Manifestation of Coagulopathy in Patients on The Background of Covid-19

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ABSTRACT

Coronavirus infection (COVID-19), an acute infectious disease caused by the SARS-CoV-2 virus, is characterized by activation of the hemostasis system, which in the most severe cases can lead to the development of consumption coagulopathy. Coronavirus disease 2019 (COVID-19) in severe cases leads to a cytokine storm, a systemic inflammatory response, and coagulopathy, which is one of the worst prognostic factors. Coagulopathy in COVID-19 is accompanied by a pronounced increase in the level of D-dimer and fibrin/fibrinogen breakdown products, while the deviation of other indicators (prothrombin time, activated partial thromboplastin time, platelet count) at the onset of the disease is relatively rare. This article will consider the role and intensive care of coagulopathy against the background of coronavirus infection.

Keywords: coronavirus infection, coagulopathy, anticoagulant therapy, D-dimer, pro-inflammatory cytokines.

Introduction. COVID-19 is caused by a huge number of phenotypes, ranging from a non-symptomatic course to complicated multiple organ failure and death. The calculated mechanisms for the formation of multiple organ failure are multifaceted, they contain hypercoagulation with the formation of blood clots in both micro- and macrocirculatory beds. The formation of DIC syndrome is manifested by a serious predictor of death (among patients with a fatal outcome occurred in 71.4% patients and was observed in only 0.6% of surviving patients) [1]. There is also a significant increase in D-dimer and prothrombin with a parallel decreasing number of fibrinogen by 10-14 per day in patients with a fatal outcome [1]. This suggests that these results need to be tracked . A significant level of D-dimer (above 1 μg/mL) is one of the solid independent risk factors for death in this population [2].

The purpose of this work: To determine the incidence, clinical manifestations of coagulopathic disorders andto identify risk factors for the development of coagulopathic disorders in COVID-19 patients.

Materials and methods: Analysis of research conducted and research literature published in scientific publications.

Results: Thrombocytopathy and endotheliopathy that form during coronavirus infection lead to the so-called thromboinflammation, which, as it turned out, is most manifested in the pulmonary vessels. Scientists from Italy were the first to describe this syndrome as MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) - microvascular obstructive thromboinflammatory syndrome of pulmonary

vascular lesions. They also noted that this the condition has significant differences from the classic acuterespiratorydistress syndrome [8].

Coagulopathy is expressed by increased fibrinogen levels, increased levels of D-dimers, and smaller modifications of prothrombin time, aHTV, and platelet count in the early stages of infection. An increase in IL-6 levels correlates with an increase in fibrinogen levels. Coagulopathy is associated with the severity of the disease and resulting thromboinflammation, and not with its own viral activity. An increased D-dimer on enrollment is associated with an elevated mortality rate and an increase in D-dimer after hospitalization precedes multiple organ failure and obvious DIC syndrome [9].

According to a one-center retrospective study in China in patients with severe pneumonia in COVID-19 who were in the intensive care unit (n = 81), the incidence of vein thrombosis of the lower extremities was 25% [12]. The presence of obvious disseminated intravascular coagulation indicates the development of coagulopathy of consumption, when it may be necessary to replenish the missing components of the blood coagulation system. The occurrence of DIC is associated with poor Forecast. Venous thrombosis and pulmonary embolism (PE) are common complications of COVID-19. In addition to deep vein thrombosis of the lower legs and PE, cases of arterial thrombosis and thrombosis in extracorporeal contours have been described [13].

Evidence of COVID-19-related pathological clotting parameters has emerged in the following reports from China. The final characteristics of the first 99 patients hospitalized in Wuhan indicated that 6% had increased activated partial thromboplastin time (APTT), 5% increased prothrombin (PT), 36% had an increased D-dimer and increased biomarkers of inflammation, including interleukin-6. IL-6), erythrocyte sedimentation rate and C-reactive protein. Thrombocytopenia occurred in only 12%, yet 5 patients had other co-infections (1 bacterial, 4 fungal) and 4 had septic shock. [10]

AT the heart of COVID-19 is multisystem inflammation with bleeding disorders. In COVID-19, levels of various pro-inflammatory cytokines are elevated, and the cytokine storm is responsible for the progression and modification of the disease. Tumor necrosis factor a, IL-1β, IL-6, interferon-γ and granulocytic colony-stimulating factor are typical cytokines that mediate inflammation and coagulation. Cytokine storm leads to systemic intravascular coagulation, multiple organ failure, and death [13].

