Review Article

Coagulopathy in COVID-19

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ABSTRACT

Hemostatic derangement is a hallmark in severe COVID-19. Markedly elevation of D-dimer and fibrinogen degradation product levels were observed in patients with severe COVID-19 higher and 71.4% of nonsurvivors met the International Society of Thrombosis and Haemostasis criteria of disseminated intravascular coagulation (DIC). Although the clinical and epidemiological features of COVID-19 have been well-described, the underlying mechanism influencing disease severity remains to be elucidated. Herein, the aim of this review article is to evaluate hemostasis in the pathogenesis of COVID-19 and its role in the management of this unprecedented pandemic.

KEY WORDS: Acute respiratory distress syndrome, anticoagulant, coagulopathy, COVID-19, D-dimer, disseminated intravascular coagulopathy, heparin

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INTRODUCTION

Since the outbreak of the coronavirus disease 2019 (COVID-19), scientists and health-care workers around the globe are working incessantly to understand and combat the pandemic. Registered clinical trials are ongoing in hopes of finding timely and effective therapies. Up till now, no specific antiviral treatment exists, and management is mainly symptomatic treatment and organ support in the intensive care unit for severely ill patients. Although the clinical and epidemiological features of COVID-19 have been well-described,[1-5] the underlying mechanism influencing disease severity remains to be elucidated. There has been growing concern about COVID-19-associated coagulopathy and disseminated intravascular coagulation (DIC).[6,7] An urgent need to identify the pathophysiologic factors is paramount, which can guide future treatment strategy in addressing the rising mortality. Herein, we aimed to evaluate hemostasis in the pathogenesis of COVID-19 and its role in the management of this unprecedented pandemic.

PATHOPHYSIOLOGY OF COAGULOPATHY IN COVID-19

Cytokine storm has been the most discussed theory explaining the varying disease severity in patients with COVID-19. Lung injury is thought as a result of the direct viral invasion and dysregulated, overactive host response driven by pro-inflammatory cytokines-the "cytokine storm."[8] Cytokine release syndrome (CRS), "cytokine storm" is an acute systemic inflammatory response to a variety of insults (e.g., infection, drugs) characterized by increased levels of pro-inflammatory cytokines (interleukin [IL]-1, IL-5, IL-8, IL-6, interferon γ), and activation of T lymphocytes, macrophages, and endothelial cells.[9] The theory is supported by the high serum levels of pro-inflammatory cytokines, inflammatory

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markers, and lymphopenia observed in critically ill patients with COVID-19.[10,11]

The cytokine storm has been the current focus of studies and clinical trials of immune-modulating therapies are emerging. A multicenter, randomized control trial of tocilizumab (IL-6 receptor antibody) has been approved in China for the treatment of COVID-19 patients with elevated IL-6 (ChiCTR2000029765). We observed markedly elevation of D-dimer in patients with COVID-19 treated with tocilizumab. Although thromboembolic events associated with tocilizumab use has not been reported, whether tocilizumab is prothrombotic remains to be elucidated. A study of tocilizumab use in rheumatoid arthritis and Castleman disease found that serum IL-6 and soluble IL-6R increases after its use.[12] Another study by Meley *et al*. found that tocilizumab use can contribute to the inflammatory status of mature dendritic cells through IL-6 receptor subunit modulation.[13] Regardless, significant abnormal coagulation function observed in COVID-19 implies the presence of other pathophysiologic factors contributing to disease progression, which could not be solely explained by CRS.

Inflammation and coagulation are the two important host defense mechanisms against injury and infection.[14] Sepsis is a dysregulated host response to infection leading to life-threatening organ dysfunction.[15] Although bacterial infection represents the majority of sepsis cases, viral infection (SAR-CoV-2) can cause sepsis. Coagulopathy commonly occurs in sepsis and arises as a result of an activated coagulation, which serves as an important host response to infection. Continued systemic inflammatory response and activated coagulation results in diffuse tissue hypoxia and organ failure.

