COVID-19 and Implications in Hemostasis and Viscoelastic Testing

What is COVID-19?

Coronavirus Disease 2019 (COVID-19) is an infection caused by the novel coronavirus, SARS-CoV-2, and is characterized by flulike symptoms, such as fever and cough. Some patients may develop dyspnea, tachypnea and/or pneumonia with disturbed gas exchange.[1] In severe cases, the disease may lead to acute respiratory distress syndrome (ARDS), sepsis and multiorgan failure.[2]

COVID-19 severity can be classified as mild, moderate, severe or critical.[3–5]

Classification	Symptoms
Asymptomatic	None
Mild	Mild clinical symptoms and no signs of pneumonia
Moderate	Fever and respiratory symptoms
Severe	Patients with any of the following: respiratory distress with respiratory rate ≥30 breaths/min, SpO2 ≤93% at rest, PaO2/FiO2 ≤300 mm Hg (mmHg = 0.133 kPa)
Critical	Patients with any of the following: respiratory failure requiring mechanical ventilation, shock or other organ failure requiring admission to Intensive Care Unit (ICU)

Comorbidities and COVID-19

Patients with certain comorbidities may be at higher risk for severe SARS-CoV-2 infection. The following disorders have been shown to be associated with increased COVID-19 severity.[6]

- Hypertension
- Cerebrovascular disease
- Diabetes
- Chronic obstructive pulmonary disease
- Cardiovascular disease

The information in this document is accurate as of posting time. However, as the situation surrounding COVID-19 continues to evolve, it's possible that some data will have changed since publication. While IL is trying to keep COVID-19 content as up to date as possible, we also encourage readers to stay informed on news and recommendations by referencing guidelines published by the ISTH, ASH, CDC, and WHO and consulting with local healthcare authorities.

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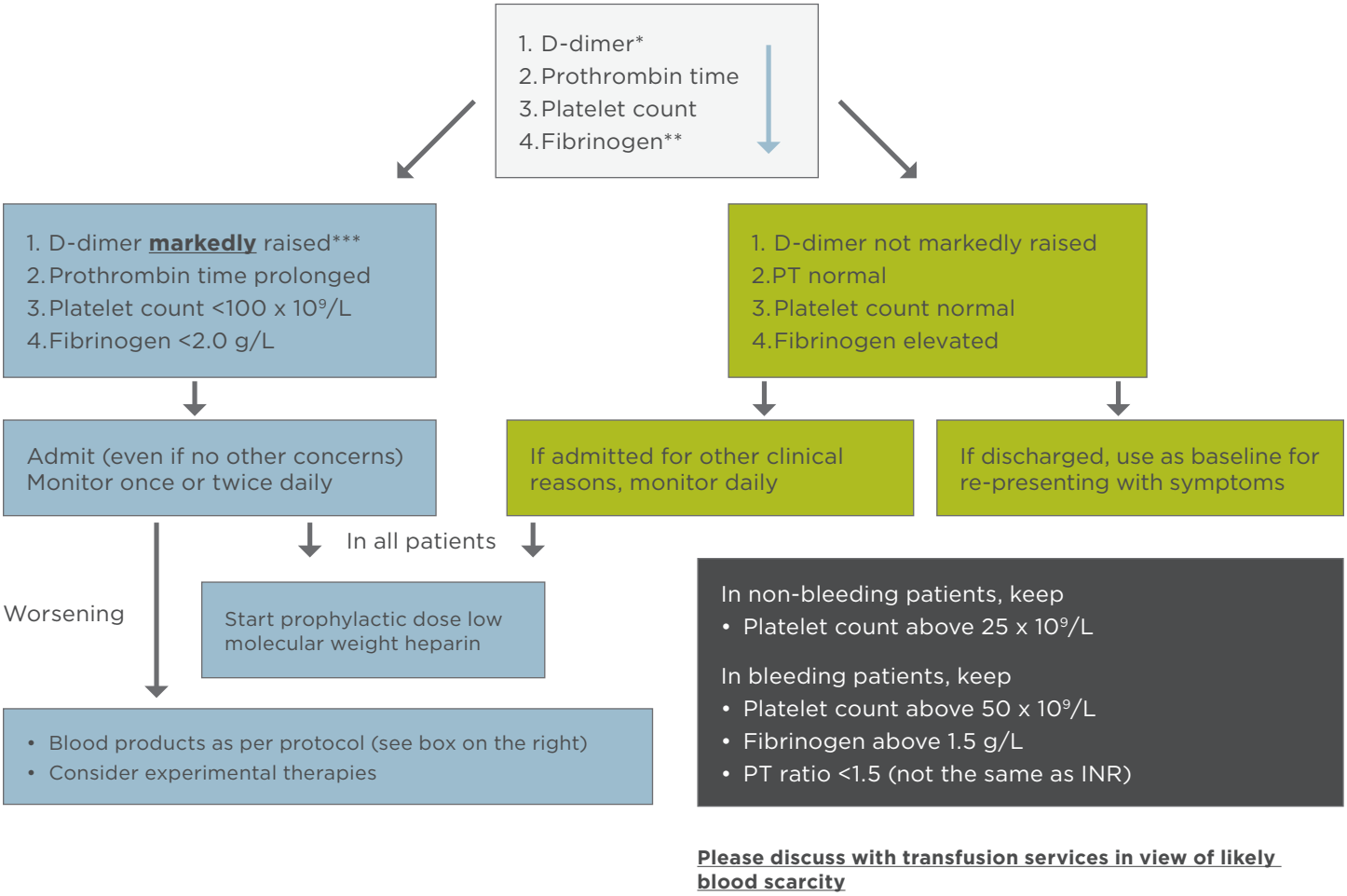
COVID-19 and Hemostasis

