Options for the development of coagulopathy in COVID-19

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ABSTRACT

The mechanisms of COVID-19-associated coagulopathy (CAC) are complex and differ in many ways from the standard mechanisms of thrombosis in critically ill patients. This review presents the pathogenesis, diagnosis and comparison of different types of coagulopathy with SAS. In the course of COVID-19 infection, the number of cases of sudden death outside the hospital has increased. One possible reason is the high rate of serious thrombotic events in patients with COVID-19. However, the pathogenesis of these life-threatening events is multifactorial and requires independent discussion.

Keywords: COVID-19-associated coagulopathy , sepsis-induced coagulopathy , thromboelastography , rotational thromboelastometry

Introduction. Most patients with COVID-19 develop symptoms of a respiratory infection, some progressing to more severe systemic illness characterized by persistent fever, lung injury with acute respiratory distress syndrome (ARDS), coagulopathy, multiple organ failure (MOF) , shock , and high mortality [1].

Careful monitoring of patients with COVID-19 has shown that changes in the blood coagulation system in almost 50% of patients resemble systemic coagulopathies , such as disseminated intravascular coagulation (DIC) and thrombotic microangiopathies (TMA) [2]. In addition, it turned out that COVID-19-associated coagulopathy also has features that distinguish it from DIC and TMA [3]. Another very important finding in patients with severe COVID-19 is the tendency to thromboembolic complications in the venous and arterial systems [4]. High mortality and its direct relationship with thromboembolic complications make coagulation complications leading in the study of COVID-19 [5].

This, in turn, raises questions about the potential role of anticoagulants and their optimal dosing in the prevention and treatment of patients with COVID-19 [6, 7]. The effectiveness of prophylactic and therapeutic use of anticoagulants in this context is ambiguous. The pathophysiology of COVID-19-associated coagulopathy (CAS) is complex and is likely to differ greatly from the standard mechanisms of thrombosis reported in critically ill patients. This review presents the pathogenesis, diagnosis and comparison of various well-characterized types of coagulopathy with SAS.

In accordance with the recommendations, patients with coronavirus infection (COVID-19) as thrombotic biomarkers, it is necessary to evaluate D- dimer levels , fibrinogen levels, prothrombin time (PTT) and activated partial thromboplastin time (APTT), platelet count.

The same guidelines indicate that in order to make a decision on hospitalization in all patients infected with SARSCoV-2, the initial concentration of D- dimers , PTT and platelet count should be determined [6]. In hospitalized patients with COVID-19, especially in severe cases of infection, systematic monitoring of hemostasis parameters becomes necessary [8]. Severe thrombocytopenia, increased D- dimer concentration , prolongation of the PTT, and worsening hypofibrinogenemia may indicate the development of DIC. N. Tang et al . in their

study showed that DIC developed in 71.4% of patients with COVID-19 who subsequently died, and only in 0.6% of patients with COVID-19 who survived [9].

However, concerns have been raised about the use of D- dimer as a biomarker in COVID-19 infected patients. D- dimer has low specificity, and elevated levels are often observed in the elderly, in women , with malignant neoplasms, surgery, pregnancy, physical inactivity, drug use, systemic connective tissue diseases, end-stage renal disease and previous thromboembolism [10].

In addition, D- dimer reflects a later stage in the hemostatic process and is released when the clot is broken down by fibrinolytic processes. Other standard laboratory tests, including TT and APTT, measure plasma clotting activity and ignore other clotting components such as platelets and fibrinolysis . Platelet counts and fibrinogen concentrations also require static measurements without any information about their functionality [11].