The pathophysiology of pulmonary coagulation and fibrinolysis in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) resembles that of sepsis.[16,17] In ALI, normal hemostatic balance is disrupted and is characterized by activated coagulation and suppressed fibrinolysis. Procoagulable state is initiated by tissue factors (TF) from the enhanced expression on endothelial cells and monocytes mediated by different inflammatory cytokines (tumor necrosis factor alpha, IL-1α, and nuclear factor kappa B). On the other hand, accelerated breakdown and/or decrease in the production of activated protein C (APC), antithrombin, and TF pathway inhibitor (TFPI) in the anti-coagulation pathway leads to shifted hemostasis. This results in abundant microthrombi formation within the pulmonary vasculature, and subsequently, impairs ventilation/perfusion and contributes to progressive respiratory failure. Pathologic findings observed in lung specimens of patients with COVID-19 are consistent with pulmonary coagulopathy, which revealed diffuse alveolar damage, proteinaceous exudates, fibrotic clots in small airways and disseminated intravascular thrombosis.[18,19] Excess thrombin formation leads to consumptive thrombocytopenia, depletion of coagulation factor and secondary fibrinolysis (evidenced by elevated serum D-dimer, fibrinogen degradation product (FDP), and low fibrinogen levels), and eventually DIC.

DERANGED HEMOSTASIS IS ASSOCIATED WITH POOR PROGNOSIS IN COVID-19

Hemostatic derangement is a prominent feature observed in patients with COVID-19. Elevated D-dimer, prolonged prothrombin time (PT), and reduced platelets have been reported in severe cases in most cohorts.[2-6] A study by Han *et al*. evaluating coagulation function of 94 patients with COVID-19 found that the level of antithrombin (AT) was significantly lower, and levels of D-dimer, fibrin/FDP, and fibrinogen (FIB) were significantly higher in COVID-19 patients compared to healthy controls.[20] The presence of abnormal coagulation function in patients with COVID-19 indicates that homeostasis and fibrinolysis may play a pivotal role in the disease progression.[7] More importantly, patients with severe COVID-19 developed a greater extent of coagulation abnormalities (higher D-dimer and FDP) compared to patients with mild COVID-19, and progressive worsening of coagulation function was positively correlated with disease severity.[7,20]

One cohort of 201 patients by Wu *et al*. concluded that organ and coagulation dysfunction (e.g., higher lactate dehydrogenase [hazard ratio (HR), 1.61; 95% confidence interval (CI), 1.44–1.79; and HR, 1.30; 95% CI, 1.11–1.52, respectively] and D-dimer [HR, 1.03; 95% CI, 1.01–1.04; and HR, 1.02; 95% CI, 1.01–1.04, respectively]) are risk factors associated with the development of ARDS and progression to death.[21] For nonsurvivors with ARDS, D-dimer (difference, 2.10 μg/mL; 95% CI, 0.89-5.27 μg/mL; $P = 0.001$) was significantly elevated compared to patients with ARDS who survived. Importantly, Tang *et al*. studied coagulation parameters in 183 patients. Comparing survivors and nonsurvivors, D-dimer and FDP levels were significantly higher in non-survivors and 71.4% of nonsurvivors met the International Society of Thrombosis and Haemostasis (ISTH) criteria of DIC. The median time from admission to the development of DIC was 4 days.[1] Based on the currently available literature, coagulopathy is common in COVID-19 and could be the underlying pathogenesis leading to the progression of ARDS, Multi-organ dysfunction syndrome (MODS), and DIC.

HEMOSTASIS AND ITS ROLE IN MANAGEMENT OF COVID-19

Risk stratification and disease monitoring

D-dimer greater than 1ug/mL is a significant risk factor associated with poor prognosis in COVID-19.[4] Early and serial monitoring of hemostatic markers (PT, D-dimer, platelet, and fibrinogen) should be performed in all COVID-19 patients who required hospitalization. This can be helpful in risk stratification and identify patients at risk of worsening illness during hospitalization.

