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Review in Hematology

The pathogenesis of COVID-19: Hypercoagulation and D-dimer in thrombotic complications

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Abstract

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused a new coronavirus disease (COVID-19), which is highly contagious and its pathogenesis has not been fully elucidated. In COVID-19, the inflammation and blood coagulation systems are excessively activated. SARS-CoV-2 damages endothelial cells and pneumocytes, which leads to disruption of hemostasis in SARS. Thromboembolism is the main cause of mortality in patients with COVID-19. Clots, including pulmonary embolism (PE) and deep vein thrombosis (DVT), ranging from minor to fatal complications of the SARS-CoV-2 infection are known. Individuals with pre-existing diseases are more susceptible to the development of blood clots and poor outcomes. High levels of circulating cytokines and D-dimer (DD) are influential biomarkers of poor outcomes in COVID-19. The latter occurs as a result of hyperfibrinolysis and hypercoagulation. Plasmin is a key player in fibrinolysis and is involved in the cleavage of many viral envelope proteins, including SARS-CoV. Due to this function penetration of viruses into the host cell occurs. In addition, plasmin is involved in the pathophysiology of acute respiratory distress syndrome (ARDS) in SARS and promotes the secretion of cytokines, such as IL-6 and TNF, from activated macrophages. The focus of existing treatment to alleviate fibrinolysis in patients with COVID-19 is the use of systemic fibrinolytic therapy given thrombotic pathology in severe forms of COVID-19 which may lead to death. However, fibrinolytic therapy may be harmful in the advanced stages of COVID-19, when the status of disseminated intravascular coagulation (DIC) changes from suppressed fibrinolysis to its enhancement during the progression of the disease. This narrative review aims to elucidate the pathogenesis of COVID-19, which will further help in precise diagnosis and treatment.

Take-home message: The COVID-19 virus disrupts haemostasis and thromboembolism by over activating the inflammation and blood coagulation systems. High levels of cytokines and D-dimer are indicators of pre-existing diseases and blood clots. Systemic fibrinolytic treatment can reduce severe fibrinolysis in COVID-19, which is caused by plasmin. In the late stages of DIC, when fibrinolysis increases, it may be dangerous. To improve therapy and results, understanding COVID-19 pathogenicity is critical.

Keywords: SARS-CoV-2; COVID-19; inflammation; blood coagulation; thromboembolism; circulating cytokines; D-dimer.

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INTRODUCTION

The novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has a high level of infectivity and thus morbidity, and mortality [1,2]. There is an urgent need to understand the pathogenicity of the virus and its interaction with the biological protective systems of the body [3–5]. The inflammatory response and the clotting system frequently offer efficient protection against this pathogen (SARS-CoV-2) [6]. The interaction between these two systems opens up potential opportunities for new therapeutic methods. Abnormally high levels of circulating D-dimer (DD) are the main predictor of poor treatment outcome and indicate overactivity of the coagulation and fibrinolytic systems in COVID-19 [7,8]. This review describes the effect of the SARS-CoV-2 virus on the fibrinolytic system and suggests a potentially new therapeutic modality to mitigate the effect of the virus in COVID-19.

Etiology and pathogenicity of COVID-19

SARS-CoV-2 is an RNA-beta-coronavirus of zoonotic origin closely related to SARS-CoV and MERS-CoV according to full genome sequencing [9,10]. The virus is highly contagious via human-to-human respiratory transmission [11]. Moreover, the basic pathogenesis of COVID-19 is similar to that of SARS and MERS. The respiratory tract and lung tissue are the target organs in this infection [12–14]. In addition, autopsies of COVID-19 patients reveal severe vascular lesions [15]. This specific tropism of SARS-CoV-2 towards lung epithelial cells and the vascular system can explain its etiotropic nature. The adhesion protein on the glycoprotein surface of SARS-CoV-2 consists of two domains: the receptor-binding domain (S1), which is combined with high affinity with angiotensin-converting enzyme receptor 2 (ACE2) on human membranes, pneumocytes, and vascular endothelial cells [5,11], and the S2 domain to anchor the virus on the target cell membrane [8]. Based on its homology with SARS-CoV, it was reported that SARS-CoV-2 requires the host cell protease to achieve infectivity and spread [16]. The S2 protein is proteolytically activated by transmembrane serine protease 2 (TMPRSS2) after binding to the ACE2 receptor [17]. Due to its high affinity towards several receptors, COVID-19 has a wide spectrum of clinical severity ranging from mild pneumonia to a severe illness that can lead to acute respiratory distress syndrome (ARDS) [11]. The ARDS-like features in COVID-19 are significantly different from those observed in patients with sepsis [18]. The main clinical laboratory findings associated with poor outcome are lymphopenia, abnormal liver function, increased serum ferritin and C-reactive protein levels, and DD [11,19,20]. A high level of DD in blood plasma is consistently considered a major predictor of mortality, suggesting that abnormal coagulation plays a key role in COVID-19 pathogenesis [3].

