Coagulopathy of Coronavirus Disease 2019

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Objectives: Recent studies have reported a high prevalence of thrombotic events in coronavirus disease 2019. However, the significance of thromboembolic complications has not been widely appreciated. The purpose of this review is to provide current knowledge of this serious problem.

Design: Narrative review.

Data Sources: Online search of published medical literature through PubMed using the term “COVID-19,” “SARS,” “acute respiratory distress syndrome,” “coronavirus,” “coagulopathy,” “thrombus,” and “anticoagulants.”

Study Selection and Data Extraction: Articles were chosen for inclusion based on their relevance to coagulopathy and thrombosis in coronavirus disease 2019, and anticoagulant therapy. Reference lists were reviewed to identify additional relevant articles.

Data Synthesis: Coronavirus disease 2019 is associated with a strikingly high prevalence of coagulopathy and venous thromboembolism that may contribute to respiratory deterioration. Monitoring coagulation variables is important, as abnormal coagulation tests are related to adverse outcomes and may necessitate adjuvant antithrombotic interventions. In the initial phase of the infection, d-dimer and fibrinogen levels are increased, while activated partial prothrombin time, prothrombin time, and platelet counts are often relatively normal. Increased d-dimer levels three times the upper limit of normal may trigger screening for venous thromboembolism. In all hospitalized patients, thromboprophylaxis using low-molecular-weight heparin is currently recommended. The etiology of the procoagulant responses is complex and thought to be a result of specific interactions between host defense mechanisms and the coagulation system. Although the coagulopathy is reminiscent of disseminated intravascular coagulation and thrombotic microangiopathy, it has features that are markedly distinct from these entities.

Conclusions: Severe acute respiratory syndrome coronavirus 2/ coronavirus disease 2019 frequently induces hypercoagulability with both microangiopathy and local thrombus formation, and a systemic coagulation defect that leads to large vessel thrombosis and major thromboembolic complications, including pulmonary embolism in critically ill hospitalized patients. d-dimers and fibrinogen levels should be monitored, and all hospitalized patients should undergo thromboembolism prophylaxis with an increase in therapeutic anticoagulation in certain clinical situations. (Crit Care Med 2020; 48:1358–1364)

Key Words: coagulopathy; coronavirus; coronavirus disease 2019; disseminated intravascular coagulation; hypercoagulability; thromboembolism

Increasing communications worldwide have reported that hospitalized, critically ill coronavirus disease 2019 (COVID-19) patients are frequently developing laboratory abnormalities compatible with hypercoagulability and clinically a high prevalence of thromboembolic events (1). In addition to deep vein thrombosis (DVT) and pulmonary embolism (PE), thrombosis in extracorporeal circuits and arterial thrombosis have been reported (2). Patients with COVID-19 often present with dyspnea, hypoxemia, and hemodynamic instability with acute respiratory distress syndrome (ARDS), and in such clinical condition, venous thromboembolism (VTE) may be overlooked (3, 4). Standard imaging in critically ill patients utilizing contrast-enhanced CT may not always be feasible, and additionally, concerns exist with disease transmission to health-care staff.

Ranucci et al (5) recently reported comprehensive coagulation analyses including d-dimers, fibrinogen levels, and viscoelastic testing in the COVID-19 patients with ARDS, and reported the procoagulant profile on ICU admission with median d-dimer levels of 5.5 mg/L (10 times the upper limit of normal), fibrinogen levels of 7.8 g/L, and increased clot strength by thromboelastometry. Panigada et al (6) performed a similar analysis and also noted increased fibrinogen levels, enhanced platelet activation, and increased viscoelastic variables. Beyond

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VTE, the relevance of microthrombus formation to organ dysfunction and acro-ischemic change has also been suggested (7–9). Although the number of postmortem pathologic reports are limited, Luo et al (10) described vascular wall thickening, stenosis of the vascular lumen, and microthrombus formation accompanying the findings of ARDS. Similar pathologic findings are found in small vessels of other organs (8–11). Magro et al (12) reported the deposition of C5b-9 (membrane attack complex), C4d, and mannose-binding lectin-associated serine protease-2 in the lung capillaries and the skin microvasculature. Notably, the deposition was co-localized with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein. A recent report also noted mononuclear and polymorphonuclear leukocyte infiltration and pulmonary microcirculation along with apoptosis as induced by caspase 3 staining (13).

