

COMMENTARY

COVID-19 associated coagulopathy and thromboembolic disease: Commentary on an interim expert guidance

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1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative pathogen of a new infectious disease, coronavirus disease 2019 (COVID-19), that first occurred in late December 2019 in the city of Wuhan in Hubei Province, China. It has since spread globally, resulting in a World Health Organization (WHO) declared pandemic, with as yet (April 28, 2020) >3 million confirmed cases and >200 000 confirmed deaths. As for every new disease, clinicians, hospitals, and governments struggle to find optimal clinical and public health measures to contain its spread and burden. For this, information from scientific research is crucial, and fortunately we see a rapidly accumulating output of studies. However, keeping up with the increasing output and its content and quality is a challenge for everyone involved in this outbreak, especially those at the front lines of patient care. Scientific journals and societies can play an important role in summarizing and channeling the data, and review articles are a great help.

In this process, more and more information is becoming available on an important aspect of COVID-19, that is, its relation with the hemostatic system and thromboembolic disease. Two different patient groups are involved whose care requires attention: (i) patients with COVID-19 who are at risk of a coagulopathy and thrombotic complications and (ii) patients with (new or a history of) thromboembolic disease whose treatment may be affected due to the current COVID-19-related measures. A recent review published in the *Journal of the American College of Cardiology (JACC)* and endorsed by the ISTH,

the North American Thrombosis Forum, the European Society of Vascular Medicine, and the International Union of Angiology and supported by the European Society of Cardiology Working Group on the Pulmonary Circulation and Right Ventricular Function covers pathogenesis, epidemiology, management, and outcomes related to these 2 groups, hence creating an important resource for clinicians and researchers.¹

We address the clinical guidance and research priorities as discussed in this review.

2 | PATIENTS WITH COVID-19

2.1 | COVID-19 and coagulopathy

COVID-19 may predispose to both venous and arterial thromboembolic disease, due to coagulation activation caused by a combination of excessive inflammation, platelet activation, endothelial dysfunction, and stasis of blood flow as a result of immobility. Measuring markers for these phenomena is important to improve understanding of the pathogenesis of thromboembolic disease in these patients. At the same time, hemostatic abnormalities are important as an indication for disease severity, varying from slight increases in D-dimer and marginally prolonged coagulation tests to clinical diffuse intravascular coagulation (DIC). Several studies have described such abnormalities, that is, thrombocytopenia, increased D-dimer levels, prolonged prothrombin time (PT) and associated International Normalized Ratio (INR) and thrombin time, and occasionally shortened activated partial thromboplastin time (APTT) in these patients.²⁻⁶

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Strong differences between COVID-19 patients who died and survived were recently described by Tang et al⁷ with respect to levels of D-dimer and fibrin degradation products as well as PT prolongation. Seventy-one percent of patients who died fulfilled the ISTH criteria for DIC, compared with only 0.6% among survivors. In another study, including 94 patients with COVID-19, PT prolongation and decreased fibrinogen values also predicted severe disease.⁸ For monitoring disease severity, it can therefore be recommended to measure D-dimer, PT, and platelet counts in patients with COVID-19, but more data to confirm these findings are urgently needed.

For research purposes, it is of interest to determine mechanisms leading to coagulopathy and to establish whether the hemostatic changes are a specific effect of SARS-CoV-2 or a consequence of general illness and comparable to the situation in patients suffering from similar symptoms due to other infectious disease. Of interest in this respect is that an effect of other coronaviruses on blood coagulation and thrombosis has previously been shown.⁹

2.2 | COVID-19 and venous thrombotic disease

2.2.1 | Venous thromboembolism prophylaxis

In line with general guidelines, the WHO interim guidance statement recommends prophylactic once-daily low-molecular-weight heparins (LMWHs), or prophylactic twice-daily subcutaneous unfractionated heparin (UFH) in hospitalized patients with COVID-19 with comorbidities, patients who are bedridden, and those requiring intensive care, unless there are contraindications, in which case mechanical venous thromboembolism (VTE) prophylaxis (eg, intermittent pneumatic compression) should be considered.¹⁰ There may be situations particular to COVID-19 that can lead to individualized risk stratification, such as DIC, bleeding complications, or an increased VTE risk (see below). Extended prophylaxis may be necessary when immobilization is prolonged during a lengthy illness or recovery phase. These topics require further study.