Early reports indicate that patients with COVID-19 may develop abnormalities in hemostasis laboratory testing.[5,7,8] In a recent meta-analysis, elevations of D-dimer were reported in 20.4% of COVID-19 patients.[9] These abnormalities have subsequently been correlated with disease severity and outcomes including mortality.[10–23] Moreover, thrombotic complications including venous thromboembolism (VTE) have been reported in 16–42.7% of patients with COVID-19.[24–26] The pathogenesis of the coagulopathy associated with COVID-19 is an area of active investigation. Preliminary hypotheses suggest hyperinflammation and associated immunothrombosis may be responsible.[27–29]

Role of Hemostasis Testing in Coagulopathy and COVID-19

Hemostasis testing provides important information for the management of COVID-19, especially in severe cases. The International Society on Thrombosis and Haemostasis (ISTH) "interim guidance on recognition and management of coagulopathy in COVID-19" recommends the use of hemostasis assays, D-dimer, prothrombin time (PT), platelet count and fibrinogen to assess prognosis in COVID-19 patients who require admission.[30]



Algorithm for the management of coagulopathy in COVID-19 based on simple laboratory markers.

*The list of markers is given in decreasing order of importance.

**Performing fibrinogen assays may not be feasible in many laboratories but monitoring the levels can be helpful after patient admission.

***Although a specific cut-off cannot be defined, a three- to four-fold increase in D-dimer values may be considered significant. Any one of the values in this table may be considered significant.

Figure 1 Adapted from: Thachil J, Tang N, Gando S, *et al.* ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost.* 2020;18(5):1023–6. doi:10.1111/jth.14810.

Impact of COVID-19 on Hemostasis Markers

Publications have reported the following changes in hemostasis assays in patients with COVID-19:

Assay	COVID-19 impact
APTT	Normal[7, 9, 11, 16–20, 26, 31–36]
PT	Normal to ↑[7, 9, 11, 16–20, 26, 31–36]
Thrombin Time	Normal to ↑[11, 33]
Fibrinogen	↑↑[11, 17, 18, 20, 26, 32, 34–36]
Platelet Count	↓[37, 38]
D-Dimer	↑↑↑[7, 9, 11, 13–20, 26, 31–36, 39–41]
FDP	↑↑[11, 18, 32]
Antithrombin	Normal to ↓[11, 26, 32, 34–36]
Protein C	Normal to ↑[36]
Free Protein S Antigen	Normal to ↓[11, 32, 34–36]
Factor V Activity	Normal[26]
Factor VIII Activity	↑↑[26, 36, 42]
VWF:Act, VWF:Ag or VWF:RCo[15]	Normal to ↑↑[26, 36, 42]
Lupus Anticoagulant	Normal to Present[26, 43–46]
Anti-Cardiolipin IgA/IgM/IgG	Normal to ↑[43, 47]
Anti-β_2 Glycoprotein I IgA/IgM/IgG	Normal to ↑[43, 47]
ADAMTS13 Activity	Normal to ↓[11, 32, 34–36, 42]

APTT = activated partial thromboplastin time
FDP = fibrin degradation products
VWF:Act: von Willebrand Factor Activity
VWF:Ag: von Willebrand Factor Antigen
VWF:RCo: von Willebrand Factor Ristocetin Cofactor Activity

Viscoelastic Testing

Early reports also suggest hypercoagulability in patients with COVID-19, defined by short clot formation times and increased clot firmness from viscoelastic testing.[34–36, 48, 49] In addition, there has not been evidence of secondary hyperfibrinolysis, supporting severe hypercoagulability, rather than a consumptive coagulopathy as part of the pathogenesis of SARS-CoV-2 infection.[48] These preliminary findings indicate that viscoelastic testing may have a role in the rapid identification of patients with severe COVID-19. Moreover, viscoelastic testing may have clinical utility in assessing a patient's response to anticoagulant therapy.

