Coagulation Dysfunction

A Hallmark in COVID-19

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• ***Context.***—**The coronavirus disease 2019 (COVID-19) is a highly contagious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coagulation dysfunction is a hallmark in patients with COVID-19. Fulminant thrombotic complications emerge as critical issues in patients with severe COVID-19.**

Objective.—**To present a review of the literature and discuss the mechanisms of COVID-19 underlying coagulation activation and the implications for anticoagulant and thrombolytic treatment in the management of COVID-19.**

Data Sources.—**We performed a systemic review of scientific papers on the topic of COVID-19, available online via the PubMed NCBI, medRxiv, and Preprints as of May 15, 2020. We also shared our experience on the management of thrombotic events in patients with COVID-19.**

Conclusions.—**COVID-19–associated coagulopathy ranges from mild laboratory alterations to disseminated intravascular coagulation (DIC) with a predominant phenotype of thrombotic/multiple organ failure. Characteristically, high D-dimer levels on admission and/or continuously increasing concentrations of D-dimer are associated with disease progression and poor overall survival. SARS-CoV-2 infection triggers the immune-hemostatic response. Drastic inflammatory responses including, but not limited to, cytokine storm, vasculopathy, and NETosis may contribute to an overwhelming activation of coagulation. Hypercoagulability and systemic thrombotic complications necessitate anticoagulant and thrombolytic interventions, which provide opportunities to prevent or reduce "excessive" thrombin generation while preserving "adaptive" hemostasis and bring additional benefit via their anti-inflammatory effect in the setting of COVID-19.**

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The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly from an epidemic outbreak in the region of Wuhan, China, to an ongoing global pandemic[1–4] with more than 4.7 million cases and more than 320 000 deaths around the world.[5] The clinical consequence of the virus infection varies from asymptomatic, mild symptoms, severe illness, and sepsis to death. Patients with COVID-19 often present with fever, cough, myalgia, fatigue, and shortness of breath. Less frequent symptoms include headache, sore throat, fatigue, nausea and vomiting, anosmia and ageustia,[1,6] skin rashes,[7,8] and Kawasaki-like symptoms in children.[9–11] Emerging data suggest that approximately 15% of symptomatic patients progress to acute respiratory distress syndrome (ARDS), which requires hospitalization and intensive care unit (ICU) care.[1,12] Although the mortality rate of COVID-19 ranges from 0.1% and 16.4% and varies from country to country,[1,5] the overall rate is lower than those of SARS and Middle East respiratory syndrome (MERS).[12] Advanced age and the comorbidities with obesity, hypertension, or diabetes mellitus may predispose patients to an increased risk of severe disease and death.[13,14]

SARS-CoV-2 invades host cells through binding of its surface spike protein to the cell receptor angiotensin-converting enzyme 2 (ACE2), which is widely expressed in arterial and venous endothelial cells, lung type II alveolar cells, arterial smooth muscle cells in most organs, enterocytes of the small intestine, neural cortex, and brainstem.[15,16] The wide distribution of ACE2 receptors may partially explain the broad spectrum of clinical presentations of COVID-19. Numerous evidence suggests that multiple organs and systems are involved in COVID-19, including lung, heart,[17,18] gastrointestinal tract,[19] liver,[20,21] brain,[22] kidney,[14,23] blood,[24] skin,[25,26] and vascular,[9] coagulation,[27,28] and immune systems.[29] Coagulopathy and fulminant thrombotic complications emerge as critical issues in patients with severe COVID-19 and are associated with high mortality. Herein, we summarize coagulation abnormalities uniquely associated with COVID-19 and discuss the potential mechanisms as well as implications for anticoagulant and thrombolytic treatment for patients with COVID-19.