2.2.2 | Diagnosis of VTE

For several reasons, diagnosing VTE in patients with COVID-19 may be challenging; as described above, elevated D-dimer levels is a common nonspecific finding in patients with COVID. However, clinical probability dependent D-dimer levels could be used even in these patients.¹¹⁻¹³ For critical patients with severe acute respiratory distress syndrome who require prone positioning, radiological imaging for PE may not be directly possible. An option may be to consider echocardiography to assess for signs of worsening right ventricular overload, especially in patients experiencing hemodynamic collapse.¹⁴ Nevertheless, suspicion for VTE should be high in the case of hypoxemia disproportionate to other known respiratory pathologies, acute unexplained right ventricular dysfunction, or unexplained

leg swelling or pain. In the latter situation, bedside 2-point compression ultrasonography may help in avoiding computed tomography scanning if proximal deep vein thrombosis (DVT) is confirmed.

2.2.3 | Incidence of VTE

At present, case reports or series have described high incidences of VTE such as a study from China, where 20 of 81 patients (25%) with severe COVID-19 admitted to the intensive care unit (ICU), developed VTE. From the paper, it is not clear if this was a consecutive patient series or whether these were patients with a clinical suspicion for VTE, hence the 25% is difficult to interpret. Notably, none of the patients had received VTE prophylaxis.¹⁵ In a recent study from the Netherlands, a cohort of 184 patients with severe COVID-19 from 3 academic medical centers was described, in whom the cumulative incidence of VTE was 27% (95% confidence interval, 17-37), predominantly PE (80% of the cases). All patients received pharmacological prophylaxis.¹⁶ In a French prospective study in 150 critically ill COVID-19 patients, 25 patients were found to have PE and 3 DVT (19%).¹⁷ These findings still require validation from other consecutive patient cohorts, also in other settings, to determine whether the VTE risk varies according to clinical situations (home, hospital, ICU) and patient characteristics. It is possible but unknown that VTE remains underdiagnosed in patients with severe COVID-19 due to the diagnostic hurdles. A research priority would be to accurately establish VTE incidence and compare this to incidences related to other viral infectious disease, to distinguish a direct relation from a general consequence of severe illness.

2.2.4 | Role for empiric therapeutic anticoagulation

A recent study from Wuhan described that anticoagulant therapy mainly with LMWH appeared to be associated with better prognosis in patients with severe COVID-19.¹⁸ However, this finding was based on a subgroup analysis (N = 97) in which confounding by indication may have affected the results. Nevertheless, in view of these results, the hemostatic derangements discussed above and the frequent occurrence of VTE, some clinicians have used intermediate-dose or full-dose (therapeutic) parenteral anticoagulation (rather than prophylactic dosing) for routine care of patients with COVID-19, hypothesizing that it may confer benefit to prevent and/or treat (microvascular) thrombosis.

2.3 | COVID-19 and arterial thrombotic disease

As for VTE, the incidence of acute coronary syndrome (ACS) in relation to COVID-19 is as yet unknown, let alone whether this differs from other comparable clinical situations like influenza or other viral illnesses. The latter cases have been attributed to a combination of systemic inflammatory response syndrome

and localized vascular/plaque inflammation.¹⁹ Anecdotal cases of patients with COVID-19 presenting with ACS due to plaque rupture have been mentioned but no such cases have been published. Type I myocardial infarction should be considered in the proper context (including classic symptoms, electrocardiographic changes, and focal wall motion abnormalities). In presentations consistent with ACS due to plaque rupture, dual antiplatelet therapy and full-dose anticoagulation per American College of Cardiology (ACC)/American Heart Association and the European Society of Cardiology guidelines should be administered unless there are contraindications.²⁰

2.4 | COVID-19, treatment, and thrombotic disease

2.4.1 | Investigational therapies for COVID-19 and thrombotic disease

Several investigational agents are being tested in the management of COVID-19, especially for patients who develop severe disease. Some of these drugs have clinically important interactions with antiplatelet or anticoagulant agents. A few of these investigational agents have been associated with risk for thrombotic events or for thrombocytopenia, requiring further study (see Table 3 in Bikdeli et al¹ for a listing).

2.4.2 | COVID-19 and interventional therapies for VTE and ACS

Generally, considerations are needed for procedure-based therapies related to VTE and ACS to preserve personal protective equipment, hospital resources including inpatient and ICU beds, and minimize exposure for patients and health care workers:

For patients with intermediate- and high-risk VTE, the use of catheter-directed (thrombolytic) therapies should be limited to the most critical situations, also considering that there are minimal available data to indicate lower mortality from routine use of advanced VTE therapies.^{14,21} Indiscriminate use of inferior vena cava filters should be avoided but may be considered in the situation of recurrent PE despite optimal anticoagulation, major bleeding on anticoagulation, or other absolute contraindications to anticoagulation such as severe thrombocytopenia.

