Review Article

COVID-19 ASSOCIATED HYPERCOAGULABILITY: MANIFESTATIONS, MECHANISMS, AND MANAGEMENT

Michael A. Mazzeffi, Jonathan H. Chow, and Kenichi Tanaka

Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, Maryland

ABSTRACT—Patients with severe coronavirus disease-2019 (COVID-19) frequently have hypercoagulability caused by the immune response to the severe acute respiratory syndrome coronavirus-2 infection. The pathophysiology of COVID-19 associated hypercoagulability is not fully understood, but characteristic changes include: increased fibrinogen concentration, increased Factor VIII activity, increased circulating von Willebrand factor, and exhausted fibrinolysis. Anticoagulant therapy improves outcomes in mechanically ventilated patients with COVID-19 and viscoelastic coagulation testing offers an opportunity to tailor anticoagulant therapy based on an individual patient's coagulation status. In this narrative review, we summarize clinical manifestations of COVID-19, mechanisms, monitoring considerations, and anticoagulant therapy. We also review unique considerations for COVID-19 patients who are on extracorporeal membrane oxygenation.

CLINICAL MANIFESTATIONS OF COVID-19 ASSOCIATED HYPERCOAGULABILITY

The immune response to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection leads to coagulation system activation and hypercoagulability in many patients with coronavirus disease-2019 (COVID-19). Studies from France, the Netherlands, the United Kingdom, and the United States estimate a venous thromboembolism (VTE) incidence between 8% and 69% (Table 1) (1–10). Pulmonary embolism occurs in critically ill COVID-19 patients at twice the rate observed in influenza patients (10). Ninety percent of patients do not have evidence of deep venous thrombosis, suggesting that pulmonary embolism occurs *de novo* in most cases (10). Ischemic stroke, ST elevation myocardial infarction, and limb ischemia also occur and may be the heralding symptom (11–14).

Autopsies of COVID-19 patients have shown that SARS-CoV-2 causes endothelialitis and microvascular thrombosis (15). These changes result in hypoxemia if poorly ventilated lung regions become hyperperfused and intrapulmonary shunting occurs (16). Patient-specific risk factors for thrombosis have not been elucidated, but may include: total viral inoculum, magnitude of inflammation, and predisposing cardiovascular disease. Severity of illness is strongly associated with thrombotic risk and patients admitted to the intensive care unit (ICU) have a 5-fold higher incidence of VTE (8).

COVID-19 ENDOTHELIALITIS

Endothelial cells maintain normal vascular homeostasis and have been called the gatekeeper of vessel health (17). Endothelial cells modulate platelet activity, regulate inflammation, and maintain the physiologic barrier between intravascular and extravascular compartments (17). Endothelial cells normally express anticoagulant molecules including PGI_2 (prostacyclin), nitric oxide, tissue factor pathway inhibitor, and thrombomodulin (18). Under conditions of inflammation or stress, endothelial cells become altered and they express procoagulant molecules including thromboxane A_2, tissue factor, plasminogen activator inhibitor-1 (PAI-1), and Factor VIII.

Varga et al. first described endothelialitis in three patients who died from COVID-19. All patients showed histological signs of endothelial cell infection in the kidneys, lungs, intestine, and heart. Histologic analyses further demonstrated perivascular inflammation with lymphocytes and mononuclear cells (19). These findings were confirmed by Ackermann et al. (15) who found evidence of endothelial cell infection in the lungs of COVID-19 patients with a profound T cell response, which differed from influenza patients who had more of a neutrophil response.