Coagulation and fibrinolysis

The extrinsic pathway starts when a tissue lesion increases the expression of activated tissue factor (aTF) in the endothelium. This activates FVII, which in turn activates FX, causing the aTF-FVIIa-FXa complex to form. This complex and the thrombin it makes can send proinflammatory signals into cells through protease-activated receptors 1 and 2 (PAR 1 and 2) [21]. On the other hand, the protein C complex containing thrombin, thrombomodulin, and activated protein C deactivates FVIIIa and FVa (acceleration factors) and leads to the slowing of the blood coagulation process [9,22]. This anticoagulation pathway (protein C complex) requires an intact vascular endothelium expressing endothelial cell protein C receptor (EPCR) [12]. The damaged endothelium releases EPCR

(soluble EPCR) that actively binds to the free activated protein C complex, and the loss of its anticoagulant part results in hypercoagulation [20]. Besides, the EPCR-protein C complex has a cytoprotective effect under normal conditions [23]. This complex activates PAR1 signaling to create anti-inflammatory and anti-apoptotic effects [24]. The activated fibrinolytic system of endothelial cells is crucial for dissolving the fibrin clot and facilitating tissue recovery. Plasmin and serine proteases are the key players in this system, responsible for fibrin degradation [25].

COVID-19 and coagulation-fibrinolytic dysfunction

Reports of patients with COVID-19 infection indicate increased thrombosis and fibrinolysis and less bleeding [9,26]. Atypical disseminated intravascular coagulation (DIC) is also seen in COVID-19 [27], as thrombocytopenia, hypofibrinogenemia, hemolytic anemia, and bleeding are underrepresented [19]. Of all the signs, high levels of DD in blood plasma are the most prominent prognostic factor in patients with COVID-19 infection [28].

Recent clinical observations suggest that people with COVID-19 have a high risk of DVT and dying, and anticoagulant therapy can improve their chances [11].There is a general idea that most COVID-19 patients need thromboprophylaxis, and some authors say that this treatment should be kept up after the in-hospital treatment is done [29].

Coagulation disorders include a long prothrombin time, low antithrombin activity, and high levels of fibrinogen and DD. However, scientists still don not know why people with COVID-19 have problems with how their blood clots and breaks down [30].

The detection of a very high level of DD in blood plasma is an indication of hyperfibrinolysis in COVID-19. The close relationship between the high level of DD in blood plasma and poor treatment outcomes raises several thoughts. Anticoagulant therapy almost never lowers mortality, except in a small group of patients, whose DD levels in blood plasma were six times higher than normal [31]. Even though the oxygenation rates of patients with ARDS caused by COVID-19 went up when they used the fibrinolytic agent Alteplase, this had no effect on their overall survival; all of them died [32]. This treatment was based on animal studies, which indicated that fibrinolytic drugs could improve lung function and alleviate inflammation in ARDS-like models [33]. Based on what we know so far, patients with COVID-19 should not be given fibrinolytic drugs [34]. And, hyperfibrinolysis plays a key role in the high pathogenicity and infectivity of SARS-CoV-2 (Figure 1).

Figure 1 shows the assumed relationship between coagulation and inflammation in patients with SARS-CoV-2 infection. Attachment proteins in the coronavirus envelope first bind to angiotensin-converting enzyme 2 (ACE2) receptors on the surface of epithelial cells (e.g., EC, endothelial cells).The adhesion protein is then cut by transmembrane serine protease type II (TMPRSS2), which makes it easier for the virus to get inside. The SARS-CoV-2 virus damages the EC, activates the coagulation cascade via TF-FVIIa (tissue factor pathway), and enhances fibrin formation (hypercoagulable state). This hyperactivation of the fibrinolytic system leads to an increase in plasmin production. Plasmin binds to the EC-plasmin receptor and degrades fibrin, resulting in high levels of DDI in blood plasma. Membrane plasmin, which is a potent serine protease, can cleave the protein S of the virus, thus promoting its entry into host cells. This common function of viral cleavage with TMPRSS2 contributes to the infectivity of the virus and facilitates its spread. In addition, overproduction of plasmin (increased plasma receptor occupancy) activates receptor 1 and 2 (PAR 1, 2) signaling pathways activated by proteases involved in inflammation and immune responses. The EPCR-protein C

