n=50. Research n=92**	**Group 2.** **Patients n=50. Research n=98**	**Group 3.** **Patients n=50. Research n=95**	**Difference in %, reliability** **(p1-2;p1-3; p1-3)**
1. Average maximum platelet count values and limits of fluctuations (thousands in µl)	244±136 (64-720 thousand in µl)	239±85 (86-456 thousand in µl)	268±103 (111-584 thousand in µl)	Nd
2. Average minimum values (thousands in µl) and limits of fluctuations	157±95 (40-516 thousand in µl)	140±76 (43-328 thousand in µl)	194±70 (63-366 thousand in µl.	Nd

3. Normal values (% of total)	40 out of 70 (57.2%)	42 out of 74 (56.8%)	41 out of 53 (77.3%)	p1-3 <0.0 3 p2-3 <0.0 3
5. High values	4 out of 70 (5.7%)	1 in 74 (1.3%)	3 out of 53 (5.7%)	Nd
6. Low values	26 out of 70(37.1%)	31 out of 74(41.9%)	9 out of 53(17.0%)	p1-3 <0.0 3 p2-3 <0.0 3
7. No data	P=0	P=0	P=1 out of 50(2%)	-
8. Dynamics of indicators in the hospital, number of patients studied	n=50	n=50	n=48	
8a. No dynamics	8 out of 51(15.7%)	9 out of 50% (18%)	11 out of 48 (22.9%)	Nd
8b. Decline	24 out of 51(47.0%)	29 out of 50 (58%)	11 out of 48 (22.9%)	p1-3 <0.0 3 p2-3 <0.0 1
8c. Increase	19 out of 51(37.3%)	12 out of 50 (24%)	26 out of 48 (54.2%)	p1-3> 0.05 p2-3 <0.0 1
8d. No information	n=0	n=0	n=1 out of 49 (2.04%)	-
8e. No research	n=0	n=0	n=1 out of 50(2%)	-
9. Number of cases with different platelet counts (combination of studies):	n=92 From 40 to 729 thousand per µl.	n=98 From 56 to 456 thousand in µl.	n=95 From 63 to 584 thousand in µl.	-
9a. 1st third of the total	74 out of 92 (80.5%) From 40 to 267 thousand per µl.	43 out of 98 (43.9%) From 7 to 157 thousand in µl.	58 out of 95 (61%) From 63 to 237 thousand in µl.	p1-2 <0.0 1 p1-3 <0.0 5 p2-3 <0.0 5
9b. 2nd third	14 out of 92 (15.9%) From 268 to 495 thousand per µl.	44 out of 98 (44.9%) From 158 to 308 thousand. in µl	33 out of 95 (34.8%) From 238 to 412 thousand in µl.	p1-2 <0.0 2 p1-3 <0.0 5
9c. 3rd third	4 out of 92 (4.3%) From 496 to 720 thousand per µl.	11 out of 98 (11.2%) From 309 to 456 thousand in µl.	4 out of 95 (4.2%) From 413 to 584 thousand per µl.	Nd

Impaired renal function in patients with HIT syndrome, in our opinion, is one of the most significant risk factors for its

development. A close connection between negative outcomes with COVID-19 and thrombosis in patients with the development of acute kidney injury was previously shown in a study by authors from the clinic of the Faculty of Medicine of the People's Friendship University of Russia (Moscow, Russian Federation), [24].

A progressive decrease in the number of platelets during the treatment period was also most often observed in our study in patients of group 2 with AKI - in 58% of cases, which was 2.53 times more often than in the group recovered from pneumonia. During the observation period, heparins were discontinued in all 5 cases of verified HIT syndrome, with replacement with direct-acting oral anticoagulants (dabigatran, xarelto).