LINK BETWEEN INFLAMMATION AND COAGULATION

Coagulation is an integral part of host immunity, isolating pathogens and preventing their replication. Humans have evolved a complex crosstalk between inflammation and coagulation. Interleukin-6 (IL-6), which is produced by macrophages,

Table 1. **Select studies of venous thromboembolism in COVID-19**

Author	Patient population	Thrombosis incidence	Notes
Artifoni et al. (1)	71 hospitalized patients France	22.5% incidence of any VTE 21% with DVT and 10% with PE	Strong association between D-dimer concentration and VTE Patients with D-dimer >3 ug/mL had over 60% incidence of VTE Higher incidence of mechanical ventilation and ICU admission in VTE patients All patients with VTE received prophylaxis with LMWH
Bompard et al. (2)	137 patients, 24 critically ill France	24% incidence of PE	All hospitalized patients received LMWH prophylaxis One-third of PEs proximal and two-third distal 20% of PE patients had associated right heart strain Median D-dimer concentration nine times higher in patients with PE
Desborough et al. (3)	66 critically ill patients United Kingdom	15% incidence of VTE 9% with DVT and 8% with PE	All thromboses were confirmed by ultrasound or CT Patients with VTE had longer ICU and hospital stay Major bleeding in 10.6% of patients, but five of seven patients with bleeding were on ECMO
Klok et al. (4)	184 critically ill patients the Netherlands	31% cumulative incidence of thrombosis over time PE was the most common type of thrombosis comprising 81%	Cohort was 76% male All patients received VTE prophylaxis, but regimen differed by hospital
Llitjos et al. (5)	26 critically ill patients France	69% incidence of VTE	Incidence of VTE significantly higher in patients receiving prophylactic versus therapeutic anticoagulation
Lodigiani et al. (6)	388 patients, 61 critically ill Italy	8% incidence of VTE	Half of VTEs detected within 24 h of admission All critically ill patients received prophylaxis with LMWH
Maatman et al. (7)	109 critically ill patients United States	28% incidence of VTE	58% had hypercoagulability on thromboelastography Median D-dimer two times higher in patients with VTE Troponin concentration significantly higher in patients with VTE
Middeldorp et al. (8)	198 hospitalized patients, 75 critically ill Netherlands	42% cumulative incidence of VTE at day 21 59% cumulative incidence in ICU patients	VTE associated with increased hazard of death; HR = 2.4 (95% CI = 1.02, 5.5) Patients with VTE required ICU admission more frequently All patients received prophylaxis with LMWH
Nahum et al. (9)	34 critically ill patients France	65% of patients had DVT at admission 79% had DVT within 48 h of admission	All patients in the cohort had Duplex examinations of both lower limbs performed 53% of patients had bilateral DVTs
Poissy et al. (10)	107 critically ill patients France	21% incidence of PE	Incidence of PE was twice as high in COVID-19 patients when compared with historical cohort of influenza patients 20 of 22 patients who had PE were receiving VTE prophylaxis

CI indicates confidence interval; COVID-19, coronavirus disease-2019; CT, computed tomography; DVT, deep venous thrombosis; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; ICU, intensive care unit; LMWH, low molecular weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism.

stimulates production of acute phase proteins including C-reactive protein and fibrinogen from the liver within 2 to 6 h (20). IL-6 and IL-1β increase PAI-1 expression through Janus kinase (JAK) signaling, and mitogen-activated protein kinase (MAPK) (21).

Inflammatory cytokines stimulate endothelial cells to release procoagulant molecules. Specifically, IL-8 and tumor necrosis factor-α (TNF-α) trigger the release of ultra-large von Willebrand factor (ULVWF) multimers from endothelial cells in a concentration-dependent manner (22). IL-6 soluble IL-6 receptor (sIL-6R) complex triggers release of ULVWF multimers from endothelial cells, but to a lesser extent than IL-8 or TNF-α (22). Conversely, IL-6, but not IL-8 or TNF-α, inhibits a disintegrin and metalloproteinase with thrombospondin type 1 motif member 13 (ADAMTS13), reducing ULVWF multimer cleavage and enhancing platelet adhesion and aggregation (22).

