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# THE MECHANISM OF BLOOD COAGULATION IN COVID-19 PATHOGENESIS

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**ABSTRACT** — One of the formidable complications of SARS-COV-2 infection leading to death is coagulopathy. The mechanisms of the development of this pathology at the present stage have not been studied, and clinical blood tests indicate that against the background of normal blood clotting indices, only the Ddi-D-dimer protein exceeds the norm many times over. The aim of the study was to study and analyze biochemical parameters in patients of Primorsky Region (Russia) infected with SARS-COV-2 against the background of concomitant vascular pathology and the development of DIC syndrome. The authors came to the conclusion about the existence of two mechanisms of circulatory disorders in the vessels of the microvasculature, associated with the violation of the integrity of the vascular wall and destruction of erythrocytes. Further research is needed to study the mechanisms of SARS-CoV-2 aggression, leading to thrombotic complications.

**KEYWORDS** — SARS-COV-2, COVID 19, coagulopathy, blood coagulation factors, prothrombin time, prothrombin index, Ddi - D-dimer, DIC syndrome.

## INTRODUCTION

The global COVID-19 pandemic represents a health emergency of unprecedented proportions. [11] Recent clinical data have shown that coronavirus disease 2019 (COVID-19) is associated with a significant risk of thrombotic complications ranging from microvascular thrombosis, venous thromboembolism, and strokes [6]. Importantly, thrombotic complications are markers for severe COVID-19 and may be associated with multiple organ failure and increased mortality. According to the literature, when infected with SARS-CoV-2, patients are predisposed to thrombotic complications in both the venous and arterial bloodstream due to excessive inflammation, platelet activation, endothelial dysfunction, and congestion leading to the development of disseminated intravascular coagulopathy (DIC syndrome).

Currently, there is no comprehensive understanding of the pathogenesis, treatment strategy and outcomes in patients with COVID-19 who develop venous or arterial thrombosis, especially in patients with preexisting thrombotic disease before the development of COVID-19 [3, 7]. The development of measures for the prevention and treatment of concomitant thrombotic disease during the COVID-19 pandemic is required. Al-Samkari H., Karp Leaf RS, Dzik WH, (2020) noted that elevated D-dimer levels in coronavirus disease 2019 (COVID-19) patients are inconsistent with observed bleeding rates, necessitating randomized trials to determine any potential prospects for enhanced effective anticoagulant prophylaxis in patients with COVID-19 [1].

Absence of general immunity in human to COVID-19 has contributed to a large number of infected patients around the world amid uncertainty about the treatment of complications arising from this viral disease [5, 9]. More than a million deaths in the world did not give an answer either about the causes of death, or about the features of the induction of pathomorphological changes by the SARS-CoV-2 virus [4, 12]. The high incidence of thromboembolic complications and high mortality suggest an important role for coagulopathy caused by COVID-19 [8].

Further research is needed to study the molecular mechanisms of coagulopathy in SARS-CoV-2 infection in order to develop conservative therapy to eliminate the pandemic. Although prophylactic drugs such as low molecular weight heparins (LMWH) are recommended by the International Society for Thrombosis and Hemostasis (ISTH) and the American Society of Hematology (ASH), their best effective dosage has not been determined at the present stage. These facts determined the direction of our research.

### *Aim of research*

To determine the features of the mechanisms of coagulopathy caused by COVID-19 when infected with SARS-CoV-2.

## MATERIAL AND METHODS

We studied the data of patients with laboratory-confirmed infection with SARS-CoV-2 and the development of the clinical picture of COVID-19, hospitalized in Primorsky Krai (Russian Far East) from March to July 2020. Data analysis was carried out in the dynamics of the disease for any thromboembolic complication, including venous thromboembolism (VTE), ischemic stroke, and acute coronary syndrome (ACS) / myocardial infarction (MI). The analysis of the clinical examination data from the recovered and patients with lethal outcomes was carried out in terms of prothrombin time (PT), international normalized ratio (INR), blood ferritin and platelet count, and the level of fibrinogen in the blood. The content of the D-dimer protein (Ddi), which is formed during the breakdown of fibrin and is the basis of blood clots, was also taken into account. The distribution of the clinical data material is shown in Table 1.

## RESULTS

Analysis of the data showed that among the patients infected with SARS-CoV-2, males prevailed, accounting for 54.8% of the number of patients included in the study group. Coagulopathy has been reported in nearly 95% of patients with severe COVID-19. Complications leading to death were severe disseminated intravascular coagulation (DIC syndrome). In the group with fatal outcomes, male patients predominated, accounting for 57% of the total number of deaths and about 56% of the number of COVID-19 hospitalized cases in men.

We noted that coagulopathy against the background of COVID-19 has shown that indicators such as PTT, PTI, platelet count, fibrinogen level in the blood of both men and women in the fatal group do not exceed framework of normal indicators. However, the measurement of the D-dimer levels showed that in deceased patients its content in all cases exceeds the normal values from 4 to 17 times, and in male patients with a predominance of the value in all age groups in comparison with female patients (Table 2).