complex is probably overwhelmed by hypercoagulation, thus losing its cytoprotective activity. This virus-related procoagulation-inflammatory state also involves macrophages. The pathophysiological paradigm explains the increased infectivity of the virus and the relationship between high D-dimer production and the cytokine storm (mainly IL-6, IL-10, and TNF) in COVID-19 [35].

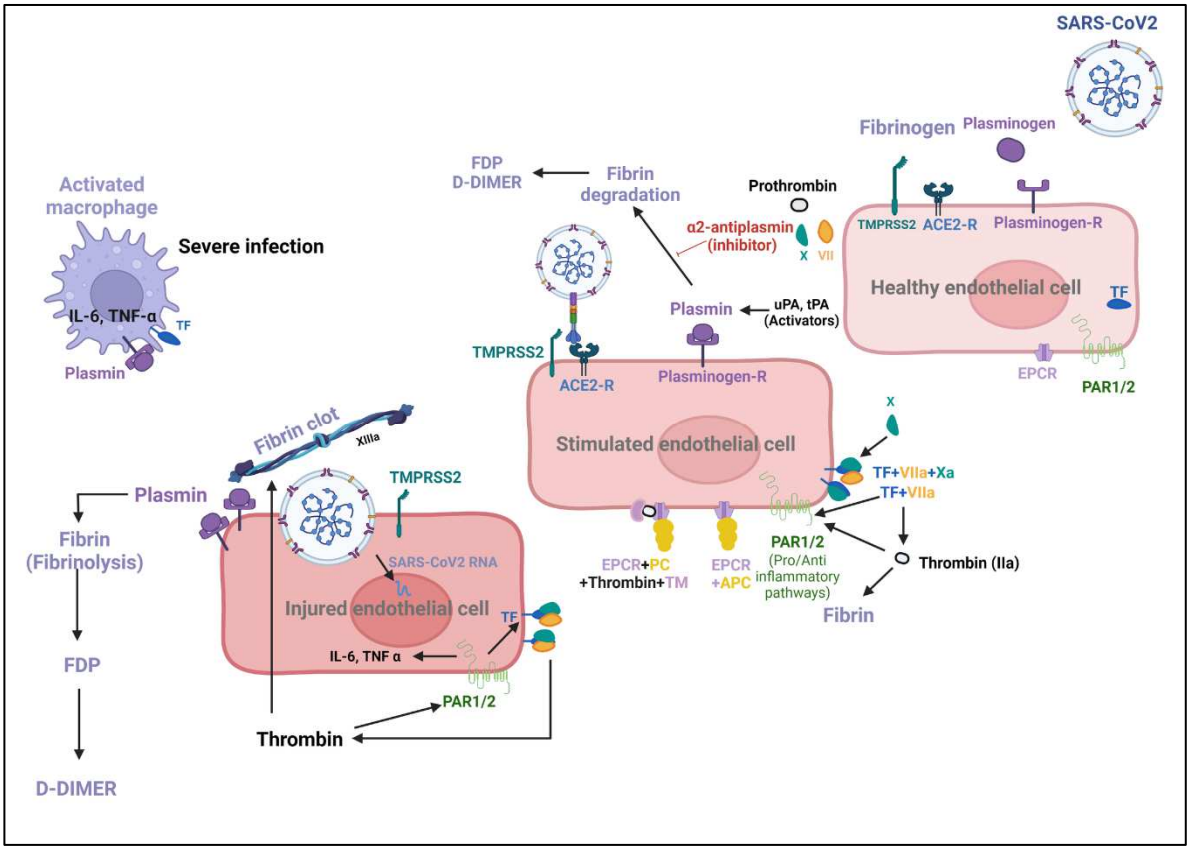

Figure 1. Role of fibrinolysis in COVID-19 pathogenicity.