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ABNORMAL COAGULATION PARAMETERS IN COVID-19

A broad range of laboratory coagulation parameter abnormalities was reported in patients with COVID-19, including alterations in D-dimer, prothrombin time (PT), fibrinogen, fibrinogen degradation products (FDPs),[30–35] platelet count and antithrombin,[34] and coagulation factor VIII and von Willebrand factor (VWF).[36,37] The characteristic changes of coagulation parameters in patients with COVID-19 include moderately elevated levels of D-dimer and FDPs, with increased fibrinogen and platelet count in the early phase of the disease, suggesting an "adaptive" coagulation activation in response to the virus infection and inflammation. As the disease progresses, elevated D-dimer, prolonged PT, and decreased platelet count are associated with more severe disease and mortality. A multicenter retrospective study of 1099 patients from 552 hospitals around China suggests that D-dimer levels are more profoundly elevated in patients with more severe COVID-19 (65 of 109, 59.6%) than in those with a less severe form of the disease (195 of 451, 43.2%). The study also found that decreased platelet count (severe versus nonsevere, 57.7% [90 of 156] versus 31.6% [225 of 713]) was associated with more severe disease.[13] These results were consistent with a meta-analysis of 26 studies including 1374 patients with severe and 4326 with less severe COVID-19, showing that elevated D-dimer levels and decreased platelet count were associated with disease severity, with odds ratio of 3.17 (95% CI, 1.86–5.41) and 2.84 (95% CI, 2.00–4.04), respectively.[38] The increase in D-dimer and fluctuation of D-dimer concentration mirror the disease activity.[30,36,39] In a cohort of 449 patients, we analyzed the association between coagulation parameters and the mortality rate in patients with severe COVID-19. The results showed that elevated D-dimer levels, prolonged PT, and advanced age were associated with higher 28-day mortality rate, while higher platelet count was associated with lower 28-day mortality rate.[40] Particularly, elevated D-dimer levels on admission and continuously increasing concentrations of D-dimer (3- to 4-fold) over time were associated with higher mortality rate.[30] Moreover, 71% (15 of 21) of nonsurvivors with COVID-19 met the criteria for DIC when compared to 0.6% (1 of 162) for survivors, acknowledging that systemic coagulation activation and consumption may occur in severe patients as a result of infection/sepsis, cytokine storm, and impending organ failure.

Anti-phospholipid antibodies, including lupus anticoagulant and/or anti-cardiolipin immunoglobulin (Ig) A, anti–β_2 glycoprotein I (aβ2GPI) IgA and IgG, were also reported in patients with COVID-19 from several studies.[37,41–43] Lupus anticoagulant, IgG, and IgM types of anti-cardiolipin and aβ2GPI have been associated with antiphospholipid syndrome with hypercoagulability; these antibodies are also common and transiently present after critical illness and various infections. In particular, the production of IgA antiphospholipid antibodies is likely attributable to mucosal immunity. Therefore, the presence of these antibodies alone is not necessarily associated with thrombotic events.[41] Nevertheless, the clinical relevance of these antibodies remains largely unknown in the setting of COVID-19. It is noteworthy that positive findings from lupus anticoagulant laboratory tests and prolonged activated partial thromboplastin time (aPTT) have to be carefully evaluated in the presence of elevated plasma C-reactive protein and concurrent heparin use to preclude the interference from preanalytic and analytic variables.[44]

Elevated VWF antigen and activity in COVID-19 were first reported in a critically ill patient. VWF antigen and collagen-binding activity were elevated 5-fold over baseline, in concert with marked elevation of D-dimer at the point of disease worsening, indicating that endothelial activation plays an important role in the progression of the disease.[36] The same magnitude of increase in VWF levels was observed in a cohort study including 150 patients with severe COVID-19.[37] In this cohort, 43% (64 of 150) of patients presented clinically with relevant thrombotic complications, indicating that the massive release of VWF from activated endothelial cells and their accumulation in the circulation might additively contribute to arterial microvascular thrombus formation.