Neutrophils are a critical part of innate immunity and sIL-6R is shed from apoptotic neutrophils increasing the number of cells that can respond to IL-6 stimulation (23). Neutrophils trigger shedding of thrombomodulin in concert with TNF-α, which impairs activation of Protein C, an endogenous anticoagulant (24). Local TNF-α, IL-6, sIL-6R, and IL-8 levels are

TABLE 2. **Comparison of coagulation parameters in sepsis-induced coagulopathy and COVID-19**

Coagulation parameter	Sepsis-induced coagulopathy	COVID-19
Platelet count	Decreased in most patients	Normal in most patients
Factor VIII activity	Increased	Severely increased
Fibrinogen	Normal or decreased in most patients	Severely increased
Thrombin antithrombin complex	Increased	Increased
VWF antigen	Increased	Severely increased
Thromboelastometry (TEM)		
EXTEM clot formation time	Normal in most patients	Decreased in most patients
EXTEM maximum clot firmness	Normal or decreased in most patients	Increased in most patients
FIBTEM maximum clot firmness	Normal or decreased in most patients	Severely increased in most patients
Thromboelastography (TEG)		
Kinetic time	Normal in most patients	Decreased in most patients
Maximum amplitude	Normal or decreased in most patients	Increased in most patients

VWF indicates von Willebrand factor.

acutely elevated during inflammation, promoting coagulation and transmigration of immune cells.

COAGULATION CHANGES IN COVID-19

Some of the coagulation changes that occur in COVID-19 are similar to typical sepsis-induced coagulopathy, while others are distinct (Table 2) (25, 26). Figure 1 summarizes mechanisms contributing to hypercoagulability. Respiratory viral infection increases tissue factor expression on endothelial cells 4 to 5-fold, which activates the extrinsic pathway and enhances thrombin generation (27). Infected monocytes also express tissue factor, which synergistically drives thrombin generation (28). Coagulation is propagated through the intrinsic pathway and shutdown is overwhelmed because of high Factor VIII activity and depletion of endogenous anticoagulants including Protein C and antithrombin. The fibrinolytic system is activated by tissue plasminogen activator, urokinase plasminogen activator, Factor XIa, and Factor XIIa, but plasmin activity cannot keep pace with fibrin formation, as fibrinolysis inhibitors including plasminogen activator inhibitor-1 are increased during sepsis and appear to be unusually high with severe coronavirus infection (29).

Characteristic changes in coagulation that occur in critically ill COVID-19 patients include: severely elevated fibrinogen concentration (600 mg/dL–900 mg/dL), increased Factor VIII activity (>300% in many patients), increased thrombin-antithrombin complexes, and low-normal antithrombin and Protein C activity (30–33). Thromboelastometry (TEM) and thromboelastography (34) show decreases in clot formation time and kinetic time, as well as increases in maximum clot firmness (MCF) and maximum amplitude (MA) (Fig. 2). These tests provide a good screening tool to identify hypercoagulable patients, particularly when D-dimer is elevated (30, 35).

IMPLICATIONS OF ELEVATED D-dimer

Fibrinogen concentration reaches 600 mg/dL to 900 mg/dL in critically ill COVID-19 patients, whereas a normal value is 200 mg/dL to 400 mg/dL (30, 36, 37). Increased D-dimer occurs in parallel with hyperfibrinogenemia in many patients. Desborough et al. (3) described a series of 10 COVID-19 patients in the United Kingdom who had ultrasound or computed tomography confirmed VTE. The median D-dimer concentration was higher in patients with VTE compared with controls (69.1 mg/L vs. 2.1 mg/L). Ranucci et al. (36) showed reductions in fibrinogen from 780 mg/dL to 580 mg/dL and in D-dimer from 3.5 mg/L to 2.5 mg/L in an Italian cohort of COVID-19 patients who were treated with low-molecular weight heparin and clopidogrel, suggesting that hyperfibrinogenemia and reactive fibrinolysis may be modifiable.
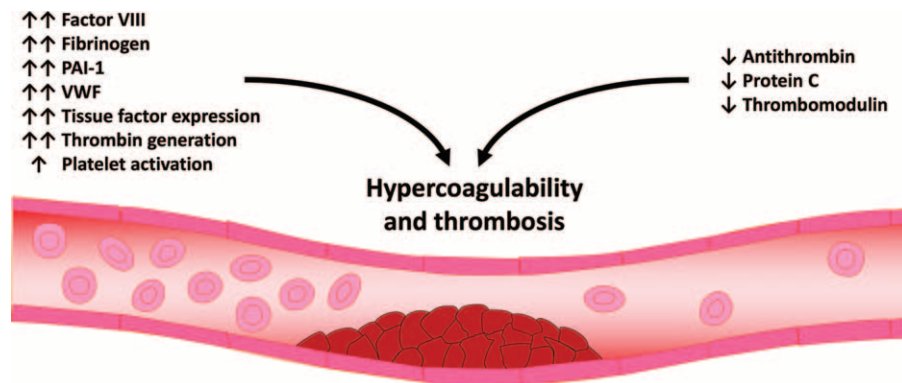