Because of its anti-inflammatory, antithrombin, and antioxidant properties, the ACE2 enzyme protects endothelial cells and pneumocytes [36,37]. The loss of ACE2 protective effects, as seen in aging, diabetes, and cardiovascular disease, causes cellular damage and deleterious effects, including an increase in oxidative stress and thrombosis [8]. It should be noted that administration of recombinant ACE2 to ACE-deficient mice with induced lung damage protects them from the development of the ARDS-like syndrome [37]. The high mortality rate in elderly COVID-19 patients with comorbidities associated with endothelial dysfunction suggests that this protective effect of ACE2 can be important for survival [18]. Accordingly, it was suggested that COVID-19 patients can be treated with human recombinant soluble ACE2 [25,38]. Despite evidence of increased ACE2 expression in cardiovascular patients treated with ACE inhibitors (ACE-I) and angiotensin receptor blockers, the actual effect of these drugs on COVID-19 has been reported to be controversial [30]. It is important to mention that ACEs have antifibrinolytic effects on people [30], and recent recommendations suggest that it is advisable for patients with cardiovascular diseases to continue taking these drugs.

Transmembrane serine protease 2 plays a key role in the infectivity of SARS-CoV-2. The cleavage of coronavirus protein S by TMPRSS2 is not limited to SARS-CoV-1 and 2 [15]. Other viruses penetrate host cells using this pathway, such as H1N1 and herpes influenza viruses [7]. In vitro studies have indicated that inhibition of TMPRSS2 does not completely block virus entry into host cells [16]. Camostat mesylate, a potent serine protease inhibitor that effectively inhibits TMPRSS2, is in clinical trials to reduce viral infectivity in patients with COVID-19 [30].

Even though TMPRSS2 is the main enzyme that helps SARS-CoV-2 get into the host cell, the same thing can be done by other serine proteases [33]. Serine proteases, trypsin, elastase, and furin can cleave protein S in the viral envelope of SARS-CoV and MERS-CoV [15]. Furin is a part of the trans-Golgi network, and endothelial and pneumocytic cells have a lot of it.It was recently reported to cleave SARS-CoV-2 as well [6]. Furin can also cleave the protein S of non-coronaviruses such as West Nile virus, Zika virus, and respiratory syncytial virus (RS) [22].

Plasmin that is attached to the plasmin receptor on the cell membrane can cut like furin [39]. Plasmin cleavage activity was first described for the H1N1 influenza virus [15]. However, plasmin cleavage activity (furin-like) against SARS-CoV-2 requires clarification [26]. Because of this, the virus can't get into the cell without a specific combination of ACE2 and the cleavage of TMPRSS2 [37].Other serine proteases, such as plasmin, can take the place of ACE2 in this last step.

Autopsies of people who had a severe case of COVID-19 showed that there were a lot of fibrin deposits in the bed [28], which means that plasmin activity was higher. In addition to virus cleavage activity, plasmin can activate human macrophages, contributing to the production of pro-inflammatory cytokines such as IL-6, IL-8, IL-10, and TNF [23,40]. The increasing level of plasma IL-6 is a marker of the cytokine release syndrome in COVID-19 and leads to poor outcomes [9]. Therefore, high plasmin activity can contribute to the virus's ability to keep spreading and to the fact that COVID-19 has too much inflammation and an immune response.

ARDS is the most difficult clinical finding and the main cause of death in patients with COVID-19-associated pneumonia [19]. Pneumocytes and endothelial cells in pulmonary alveoli have similar protective biological mechanisms [3]. Some COVID-19 patients are procoagulable with catastrophic microvascular damage in the lungs [30]. MERS-CoV, SARS-CoV, and SARS-CoV-2 coronaviruses target cells with high expression of ACE2 and TMPRSS2, such as endothelial cells and pneumocytes [11,41]. ACE2 has an important protective function in these cells. It has been reported that lung damage in ARVI depends on the balance between coagulation activity and the degree of the fibrinolytic process [15]. It is also known that plasminogen-plasmin activity is increased in ARDS [41]. Levels of procoagulant components in bronchoalveolar lavage of patients with ARDS, such as plasmin products and fibrinolytic degradation, are significantly higher than in patients without ARDS. The assumption of the role of the fibrinolytic system in the ARDS genesis in patients with COVID-19 is confirmed by the results of the study of mice deficient in plasminogen activator inhibitor-1 (PAI-1) [12]. The results show that tPA and uPA contribute to the development of lung lesions in coronavirus infection, and PAI has a protective function in this condition [31]. It indicates that partial inhibition of the hyperfibrinolytic process in COVID-19 can mitigate the development of ARDS. The activated coagulation-plasmin-fibrin pathway in ARDS triggers the secretion of various proteases, such as elastase, and a strong cytokine response manifested by activated leukocytes and macrophages. The cytokine release syndrome has not yet been fully characterized in patients with