In critically ill COVID-19 patients, there appear to be at least two separate pathologic coagulation pathologic processes that are important in producing clinical manifestations. In the microcirculation of the lung and potentially other organs, there is local direct vascular and endothelial injury producing microvascular clot formation and angiopathy (13, 14). Post mortem biopsy of the lung revealed mononuclear and polymorphonuclear infiltration along with apoptosis of endothelial and mononuclear cells (13). In the systemic circulation, due to hypercoagulability with hyperfibrinopenemia, there is also the potential for large vessel thrombosis and major thromboembolic sequelae including PE that is reported in 20–30% of ICU patients (15–17) (Fig. 1). Because of the important role of coagulation activation in critically ill COVID-19 patients, this review summarizes the current knowledge about the coagulopathy and role of anti-coagulation in these patients.

**PREVALENCE OF COAGULOPATHY AND DISSEMINATED INTRAVASCULAR COAGULATION**

Coagulopathy is a common feature of SARS-CoV-2 infection, and an increase in d-dimer is the most common finding. One of the larger initial studies found abnormally elevated d-dimer levels in 260 of 560 cases (46.4%) with a prevalence of 43% in nonsevere patients compared with 60% in critically ill ICU patients (18). In another series, elevated d-dimers were associated with a poor prognosis (19). More recently, Zhang et al (20) examined 343 cases and showed that d-dimer levels of over 2.0 mg/L could predict mortality with a sensitivity of 92.3% and a specificity of 83.3%. Tang et al (21) reported increased d-dimers and fibrin degradation products along with mildly to moderately increased prothrombin times (PTs) and activated partial thromboplastin times (aPTT) in COVID-19. Of note is they reported that 71.4% of nonsurvivors fulfilled the criteria of sepsis-induced coagulopathy, while 0.6% of the survivors met the criteria.

Platelet counts in COVID-19 patients are variable depending on the reported studies. A meta-analysis reported significantly lower platelet counts in critically ill COVID-19 patients with weighted mean difference of −31 × 10^9/L (95% CI, −35 to −29 × 10^9/L), and thrombocytopenia defined as below the lower limit of the range was associated with more than fivefold higher risk of severe disease, which may reflect secondary infections (22). However, as noted above, thrombocytopenia is not a significant finding initially in COVID-19 (23). Huang et al (24) reported platelet counts of less than 100 × 10^9/L in only 8% of ICU and 4% in non-ICU patients initially at admission. Yin et al (25) compared the platelet count between COVID-19–associated ARDS patients and non-COVID-19 ARDS patients and reported minor clinical differences in platelet counts (215 ± 100 vs 188 ± 98 × 10^9/L). The lack of thrombocytopenia reflects that this is not a consumptive coagulopathy typical of disseminated intravascular coagulation (DIC). The potential for increases in platelet counts in COVID-19 patients is suspected to be caused by increased proinflammatory cytokines such as interleukin (IL)-1β and IL-6 produced by the macrophages and monocytes in the lung (26), and activated platelets may contribute to the lung injury (27). Interestingly, only 6.4% of COVID-19 patients who died met DIC criteria of the International Society on Thrombosis and Haemostasis (ISTH) (28). More recent data suggests the COVID-19

**Figure 1.** Various types of thrombus formation in coronavirus disease 2019 (COVID-19). Venous thrombosis and pulmonary thromboembolism are common complications in COVID-19. Increased fibrinogen and factor VIII, activated coagulation, direct viral endothelial infection and endothelial injury, and increased platelet-vessel wall interaction activation play roles in the development of thrombotic complications. In addition, there may be pulmonary microvascular coagulation in COVID-19. The prevalence of arterial thrombosis is also high and involvement of antiphospholipid antibodies has been suggested.
coagulopathy is different from common bacterial infection-induced DIC with relatively minimal changes in platelet counts, antithrombin levels, PT, and aPTT (21, 29).

The association with increased microvascular thrombosis, increased levels of lactate dehydrogenase (LDH) and ferritin, and mild increases in PT and aPTT are reminiscent of thrombotic microangiopathy (30). Although thrombocytopenia and hemolytic anemia are uncommon in COVID-19, clinical presentations of increased D-dimers, vascular endothelial injury, and multiple organ damage are also common features of atypical hemolytic uremic syndrome (12).