Thus, the analysis of the data showed that there are differences in pathological changes in blood parameters depending on the gender of the patients. There is a high incidence of deep vein thrombosis and pulmonary embolism, and a high mortality rate in patients despite the use of standard doses of low molecular weight heparin (LMWH) recommended by the International Society for Thrombosis and Hemostasis (ISTH) and the American Society of Hematology (ASH).

At the same time, at the present stage, an adequate effective dosage has not been determined, which, in our opinion, is associated with a dead-end concept of vascular thromboembolism. The most informative are the blood levels of D-dimer protein and ferritin, which sharply differ from the normal values. In men with a fatal outcome as a result of COVID-19, this figure exceeds the norm by up to 17 times, in women from 3 to 4 times. PTT in men with a lethal outcome is within the normal range; in women it exceeds the norm by 1.5 times.

PT in women corresponds to norm, in men it is 30% lower. The number of platelets in women is below normal in 90%, in men it is higher than normal in only 1 case. Fibrinogen in men in some cases slightly exceeds the norm, and in women it is below the norm in 70% of cases. A decrease in platelet counts was observed in deceased intensive care patients compared with patients who were not treated in intensive care unit.

These data indicate that DIC is a syndrome against the background of SARS-CoV-2 infection and the development of an aggressive form of COVID-19, accompanied by the formation of structures that disrupt the patency of small and large vessels of the visceral and nervous systems may have other mechanisms and participants in pathogenetic manifestations. Some blood clotting parameters may be below normal as a result of anticoagulation treatment.

Discussion. The features of coagulopathy associated with COVID-19 have been noted in many studies [1]. Therefore, despite the fact that there is prophylactic anticoagulant therapy, there is an urgent need for studies of the real pathogenesis of thromboembolic complications and thromboprophylaxis strategies in the conservative treatment of SARS-CoV-2 infection. A noticeable increase in the level of D-dimer is associated with the development of intravascular thromboembolism (VTE) and can be used to predict and identify the risk of complications. Pulmonary microvascular thrombosis may be involved in progressive pulmonary failure. In COVID-19, the main risk factors for the development of complications leading to death are old age, male sex and the presence of concomitant diseases, especially arterial hypertension [2,10]. The lack of understanding of the pathophysiology of COVID-19, as well as the definition of an effective therapy strategy, is accompanied by severe clinical manifestations and poor outcomes in a large number of patients. The standard or increased dosage of LMWH in the group of resuscitated patients, venous and arterial thrombotic events indicate the need to revise the pathogenesis of COVID-19. Further research is urgently needed to investigate the mechanisms of SARS-CoV-2 aggression leading to thrombotic complications.

***Table 1.*** *Distribution of hospitalized patients with severe manifestations of coronavirus infection by the groups of age and gender*

| № of group* | Age | Men | Women | Total | Recovered | Died |
|---|---|---|---|---|---|---|
| | | | | | m/w | m/w |
| VII | 21–30 | 1 | 1 | 2 | 1/1 | 0/0 |
| VIII | 31–40 | 2 | 4 | 6 | 2/4 | 0/0 |
| IX | 41–50 | 9 | 4 | 13 | 5/4 | 4/0 |
| X | 51–60 | 8 | 6 | 14 | 6/3 | 3/2 |
| XI | 61–70 | 7 | 5 | 12 | 0/2 | 7/3 |
| XII | 71–80 | 6 | 5 | 11 | 0/0 | 6/5 |
| XIII | More than 80 | 1 | 3 | 4 | 1/0 | 0/3 |
| Total | | 34 | 28 | 62 | 15/14 | 19/14 |

** Official international numbering of age groups distribution*

***Table 2.*** *Indicators of blood clotting in patients with different outcomes of the disease*

| Blood count rates | Norm | | Recovered | | Died | |
|---|---|---|---|---|---|---|
| | Men | Women | Men | Women | Men | Women |
| | | | 15 | 14 | 19 | 14 |
| D-dimer, μg / μl | 0–0.5 | 0 | 0 | 0 | 1.14–8,8 | 1.47–2.44 |
| PTT, Sec. | 11 | 16 | 10.4 | 15.3 | 12.4–15.4 | 11.7–26.1 |
| PTI, % | 80 | 105 | 102 | 80–98 | 52.8–66.7 | 81.5–91 |
| Thrombocytes Units / μl | 200–400 | 180–320 | 300 | 240 | 208–478 | 133–170 |
| Fibrinogen, g/l | 2–4 | 2–4 | 2 | 3 | 2.45–4.8 | 1.29–2.51 |
| Ferritin, ng/mL | 30–250 | 10–125 | 64 | 59 | 152 | 966–1154 |

## CONCLUSIONS

1. A large number of arterial and venous thromboembolism diagnosed within 24-48 hours after hospitalization, high mortality among patients with COVID-19 suggest an urgent need to study the specific mechanisms of DIC-syndrome in SARS-CoV-2 infection and develop pathogenetically informed strategy of conservative treatment, as well as justification of the efficacy and safety of thrombi prophylaxis in outpatients with COVID-19.
2. An increase in D-dimer levels is the most informative and most significant change in blood coagulation parameters in patients with severe COVID-19, and gradually increasing values can be used as a predictor of a worse outcome.
3. The pathophysiology and mechanisms of coagulopathy in COVID-19 are not associated with the mechanisms of blood coagulation, but complicate their course.

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