PULMONARY COAGULOPATHY IN COVID-19

The lung is the first and main battlefield upon SARS-CoV-2 invasion through the airway. The viral particles may elicit innate immune responses via the activation of resident alveolar macrophages and the complement cascade through the lectin pathway. Upon complement activation, the membrane attack complex can directly cause endothelial cell damage. Leukocytes, recruited by C3a and C5a to the site of infection, together with macrophages, are responsible for releasing proinflammatory cytokines such as interleukin (IL) 1, IL-2R, IL-6, IL-8, tumor necrosis factor α (TNF-α), and interferon-γ (INF-γ),[45,46] resulting in massive vascular endothelial and alveolar epithelial cell damage and coagulation activation. The more powerful coagulation activation may be driven by the expression and exposure of tissue factor (TF) from damaged alveolar epithelium, macrophages, and endothelium.[47] Histology from minimally invasive autopsies showed edematous and widened blood vessels, with modest infiltration of monocytes, lymphocytes, and thrombi.[48] Interstitial infiltration of inflammatory cells was widely observed in the lung dissection of patients with mild, severe, and fatal COVID-19.[48–53] The inflammatory exudates and accumulation of fluids in the alveolar spaces result in hypoxia and ventilation perfusion mismatch that further exacerbate endothelial cell disruption, tissue factor expression, and activation of the coagulation cascade, leading to a vicious cycle within pulmonary vasculature with diffuse microthrombi and hemorrhage.[54] Pulmonary coagulopathy is believed to be a more localized process, at least initially, with changes in fibrin turnover being restricted to the site of infection.[51,55] Initial minimal thrombin, together with coagulation factors in the alveolar spaces, as a result of blood vessel leakage, enables the amplification of coagulation cascades resulting in fibrin deposition in the bronchoalveolar spaces.[55] These immune-inflammatory-hemostatic changes correlate with severity of inflammation and ARDS progression. In a cohort of 201 hospitalized patients with COVID-19, early in the epidemic crisis in Wuhan, 41.8% (84 of 201) of patients developed ARDS; of those, slightly more than half died. Neutrophilia, and elevated D-dimer and lactate dehydrogenase levels, were associated with both ARDS development and progression from ARDS to death.[33] Moreover, fibrinolytic activity in the lung is depressed owing to local or blood-derived elevation of fibrinolytic inhibitors including plasminogen activator inhibitor (PAI)-1, PAI- 2, and α-2-antiplasmin.[56–59] These biological mechanisms are likely responsible for the common findings of elevated

plasma D-dimer concentrations and spreading hyaline thrombosis, hemorrhagic change, pulmonary infarction, and pulmonary interstitial fibrosis in patients with severe COVID-19.[48–50]

One recent study[50] also emphasized prominent capillary thrombosis characterized by thickened alveolar capillaries with surrounding edema and fibrin thrombi in the bed of capillaries and small vessels with the signs of cardiomegaly and right ventricular dilatation, pointing to the potential development of pulmonary artery hypertension and heart failure due to thromboses in the lung. COVID-19 shares similar features in lung pathology with SARS, characterized by edema, inflammatory cell infiltration into the walls of the pulmonary microvasculature, marked hemorrhagic necrosis, and vessel microthrombi mostly confined to the lung and pulmonary tissue infarction, in the context of septal inflammation and diffuse alveolar damage.[60]

VENOUS AND ARTERIAL THROMBOTIC DISORDERS IN COVID-19

Mounting evidence demonstrates that COVID-19 is associated with thrombotic complications in all organs of the body, emerging as one of the major causes of death in COVID-19. An earlier study from Wuhan[61] reported that the incidence of venous thromboembolism (VTE) in COVID-19 patients in the ICU was 25% (20 of 81). A more in-depth study from the Netherlands[62] showed a remarkably high cumulative incidence (n = 31, 31%) of thrombotic complications in 184 patients in the ICU despite the use of standard weight–based VTE prophylaxis. These results were confirmed by a larger cohort study from Milan.[63] The thrombotic events include pulmonary embolism, deep venous thrombosis, ischemic stroke, myocardial infarction, and systemic arterial embolism.[17,62,63] Likewise, the high incidence of pulmonary embolism was reported by 2 French groups in critically ill COVID-19 patients.[37,64] As compared with patients in general wards, the incidence of VTE in patients with COVID-19 was much higher in the ICUs (ICU versus general wards, 47% [35 of 75] versus 3% [4 of 123]).[65,66] ICU-associated conditions including ventilation, central line catheterization, and immobilization may not be sufficient to explain the high incidence of VTE in COVID-19 patients. In the same ICU setting, the frequency of pulmonary embolism in COVID-19 patients (22 of 107, 20.6%) is much higher than that in both the ICU controls (12 of 196, 6.1%) and influenza series (3 of 40, 7.5%).[64] These thrombotic complications were associated with an increased risk of death.[66] The death caused by lethal thrombotic complications, including pulmonary embolism, myocardial infarction, or stroke in COVID-19, may be largely underestimated without an autopsy evaluation.

Acute respiratory infections are associated with a high risk of cardiovascular-related death, especially in older patients and those with preexisting cardiovascular disease.[67,68] More recently, ischemic stroke and myocardial infarction were also reported in younger patients with COVID-19. The incidence of stroke among hospitalized patients with COVID-19 was approximately 5% in Wuhan.[69] Stroke due to large-vessel occlusion, normally seen in the elderly, unexpectedly developed in 5 young patients, the youngest only 33 years old.[70] In addition, cyanosis, livedo reticularis, and ischemic limb gangrene were frequently identified in COVID-19 patients in critically ill condition, indicating the development of thrombotic microangiopathy, which is likely triggered by hypoxia, ischemia, and acute inflammation response.