**CHANGES IN COAGULATION AND FIBRINOLYSIS**

The coagulation cascade is activated in viral infections as a host defense to limit the spread of the pathogens (31). Initially, an adaptive hemostasis response occurs that is associated with a systemic inflammatory response. As a result of increased inflammatory activity, fibrinogen is significantly increased, and thrombin generation occurs (32). The enhanced cytokine production during virus infection also stimulates additional procoagulant reactions, with increased tissue factor expression, a major initiator of the activation in coagulation. However, other factors such as phosphatidylserine on the cellular membrane, neutrophil extracellular traps, and damage-associated molecular patterns (DAMPs) may also be involved in the procoagulant profile in COVID-19 (33). In some cases, the presence of antiphospholipid antibodies that can induce arterial thrombosis is reported (2), and the relevance to stroke and acute coronary disease should be examined in future studies.

There is an association between bronchoalveolar coagulation/fibrinolysis and the pathogenesis of ARDS that enhances intrapulmonary deposition of fibrin (34). In cases of bacterial infection, measurement of coagulation and fibrinolysis factors in bronchoalveolar lavage fluid (BALF) have demonstrated enhanced intrapulmonary thrombin generation, insufficiently balanced physiologic anticoagulation, and suppressed fibrinolysis mediating the pathogenesis of ARDS (35). In COVID-19, procoagulant activity is increased through tissue factor pathway, and plasmin activity suppressed by the reduced urokinase-type plasminogen activator and increased plasminogen activator inhibitor-1 (36, 37). By contrast, Ji et al (38) reported activated plasmin and increased fibrinolytic activity resulting in D-dimer elevation in COVID-19 and reported that the preexisting increased plasmin activity recognized in hypertension, diabetes, and cardiovascular disease enhances the virulence and infectivity of the SARS-CoV-2 virus by cleaving its spike proteins. The pathologic findings of ARDS in COVID-19 suggest the inflammation and diffuse alveolar damage with exudates that mimic sepsis-induced ARDS are lymphocyte predominant (39).

Gattinoni et al (40) hypothesized that there are two distinct types of lung damage in ARDS. Type-L is characterized by the low elastance and high compliance, which is rarely seen in ARDS, while type-H shows high elastance and low compliance that is the typical style of ARDS. They explain the primary cause of hypoxemia in type-L is perfusion defects presumably caused by vasoconstriction and high shunt fraction. In contrast, the high elastance in type-H is thought to be induced by lung edema. We hypothesize that the intravascular coagulation and clot formation, in addition to the vasoconstriction, contribute to the disturbance of perfusion. The findings as mentioned above suggest that the procoagulant changes are present in both intra-alveolar and intravascular spaces (Fig. 2). Indeed, Dolhnikoff et al (41) reported the fibrinous thrombi in pulmonary artery in areas of both damaged and preserved lung parenchyma. The endothelial damage in the pulmonary capillary is also accelerated by the vascular endothelial damage. SARS-CoV-2 infects endothelial cells through an angiotensin-converting enzyme 2 receptor (42); the rapid viral replication causes massive endothelial cell apoptosis and triggers the loss of anticoagulant function of the vascular lumen. In addition to the derangement of coagulation/fibrinolysis and platelet function, endothelial dysfunction contributes to the procoagulant change in COVID-19 (Fig. 3).