There are three pathogenetic mechanisms in the development of thrombosis in coronavirus infection: the release of cytokines, netosis, antiphospholipid antibodies. SARS-CoV-2 is a single-stranded RNA coronavirus belonging to the family*, Coronaviridae*, a genus of beta-coronavirus that invades human cells by binding a "spike protein" (S protein) to the angiotensin-converting enzyme 2 (ACE2) receptor, acting as the main SARS-CoV-2 receptor, resulting in suppression of ACE2 and higher expression of angiotensin II [14]].

Angiotensin II has pronounced vasoconstrictor properties, and also increases hypercoagulation by enhancing the production of tissue factor and a plasminogen activator inhibitor (Forrester S., 2018).. Binding of the "spike protein" to ACE2 leads to the production of inflammatory cytokines, including the chemoattractant of protein 1 monocytes (MSP-1), transforming growth factor-beta 1 (TGF-β1)), tumor necrosis factor alpha (TNF-α)), interleukin (IL)-1β and IL-6, which are involved in hypercoagulation. Released cytokines provoke interstitial inflammation, endothelial damage and activation of coagulation, in the pathogenesis of which a key role belongs to the tissue factor. It is secreted by monocytes, as well as damaged or activated by the action of cytokines endothelial cells. The release of TF leads to activation of the external pathway of blood coagulation [15].

In 15 out of 21 fatal patients, obvious DIC syndrome was diagnosed according to the ISTH criteria with an average onset 4 days after admission; only 1 in 78 discharged patients showed signs of DIC syndrome. At the time of hospitalization, the deceased showed signs of progressive DIC syndrome with a decrease in fibrinogen, an increase in D-dimer and an

increase in PV 10 days after hospitalization, although information on signs of sepsis was not provided. Suggesting that antithrombin levels decreased in the later stages of hospitalization in non-survivors, in most they were not below the allotted norm [11].

Hyperinflammatory reactions lead to tissue damage, disruption of the endothelial barrier and uncontrolled activation of coagulation [16]. Direct viral damage to the endothelium is also crucial for activating coagulation. Another mechanism for involving hemostasis in the pathogenesis of COVID-19 is the production of antiphospholipid antibodies. Chinese authors described 3 patients with COVID-19 in whom thrombotic complications manifested by thrombosis of the arteries of the extremities, ischemic strokes, arose on the 3rd, 10th and 18th days of the disease. During a detailed examination, all were found to have antibodies to β 2-glycoprotein-1 related to immunoglobulins (Ig) of classes G and A, as well as anticardiolipin antibodies related to IgA [17].

Antithrombotic therapy of COVID-19 associated coagulopathy uses low-molecular and unfractionated heparin (LMWH, UFH). At the moment, preference is given to LMWH. The administration of low molecular weight heparins at least in prophylactic doses is indicated for all hospitalized patients and should continue at least until discharge. To date, the issues relating to pathogenetically based prevention and therapy, with the impact on all links of viral inflammation and caogulopathy in such patients, have not been finally resolved and require clarification . This determines the need for research in this direction to choose the method and scope of treatment of this pathology in this category of patients.

Already the first autopsies showed that the lungs in COVID-19 had diffuse edema, as well as a pattern of ARDS, microangiopathic, hemorrhagic and thrombotic phenomena. The studied lungs were characterized by widespread alveolar damage, the presence of a significant number of CD4 + limfocytes aggregated around small thrombosed vessels, and concomitant bleeding [18].

Excess production of pro-inflammatory cytokines, elevated levels of damaging molecular patterns, and endothelial damage underlie disseminated intravascular coagulation (DIC) occurring in severe infections and/or sepsis, which is characterized by decreased levels of blood clotting factors associated with increased fibrinolysis. Although COVID-19-associated coagulopathy (thrombocytopenia, increased D-dimer levels, and prolonged prothrombin time) resembles that seen in DIC syndrome associated with sepsis, most cases cannot be classified as having DIC syndrome on the Scale of the International Society of Thrombosis and Hemostasis (ISTH) for specific laboratory features (very high levels of D-dimer and moderate thrombocytopenia), at least in the early stage of COVID-19 infection. Several mechanisms are thought to underlie the prothrombotic changes in COVID-19. These are disseminated intravascular coagulation (DIC syndrome), pulmonary intravascular coagulopathy (LVC) or microvasculatory obstructive thromboinflammatory syndrome of the lungs (MicroCLOTS), secondary hemophagocytic lymphohistiocytosis, thrombotic microangiopathy (TMA) and endothelialitis [19].