For timely diagnosis of HIT syndrome and urgent transition to therapy with other antithrombotic drugs in patients with covid-19, in our opinion, dynamic assessment (monitoring) of hemostasis indicators and control of platelet levels during anticoagulant therapy in all patients with covid-19 in ICU departments should be used. Its necessity was previously substantiated in the work of Yu.L.Ketsko and O.V.Tereshin from the clinic of the Samara Medical University Reaviz [23].

In our study, using such diagnostics, the connection between the development of HIT syndrome in patients with COVID-19 and pneumonia receiving anticoagulant therapy with heparins was verified in cases of a disease complicated by the simultaneous development of acute kidney injury. The risk group for developing heparin-dependent thrombocytopenia in COVID-19 was mainly patients with an initial decrease in this indicator. According to diagnostic data carried out before this hospitalization, 17 cases of deep thrombocytopenia were identified in 216 patients (7.8%) with a platelet count from 21 to 80 thousand per μl (Table 5).

Table 5. The nature and frequency of detected pathology of the hematopoietic organs in 3 groups of patients according to the study data before hospitalization

Diseases of the hematopoietic system. **Indicators.**	**Group 1. Deceased patients with COVID-19 without AKI** **n=75**	**Group 2. Deceased patients with COVID-19 with AKI** **n=77**	**Group 3. Patients with COVID-19** **Discharged from hospital** **n=64**	**Difference in %, reliability** **(p1-2;p1-3; p1-3)**
Frequency of diseases of the hematopoietic organ system before current hospitalization:	n=21 (28%)	n=37 (48%)	n=9 (14.1%)	p1-2 <0.05 p1-3 nd p2-3 <0.01
Anemia: light moderate severity	n=20 (26.7%) n=14 (70%) n=6 (30%)	n=26(33.8%) n=18 (69.2%) n=8 (30.8%)	n=9 (14.1%) n=6 (66.7%) n= 3 (33.3%)	p 2-3<0.05 nd nd
Thrombocytopenia: 21-80 thousand 81-134 thousand	n=8 (10.7%) n=5 (62.5%) n=3 (37.5%)	N=11(14.3%) n=8 (72.7%) n=3 (27.3%)	n=10 (15.6%) n=4 (40%) n=6 (60%)	Nd
B-cell lymphocytic leukemia 1-2 tbsp.	n=0	n=1 (1.3%)	n=0	-

Analysis of the effectiveness of oral anticoagulants and antiplatelet agents affecting blood clotting in patients with COVID-19 and pneumonia in 3 selected groups allowed us to note a negative impact on patient survival rates of the use of a combination of heparin and aspirin in medium doses (125 mg/day), (Table 6). At the same time, we did not note any signs of a possible negative effect of combinations of heparins with such oral antithrombotic drugs as apixaban, rivaroxaban (direct-acting anticoagulants, selective inhibitors of coagulation factor Xa) and clopidogrel (P2 Y12 blocker platelet receptors), on the risk of developing AKI and patient survival rates.

Table 6. Per os anticoagulants and antiplatelet agents used in the treatment of patients with COVID-19 and pneumonia (in table)

Drugs, doses. No drugs	Group 1. Deceased patients with COVID-19 without AKI who received drugs n=36 out of 75 (48%) n=39(52%)	Group 2. Deceased patients with COVID-19 with AKI who received drugs n=37 out of 77(48%) n=40(52%)	Group 3. Patients with COVID-19, AKI and CKD, discharged and receiving medications. n=14 out of 64 (21.8%) n=50(78.2%)	Significance of differences (p1-2;p1-3;p1-3) p1-2 nd P1-3 < 0.03 P2-3 < 0.02 p1-2 nd p1-3 < 0.03 P2-3 < 0.02
1. Aspirin Dose 100 mg/s Dose 125 mg/s Dose 250 mg/s	n=24 out of 75 (32%) n=2 (8.3%) n=22 (91.7%) n=0	n=26 out of 77(33.7%) n=3(11.5%) n=20 (77%) n=3(11.5%)	n=7 out of 64 (10.9%) n=3 n=4 n=0	p1-2 nd p1-3 < 0.03 p2-3 < 0.03 nd nd -
2. Apixaban Dose 5 mg/s Dose 10-20 mg/s	n=3 (4%) n=0 n=3	n=11 (14.3%) n=7 n=4	n=6 (9.4%) n=6 n=0	Nd - -
3. Clopidogrel Dose 75 mg/s Dose 600 mg/s	n=5 (6.7%) n=5 n=0	n=6 (7.8%) n=2 n=4	n=2 (3.1%) n=2 n=0	Nd - -
4. Rivaroxaban Dose 15 mg/day Dose 20-30 mg/day	n=6 (8%) n=2 n=4	n=6 (7.8%) n=6 n=0	n=2 (3.1%) n=0 n=2	Nd - -
5. Warfarin (2.5 mg tablet) Dose 1.75 mg/day	n=0 n=0	n=0 n=0	n=2 (3.1%) n=2	nd -

