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Coagulation dysfunction: A hallmark in COVID-19

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Abstract

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, online available 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 is 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.

INTRODUCTION

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 into an ongoing global pandemic [1-4] with more than 4.7 million cases and over 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 ageusti [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 lands between 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]. The 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], vascular [9] and 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 anti-coagulant and thrombolytic treatment in patients with COVID-19.

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 (FDP) [30-35], platelet count and antithrombin (AT) [34], and coagulation factor VIII (FVIII) 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 FDP, 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. While, as the disease progressed, elevated D-dimer, prolonged PT and decreased platelet count were associated with more severe disease and mortality. A multi-center study retrospectively reviewed 1099 patients from 552 hospitals around China suggest that D-dimer is more profoundly elevated in patients with more severe COVID-19

(65/109, 59.6%) than those with a less-severe form of the disease (195/451, 43.2%). They also found that decreased platelet count [severe vs non-severe, 57.7% (90/156) vs 31.6% (225/713)] was associated with more severe disease [13]. These results were consistent with a meta-analysis of 26 studies including 1374 severe and 4326 less-severe patients with COVID-19, showing that elevated D-dimer and decreased platelet count were associated with the disease severity, with the odds ratio (OR) of 3.17 (95% confidence interval (CI), 1.86-5.41) and 2.84 (95% CI, 2.00-4.04), respectively [38]. The increased 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 severe COVID-19 patients. The results showed that elevated D-dimer, 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 on admission and continuously increasing concentrations of D-dimer (3- to 4-fold) over time were associated with the higher mortality rate [30]. Moreover, 71% (15/21) of non-survivors with COVID-19 met the criteria for DIC when compared to 0.6% (1/162) in 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.

Antiphospholipid antibodies (aPL) including lupus anticoagulant (LAC), and/or anticardiolipin (aCL) IgA, anti-β_2 glycoprotein I (aβ2GPI) IgA and IgG were also reported in patients with COVID-19 from several studies [37, 41-43]. LAC, IgG and IgM

types of aCL and aβ2GPI have been associated with antiphospholipid syndrome (APS) with hypercoagulability, while these antibodies are also common and transiently present following critical illness and various infections. In particular, the production of IgA aPL is likely attributable to the 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 laboratory LAC studies and prolonged aPTT have to be carefully evaluated in the presence of elevated plasma C-reactive protein and concurrent heparin uses to preclude the interference from pre-analytic 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 5-fold elevated 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% (64/150) 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 (MAC) can directly cause endothelial cell damage. Leukocytes, recruited by C3a and C5a to the site of infection, together with macrophages are responsible for releasing pro-inflammatory cytokines such as interleukin (IL)-1, IL-2R, IL-6, IL-8, tissue necrosis factor (TNF)-α, and interferon-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 exposing 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 organ 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 viscous 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% (84/201) patients developed ARDS, of those slightly more than half died. Neutrophilia, elevated D-dimer and LDH were associated with both ARDS development and progression from ARDS to death [33]. While, fibrinolytic activity in the lung is depressed due to local or blood derived elevation of fibrinolytic inhibitors including plasminogen activator inhibitor (PAI)-1, PAI- 2, and alpha-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 also emphasized prominent capillary thrombosis characterized by thickened alveolar capillaries with surrounding edema and fibrin thrombi in the bed of the capillaries and small vessels with the sign of cardiomegaly and right ventricular dilatation, pointing towards the potential development of pulmonary artery hypertension and heart failure due to thromboses in the lung [50]. 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 complicated with thrombotic complications all over the body from head to toe, emerging as one of the major causes of death in COVID-19. An earlier study from Wuhan reported the incidence of venous thromboembolism (VTE) in COVID-19 patients, in the ICU, was 25% (20/81) [61]. A more profound study from the Netherlands 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 [62]. These results were confirmed by a lager cohort study from Milan [63]. The thrombotic events include pulmonary embolism (PE), deep venous thrombosis (DVT), ischemic stroke, myocardial infarction, and systemic arterial embolism [17, 62, 63]. Likewise, the high incidence of pulmonary embolism (PE) was reported by French groups in critically ill COVID-19 patients [37, 64]. Compared with patients in general wards, the incidence of VTE in patients with COVID-19 was much higher in the ICUs [ICU vs general wards, 47% (35/75) vs 3% (4/123)] [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 PE in COVID-19 patients (22/107, 20.6%) is much higher than that in both the ICU controls (12/196, 6.1%) and influenza series (3/40, 7.5%) [64]. These thrombotic complications were associated with an increased risk of death [66]. The death caused by