**INFLAMMATORY THROMBUS, MICROCIRCULATORY INJURY, AND ORGAN DYSFUNCTION**

Various proinflammatory cytokines are known to be elevated in COVID-19, and a "cytokine storm" is estimated to be relevant in the progression and modification of the disease. Tumor necrosis factor-α, IL-1β, IL-6, interferon-γ, and granulocyte-macrophage colony stimulating factor are the representative cytokines that mediate inflammation and coagulation. Elevation in the circulating blood cytokine levels is also increased in the lung. Xiong et al (43) revealed increased levels of chemokines such as monocyte chemotactic protein 1 (MCP-1), interferon-inducible protein-10, macrophage inflammatory protein-1α in the BALF obtained from COVID-19 patients. This cytokine storm leads to the systemic intravascular coagulation, multiple organ dysfunction syndrome (MODS), and fatal outcome (9). Indeed, Cao et al (44) integrated data obtained from more than 46,000 COVID-19 cases, and reported that the prevalence of ARDS was 28.8%, that of MODS was 8.5%, and the fatality rate was 6.8%. Therefore, the regulation of the overproduced cytokines is a focus of treatments targeting suppression of IL-1 family and IL-6 currently in trials (26). The multiple inflammatory mediators also can produce microcirculatory injury and thrombus formation. In the postmortem evaluation of COVID-19 pulmonary tissues, the arterial vessels demonstrated neutrophilic and mononuclear cellular infiltration, and apoptosis of endothelial cells and mononuclear cells based on caspase 3 immunostaining (13).

Mehta et al (45) reported that severe COVID-19 resembles hemophagocytic lymphohistiocytosis (HLH) most frequently triggered by viral infection, a clinical scenario with uncontrolled cytokine production and typically presentation of fever, splenomegaly, cytopenia of two or more lineages, increased ferritin, low fibrinogen level, and MODS, including ARDS (46, 47). Chest radiographic findings in HLH include bilateral
ground-glass opacities and consolidation that are similar to COVID-19. In laboratory testing, hyperferritinemia and high LDH levels are common, but low fibrinogen levels and cytopenias of more than two cell lineages by hemophagocytosis are not reported in COVID-19. Taken together, it may be reasonable to think that the pathophysiology of COVID-19 overlaps with low-grade HLH, and the differences and similarities of HLH and COVID-19 should be examined in future studies.

VENOUS THROMBOEMBOLISM AND PULMONARY EMBOLISM

Immobilization, inflammation, activated coagulation, and suppressed fibrinolysis increase the risk of VTE and PE. Increasing reports have indicated an increased risk of VTE and PE in COVID-19 (1, 48). Cui et al (49) examined thrombosis in nonsymptomatic lower limbs by ultrasonography in COVID-19 pneumonia patients treated in ICU and reported that the prevalence was 25% (20/81). In another study in SARS-CoV-1 infected patients, it was reported that 20.5% of patients had DVT, and 11.4% had PE (50). Klok et al (15) studied 184 ICU patients and confirmed VTE in 27% and arterial thrombotic events in 3.7% patients. It should be kept in mind that the prevalence of VTE and PE is underestimated since the access to contrast-enhanced CT may be limited in critically ill patients for practical reasons. D-dimer levels can also not accurately differentiate between the presence of thrombosis and high levels due to the critical illness state. Therefore, all critically ill patients should receive VTE prophylaxis, preferably using low-molecular-weight (LMW) heparin regardless of their D-dimer level. In case of sudden deterioration, increased oxygenation requirements, right heart failure, and/or shock, a very high suspicion for PE should be maintained (51).

COAGULATION DISORDERS OF SARS-COV-2 INFECTION IN PREGNANCY

The effect of SARS-CoV-2 infection on pregnancy is not clear, and Liu et al (52) reported pregnancy and childbirth did not aggravate the course of COVID-19 pneumonia in the small case study (15 cases). However, Dashraath et al (53) suggested that 2% of pregnant women will require mechanical ventilation, 9% will have fetal growth restriction, and 43% will deliver preterm. In addition, since there are changes in coagulation/fibrinolysis that occur naturally during pregnancy, with hyperfibrinogenemia, there are considerable concerns for the risk of pregnant patients for thrombotic complications and coagulopathy. ISTH released an interim guideline for the management of COVID-19–associated coagulopathy and DIC in pregnant women (54), and this guidance recommends: admission of any patients with markedly raised D-dimer, prolonged PT, platelet count less than 100 × 10^9/L, or fibrinogen less than 2 g/L, even in absence of other concerns, with the consideration for the use of prophylactic LMW heparin in all patients who require hospital admission in the absence of contraindications.

COAGULATION DISORDER IN CANCER PATIENTS

Patients with cancer are more susceptible to SARS-CoV-2 infection due to immunosuppression, poor nutrition,
comorbidities, and immobilization (55). COVID-19 affected cancer patients require specific attention as they are prone to thromboembolic complications, and thromb prophylaxis is mandatory. However, evidence on the clinical course of COVID-19 in cancer patients is scarce so far, and more studies are warranted.