COVID-19 [17]. However, there is evidence that the high viral load in the lungs of COVID-19 patients is associated with an acute inflammatory response involving epithelial cells and activated macrophages, which are primarily responsible for the secretion of cytokines such as TNF, IL-6. IL-8, IL-1β, and CXCL10 [42].

Interaction of coagulation with viral inflammation

Viruses affect the system that keeps blood from clotting by turning on or off platelet aggregation, clotting, and fibrinolysis [15].There is more and more evidence that viral infections involve a common process that links blood clotting to inflammation. The inflammatory response activates the coagulation system. Virus-associated hemostasis frequently causes a procoagulant-thrombotic effect. Similar changes can be seen in cytomegalovirus, hepatitis C, and HIV infections. In contrast, Ebola, Dengue, and other hemorrhagic viruses, which can also cause endothelial damage, are associated with increased anticoagulant action and fatal bleeding. Viruses affecting endothelial cells can contribute to the TF-VIIa-Xa-EPCR complex, a procoagulant pathway that can activate PAR2 and induce an innate immune response. During viral infection, PAR2 activation triggers toll-like receptor 4 (TLR4) to modulate the inflammatory response. On the other hand, some viral infections can increase thrombin production and activate the EPCR-aPC complex, which stimulates PAR1 signaling to produce a cytoprotective effect [8,23,36].

Therefore, when a virus gets into the body, the coagulation problems that happen depend on how the virus affects the balance between the procoagulant and anticoagulant pathways. A severe inflammatory response can be caused by a virus that mostly makes the procoagulant and fibrinolytic systems work. A virus that activates the anticoagulant pathway can cause a moderate inflammatory response [13]. Patients with Dengue hemorrhagic fever, for example, make antibodies against the virus. These antibodies can turn on plasminogen and fibrinolysis, which can cause bleeding. In contrast, SARS-CoV-2 causes hyperfibrinolysis without any significant bleeding [30].

COVID-19 treatment review

Although several therapeutic agents have been evaluated to treat COVID-19, none has proven effective. Similarities in the clinical features of coronavirus infections offer clinicians therapeutic modalities based on the SARS and MERS epidemics. However, the efficiency results of the registered treatment methods for SARS and MERS are contradictory [17,19,22].

Lopinavir-ritonavir, which is an aspartate protease inhibitor mixed with a CYP450 inhibitor to lengthen its half-life, doesn't help COVID-19 patients in any way, according to reports. Ribavirin, which is a nucleotide analogue that stops viral RNA-dependent RNA polymerase from working, is also said to do nothing good [16]. Remdesivir, a potent RNA polymerase inhibitor, has been used effectively for a short period of time until patients with COVID-19 recovered [5].

Antimalarial drugs like chloroquine and hydroxychloroquine have a good effect on the immune system because they stop lysosome activity and autophagy [12]. Hydroxychloroquine stops SARS-CoV-2 from getting into host cells through the endosomes and lowers the production of cytokines in the lab [26]. Also, it has been said that hydroxychloroquine doesn't work to prevent COVID-19 in ambulatory patients after medium- or high-risk exposure and has no effect on how the disease progresses in hospitalized patients [41].

High levels of IL-6 in the plasma of COVID-19 patients can be a reason to use tocilizumab, a monoclonal antibody to the IL-6 receptor that can protect against the cytokine storm. However, its

effect on viral replication and infectivity is questionable [18]. In Japan, one has recently offered to treat COVID-19 patients with heparin and Nafamostat mesylate, a synthetic serine protease inhibitor with antitrypsin and antifibrinolytic effects. Nafamostat is also being investigated because of its ability to block MERS-CoV entry into host cells [37].