FIG. 1. **Figure shows a summary of the coagulation changes that occur in COVID-19.** Factor VIII activity, fibrinogen concentration, PAI-1, VWF, tissue factor expression, and thrombin generation are severely elevated in COVID-19. Platelet activation is also increased, while antithrombin, protein C, and thrombomodulin are decreased, leading to a hypercoagulable state and thrombosis in some patients. Figure created with Motifolio Toolkit (Motifolio Inc, Ellicott City, Md). PAI-1 indicates plasminogen activator inhibitor-1; VWF, von Willebrand factor; COVID-19, coronavirus disease-2019.
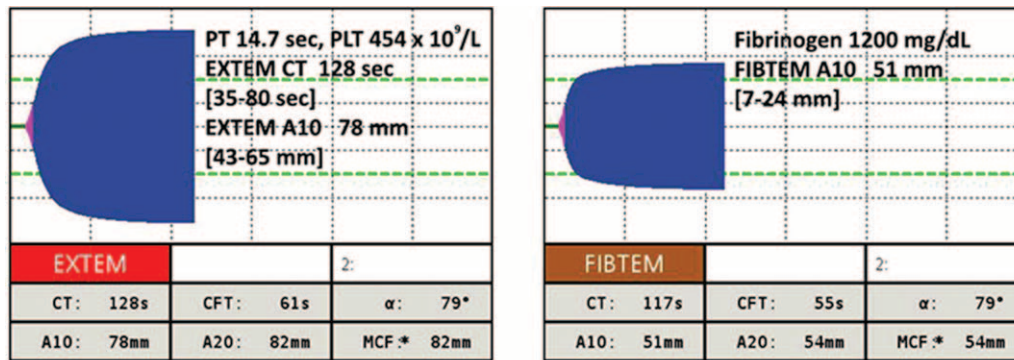
Fig. 2. **Figure shows thromboelastometry tracings from a critically ill patient with severe acute respiratory distress syndrome related to SARS-CoV-2 infection who was on extracorporeal membrane oxygenation.** The EXTEM and FIBTEM tracings show a slightly prolonged clotting time, but maximum clot formation on both EXTEM and FIBTEM is severely increased reflecting hypercoagulability. Normal ranges for tests are shown in brackets. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus-2.

D-dimer has become part of routine laboratory testing for critically ill COVID-19 patients and is considered a marker of disease severity. Zhang et al. reported that elevated D-dimer was a predictor of death in Chinese patients with COVID-19. In a study of 343 patients, there were 12 deaths in 67 patients who had an admission D-dimer ≥ 2.0 mg/L, and one death in 276 patients who had an admission D-dimer < 2.0 mg/L, hazard ratio $= 51.5$ (95% CI $= 12.9$–206.7; $P < 0.001$) (38). Notably, patients with elevated D-dimer were older and had more comorbidities including diabetes mellitus and cardiovascular disease, which were not controlled for adequately in the analysis. Similarly, Desborough et al. (3) found that patients who died were older (64 years vs. 55 years; $P = 0.01$) and were more likely to have diabetes mellitus and cardiovascular disease. There was a non-significant trend toward higher D-dimer (7.8 mg/L vs. 2.1 mg/L; $P = 0.28$) in patients who died, but the number of patients was relatively small limiting statistical power (3). Interestingly, COVID-19 patients do not consistently have signs of systemic fibrinolysis on viscoelastic coagulation testing (37, 39). Hence, D-dimer elevation is probably caused by both intravascular and extravascular fibrinolysis and impacted by the degree of lung injury, glomerular filtration rate, and baseline coagulation status.