In the available literature on the results of the use of non-steroidal anti-inflammatory drugs (NSAIDs), we have not

identified any data on the negative impact of the drug on the life prognosis of severe patients with COVID-19.

Another negative side of the anticoagulant and antiplatelet therapy carried out in patients with COVID-19 and pneumonia could be hemorrhagic complications. In our work, we analyzed the incidence of perioperative and spontaneous bleeding in them with blood loss in the amount of 150-500 ml/day (Table 7).

Table 7. Frequency of bleeding of various organ localizations during hospital treatment of patients with covid-19 and pneumonia in 3 groups

Diseases with blood loss in hospital	**Group 1. Deceased patients with COVID-19 without AKI** **n=75**	**Group 2. Deceased patients with COVID-19 with AKI** **n=77**	**Group 3. Patients with COVID-19. Discharged from hospital** **n=64**	**Difference in %, reliability** **(p1-2;p1-3; p1-3)**
Gastrointestinal bleeding	n=2 (2.7%)	n=3 (3.9%)	n=1(1.6%)	Nd
Erosive colitis	n=2 (2.7%)	n=0	n=0	-
Erosive gastritis, gastroduodenitis	n=12 (16%)	n=11(14.3%)	n=1 (1.6%)	Nd
Uterine fibroids, bleeding, hystrectomy	n=6 (8%)	n=5 (6.5%)	n=4 (6.2%)	Nd
Total cases with blood loss	22 (29.3%)	19 (24.7%)	6 (9.4%)	p1-2 nd p2-3 nd p1-3 < 0.05

During the analysis, we noted that the maximum rate of bleeding was in the 1st group - 29.3% and the 2nd group of deceased patients with AKI - 24.7% and the lowest in the 3rd group of discharged patients - 9.4%, a difference between groups 1 and 3 was significant (p1-3<0.03). Therapy with hemostatic drugs was most often used in the 2nd group of those who died with AKI - in 13% of patients and least often in the 3rd group - in 3.1%, the difference is not significant (Table 8).

Table 8. Hemostatic therapy drugs used in the treatment of patients with covid-19 and pneumonia in 3 compared groups

Drug groups (frequency of application ni in %)	Group 1. Deceased patients without proven AKI. n=75	Group 2. Deceased patients with AKI criteria. n=77	Group 3. Discharged patients with AKI or CKD. n=64	Difference in %, reliability (p1-2;p1-3;p1-3)
Hemostatic, total drugs	n=6 out of 75 (8%)	n=10 out of 77(13%)	n=2 out of 64 (3.1%)	Nd
1.Menandione (vicasol) 10 mg/ml Dose 10-20 mg/day Dose 30 mg/day	n=3 out of 75(4%) n=3 n=0	n=0 n=0 n=0	n=1 out of 64 (1.6%) n=0 n=1	nd - -
2. Tranexam (250 mg tablet) Dose 500 mg/day	n=0 n=0	n=5 out of 77 (6.5%) n=5	n=0 n=0	- -
3. Etamsylate (125 mg/ml-2.0 amp.) Dose 750 mg/day	n=3 out of 75 (4%) n=3	n=5 out of 77 (6.5%) n=5	n=1 out of 64 (1.6%) n=1	Nd -