DISTINCT FEATURES OF COAGULOPATHY ASSOCIATED WITH COVID-19

In most cases, despite increases in D-dimer levels, platelet count and fibrinogen are not substantially reduced in patients with COVID-19, consistent with an ongoing acute phase response. Uniquely, in most cases, aPTT is nearly normal, which is different from what has been observed in similar diseases (ie, SARS and MERS). The mechanism for near normal aPTT in COVID-19 is not fully understood, although a dramatic increase in levels of factor VIII during inflammation is a plausible explanation.[36] The most common coagulation abnormalities in SARS patients include mild thrombocytopenia, prolonged aPTT, and slightly elevated D-dimer levels, whereas PT remained normal in most cases.[71–73] These abnormalities were self-limited in most cases and reactive thrombocytosis was also observed during the disease course, probably due to increased thrombopoietin levels in SARS patients.[72,73] A typical consumption coagulopathy (ie, DIC) does develop in late-stage disease with markedly prolonged PT and aPTT, thrombocytopenia, and elevated D-dimer levels.[73,74] In MERS, thrombocytopenia is one of the most common coagulation abnormalities.[75,76] Profound thrombocytopenia is an indicator of disease progression.[77–79] Like SARS, "noxious" DIC with bleeding is one of the major complications reported in fatal MERS-CoV cases.[78,80,81]

Interestingly, in our study,[40] only 21.6% (97 of 449) of patients met the sepsis-induced coagulopathy (SIC) criteria (total score $\geq$4) when they were classified as severe cases, and D-dimer levels appear to be a more sensitive marker for coagulopathy than both platelet count and SIC criteria in COVID-19. This suggests that coagulation abnormalities in patients with severe COVID-19 are not identical to SIC in general. There has been debate in the field on how to interpret these laboratory parameters and the discrepancy between an overt laboratory "DIC" and lack of typical signs of clinical DIC, such as oozing or massive bleeding. The phenotype of "DIC" in COVID-19 patients seems to be mimicking "thrombotic/multiple organ failure DIC" characterized by digital gangrene and multiple ischemic organ failure from extensive macrothrombi or microthrombi. Prolonged PT and minimally affected aPTT also suggest a predominant TF-FVIIa–mediated activation of the extrinsic coagulation pathway in patients with COVID-19. It is noteworthy that the liver appears to sustain its production of coagulation components needed for the intrinsic pathway.[20,82] The concepts of "local DIC"[83] and "pulmonary intravascular coagulopathy"[84] have been proposed to distinguish COVID-19–associated coagulopathy from macrophage activation syndrome with DIC. Diffuse pulmonary intravascular coagulopathy, increased plasma D-dimer levels (reflecting pulmonary vascular bed thrombosis with fibrinolysis), and elevated cardiac enzyme concentrations (reflecting emergent ventricular stress induced by pulmonary hypertension) in the face of normal concentrations of fibrinogen and platelets are key early features of severe pulmonary intravascular coagulopathy related to COVID-19.[84]

INFLAMMATION AND THROMBOSIS IN COVID-19

Inflammation-induced thrombosis is a well-known entity and is a vital part of the immune system's response to injury

and infection. Systemic inflammation is a potent prothrombotic stimulus, which can upregulate platelet activity and procoagulant factors, downregulate natural anticoagulants, and inhibit fibrinolytic activity, resulting in coagulation activation and hypercoagulability. The complex interactions between inflammation and hemostasis involve innate immunity, proinflammatory cytokines, chemokines, adhesion molecules, tissue factor expression, platelet and endothelial activation, and microparticles. In turn, coagulation also enhances inflammation. The activated coagulation products, including thrombin, FXa, fibrin, and the TF–FVIIa complex through activating protease-activated receptors (PARs), can induce secretion of proinflammatory cytokines and growth factors, leading to a vicious cycle.[47,85] Here, we briefly highlight 3 mechanisms potentially associated with COVID-19.