On the other hand, coagulation analysis of whole blood can be quickly performed using thromboelastography (TEG) or rotational thromboelastometry (ROTEM), which measure the ability of whole blood to form and maintain clot formation [12]. Currently, several reports have been published describing the early experience with the use of TEG or ROTEM for research in patients admitted with severe COVID-19 to intensive care facilities in Italy and the USA [13]. M. panigada et aL . demonstrated a hypercoagulable profile measured by TEG in 24 patients admitted to the intensive care unit (ICU) with COVID-19 [13]. They noted that reaction time (R) and clot formation time (K) were shorter than in the control population. K-angle and MA values were higher than in the control population, while clot lysis at 30 min (LY-30) was lower in 100% of patients with COVID-19.

Similar results were obtained using TEG TK Maatman et aL . and F.L. Wright et aL ., who showed a COVID-19-associated hypercoagulable state related to impaired fibrinolysis (defined by LY-30 < 0.8%) [14, 15]. Patients with a hypercoagulable profile and/or impaired fibrinolysis had a higher incidence of venous thrombosis (40% versus 5%, p = 0.013) [15]. Just like JR Mortus et aL . found high MA in 19 of 21 patients with severe COVID-19 as measured by TEG [16].

Finally, V. Pavoni et aL . demonstrated significant evidence for a hypercoagulable state in severe COVID-19 from the ROTEM platform with improved fibrinogen clot density after 10 days of illness. This indicates the possibility of a dynamic assessment of coagulation changes that accompany an increase or decrease in inflammatory parameters [17]. JR Mortus , S.E. Manek , L.S. Brubaker et aL . found that more than half of patients admitted to the intensive care unit (ICU) at Baylor Medical Center Saint - Luc had clinically significant thromboses, which were diagnosed only on the basis of thromboelastography (TEG) parameters. All patients received standard anticoagulant prophylaxis for deep vein thrombosis upon admission to the ICU and therapeutic anticoagulation (infusion of heparin or enoxaparin (2 mg/kg/ day)) for thrombotic complications. All patients underwent TEG and TEG with heparinase correction upon admission to the ICU . Hypercoagulability was defined as increased fibrinogen activity at an angle greater than 73° or a maximum amplitude (MA) greater than 65 mm on a heparinase- adjusted TEG [17].

This cohort study included 21 patients (mean age (SD) 68 (11) years (range 50-89 years); 12 (57%) men). Among these patients, 20 (95%) had comorbidities with a mean follow-up (SD) of 3(2), comorbidities each (range 1 to 7 comorbidities). The mean (SD) follow-up was 11 (4) days. Cohort international normalized ratio (INR), thromboplastin and platelet levels were within normal ranges, but fibrinogen and D- dimer levels were elevated. A total of 19 patients (90%) had TEG hypercoagulability , including 14 patients (74%) with TEG hypercoagulation by fibrinogen activity and MA criteria and 5 patients (26%) with TEG hypercoagulability with MA criteria alone. 13 patients (62%) showed clinical signs of thrombotic events. A total of 46 events were recorded, ranging from 1 to 8 events per patient. There were no statistically significant differences in

prothrombin time, INR, partial thromboplastin time, or platelet levels between 10 patients with at least 2 thrombotic events and 11 patients with fewer than 2 events. In the same patients, MA TEG was significantly higher in the high thrombotic event rate group than in the low thrombotic event rate group (mean (SD), 75 mm vs. 61 mm; p = 0.01). Elevated MA was observed in 10 patients (100%) in the high thrombotic event group compared with 5 patients (45%) in the low thrombotic event group. MA TEG provided 100% sensitivity and 100% predictive value in the diagnosis of thrombotic events. Underdiagnosis or undertreatment of hypercoagulation may explain the high rate of unexplained deaths from COVID-19. They may be associated with potentially preventable microvascular and macrovascular thrombosis and subsequent cardiovascular complications, including myocardial injury and infarction.

In this context, TEG may be critical to accurately identify patients at increased risk of thrombosis and, if necessary, to avoid unnecessary anticoagulation in patients at low risk of thrombosis. In particular, the diagnosis of TEG-MA hypercoagulability gives 100% sensitivity and 100% predictive value in assessing the occurrence of multiple thromboses in SAS [17]. Thus, studies to identify the most informative biomarkers for decisions to increase anticoagulant prophylaxis in patients with severe COVID-19 are developing rapidly and are increasingly focusing on TEG and ROTEM.