In this study, we also analyzed the initial blood coagulation parameters in 3 groups of patients with COVID-19 and their dynamics during hospital treatment. Assessing the nature of changes in the phases of the blood coagulation cascade in the studied groups of patients, we noted that the APTT indicator, reflecting the phase of blood thromboplastin formation, was the highest in the 1st group of deceased patients who did not have reliable signs of AKI, exceeding the average maximum values of patients of the 3rd group by 35.1%, the difference is significant ($p<0.01$), table 9.

Table 9. Frequency of changes in activated partial thromboplastin time (APTT) in 3 groups of patients with covid-19 and pneumonia during the period of hospital treatment.

Activated partial thromboplastin time (APTT) ***Normal 22-31 sec*** ***Indicators***	**Group 1. Patients, n=50** **Research, n=119**	**Group 2. Patients n=50** **Research, n=107**	**Group 3. Patients, n=50** **Research, n=44**	**Reliability of differences**
1. Average maximum blood APTT values (sec) and limits of fluctuations	51.5±38.5 (20.2-200 sec)	44.8±35.8 (19.1-200 sec)	33.4±12. (19.6-94.2 sec)	Nd
2. Average minimum values (sec)	33.1±23.3 (19.8-134 sec)	28.8±7.1 (18.3-63.2 sec)	28.6±5.5 (18.9-40.9 sec)	Nd
3. Normal values (% of total)	36 out of 69 (52.2%)	34 out of 66 (51.6%)	28 out of 45 (62.3%)	Nd
5. High values	25 out of 69 (36.2%)	30 out of 66 (45.4%)	15 out of 45 (33.3%)	Nd
6. Low values	8 out of 69 (11.6%)	2 out of 66 (3%)	2 out of 45 (4.4%)	Nd
7. No data	4 out of 50 (8%)	3 out of 50 (6%)	13 out of 50 (26%)	P1-3 <0.05 P2-3 <0.05
8. Dynamics in the hospital	n=38	n=40	n=18	
8a. No dynamics	6 out of 38 (15.8%)	18 out of 40 (45%)	2 out of 18 (11.1%)	P1-2 <0.0 1 P2-3 <0.0 1
8b. Decline	13 out of 38 (34.2%)	7 out of 40 (17.5%)	11 out of 18 (61.1 %)	P1-2> 0.05 P1-3 <0.0 2 P1-3 <0.0 01
8c.Increase	19 out of 38 (50%)	15 out of 40 (37.5%)	5 out of 18 (27.2 %)	P1-3 <0.0 3
8d. No information	11 out of 50 (22%)	7 out of 50 (14%)	19 out of 37 (51.3%)	P1-3 <0.05 P2-3 <0.0 1
8e. No research	4 out of 50 (8%)	3 out of 50 (6%)	13 out of 50 (26%)	P1-3 <0.05 P2-3 <0.05

The average maximum indicator in the 2nd group was also 25.4% higher than the indicator in the 3rd group (significant; p <0.02). From these data we can conclude that in the deceased patients of these two groups, laboratory signs of hypocoagulation associated with suppression of thromboplastin formation were observed during hospital treatment, probably due to medication, since 92-97% of them received therapy with various types of heparins (as did 75 % of patients in group 3). During the initial period of hospital treatment, differences in APTT levels in the groups were less

pronounced and non-significant, which was reflected by the average minimum APTT values. During the period of treatment in the hospital, the most frequent increase in the indicator was also observed in the 1st group - in half of the patients, the difference from the 3rd group was significant - by 22.8% (p <0.03), and a decrease - in the 3rd group - in 61.1% of patients, the difference is significant and compared with the indicator of the 1st group by 26.9% (p <0.02) and the 2nd group - by 43.6% (p <0.001). These data indicate that hypocoagulation with a decrease in APTT had a longer duration in the groups of deceased patients, while heparin therapy in them had an average longer period than in the group of recovered patients.