COAGULATION ASSESSMENT IN COVID-19 PATIENTS

Viscoelastic coagulation testing offers a useful tool to identify hypercoagulable COVID-19 patients. TEM and TEG offer an advantage over traditional plasma-based coagulation tests, such as prothrombin time and activated partial thromboplastin time, which are normal in most patients with COVID-19 (30, 35, 36). TEM shows a reduced clot formation time (CFT), increased angle, and increased MCF in COVID-19 patients with hypercoagulability (35), while TEG shows a reduced kinetic time (K), increased angle, and increased MA (30). The increased MCF in COVID-19 patients is mainly due to increased fibrinogen concentration, as is shown by a markedly increased FIBTEM MCF (Fig. 2).

Enhanced primary hemostasis related to increased VWF release from endothelial cells is difficult to demonstrate with routine plasma-based coagulation tests, but is almost certainly a factor in COVID-19 associated hypercoagulability, as VWF antigen levels are increased five times above the upper limit of normal (30). One approach to monitor for hypercoagulability using commonly available laboratory tests is to measure fibrinogen concentration, Factor VIII activity, D-dimer, and viscoelastic coagulation parameters. In combination, these tests should demonstrate hypercoagulability in most COVID-19 patients, allowing for tailored anticoagulant therapy. Testing for antiphospholipid antibodies should also be considered for patients who demonstrate clinical signs of hypercoagulability (40).

ANTICOAGULANT THERAPY FOR COVID-19 PATIENTS

Anticoagulant therapy is associated with improved survival in critically ill COVID-19 patients and the benefit of anticoagulation is greatest when there is more coagulation system activation (41, 42). Two cohort studies, one from China and one from the United States, demonstrated a mortality benefit when critically ill COVID-19 patients received either prophylactic or therapeutic anticoagulation. In the largest cohort study from New York City, 786 of 2,773 patients received intravenous unfractionated heparin and survival was improved in patients on mechanical ventilation (n $= 395$) (41). In this study, a longer duration of anticoagulation was independently associated with a reduced risk of in-hospital death; hazard ratio $= 0.86$ per day, (95% CI $= 0.82$–0.89) and the incidence of serious bleeding was low at 3% (41).

The optimal degree of anticoagulation for critically ill COVID-19 patients is not known and it appears that VTE prophylaxis may not be adequate for a large proportion of patients. In one study of COVID-19 patients in the United States, up to 40% developed VTE, despite prophylaxis with unfractionated heparin or low molecular weight heparin (43). In a separate study of Italian patients, VTE prophylaxis with low molecular weight heparin was combined with antithrombin concentrate to keep antithrombin levels above 70% and clopidogrel when platelet count was above 400×10^9/L (44). This combination therapy leads to mitigation of hypercoagulability on viscoelastic coagulation testing (44). To our knowledge no

studies have compared the efficacy of prophylactic anticoagulation with therapeutic anticoagulation in critically ill COVID-19 patients.

Intravenous direct thrombin inhibitors may be beneficial in critically ill COVID-19 patients with hypercoagulability. Direct thrombin inhibitors bind to both circulating and clot-associated thrombin; whereas heparin–antithrombin complex binds only to circulating thrombin (45). Bivalirudin has a short half-life of approximately 25 min, which is prolonged when glomerular filtration rate is less than 30 mL/min and reaches 3 h when patients require renal replacement therapy (46). Argatroban has a half-life of approximately 45 min, but its half-life is prolonged in cases of acute hepatic dysfunction or cirrhosis (46). Novel oral anticoagulants are not typically used for treatment of critically ill COVID-19 patients because of their long half-lives, but they may be useful in the outpatient setting.

Other potential treatment options for COVID-19-associated hypercoagulability include: tissue plasminogen activator and recombinant thrombomodulin. In a case series of three critically ill COVID-19 patients with elevated D-dimer, tissue plasminogen activator treatment led to improved pulmonary gas exchange in all patients, with one patient having a durable response (47). A bolus of 25 mg was given over 2 h followed by a 22 h, 25 mg infusion (47). One patient had a 4-fold improvement in their P/F ratio after 11 h.