Due to their ease of testing and their properties as a single test that can evaluate the various components and stages of coagulation and platelet function at the bedside, TEG or ROTEM are ideal for preliminary thrombotic risk assessment in patients with moderate or severe COVID-19 [18] .

Abnormalities in laboratory studies of the hemostatic system in patients infected with severe SARS-CoV-2 indicate activation of the blood coagulation system consistent with sepsis- induced coagulopathy (SIC) or DIC. However, as various experts emphasize, hemostasis disorders in COVID-19 have characteristics that distinguish them from DIC in sepsis. Recently published results of a study show that severe infection with SARS-CoV-2 causes a significant suppression of the fibrinolytic system, which is manifested, among other things, by the complete absence of thrombus lysis on thromboelastography (TEG; parameter LY30 = 0%) [15]. These results are surprising because D- dimer , a high concentration of which is so common in patients with COVID-19, is the result of the breakdown of fibrin by the main component of the fibrinolytic system, plasmin. With a large amount of polymerized fibrin in the bloodstream of patients with COVID-19, even a small fibrinolytic activity is sufficient to produce a large amount of D- dimer [15].

An alternative theory is that SARS-CoV-2 first activates the fibrinolytic system, which then becomes depressed [15]. An important and distinguishing feature of SARS-CoV-2-associated coagulopathy is that hemorrhagic diathesis is almost non-existent. To emphasize the difference between blood clotting disorders in people infected with SARS-CoV-2 and other coagulopathies , experts have proposed the term “COVID-19-associated coagulopathy ” (CAC) [19]. Summarizing published data, it should be assumed that in response to SARS-CoV-2 infection, the hemostatic system increases its prothrombotic potential in mechanisms that depend mainly on a strong inflammatory response (the so-called cytokine storm) and endothelial damage, and also, possibly, from the suppression of the fibrinolytic system. It should not be forgotten that, in addition to changes in microcirculation, patients with COVID-19 also tend to form blood clots in larger vessels.

The clinical and laboratory features of CAC overlap with hemophagocytic syndrome, antiphospholipid syndrome, and thrombotic microangiopathy. Hemophagocytic syndrome / hemophagocytic lymphohistiocytosis . Hemophagocytic syndrome (HPS), or hemophagocytic lymphohistiocytosis (HLH), is a hyperinflammatory syndrome characterized by excessive activation of immune cells such as macrophages, natural killer cells , and cytotoxic T cells. Acquired HPS/HLH is due to large amounts of pro-inflammatory cytokines (TNFa

, interferon- Y , IL-1, IL-2, and IL-6) released from activated macrophages and lymphocytes secondary to various triggers, including viral infection [20]. Diagnosis is based on five criteria (fever, splenomegaly , decrease in two cell lines, hypertriglyceridemia and/or hypofibrinogenemia , and hemophagocytosis) [21]. Three additional criteria have recently been introduced, which include low/no natural killer cell activity , hyperferritinemia , and high levels of soluble interleukin-2 receptors. Although there are some similarities between and SAS, such as the development of a "cytokine storm " in COVID-19, the clinical and laboratory findings of typical HPS/H_H are not characteristic of COVID-19, with the exception of fever and hyperferritinemia [22]. A recent retrospective multicenter study of patients with COVID-19 showed elevated ferritin levels in non-survivors compared with survivors (1297.6 ng /mL vs. 614.0 ng /mL, $p < 0.01$) and for 4 ng /ml versus 6.8 ng /ml, $p < 0.0001$) [23]. Treatment of HPS/H_H requires elimination of the causative infection plus immunosuppressive treatment with corticosteroids and /or anticancer chemotherapy for refractory disease [24]. In COVID-19, hemophagocytosis has not been reported on bone marrow biopsy [25]; chemotherapy is not recommended. In contrast to HPS/H_H, severe lung injury and coagulopathy are the dominant characteristics of COVID-19.