In our study, when assessing the main indicators characterizing the 2nd phase of blood coagulation, it was noted that the time of thrombin formation from prothrombinase - prothrombin time (PT) and the international normalized ratio (INR) differed little in the 3 study groups in terms of average values both during the initial period of hospitalization and at the end of the inpatient period. High average PT values were more often detected in the 2nd group of patients - in 75.9% of cases, which was significantly more often than in the 3rd group - by 24.6% (significant difference; p <0.03) and in 1 group, by 18.5% (p <0.05), table 10. Accordingly, normal values of the indicator were determined in group 2 significantly less frequently than in groups 3 and 1 - by 24.6% and 18.5%, respectively, table 10.

Table 10. Frequency of changes in prothrombin time (PT), international normalized ratio (INR) and thrombin time (TT) in 3 groups of patients with covid-19 and pneumonia upon admission and during the period of hospital treatment

Prothrombin time (PT). ***Normal 9-12 sec*** ***Indicators***	**Group 1. Number of patients, n=50.** **Research, n=91**	**Group 2. Number of patients, n=50.** **Research, n=95**	**Group 3. Number of patients, n=50.** **Research, n=44**	**Reliability of differences**
1. Average maximum values of blood PT (seconds) and limits of fluctuations	15.8 ± 5.6 (11.0-31.0 sec)	16.2 ± 7.1 (10.5-53.6 sec)	15.0 ± 7.0 (11.4-50.6 sec)	Nd
2. Average minimum values (sec), fluctuation limits	12.9 ± 2.1 (10.1-23.3 sec)	13.2 ± 1.8 (11.1-18.1)	13.5 ±3.5 (10.8-30.2 sec)	Nd
3. Normal values, frequency of cases (% of total)	26 out of 61 (42.6%)	13 out of 54 (24.1%)	19 out of 39 (48.7%)	P1-2 <0.0 5 p1-3 nd P2-3 <0.0 3
4. High values	35 out of 61 (57.4%)	41 out of 54 (75.9%)	20 out of 39 (51.3%)	P1-2 <0.0 5 P2-3 <0.0 3 p1-3 nd
5. Low values	P=0	P=0	P=0	-

6. No data	1 in 50 (2%)	3 out of 50 (6%)	17 out of 50 (34%)	P1-2 nd P1-3 <0.0 1 P2-3 <0.0 2
7. Dynamics in the hospital, number of studies	P=34	P=33	P=12	-
7a. Without dynamics, number of cases (frequency in%)	13 out of 34 (30.2%)	8 out of 33 (24.2%)	P=0	nd
7b. Decline	7 out of 34 (20.7%)	10 out of 33 (30.3%)	5 out of 12 (41.7%)	P1-2 nd P1-3 <0.0 3 p2-3 nd
7c. Increase	14 out of 34 (41.1%)	15 out of 33 (45.4%)	7 out of 12 (58.3%)	P1-2 nd P1-3 <0.0 5 p2-3 nd
7d. No information	15 out of 50 (30%)	14 out of 50 (28%)	22 out of 33 (66.7%)	P1-2 nd P1-3 <0.0 1 P2-3 <0.0 1
7e. No research	1 in 50 (2%)	3 out of 50 (6%)	17 out of 50 (34%)	P1-2 nd P1-3 <0.0 1 P2-3 <0.0 2
International normalized ratio (INR). *Norm 0.95-1.10*	Number of patients, n=50. Research,n=107	Number of patients, n=50. Research, n=113	Number of patients, n=50. Research, n=57	-
1. Average maximum INR values and limits of fluctuations	1.51 ± 0.66 (0.98-4.96)	1.55 ± 0.63 (1.02-4.11)	1.34 ± 0.63 (0.96-4.86)	Nd
2. Average minimum values, limits of fluctuations	1.18 ± 0.19 (0.93-2.06)	1.18 ± 0.16 (0.93-1.63)	1.19 ± 0.28(0.95-2.65)	Nd
3. Normal values (% of total)	18 out of 56 (32.1%)	17 out of 60 (28.3%)	17 out of 42 (40.5%)	Nd
4. High values	37 out of 56 (66.1%)	42 out of 60 (70%)	25 out of 42 (59.5%)	Nd
5. Low values	1 in 56 (1.8%)	1 in 60 (1.7%)	P=0	Nd
6. No data	2 out of 50 (4%)	2 out of 50 (4%)	14 out of 50 (28%)	P1-2 nd P1-3 <0.0 3