Most likely, DIC syndrome underlies the progression of multiple organ failure, which occurs faster in the absence of anticoagulant prophylaxis, and may also be due to the occurrence of septic complications. The thromboinflammatory response may be mediated by either endothelial damage or activation of macrophages leading to a cytokine storm [20]. This situation can be interpreted as a special kind of secondary hemophagocytic lymphohistiocytosis, and the observed increase in ferritin confirms this hypothesis. Particular mechanisms of prothrombotic changes in the hemostasis system may include direct damage to the endothelium by virus, hypoxia, DNA and histones of epithelial, endothelial and neutrophilic origin (extracellular neutrophil networks - NETs), inflammatory cytokines; dysregulation of macrophage activity and Lymphocytes; a decrease in the amount of ACE-2, accompanied by an increase in the concentration of angiotensin. complement

activation; irritation of megakaryocytes of the lungs; production of antiphospholipid antibodies; development of heparin-induced thrombocytopenia [19].

Meanwhile, there are no convincing data on the efficacy and safety of the use of prophylactic doses of anticoagulants in outpatients with infectious diseases to date. The incidence of venous thromboembolic complications in patients with COVID-19 was unexpectedly high, which determines the need to develop effective preventive comprehensive measures. The problem in the tactics of choosing intensive complex treatment is the basis for conducting scientific research to address the above issues. Pathogenetically based prevention and treatment, with an impact on all links of coronavirus inflammation and the caugulopathic process in such patients is planned for the first time in this study.

The present has generated a keen interest in the possibility of using anticoagulants in COVID-19 patients. Heparin most likely has a number of advantages over other anticoagulants due to the fact that it has not only anticoagulant properties, but also anti-inflammatory qualities (alleviating pneumonia and improving oxygenation), as well as – potentially – antiviral properties.

As an anticoagulant, heparin can dissolve blood clots in microcirculation of organs, most effectively in the vessels of the lungs. Cases of hypoxia, disproportionate lung function in pulmonary vasculopathy and increased dead space (and hemoglobinopathy) have been outlined. The use of anticoagulants is indirectly associated with a decrease in mortality in all patients, for example, in patients with more than 3 points on a scale assessing sepsis-associated coagulopathy (SIC score) [3]. It should be noted that, as with each episode of DIC syndrome, patients can progress to a hypocoagulant phenotype when the level of fibrinogen begins to decrease. Then the suspension of anticoagulant therapy should be analyzed. At the moment, the suspension of anticoagulant therapy should be analyzed. At the moment, the role of the use of thromboelastography (TEG) in addition to measuring the level of other indicators of coagulation systems in deciding whether to start or discontinue anticoagulant therapy is considered. Hypothetical, patients receiving continuous renal replacement therapy (OST) or on extracorporeal membrane oxygenation (ECMO) may have complications associated with coagulation, and proactive anticoagulant therapy in these cases will be justified. In addition to the increasing number of negative events associated with blood clotting, an increase in antithrombin 3 deficiency is added, leading to the impossibility of using heparin in anticoagulant therapy. A lot of medical organizations switched to bivalirudin when choosing anticoagulants when drawing up treatment regimens.

A small number of cases with the use of thrombolytics together with a tissue plasminogen activator (tPA) in cases of difficult-to-treat hypoxia indicates positive results associated with the normalization of the oxygenation index with prolonged infusions [4]. Patients are now being collected for comprehensive tPA studies.

The anti-inflammatory properties of heparin have positive benefits. Rising levels of D-dimer may indirectly serve as a marker of an increasing inflammatory response in the provided population. In practice, with immune-thrombotic interaction – where inflammation and thrombin formation are directly interdependent – heparin may reduce the inflammatory response by blocking thrombin formation. The meta-analysis confirms a decrease in deaths with the use of small molecule heparin in patients with acute respiratory distress syndrome (ARDS), against the background of COVID-19 [5].

As a result, heparin may have antiviral qualities, affect the surface proteins of fusion and inhibit the attachment of the virus to the cell [6].