Direct SARS-CoV-2 infection in lung epithelial cells, followed by damage to lung capillary endothelial cells, and subsequent fibrin deposition with increased u-PA fibrinolysis in the alveoli may contribute to the distinction between COVID-19 and HPS/H_H. Based on the theory of hypercytokinemia , anticytokine therapy may play an important role in the treatment of COVID-19 [26].

Antiphospholipid Syndrome

Thrombotic stroke, reported even in young patients, is a serious complication of COVID-19, and the clinical significance of the presence of anti-phospholipid antibodies is unknown [27]. Secondary antiphospholipid syndrome (PAFLS) is an acquired autoimmune thrombophilia determined by the development of arterial and venous thrombosis in the presence of antiphospholipid antibodies [28]. Antiphospholipid antibodies, i.e., lupus anticoagulant, anticardiolipin , and antibodies against p2-glycoprotein I, cause thrombocytopenia and prolonged activated partial thromboplastin time (APTT), and these findings are often the key to anti-phospholipid syndrome (APLS). Although lung damage is not common in APLS, catastrophic antiphospholipid syndrome (CAFLS), a rare but highly fatal variant, can lead to multiple organ dysfunction, including acute lung injury [29], and an overactivated complement system has been suggested [30]. While a treatment strategy to prevent thrombosis in AFLS may include combined antiplatelet and anticoagulant therapy [31], the benefit of adding antiplatelets to a therapeutic dose of unfractionated heparin or low molecular weight heparin in COVID-19 is unknown and may increase the risk of bleeding. In COVID-19 [32], in addition to anticoagulant therapy, as in the treatment of CAFLS, glucocorticoids , plasmapheresis , and/or intravenous immunoglobulin are used. Plasma convalescence therapy is being developed for COVID-19, but the use of intravenous immunoglobulins has not been studied. R. Escher et aL . [33] reported an interesting case of COVID-19 in a patient admitted to hospital with altered mental status, followed by respiratory and renal failure. A patient with COVID-19 infection demonstrated elevated levels of anticardiolipin and IgM antibodies to ß2-GP I simultaneously with dramatically elevated levels of von Willebrand factor (VWF) and factor VIII.

Thus, the studies demonstrate similarities and differences in laboratory manifestations of SAS and AFLS.

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) is a clinical disease that includes thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) and secondary TMA. TMA is characterized by the formation of a thrombus in the microvasculature (mainly

arterioles) with laboratory signs of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. Diffuse microvascular thrombi in many organs at autopsy of COVID-19 are similar to those in TMA, and changes in hematological markers resemble those in moderate MAHA, represented by a decrease in hemoglobin, an increase in lactate dehydrogenase (LDH), increased bilirubin, decreased haptoglobin , etc. and the appearance of histocytosis [34].

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is caused by autoantibody- induced depletion or inhibition of disintegrin and the enzyme metalloproteinase (ADAMTS-13), which breaks down large von Willebrand factor (VWF) multimers . In TTP, platelet microthrombi are found, along with severe thrombocytopenia and MAHA. Although acquired TTP may be caused by infection, there have been no reports of ADAMTS-13 depletion in COVID-19 to date. Rather, elevated levels of VWF have been reported in COVID-19. J.HeLms _ et aL . [35] found markedly elevated levels of VWF activity, VWF antigen, and factor VIII levels in COVID-19. In addition, lupus anticoagulant was found in almost 90% of the patients examined, suggesting that COVID-19 exhibits features resembling those of TTP and AFLS. Elevated VWF is thought to be the result of vascular injury, as VWF and factor VIII accumulate in Weibel - Palade bodies in endothelial cells. Infection of endothelial cells with SARS-CoV-2 can stimulate the release of these components, with levels increasing independently of ADAMTS13 levels. Dengue virus, a coronavirus -like virus , is known to stimulate endothelial cells to release, and in dengue fever, an association has been reported between elevated levels of circulating VWF and stroke. Signs of TTP in the form of thrombocytopenia, fever, decreased consciousness, and kidney failure can also be seen with COVID-19. However, arterial thrombosis, such as stroke and acute coronary syndrome, and microvascular (arteriolar) thrombosis predominate in TTP and are significantly less common in COVID-19.