				P2-3 <0.0 3
7. Dynamics in the hospital, number of studies	P=33	P=38	P=16	-
7a. No dynamics	13 out of 33 (39.4%)	7 out of 38 (18.4%)	1 in 16 (6.3%)	P1-2 <0.0 3 P1-3 <0.0 1 p2-3 nd
7b. Decline	5 out of 33 (15.1%)	14 out of 38 (36.8%)	9 out of 16 (56.2%)	P1-2 <0.0 3 P1-3 <0.0 01 P2-3 <0.0 5
7c.Increase	15 out of 33 (45.5%)	17 out of 38(44.8%)	6 out of 16 (37.5%)	Nd
7d. No information	15 out of 50 (30%)	10 out of 50 (20%)	21 out of 36 (58.3%)	P1-2 <0.0 2 p1-3 <0.0 2 P2-3 <0.0 1
7e. No research	2 out of 50 (4%)	2 out of 50 (4%)	14 out of 50 (28%)	P1-2 nd P1-3 <0.0 3 P2-3 <0.0 3
Thrombin time (TT). *Number of people studied. The norm is 16-25 seconds*	n=11	n=20	n=7	-
Average TT values (sec) and limits of indicator fluctuations	33.1 ± 23.3 From 19.8 to 100 sec	36.8 ± 27.1 From 11.7 to 100 sec	22.9 ± 10.5 11.2 to 49.0 sec	Nd

During the period of inpatient treatment, a decrease in PT was more often observed in patients in group 3 - in 41.7% of patients, which was significantly more often than in patients in group 1 - on average by 21% (p <0.03). Similarly, a decrease in the INR in the hospital was more often observed in the 3rd group on average in discharged patients than in the 1st and 2nd groups of deceased patients, by 41.1% (significant; p <0.001) and by 19.4 % (p<0.05), respectively. Thrombin time (TT) was assessed in groups only upon admission of patients to the hospital, and we were unable to obtain reliable statistics for the treatment period in the study. According to the average indicators obtained at the beginning of hospitalization, the average TV values were the highest in the 2nd group of deceased patients with AKI - 36.8 seconds, which was 37.8% higher than in the 3rd group (significant; p<0. 01). Thus, the data obtained on the state of the blood coagulation cascade in its 1st and 2nd phases in patients with COVID-19 and AKI, compared with the indicators of

patients without signs of acute kidney injury, suggest a connection between these mechanisms and the factors and causes of development renal damage in some patients.

The level of fibrinogen protein in the blood, which characterizes the 3rd phase of the blood coagulation cascade and fibrin thrombus formation, according to the average maximum values obtained in patients in the 3 analyzed groups during hospital treatment, was the highest in the 2nd group of patients with COVID-19 19 and AKI, exceeding the average values of the 1st group of deceased patients by 24.9% (significant; p<0.03), table 11.