TREATMENT WITH ANTICOAGULANTS

Heparin for VTE Prevention

ISTH interim guidance recommends the use of prophylactic LMW heparin in severe COVID-19 patients (51). The effect of heparin, mainly LMW heparin, is reported by Tang et al (56) showing a reduced mortality in cases with coagulopathy and treated with heparin compared with the patients who did have coagulopathy and were not treated with heparin (40.0% vs 64.2%, respectively; \( p = 0.029 \)). In the same study, increasing levels of d-dimer were related to increasing mortality in non-heparin treated patients. Heparin exhibits anti-inflammatory effects by neutralizing DAMPs to protect the endothelial cells by reducing the toxicity of histones on endothelial tight junctions, and decrease lung edema and vascular leakage (57, 58). Regarding the type and dose of heparins, we summarize the current recommendation in Table 1. Caution is required for the application of the treatment dose of heparins. The overall effectiveness is still under debate (59).

Anticoagulant Therapies for Inflammatory Thrombus Prevention

In addition to VTE prevention, anticoagulant therapy may also have anti-inflammatory effects. Glas et al (34) proposed the administration of anticoagulants such as antithrombin and activated protein C for the treatment of classical ARDS. Others have suggested therapies to reverse pulmonary microthrombi in ARDS with tissue plasminogen activator; however, supporting evidence in humans is currently unavailable (60, 61).

Antiplatelet Therapies

Although platelets may be involved in the local and systemic thrombotic response in COVID-19 coagulopathy, adding a platelet inhibitor to unfractionated heparin or LMW heparin at therapeutic doses would increase the potential for risk for bleeding. This is a known phenomenon in acute coronary syndromes where anticoagulant therapy along with antiplatelet therapy may decrease arterial thrombosis, but it is associated with increased bleeding risk that also increases adverse events and most P2Y12 inhibitors have long half-lives without the availability of any reversal agent (62). Further, platelet function testing is cumbersome, and research studies on platelet activation biomarkers are still premature. The microvascular thrombosis, DVT, and pulmonary artery thrombosis appear to be due to abnormally elevated coagulation factor levels and the absence of the usual protective effects of the vascular endothelium. The role of platelet activation in this process is less well defined and not clearly implicated.

SUMMARY

SARS-CoV-2/COVID-19 frequently induces hypercoagulability with inflammation driving increased levels of procoagulant clotting factors and disruption of the normal

### Table 1. Dosing Recommendations for Unfractionated and Low-Molecular-Weight Heparins

| Drug                   | Prophylaxis          | Treatment                  |
|------------------------|----------------------|-----------------------------|
| Dalteparin (subcutaneously) | 5,000 IU once daily | 200 U/kg daily              |
| Enoxaparin (subcutaneously) | 40 mg once daily    | 1 mg/kg bid                 |
| Nadroparin (subcutaneously) | 2,850 IU once daily | 171 IU/kg once daily        |
| Tinzaparin (subcutaneously) | 4,500 IU once daily | 175 IU/kg once daily        |
| Unfractionated heparin | 5,000 units twice/three times a day (subcutaneously) | IV titrated to target laboratory values |

IU = international units.
homeostasis of vascular endothelial cells resulting in microangiopathy, local thrombus formation, and a systemic coagulation defect leading to large vessel thrombosis and major thromboembolic complications including PE in critically ill hospitalized patients. In patients with infection-induced coagulopathies, a critical component of management is treating the underlying disease. In COVID-19, because we currently do not have a standard antiviral therapy, we believe some of the unique microvascular and macrovascular hypercoagulability clinician are observing represent thromboinflammatory responses to the continuing infection. As a result, sequential monitoring of coagulation tests every 2–3 days is recommended. Surveillance for development of VTE is important with heightened suspicion in patients with sudden decompensation not attributable to other factors. All hospitalized patients should receive VTE prophylaxis; higher than conventional doses of LMW heparin are currently being investigated in clinical trials, although many centers have adopted escalated or intermediate doses for VTE prophylaxis. Whether anticoagulation alone is sufficient to prevent these thrombotic events, especially those driven by endothelial dysfunction, is unknown. Additional strategies and studies to address all factors that result in microvascular and macrovascular thrombosis are needed.

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