Given the urgent need, it allows for unconventional treatment of COVID-19 patients. As the procoagulant state and hyperfibrinolysis coexist in COVID-19, we assume that enhanced fibrinolysis increases the infectivity of SARS-CoV-2 via a plasmin-mediated pathway. Besides, plasmin induces a proinflammatory response through macrophage activation (release of IL-6 and TNF) and enhances PAR2-TLR4 signaling [10]. In addition, increased mortality from COVID-19 is associated with conditions related to endothelial dysfunction, low ACE2 expression, and a high level of circulating plasminogen [36]. We think that pharmacological interventions that aim to reduce plasmin production can reduce the ability of the virus to spread and lessen the inflammation that comes with it in COVID-19 patients.

Tranexamic acid (TA) blocks plasminogen activation by making it harder for plasminogen to turn into plasmin. This lowers the amount of DD in the blood. TA is used to treat people with a tendency to bleed, and it can be given intravenously, orally, or in the area where the bleeding is happening. The half-life of TA is 2-3 hours, and it is mostly excreted with the urine [19]. The efficiency of the inhaled method of administration has been tested among patients with hemoptysis. Researchers reported that inhaled TA was effective and safe for the elimination of hemoptysis. Similar results were obtained in patients with hemoptysis receiving oral or intravenous TA [24]. TA is well tolerated, and the occurrence of side effects such as mild to moderate headache, muscle cramps and arthralgia, nausea, and diarrhea is rare [12]. At the same time, inhibition of fibrinolysis can increase the risk of thrombosis; there are no reports of thromboembolism with TA. Over the past two decades, TA has been used in combination with prophylactic anticoagulants (low-dose warfarin, LMWH, and DOAC) in elderly patients undergoing major orthopedic surgeries with a high risk of thrombosis and hemorrhage [18]. This combined therapeutic method provides anticoagulant, antifibrinolytic, and anti-inflammatory effects, thereby reducing thrombosis, bleeding, and signs of inflammation [8]. Therefore, it can be suggested that people with COVID-19 who have moderate to severe pneumonia be treated with TA. According to the literature, TA can be given systemically or through a closed nebulizer [8]. All patients with COVID-19 should receive an increased dosage of anticoagulants [16]. The thrombotic load in COVID-19 patients increases with the severity of the disease. Thus, the offered use of TA should exclude critically ill patients. Given the current state-of-the-art data on SARS-CoV-2 dynamics and the peculiarities of the course of COVID-19, the timeframe for drug intervention should be determined in future studies [21].

Alpha-2-antiplasmin (alpha-2-AP) is an alternative way to treat COVID-19 patients who are having trouble breathing. Alpha-2-AP is a strong plasmin absorber and is often used as alpha-2-AP replacement therapy for people who don't have enough alpha-2-AP in their bodies. Most of the time, these patients bleed after surgery, and alpha-2-AP replacement therapy is the only effective treatment for them [42]. This treatment method should be used on COVID-19 patients who are very sick and whose blood plasma has a low level of alpha-2-AP.

Features of pulmonary intravascular coagulation therapy in COVID-19

Some authors suggest that fibrinolytic drugs could be used to treat ARDS in severe cases of COVID-19 [16]. ARDS and organ dysfunction associated with the cytokine storm have been identified as causes of death in COVID-19 [4]. Also, death is linked to the high rate of thrombotic complications, such as pulmonary embolism. Even though severe COVID-19 had systemic hypercoagulation due to severe inflammation, most of the thrombosis was in the lungs. Not only were there cases of pulmonary embolism that were diagnosed with contrast computed tomography, but there were also cases of microscopic fibrin thrombosis that were often found in the pulmonary microcirculation during autopsy [28]. Pulmonary thrombosis in severe COVID-19 can be described as macroscopic or microscopic thrombosis. Although the activation of coagulation is associated with a systemic cytokine storm, since the main location of clot formation is the lungs, it can also be called pulmonary intravascular coagulation [9]. It is known that COVID-19 patients with a high DD level have poor clinical outcomes, and it is believed to reflect a direct relationship between thrombotic pathology and prognosis [15]. It has been noted that the effect of tissue factors (TF) on damaged alveolar endothelial cells and leukocyte surfaces contributes to fibrin deposition. They also noted that significantly increased expression of plasminogen activator inhibitor 1 (PAI-1) by lung epithelial and endothelial cells creates the hypofibrinolytic state [26]. Although heparin is often used to treat thrombotic pathology in COVID-19, PE is still observed in about 20% of severe cases, and there is disagreement about the intensity of anticoagulant therapy. Besides heparin, the thrombotic condition can be improved with fibrinolytic drugs that decompose already existing fibrin in the lungs [10]. The fibrinolytic drug, tissue plasminogen activator (tPA), is used systemically to treat ARDS in COVID-19 and is efficient in some patients [14]. As tPA has been reported to demonstrate an anti-inflammatory effect in addition to its fibrinolytic action, this potential of tPA will be useful in improving the prognosis of patients with COVID-19 [27].