The concept of "sepsis-induced coagulopathy (SIC)" and SIC scoring has been advocated by the ISTH.[22] SIC scoring can be used to identify COVID-19 patients at risk of DIC. Parameters in SIC scoring include platelet count, PT ratio, fibrinogen, and Sequential Organ Failure Assessment score [Table 1].

Thromboelastometry (TEG) could also be a useful tool in diagnosing alternations in coagulation and identifying COVID-19 patients at risk of DIC.[23] Studies have shown that the degree of hypocoagulability defined by TEG variables correlates with the severity of organ failure and is of prognostic value in critically ill patients.[24,25]

Circulating microvesicles (MV) are small membrane fragments that can transfer mRNA and protein between cells.[26] During viral infection, MV-TF is released from endothelial cells and activates coagulation cascade. A study by Rondina *et al*. found that measuring serum IL-8 and MV-TF activity can allow early identification of patients with influenza A/H1N1 and are of prognostic values.[27] Measuring MV-TF activity and IL-8 levels might help identifying COVID-19 patients with coagulopathy.

Management of coagulopathy in COVID-19

Although coagulopathy is common in severe COVID-19 patients, recommendation on the management of coagulopathy in COVID-19 remains scarce. A guideline by the ISTH on management of coagulopathy in COVID-19 has been recently published.[28] A practical guidance for prevention of thrombosis and management of coagulopathy and DIC of patients infected with COVID-19 is also published on thrombosis UK (https://thrombosisuk.org/covid-19-thrombosis. php).

Thromboprophylaxis in COVID-19 patients who required hospitalization

Anticoagulation therapy with low molecular weight heparin (LMWH) has shown to be associated with better prognosis in severe COVID-19 patients with coagulopathy (defined by SIC score ≥4 or D-dimer >3.0 μg/mL).[1] The ISTH guidance recommends that prophylactic dose LMWH should be considered in all patients (including noncritically ill) who require hospitalization for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count $<25 \times 10^9$/L; monitoring advised in severe renal impairment; abnormal PT or activated partial thromboplastin time is not a contraindication).[28]

Table 1. ISTH overt DIC and SIC scoring systems, adapted from J Thromb Haemost. 2019 Nov;17(11):1989-1994.

Item	Score	ISTH overt DIC	SIC
		Range	Range
Platelet count (−109/L)	2	<50	< 100
	1	≧50, <100	≧100, <150
FDP/D-dimer	3	Strong increase	-
	2	Moderate increase	-
Prothrombin time	2	≧ 6 sec	(>1.4)
(PT ratio)	1	≧3 sec, <6 sec	(>1.2, ≦1.4)
Fibrinogen (g/mL)	1	<100	-
SOFA score	2	-	≧2
	1	-	1
Total score for DIC or SIC		≧5	≧4

ISTH: International Society on Thrombosis and Haemostasis; DIC: disseminated intravascular coagulation; SIC: sepsis-induced coagulopathy; SOFA: sequential organ failure assessment. SOFA score: score is the sum of 4 items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, renal SOFA).

Besides, LWMH prophylaxis is effective in preventing venous thromboembolic events in critically ill patients.[29] Pulmonary embolism (PE) should be suspected in patients who present with respiratory distress, sudden deterioration of oxygen saturation and hemodynamic instability. Case reports of acute PE in COVID-19 patients have been reported.[30,31]

Disseminated intravascular coagulation in COVID-19 patients

General principles include both treatment of underlying infection and correcting coagulopathy. Blood product transfusions should be considered in patients with major bleeding, while patients with milder bleeding can be closely monitored and management expectantly. We acknowledge that there are considerable differences in the therapeutic approach to DIC across different countries and the availability and approval status of anticoagulant agents varies among countries. Evidence supporting the use of the most-studied anticoagulant agents is summarized in the following section (LMWH has been discussed as above).