Inference. The choice of schematic treatments for seriously ill COVID-19 patientsis compounded by the incessantly changing data from surveys and general episodes. As a result, as with all health care providers treating COVID-19 patients, it is a priority to make the most informed decisions based on a significant

number. Ofthe studies included in the peer review, we come to these conclusions that:

- All patients with coronavirus infection are accordingly required to undergo examinations for the level of D-dimer, platelets, as well as for prothrombin time (PTV) [7].
- All patients with coronavirus infection are recommended to prescribe anticoagulants in prophylactic doses, mainly low molecular weight heparin, if there are no contraindications, for example, acute renal damage (AKI), in which it is advisable to use unfractionated heparin.
- The use of anticoagulants in therapeutic doses is probably considered only for patients at high risk of developing coagulopathy showing symptoms of organ dysfunction caused by the formation of microthrombi, either with confirmed thromboembolism of large vessels or with serious suspicions of it. Detection of patients at significant risk through laboratory tests for coagulopathy includes: measurement of platelet levels, fibrinogen, fibrinogen breakdown products, D-dimer levels, thromboelastography, and prothrombin time. It should be noted that some medical institutions prescribe anticoagulants in therapeutic doses to all patients, if there are no direct contraindications.
- The use of acetylsalicylic acid should be considered in cases with an increase in troponin and cardiac dysfunction.

References:

1. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020. doi:10.1111/jth.14768
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3
3. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020. doi:10.1111/jth.14817
4. Wang J, Hajizadeh N, Moore EE, et al. Tissue Plasminogen Activator (tPA) Treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): A Case Series. J Thromb Haemost. 2020. doi:10.1111/jth.1482
5. Li J, Li Y, Yang B, Wang H, Li L. Low-molecular-weight heparin treatment for acute lung injury/acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. Int J Clin Exp Med. 2018;11(2):414-422.
6. Mycroft-West CJ, Su D, Elli S, et al. The 2019 coronavirus (SARS-CoV-2) surface protein (Spike) S1 Receptor Binding Domain undergoes conformational change upon heparin binding. bioRxiv. 2020:2020.02.29.971093. doi:10.1101/2020.02.29.971093
7. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020. doi:10.1111/jth.14810
8. Ciceri F, Beretta L, Scandroglio AM, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): An atypical acute respiratory distress syndrome working hypothesis. Critical Care and Resuscitation 2020; 22 (2): 95–7. DOI: 10.3316 / informit.196503333515429.
9. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020; 135 (23): 2033–40. DOI: 10.1182 / blood.2020006000.
10. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–513.
11. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with

novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–847.
12. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020 Jun;18(6):1421-1424. doi: 10.1111/jth.14830. Epub 2020 May 6. PMID: 32271988; PMCID: PMC7262324.
13. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020 Dec;9(1):727-732. doi: 10.1080/22221751.2020.1746199. PMID: 32196410; PMCID: PMC7170333.
14. Paz Ocaranza, M., Riquelme, J.A., García, L. et al. Counter-regulatory renin–angiotensin system in cardiovascular disease. Nat Rev Cardiol 17, 116–129 (2020). https://doi.org/10.1038/s41569-019-0244-8
15. Galstyan G.M. Coagulopathy in COVID-19. Pulmonology. 2020;30(5):645-657. https://doi.org/10.18093/0869-0189-2020-30-5-645-657
16. Colling ME, Kanthi Y. COVID–19-associated coagulopathy: An exploration of mechanisms. Vascular Medicine. 2020;25(5):471-478. doi:10.1177/1358863X20932640
17. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y, Zhang S. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med. 2020 Apr 23;382(17):e38. doi: 10.1056/NEJMc2007575. Epub 2020 Apr 8. PMID: 32268022; PMCID: PMC7161262.
18. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, Baghbanzadeh M, Aghamohammadi N, Zhang W, Haque U. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol. 2020 Jun 1;49(3):717-726. doi: 10.1093/ije/dyaa033. PMID: 32086938; PMCID: PMC7197734.
19. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res. 2020 Jun;220:1-13. doi: 10.1016/j.trsl.2020.04.007. Epub 2020 Apr 15. PMID: 32299776; PMCID: PMC7158248.
20. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev. 2020 Jun;19(6):102537. doi: 10.1016/j.autrev.2020.102537. Epub 2020 Apr 3. PMID: 32251717; PMCID: PMC7195002.