Table 11. Frequency of changes in fibrinogen concentrations in the blood in 3 groups of patients with covid-19 and pneumonia during the period of hospital treatment

Fibrinogen. ***The norm is 2.0-3.9 g/l.*** ***Indicators***	**Group 1. Number of patients, n=50 research, n=84**	**Group 2. Number of patients, n=50 research, n=81**	**Group 3. Number of patients, n=50. research, n=52**	**Significance of differences**
1. Average maximum values of blood fibrinogen concentration (g/l) and limits of fluctuations	4.30 ± 2.11 (1.4-9.8 g/l)	5.73 ± 2.43 (1.0-12.2 g/l)	5.58 ±2.27 (1.4-11.2 g/l)	Nd
2. Average minimum values (g/l) and limits of fluctuations	3.01 ± 1.76 (0.9-8.5 g/l)	3.53 ± 2.36 (0.9-11.0 g/l)	4.97 ± 1.87 (1.4-8.5 g/l)	Nd
3. Normal values, number of cases (% of total)	29 out of 63 (46.1%)	16 out of 63 (25.4%)	4 out of 39 (10.3%)	P1-2 <0.0 3 P1-3 <0.0 1 p2-3 nd
5. High values	20 out of 63(31.7%)	34 out of 63(54%)	32 out of 39(82%)	P1-2 <0.0 2 P1-3 <0.0 01 p2-3 <0.0 2
6. Low values	14 out of 63 (26.2%)	13 out of 63 (20.6%)	3 out of 39 (7.7%)	P1-2 nd P1-3 <0.0 5 p2-3 nd
7. No data	3 out of 50 (6%)	9 out of 50 (18%)	12 out of 50 (24%)	P1-2 nd P1-3 <0.0 5 p2-3 nd
8. Dynamics in the hospital, number of cases	n=28	n=30	n=11	-
8a. No dynamics (% of total)	4 out of 28 (14.3%)	3 out of 30 (10%)	P=0	Nd

8b. Decline	15 out of 28 (53.6%)	19 out of 30 (63.3%)	9 out of 11 (81.8%)	P1-2 nd P1-3 <0.0 2 P2-3 <0.0 5
8c. Increase	9 out of 28 (32.1%)	8 out of 30 (26.7%)	2 out of 11 (18.2%)	Nd
8d. No information	21 out of 50 (42%)	11 out of 50 (22%)	27 out of 38 (71%)	P1-2 <0.0 5 P1-3 <0.0 2 P2-3 <0.0 01
8e. No research	3 out of 50 (6%)	9 out of 50 (18%)	12 out of 50 (24%)	P1-2 nd P1-3 <0.0 5 p2-3 nd

At the same time, the values of the indicator obtained in the initial period of hospital treatment were maximum in the 3rd group of recovered patients, exceeding the values of patients in the 1st group by 39.4% (the difference is significant; p <0.01) and the indicator of the 2nd group – by 28.9% (significant; p<0.02). The incidence of a decrease in its concentration was the highest in the 3rd group of discharged patients, exceeding the level of the 1st and 2nd groups by 28.2% (significant difference; p<0.02) and 18.5% (p< 0.05).

From the data obtained, we can conclude that activation of thrombus formation mechanisms with increased fibrin formation occurred in all 3 groups of patients with COVID-19 and pneumonia, and their most rapid normalization was observed in recovered patients with resolving pneumonia (group 3).

As in the studies of other cited authors, this work noted the high significance of thrombotic mechanisms involving D-dimer or fibrinogen degradation products in the pathogenesis and outcomes of the disease in groups of deceased patients and the role of an increase in its concentration that persisted during hospital treatment in the development of AKI.

Significant differences between the 1st and 2nd groups were identified in the 2nd indicators of the dynamics of D-dimer concentration during hospital treatment - the frequency of decrease in the indicator - 18.3% more in the 1st group (p <0.05), and the frequency of increase in the indicator - higher in group 2 by 21.1% (p <0.03), table. 12.