Antithrombin

Global sepsis guidelines recommend against the use of AT because the results of a large-scale clinical trial (the KyberSept trial) reported an increased risk of bleeding.[32,33] However, subsequently, results from multiple meta-analysis of AT replacement therapy in sepsis-associated DIC have shown beneficial effects in survival.[34-37] Based on these results, the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock recommend the AT replacement therapy in DIC patients with decreased AT activity.[38]

Recombinant thrombomodulin

Although currently, no guidelines recommend the use of recombinant thrombomodulin as first-line treatment in sepsis-induced DIC. In a meta-analysis of all recombinant thrombomodulin trials, Yamakawa *et al*. found a reduction of mortality rate by 13% (relative risk: 0.87, 95%, CI 0.74–1.03).[39]

Recombinant activated protein C

Recombinant APC (drotrecogin α), once approved as a novel therapy for sepsis, has been withdrawn from the market because subsequent clinical trials failed to demonstrate improvement in morality and raised concern about bleeding.[28,40] A preclinical study of a recombinant APC variant (endotoxemia) reported reduced mortality

in animal models of sepsis, but its efficacy has not been tested in clinical trials.[41]

Potential role of anticoagulant therapy in acute respiratory distress syndrome

Anticoagulant agents, such as LMWH, AT, recombinant APC, TFPI, and recombinant thrombomodulin, have been evaluated for the treatment of ALI/ARDS. In a meta-analysis of LMWH by Li *et al*., adjunctive treatment with LMWH appears is effective in reducing 7-day and 28-day mortality, improving the PaO_2/FiO_2 ratio among ALI/ARDS patients. Although previous clinical trials of other anticoagulant agents do not suggest beneficial effects in treating ARDS, given that patients with severe COVID-19 are coagulopathic and elevated D-dimer is associated with high mortality, evaluating its potential role in treating severe COVID-19 is warranted. Besides, as natural anticoagulant possesses anti-inflammatory properties (bidirectional communication between inflammation and thrombosis), it may potentially restore proper hemostasis and attenuate inflammation.

Potential role of fibrinolytic therapy in acute respiratory distress syndrome

Microvascular thrombi and fibrin deposits are the hallmarks of ARDS.[42] Suppressed fibrinolysis is evidenced by increased levels of plasminogen activator inhibitor-1 in bronchoalveolar lavage in ARDS patients.[43] Gralinski *et al*. suggest that dysregulation of the urokinase pathway and blockade of plasmin activity by a2-plasmin inhibitor is the mechanism of ARDS in animal models of SARS.[44] Tissue plasminogen activator (tPA) has been used for the treatment of acute ischemic stroke, myocardial infarction, parapneumonic effusion, and empyema. Although current studies evaluating the therapeutic application of fibrinolytic agents in ARDS is still in the early preclinical stage, most of them have shown promising results.[45] Fibrinolytics can potentially be a therapeutic target in COVID-19 patients. Moore *et al*. recommends tPA as a novel treatment for refractory COVID-19 associated ARDS. They recommend a dose of 25 mg of tPA over 2 h followed by a 25 mg tPA infusion administered over the subsequent 22 h, with a dose not to exceed 0.9 mg/kg.[46]

Potential role of antiplatelet therapy

Antiplatelet therapy includes aspirin (cyclooxygenase inhibitor), clopidogrel, prasugrel, ticagrelor (P2Y12 inhibitors) and abciximab, eptifibatide and tirofiban (GPIIb/IIIa antagonist). Antiplatelet therapy has been shown to reduce mortality in patients with sepsis.[47] Some studies suggest that antiplatelet therapy is associated with reduced mortality and lower incidence of ARDS/ALI.[48,49] Based on existing findings, antiplatelet agents may be effective in improving outcomes in patients with COVID-19.

CONCLUSION

Coagulopathy is common in COVID-19 and coagulation markers (elevated D-dimer, prolonged PT, and thrombocytopenia) are indicators of poor outcomes. Early monitoring of coagulation markers in patients with COVID-19 can help stratify and identify patients at risk of worsening illness during hospitalization. This is of prime importance given the exponentially increasing number of cases and scarce healthcare resources. In COVID-19 patients with coagulopathy, prophylactic LMWH should be administered unless contraindicated. Therapeutic strategies targeting at restoring hemostasis might be useful in addressing this unprecedented, public health emergency.

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Conflicts of interest

There are no conflicts of interest.

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