Hemolytic -uremic syndrome

Hemolytic uremic syndrome (HUS) can also be caused by secondary infection and is a consequence of dysregulation of the complement pathway. Typical symptoms of HUS are microangiopathic hemolytic anemia (MAHA), acute kidney injury, and dysfunction of other organs. E. GavriiLaki et aL . [36] argue that COVID-19 more closely resembles the pathophysiology and phenotype of HUS than SIC/DIC. Activated complement activates platelets, causes hemolysis, and finally forms membrane attack complexes (MACs [C5b-9]), which damage cell membranes. Although studies on the complement system in COVID-19 are sparse, MERS- CoV is known to increase levels of C5a and C5b-9 in blood and lung tissue in a mouse model. In addition, C. Magro et aL . [37] described the deposition of MAC (Membrane attack complexes), C4d, and mannose -binding lectin -associated serine protease (MASP) in lung microvessels of patients with COVID-19. Activation of the complement system may be involved in endothelial injury in COVID-19, and the effect of anti-complement therapy is currently being studied .

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a prothrombotic complication that may occur after heparin treatment. As VTE prophylaxis using heparins (unfractionated or LMWH) becomes the standard of care for COVID-19, patients may be at increased risk of developing HIT. This adverse drug reaction is caused by platelet-activating antibodies that recognize multimolecular complexes of platelet factor 4 (PF4) and heparin. Patients often experience moderate to severe thrombocytopenia, manifesting as venous or arterial thrombosis (sometimes both). The risk of HIT is ten times lower for LMWH compared to unfractionated heparin, and thus LMWH is preferable for COVID-19 thromboprophylaxis . The 4Ts score, which consists of thrombocytopenia , time of onset, and other causes of thrombocytopenia, is useful for clinical diagnosis [38] but may be problematic in patients with COVID-19 . A

higher baseline platelet count in COVID-19 may obscure the clinical assessment of HIT-associated platelet decline, so clinical vigilance is needed, including appropriate laboratory evaluation of anti- HIT antibodies . If HIT is suspected, anticoagulant therapy should be changed to include fondaparinux or direct thrombin inhibitors (eg, argatroban , bivalirudin) [39]. In the course of COVID-19 infection, the number of cases of sudden death outside the hospital has increased. One possible reason is the high incidence of serious thrombotic events in patients with COVID-19. However, the pathogenesis of these life-threatening events is multifactorial and requires independent in-depth study.

Covid-19 coagulopathy and glucocorticosteroids

Coronavirus pneumonia occurs not only with severe damage to the lung tissue, but also with autoimmune systemic inflammation, rapid activation of cytokines and chemokines , called "cytokine storm ", and at the same time with a high risk of thrombosis and thromboembolism. In June 2020, a report from the British RECOVERY study was published showing a reduction in 28-day mortality in patients receiving dexamethasone . The analysis included 6,425 patients, of whom 2,104 were in the intervention group and 4,321 were in the control group. The median duration of dexamethasone use was 7 days. A lower incidence of the primary endpoint was found in the intervention group compared to the control group among patients:

■ on mechanical ventilation (29.3% vs 41.4%; relative risk 0.64; 95% CI 0.51-0.81),

■ in the group of patients who received oxygen therapy without invasive ventilation (23.3% vs 26.2%; relative risk 0.82; 95% CI 0.72-0.94).