Mild COVID-19 may rapidly develop into acute lung injury, ARDS, sepsis, and multiple organ failure. A potential etiology of suddenly worsening disease is cytokine release syndrome (CRS) and its most severe form, secondary hemophagocytic lymphohistiocytosis (sHLH).[86] Numerous studies have shown that there is an excessive production of inflammatory cytokines including IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-17, IFN-γ, IFN-γ–inducible protein 10, monocyte chemoattractant protein 1, granulocyte-colony stimulating factor, macrophage inflammatory protein 1α, and TNF-α in patients with COVID-19 with critical conditions.[1,46,86–88] Anticytokine therapy appears to be a plausible strategy to reduce the diffuse immunothrombosis. However, an experimental trial of tocilizumab, an IL-6 receptor antagonist, involving 2 patients with complications from COVID-19–induced CRS[89] showed that both patients' condition progressed to sHLH despite treatment with tocilizumab, and one developed viral myocarditis, challenging the safety and clinical usefulness of tocilizumab in the treatment of COVID-19–induced CRS.[89] Therefore, more data are needed to address the concern of whether the emergent activation of coagulation in patients with COVID-19 is purely due to an appropriate immune response to the virus, or whether there is a degree of excessive inflammation that could be targeted to help prevent progression of coagulopathy.[84]

Endothelial cells play crucial roles in normal hemostasis by maintaining the integrity of the vessel wall and expressing platelet inhibitors (ie, nitric oxide and prostaglandin I_2) and various anticoagulants such as tissue factor pathway inhibitor, thrombomodulin, endothelial protein C receptor, and heparin-like proteoglycans.[90] In endothelial cells, Weibel-Palade bodies store VWF, P-selectin, angiopoietin-2, tissue plasminogen activator (tPA), and endothelin-1, which are active participants of platelet adhesion, leukocyte recruitment, inflammation modulation, fibrinolysis, and vasoconstriction.[91] Endothelial cell disruption and dysfunction lead to increased vascular wall permeability in the pulmonary microvasculature, an essential step in the thromboinflammatory processes that results in ventilation perfusion mismatch, and a clinical phenotype of refractory ARDS, and ultimately systemic vasculopathy in COVID-19. Direct viral infection of the endothelial cells, diffuse endothelial inflammation, and cell death across vascular beds of different organs were evidenced in a series of patients with COVID-19.[92] The endotheliopathy in COVID-19 is particularly relevant for cardiovascular thrombotic complications in vulnerable patients with preexisting endothelial dysfunction as well as vasculitis in children.[9] This provides a rationale for implementing therapies to stabilize the endothelium with anti-inflammatory drugs, anticytokine drugs, ACE inhibitors, and statins, while tackling viral replication and endothelial activation biomarkers.[92]

Neutrophils have evolved into a more complex network, linking innate immunity and hemostasis.[93] In hospitalized COVID-19 patients, normal to low white blood cell counts, but an increase in neutrophils and ratio of neutrophils to lymphocytes, suggest that neutrophils play an essential role in host defense and prothrombotic process. Neutrophils not only engulf pathogens, but also undergo a process called NETosis through the activation of protein arginine deiminase 4, an enzyme responsible for citrullination of histones in the neutrophils, which leads to chromatin decondensation, nuclear rupture, and release of their granule enzymes and nuclear content to form neutrophil extracellular traps (NETs).[94] These NETs, including histones and DNA fragments, myeloperoxidase, neutrophil elastase, and cathepsin G, are an essential part of innate immunity in host defense against bacteria, viruses, and fungi.[95] NETs are implicated in the pathogenesis of various thrombotic disorders including deep venous thrombosis, myocardial infarction, and thrombotic thrombocytopenic purpura (TTP).[96] High levels of circulating histones or histone-DNA complexes seen in septic shock, thrombotic microangiopathies including DIC,[92] heparin-induced thrombocytopenia,[97] and TTP[98] are associated with disease severity and poor prognosis. Histone infusion induces intravascular coagulation with thrombocytopenia and increased levels of D-dimers[99] or TTP phenotype.[100] Anti-histone with antibodies or protein C can prevent both lung and cardiac injuries in experimental models.[101] Therefore, NETs as a potential driver of COVID-19, recently reviewed by 2 groups,[102,103] are an optional therapeutic target.