Thrombotic Complications of COVID-19 and Anticoagulation Therapy

Several studies have demonstrated a high incidence (16–43%) of thrombotic complications in COVID-19 patients[24], including:

- VTE
- Thrombosis of extracorporeal circuits (*e.g.,* extracorporeal membrane oxygenation, continuous renal replacement therapy)
- Central venous catheter-associated thrombosis

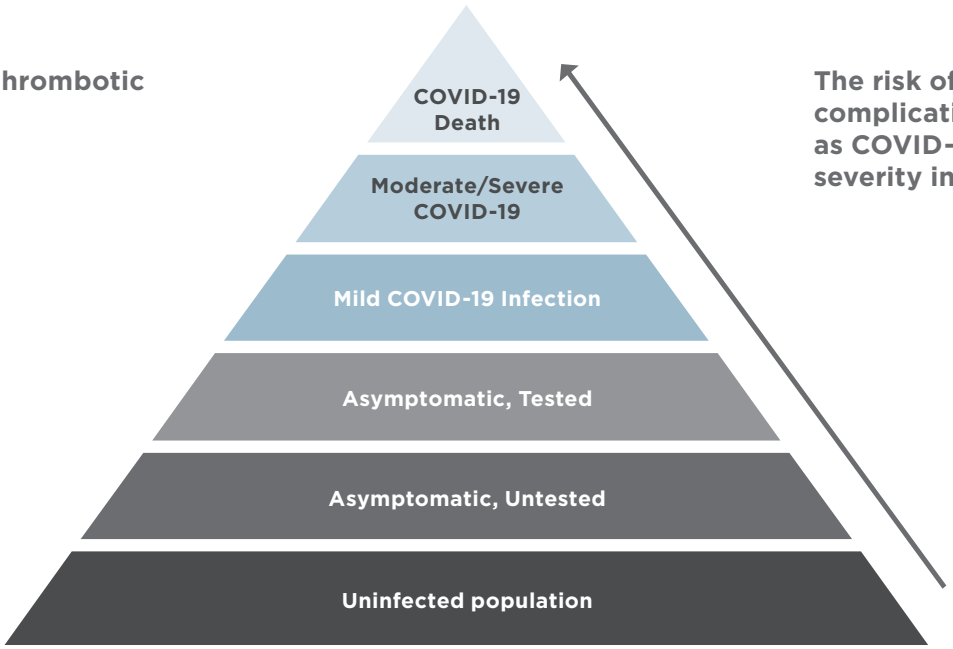
These thrombotic complications occurred, despite prophylactic or therapeutic anticoagulation, and were more likely to occur in critically ill COVID-19 patients. Despite this apparent failure of anticoagulation therapy in some patients, early studies indicate that the use of low molecular weight heparin (LMWH) is associated with reduced mortality in COVID-19 patients with coagulopathy.[50]

Current recommendations advise treating all hospitalized COVID-19 patients with standard-dose LMWH, unfractionated heparin (UFH) or fondaparinux for VTE prophylaxis, unless contraindicated (*e.g.*, bleeding, thrombocytopenia).[1, 3, 51–53] The use of intermediate dose LMWH should be considered for patients with multiple risk factors for VTE (*e.g.,* immobilization, obesity, history of VTE).[1]

Elevated FVIII activity and the presence of lupus anticoagulants make using APTT for heparin monitoring challenging. Thus, use of an anti-Xa assay to monitor UFH therapy in these patients is recommended.[3] Heparin-induced thrombocytopenia (HIT) is a risk in all patients on heparin therapy. Regular monitoring and 4T scores should be assessed and if HIT is present, patients should be converted to a non-heparin anticoagulant therapy (*e.g.,* danaparoid, argatroban, bivalirudin).[54, 55]

Increased risk of thrombotic complications

- Age
- Immobilization
- Inflammation
- Coagulopathy



The risk of thrombotic complications increases as COVID-19 illness severity increases.

Figure 2 Adapted from: Bikdeli B, Madhavan MV, Jimenez D, *et al*. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up [published online ahead of print, Apr 15, 2020]. *J Am Coll Cardiol.* 2020. doi:10.1016/j.jacc.2020.04.031.

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