lethal thrombotic complications including PE, 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 pre-existing cardiovascular disease [67, 68]. More recently, ischemic stroke and myocardial infarction (MI) 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, activated partial thromboplastin time (aPTT) is nearly normal, which was different from what was observed in similar diseases (i.e. SARS and MERS). The mechanism of near normal aPTT in COVID-19 is not fully understood, though dramatically increased levels of FVIII 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, whereas the PT remained normal in most cases [71-73]. These abnormalities were self-limited in most cases and reactive thrombocytosis was also observed during the course, probably due to the increased thrombopoietin levels in SARS patients [72-73]. A typical consumption coagulopathy (i.e. DIC) does develop in late stage disease with markedly prolonged PT, aPTT, thrombocytopenia, and elevated D-dimer [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% (97/449) patients met the sepsis-induced score (SIC) criteria (total score ≥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 severe COVID-19 patients are not identical to SIC in general. It has been debated in the field how to interpret these laboratory parameters and the discrepancy between an overt lab “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 macro- or micro- thrombi. 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 distinct 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, pro-inflammatory 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 three mechanisms potentially associated with COVID-19.

Mild COVID-19 may rapidly develop into acute lung injury, ARDS, sepsis, and multiple organ failure (MOF). A potential etiology of suddenly worsening of the 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 interleukin (IL)-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-17, Interferon (IFN)-γ, IFN-γ-inducible protein 10, monocyte chemoattractant protein 1 (MCP1), granulocyte-colony stimulating factor, macrophage inflammatory protein 1α, and TNF-α in patients with COVID-19 with critically ill conditions [1, 46, 86-88]. Anti-cytokine therapy appears to be a plausible strategy to reduce the diffuse immunothrombosis. However, an experimental trial of tocilizumab, an IL-6 receptor antagonist, in two patients complicated with COVID-19-induced CRS [89], showed that both patients 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 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 through maintaining the integrity of the vessel wall and expressing platelet inhibitors (i.e. 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, t-PA, 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 pre-existing endothelial dysfunction as well as vasculitis in children [9]. This provides a rationale for therapies to stabilize the endothelium with anti-inflammatory drugs, anti-cytokine 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 cells, but increased neutrophils and ratio of neutrophilia-to-lymphocytes (NLR) suggest that neutrophils play an essential role in host defense and prothrombotic process. Neutrophils not only engulf pathogens, but they also undergo a process called NETosis through the activation of protein arginine deiminase 4 (PAD4), an enzyme responsible for citrullination of histones (citH3) in the neutrophils, which leads to

chromatin de-condensation, 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 (MPO), and neutrophil elastase (NE), 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 DVT, 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 the disease severity and poor prognosis. Histone infusion induces intravascular coagulation with thrombocytopenia and increased 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 two groups [102, 103], is 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 necessitates anticoagulant and/or thrombolytic treatment in severe patients with COVID-19. The International Society of Thrombosis and Haemostasis and American Hematology Society recommend that all hospitalized patients with COVID-19 receive pharmacological 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 six 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 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 [35]. There is 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 (i.e. tPA) or fibrinolytic therapy (i.e. streptokinase and urokinase) 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. Based on 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 cut-off of PaO2/FiO2<60 mmHg. 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 three COVID-19 patients with severe ARDS on ventilators and heparin treatment. A transient improvement of lung function (increased PaO2/FiO2) was observed in 2 out of 3 patients along with a reduction of fibrinogen (3/3) following two 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, emerging large artery occlusions (i.e. MI and ischemic stroke) in COVID-19 necessitates 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, MOF, and even death. COVID-19-associated coagulopathy is characterized by elevated D-dimer, fibrinogen, 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 the clot formed in major organs such as cardio- or cerebral- vasculatures. In addition, the 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 in COVID-19 patients appears promising but warrants further investigation.

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