Thrombomodulin binds to activated thrombin and in concert with the endothelial protein C receptor coverts Protein C to activated Protein C. Recombinant thrombomodulin (Asahi Kasei Pharma Corporation, Tokyo, Japan) has been approved for treatment of disseminated intravascular coagulation in Japan since 2008, but is not currently available in the United States or Europe. In a recent meta-analysis that included over 1,600 patients from three randomized controlled trials, it was found to reduce mortality in patients with sepsis-induced coagulopathy, relative risk = 0.80 (95% CI = 0.65–0.98) (48). To our knowledge, there are no published reports of recombinant thrombomodulin use in critically ill COVID-19 patients, but there is a strong physiologic rationale for its use and bleeding risk is probably low because its anticoagulant action is thrombin dependent.

Aspirin would seem to be a logical treatment for COVID-19 because of its irreversible antiplatelet effects and beneficial effects in patients with cardiovascular disease. Thrombocytopenia is uncommon in COVID-19 and aspirin reduces platelet neutrophil aggregates in the lung (30, 49). Aspirin also reduces IL-6 production, which may mitigate cytokine storm (50). At present, there are no studies to support aspirin's efficacy in COVID-19, but it is widely available, has a well-described risk profile, and is unlikely to cause major bleeding in patients without prior gastro-intestinal disease. Future studies will be needed to determine whether aspirin is a useful adjunctive treatment.

SPECIAL CONSIDERATIONS FOR EXTRACORPOREAL MEMBRANE OXYGENATION

COVID-19 patients who require extracorporeal membrane oxygenation (ECMO) deserve special consideration in terms of anticoagulation because many of the coagulation changes that occur with COVID-19 are exacerbated by ECMO. For example, patients on ECMO have increased Factor VIII activity and fibrinogen concentration, as well as supra-normal thrombin generation when they are not anticoagulated (51). COVID-19 patients who require ECMO have been noted to be hypercoagulable, requiring frequent circuit and oxygenator changes. In one report of 12 veno-venous ECMO patients, four patients had thrombotic complications during cannulation, two of which led to death (52). In addition, two other patients had cannula thrombosis, one of which required emergent cannula exchange (52). For this reason, many centers use high intensity heparin protocols for COVID-19 patients on veno-venous ECMO.

Exposure of blood to centrifugal pumps and high shear stress leads to loss of large VWF multimers and platelet GP1bα receptor shedding, which causes abnormal primary hemostasis in ECMO patients and excessive bleeding during tissue injury (53–55). These changes, along with the use of higher anticoagulation targets in COVID-19 patients on ECMO, create a high risk for excessive bleeding during bedside procedures (e.g., chest drain insertion) or major surgical procedures. COVID-19 patients are at particularly high risk for airway bleeding and hemothorax given the severe tissue damage that occurs in the lungs. Given these complexities, we recommend an individualized, tailored approach to anticoagulation in COVID-19 patients on veno-venous ECMO. Hypercoagulability should be assessed using TEM or TEG, when available, and patients who are hypercoagulable should receive high intensity systemic anticoagulation with heparin or a direct thrombin inhibitor. Alternatively, patients with thrombocytopenia during ECMO and a low or normal MCF or MA might be better served with low intensity anticoagulation.

CONCLUSIONS

Coagulation system activation is common in critically ill COVID-19 patients. Severity of illness is associated with the degree of coagulation system activation and patients with chronic cardiovascular diseases appear to have a predilection for hypercoagulability and organ failure. Some studies suggest that hypercoagulability during COVID-19 is modifiable offering an opportunity for intervention. Given the widespread availability of viscoelastic coagulation testing, anticoagulant therapy can be tailored for individual patients based on these tests. In critically ill COVID-19 patients, the risk for serious bleeding appears to be low; however, patients on ECMO represent an exception to this rule because of derangements in primary hemostasis. As greater experience is gained in caring for critically ill COVID-19 patients, there will be a better understanding of which patients are likely to benefit from high intensity anticoagulation and adjunctive therapies like low dose TPA, antiplatelet drugs, and perhaps recombinant thrombomodulin.

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