ANTICOAGULANTS AND THROMBOLYTIC THERAPIES IN COVID-19

COVID-19 is complicated by extensive thrombotic complications including VTE, myocardial infarction, and stroke, which necessitate anticoagulant and/or thrombolytic treatment for patients with severe COVID-19. The International Society of Thrombosis and Haemostasis and American Hematology Society recommend that all hospitalized patients with COVID-19 receive pharmacologic thromboprophylaxis with low-molecular-weight heparin or fondaparinux.[53]

The effect of anticoagulant therapy was first retrospectively analyzed by our group.[40] Low-molecular-weight heparin (mostly used in prophylactic doses rather than therapeutic doses) did not confer an overall survival advantage. However, the regimen was associated with improved survival in the group with a high sepsis-induced coagulopathy score and in patients with D-dimer concentrations that were more than 6 times the upper limit of normal, suggesting that the timing of anticoagulation should be closely guided by laboratory coagulation parameters. A small observational study from an Italian group[35] showed that aggressive thromboprophylaxis could decrease the levels of fibrinogen and D-dimer and seemed to prevent major thrombotic events from occurring in ICU patients. There are no data yet for the use of other anticoagulants, including thrombin inhibitors, coagulation factor Xa, or PAR-1 antagonist, in COVID-19–induced thrombotic prophylaxis and treatment.

The role of thrombolytic or fibrinolytic agents in treating ARDS and thrombotic complications associated with COVID-19 is not clear yet. It has been shown that thrombolytic (ie, tPA) or fibrinolytic (ie, streptokinase and urokinase) therapy can attenuate ventilator-induced acute lung injury in rat models through decreasing capillary-alveolar protein leakage as well as local and systemic coagulation, as shown by decreased lung vascular fibrin deposition and plasma D-dimers.[104] Inhaled streptokinase seems to be a rescue therapy for severe ARDS that can improve oxygenation and lung mechanics more quickly than heparin or conventional management.[105]

The salvage use of tPA has been proposed for critically ill patients. On the basis of the natural history of ARDS[106] and the results of phase I clinical trial for systemic use of tPA in ARDS,[107] Choudhury et al[108] created a decision-analytic Markov state-transition model to simulate critically ill COVID-19 patients with ARDS, using a cutoff of P_AO_2/F_IO_2 <60 mm Hg. The results showed that tPA use was associated with reduced mortality for base case patients. When extrapolated to the projected COVID-19 eligible-for-salvage tPA use, peak mortality (deaths/100 000 patients) was reduced for both optimal social-distancing and no-social-distancing scenarios.[108] The first off-label trial of tPA was conducted by Wang et al[109] in 3 COVID-19 patients with severe ARDS who required ventilators and heparin treatment. A transient improvement of lung function (increased P_AO_2/F_IO_2) was observed in 2 of 3 patients, along with a reduction of fibrinogen (3 of 3), following 2 sequential bolus doses of intravenous infusion of tPA (25 mg) without bleeding complications. It remains to be determined whether a larger bolus (50–100 mg) or re-dosing may achieve a more sustained response. Certainly, emergent large artery occlusions (ie, myocardial infarction and ischemic stroke) in COVID-19 necessitate a more aggressive thrombolytic therapy with careful evaluation for factors that may increase the risk of bleeding.

CONCLUSIONS

SARS-CoV-2 infection triggers the immune-hemostatic response. While both systems are closely intertwined and essential for an effective immune response to limit the infection, overwhelming activation of coagulation can outweigh the beneficial effects by inducing thrombotic complications, excessive inflammation, and tissue damage, resulting in acute lung injury, respiratory dysfunction, ARDS, DIC, multiple organ failure, and even death. COVID-19–associated coagulopathy is characterized by elevated D-dimer and fibrinogen levels and prolonged PT with a predominant phenotype of thrombotic/multiple organ failure with systemic thrombotic complications in both venous and arterial vasculatures. Therefore, anticoagulants and/or thrombolytic therapies provide opportunities to prevent or reduce "excessive" thrombin generation, while preserving "adaptive" hemostasis. This essential life-saving therapy helps to limit the ongoing fibrin deposition and microthrombi formation in the airway and lung parenchyma, thereby reducing ARDS-associated mortality. It also lyses clots formed in major organs such as the cardiovasculature or cerebrovasculature. In addition, anticoagulants and thrombolytic therapies bring additional benefit via their anti-inflammatory effect in the setting of COVID-19. The combination of immunomodulatory and anticoagulant strategies for COVID-19 patients appears promising but warrants further investigation.

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