A similar relationship was not demonstrated in the group of patients who did not receive oxygen therapy or invasive ventilation (17.8% vs 14.0%; relative risk 1.19; 95% CI 0.91-1.55). Thus, dexamethasone was associated with lower 28-day mortality in patients with symptoms lasting >7 days, but not in patients with shorter duration of symptoms. This study is the first to raise the issue of the safety of corticosteroids in the treatment of severe COVID-19 infection. In addition to deaths, three serious adverse events (cerebral vasculitis , pulmonary embolism (PE) and intra-abdominal bleeding as a result of anticoagulation in the treatment of PE) were reported in the hydrocortisone group.

V.Yu. Mareev et al . studied the efficacy and safety of pulse therapy with high doses of glucocorticosteroids (GCS): methylprednisolone 1000 mg for 3 days plus dexamethasone 8 mg for another 3-5 days in 17 patients with severe coronavirus pneumonia. In addition to assessing the clinical status, the dynamics of C-reactive protein (CRP), the thrombogenesis marker D- dimer , and the degree of lung damage on computed tomography (CT) were assessed . In the study group, dyspnea significantly decreased, oxygen saturation increased, and scores on the NEWS-2 clinical status scale decreased. In the GCS group, the level of CRP decreased statistically significantly from 134 to 41.8 mg / dl (p = 0.009), but at the same time D- dimer significantly increased from 1.41 to 1.98 μg / ml (p = 0.044). A correlation was found between the dynamics of the N/L index and D-dimer in the GCS pulse therapy group, which emphasizes the relationship between chronic autoimmune inflammation and thrombus formation in COVID-19 (r = 0.49, p = 0.04) [40].

Conclusion

Thus, pulse therapy with high doses of corticosteroids has a rapid anti-inflammatory effect , but at the same time increases the level of D- dimer , which increases the risk of venous thrombosis and thromboembolism. SAS has unique features that can be defined as a new category of coagulopathy . In every COVID-19 patient who requires hospitalization, prothrombin time (PTT), D- dimer and fibrinogen concentrations, and platelet counts should be monitored. An increase in the concentration of D- dimer correlates with higher mortality, and a rapidly increasing hypofibrinogenemia heralds the development of disseminated intravascular coagulation

(DIC). However, it must be remembered that changes in laboratory results that meet the criteria for DIC may be due to causes other than SARS-CoV-2 infection (eg, bacterial superinfection or severe comorbidity). The management of coagulopathy associated with coronavirus should resemble the management of coagulopathy such as DIC and SIC, as recommended. Patients with severe COVID-19 are at high risk of developing venous thromboembolism (VTE), so every hospitalized patient with COVID-19 should be screened for deep vein thrombosis (DVT) and pulmonary embolism (PE). PE can be manifested by increased respiratory failure. Since the underlying disease (COVID-19) is manifested by respiratory failure, the healthcare team may misinterpret the deterioration of the patient's condition during the development of PE as the progression of infection in the lungs. Because of the high risk of VTE in every hospitalized patient with COVID-19 without absolute contraindications to anticoagulant therapy, thromboprophylaxis with UFH or LMWH should be considered. The incidence of venous thromboembolic complications in patients with COVID-19 turned out to be unexpectedly high, which determines the need for the development and application of effective preventive diagnostic and treatment protocols. In critically ill patients, as well as when using methods of extracorporeal circulatory support, in the absence of the ability to effectively monitor the state of the hemostasis system using traditional methods, it is advisable to use global tests (thromboelastography) if there is experience in their use and interpretation. However, the methodology for using thromboelastography in patients with COVID-19 in conditions of high frequency and multifactoriality of serious thrombotic events requires independent in-depth study. Thus, the study of the pathogenesis of COVID-19-associated coagulopathy , the development of algorithms for its diagnosis and correction at various stages of the disease, under conditions of various course options, from mild to extremely severe, predetermine the outcome of the treatment of COVID-19-associated infection, since SAS is an integrating component. interactions of the infectious process, immune response and general somatic status and determining the risk of adverse outcomes .

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