Table 12. Concentration of D-dimer (PDF) in the blood of patients with covid-19 and pneumonia in 3 selected groups

D-dimer. ***The norm is 14-500 ng/ml.*** **Indicators**	**Group 1.** **Number of patients, n=50.** **Number of research, n=128**	**Group 2.** **Number of patients, n=50.** **Number of research, n=111**	**Group 3.** **Number of patients, n=50.** **Number of research, n=111**	**Significance of differences**
1. Average maximum concentration of D-dimer in the blood and limits of fluctuations (ng/ml)	5348 ± 3518 (683-10620 ng/ml)	5485 ± 3626 (484-10436 ng/ml)	2307 ± 2188 (177-10000 ng/ml)	Nd
2. Average minimum concentration (ng/ml)	2124 ± 2528 (148-10000 ng/ml)	2793 ± 3030 (19-10000 ng/ml)	1309 ± 1350 (170-4373 ng/ml)	Nd
3.Normal values, number of cases (% of total)	9 out of 61 (14.7%)	8 out of 50 (16%)	15 of 58 (25.9%)	Nd
5.High values, number of cases (%)	52 out of 61 (85.3%)	42 out of 50 (84%)	43 of 58 (74.1%)	Nd
6. No data	O out of 50	0 out of 50	1 in 50 (2%)	-
7. Dynamics in the hospital, number of cases (% of total)	P=37 out of 50 (74%)	P=33 out of 50 (66%)	P=34 out of 49 (69.4%)	Nd
7a. No dynamics	1 in 37 (2.7%)	P=0	4 out of 34 (11.8%)	nd
7b. Decline	18 out of 37 (48.6%)	10 out of 33 (30.3%)	10 out of 34 (29.4%)	p1-2 <0.05 p1-3 nd p2-3 <0.05
7c. Increase	18 out of 37 (48.6%)	23 out of 33 (69.7%)	20 out of 34 (58.8%)	p1-2 <0.0 3 p1-3 nd p2-3 <0.05
7d. No information	13 out of 50 (26%)	17 out of 50 (34%)	15 out of 49(30.6%)	Nd
7e. No research	P=0	P=0	P=1 out of 50(2%)	-

Our data indicate the high importance of thrombotic mechanisms with the participation of D-dimer in the pathogenesis and outcomes of the disease in groups of deceased patients with AKI, and, consequently, the predominant importance of vascular damage in the mechanisms of activation of parts of the thrombotic cascade in them.

Conclusion

Thus, the course of the disease in inpatients with COVID-19 and pneumonia is characterized by a high, up to 46-56%, incidence of arterial and venous thrombosis of various locations. The thrombotic danger was largely associated with an increased level of D-dimer and the duration of its increase in the blood of patients. Some cases of a combination of thrombosis and thrombocytopenia may be due to the nature of the drug therapy and the development of heparin-associated thrombocytopenia syndrome. This variant of coagulopathy complicated the course of covid infection and heparin therapy in 2.3% of cases and mainly in patients with acute kidney injury. Thrombocytopenia in severely ill patients with COVID-19 and pneumonia was often diagnosed - in 47-58% of cases and was a significant risk factor for the development of deaths. In cases where deep thrombocytopenia was detected in patients, below 20 thousand cells per μl, its nature was assessed using the 4Ts scale, and when heparin-induced thrombocytopenia was diagnosed, the use of heparin was stopped and therapy with direct oral anticoagulants was prescribed. The incidence of organ bleeding in patients receiving anticoagulants was 15-29% and was largely associated with the existing pathology of the gastrointestinal tract and genitals; the risk of hemorrhage was aggravated by the development and progression of thrombocytopenia and limited the use of heparin therapy. Antithrombotic therapy when combining medium doses of aspirin with heparins negatively affected the life prognosis and survival of severe patients with COVID-19, pneumonia and acute kidney injury, and, on the contrary, the use of fondaparinux was associated with a reduced risk of developing acute renal failure.

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Statements and Declarations

Conflict of Interest

The authors declare no conflict of interest.

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