Differences between DIC at the late stage of COVID-19 and DIC caused by sepsis

According to the existing literature, the systemic use of tPA in the severe course of COVID-19 with ARDS needs to be done with great care. The levels of fibrin/fibrinogen degradation products (FDP) and DD go up a lot because the level of fibrinogen also goes up due to an inflammatory response in patients who later die after being hospitalized. In these patients, there is a further dramatic increase in FDP (>120 μg/ml), which is accompanied by a moderate increase in DD (approximately 20 μg/ml) when the patient's condition worsens. Consequently, there is a large difference between FDP and DD levels. Besides, the fibrinogen level rapidly decreases from approximately 4.5 g/L (day 7) to 1.0 g/L (day 10) in just 3 days. The substantial increase in FDP, the divergence of FDP and DD levels, and the significant decrease in the fibrinogen level are signs characteristic of enhanced fibrinolytic type DIC, not sepsis-associated DIC. The DIC type changes from depressed fibrinolytic to enhanced fibrinolytic with disease progression in COVID-19. Plasma tPA levels are reported to be significantly higher in severe cases of COVID-19 (with intensive therapy) than in mild cases (non-intensive therapy). It can indicate that fibrinolysis will be more active at the late stage of COVID-19 [18].

Side effects of systemic thrombolytic therapy for COVID-19 treatment

If systemic fibrinolytic therapy is given at the same time, the sharp drop in fibrinogen is very dangerous and raises fears of fatal bleeding, including brain hemorrhage [43]. The pathology of coagulation and fibrinolysis can change a lot in a short amount of time, especially in severe cases of COVID-19. Initial reports of coagulation and fibrinolysis testing in COVID-19 have primarily

emphasized DD, then PT and APTT. However, periodic testing of fibrinogen and FDP levels is also important. If the results of these tests indicate enhanced fibrinolytic DIC, systemic fibrinolytic therapy should not be prescribed [26].

On the other hand, treatment by inhalation of fibrinolysis-related substances, such as tPA and plasminogen, can be used at any stage of COVID-19 without fear of bleeding [37]. Fibrinolysis-related substances can improve alveolar ventilation by dissolving fibrin-containing exudates in the pulmonary alveolar space and breaking up fibrin clots in the microcirculation near the alveoli. Over time, it has become clear that inhaled tPA therapy works in a number of ARDS cases [12].

With severe COVID-19 and systemic fibrinolytic therapy for ARDS, there is a risk of massive bleeding if the disease stage or the pathology of coagulation and fibrinolysis are not correctly assessed. Autopsy studies showed that the incidence of thrombosis and bleeding was the same, even if no fibrinolytic therapy was given [44,45]. When combined with data on parameters like FDP, DD, and fibrinogen, it means that fibrinolytic-enhanced DIC is present in the late stage of COVID-19 [32].

Consequently, inhaled therapy with fibrinolytic agents should be planned while still in the DIC phase of the depressed fibrinolytic type (slightly increased DD level and normal fibrinogen range) or without DIC (normal platelet range) for safe use. Further research assessing tPA levels in blood plasma in both inhaled and systemic fibrinolytic therapy is required to confirm the harmlessness of inhaled therapy.

CONCLUSION

The high level of DD, which is caused by both hyperfibrinolysis and hypercoagulation, is an important coagulation biomarker of COVID-19. Plasmin is a key part of fibrinolysis, and it helps break apart the proteins on the outside of many viruses, including SARS-CoV.

Even though the coagulation/fibrinolytic state changes quickly during DIC in COVID-19, it is worrying that many articles treat DIC in COVID-19 as hypercoagulable DIC. Systemic fibrinolytic therapy is dangerous if there isn't enough monitoring of how the DIC state changes.

Inhaled fibrinolytic agents haven't been studied enough in terms of how well they work and how safe they are, so it's not clear if they will be spread evenly through the alveoli of COVID-19 patients. Besides, inhalation therapy for patients with COVID-19 can stimulate the production of harmful aerosols. Although further clinical studies are needed, we can reasonably assume that this new therapy offers a useful measure for COVID-19 patients with ARDS.

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