Recommendations from the ACC and Society for Cardiovascular Angiography and Interventions state that it is reasonable to continue optimal medical therapy and defer nonurgent cardiac procedures.²²

2.4.3 | Critical Illness with SARS-CoV-2 and management of antithrombotic agents

In critically ill patients, the risk of VTE is likely even higher, due to the hemostatic derangements, immobility, a systemic inflammatory

state, mechanical ventilation, and central venous catheters. Dose adjustment of anticoagulation may be necessary considering changed levels of coagulation factors, in addition to alterations in pharmacokinetics. Parenteral anticoagulation is recommended in most cases in which anticoagulant therapy is needed. UFH can be used in the setting of anticipated procedures or in patients with deteriorating renal function. If no urgent procedures are anticipated, LMWHs are a reasonable alternative. The dosing of UFH is preferably based on anti-Xa-level monitoring rather than on APTT, taking the coagulopathy and interaction with acute-phase proteins into account.

2.5 | COVID-19, DIC, and antithrombotic therapy

It is uncertain whether COVID-19 has unique characteristics to directly cause activation of coagulation. It is plausible that DIC develops in patients with COVID-19 due to a severe phenotype of the COVID-19 infection itself, hypoxia, and/or in the setting of secondary infections. DIC, however, appears to be rare and related to prognosis as described above.^{16,17} Regular laboratory monitoring of platelet count, PT, and fibrinogen in patients with COVID-19 is recommended to diagnose worsening coagulopathy and monitor severity. D-dimer can be added to this list but may cause confusion due to its association with presence of VTE.

2.5.1 | Management of COVID-19-related DIC

The first step in management of DIC is to identify and treat the underlying condition(s), which is challenging in patients with COVID-19 pneumonia and profound hypoxemia. LMWH prophylaxis may decrease thrombin generation and modify the course of DIC in addition to preventing VTE. Preliminary results, albeit with small number of events and limited adjustment, suggest a favorable response from LMWH prophylaxis.¹⁸

Clinically overt bleeding has hardly been reported in the setting of COVID-19. However, when bleeding occurs in COVID-19-associated DIC, or in case of a vital indication for invasive procedures, blood products support should be considered as per septic coagulopathy.²³

3 | PATIENTS WITHOUT COVID-19: MANAGEMENT OF THROMBOEMBOLIC DISEASE

Patients with a history of venous or arterial thrombotic disease receiving antithrombotic therapy may develop COVID-19. This has important implications to optimize both patient outcomes and safety for health care providers.

In general, for patients with known or new-onset thrombotic disease but without COVID-19, health care worker-patient contact should be limited to only necessary encounters. Outpatient

TABLE 1 Research priorities in COVID-19

	Patients with mild COVID-19 (outpatient)	Patients with moderate or severe COVID-19 without DIC (hospitalized)	Patients with severe COVID-19 at the ICU	Patients discharged from hospital but not yet fully recovered	Patients without COVID-19 but with comorbid thrombotic conditions who are homebound	All COVID-19 patients
Hemostatic abnormalities						To understand the pathogenesis of thromboembolic disease To establish whether the hemostatic changes are a specific effect of SARS-CoV-2 or a consequence of general illness
DIC			To determine if routine use of pharmacological VTE prophylaxis is warranted (if no overt bleeding) To determine if additional clinical characteristics and variables in the setting of DIC (eg, lymphopenia) should be considered to help risk-stratify and assess prognosis			
VTE prophylaxis	To determine the optimal method for risk assessment	To determine the optimal dose of prophylactic anticoagulation overall and in specific groups (eg, those with obesity or advanced kidney disease)	To determine the preferred method of pharmacological prophylaxis (type and dosage)	To determine the optimal total duration of prophylactic anticoagulation	To determine the optimal method of screening and risk stratification for consideration of VTE prophylaxis	To study individualized risk stratification and according prophylaxis
VTE diagnosis		To determine the role of D-dimer and diagnostic algorithms used in the non-COVID setting	To develop an appropriate algorithm for critically-ill patients, including those in prone position, with limited options for CTPA or ultrasonography.			

(Continues)

TABLE 1 (Continued)

	Patients with mild COVID-19 (outpatient)	Patients with moderate or severe COVID-19 without DIC (hospitalized)	Patients with severe COVID-19 at the ICU	Patients discharged from hospital but not yet fully recovered	Patients without COVID-19 but with comorbid thrombotic conditions who are homebound	All COVID-19 patients
VTE incidence	To determine the incidence and predictors of PE and DVT	To determine the incidence and predictors of PE and DVT	To determine the incidence and predictors of PE and DVT	To conduct population-level studies to determine the trends in incidence and outcomes of thrombotic disease in the period of reduced office visits		To accurately establish VTE incidence and compare this to incidences related to other viral infectious disease
VTE treatment			To determine if intermediate-dose or full dose (therapeutic) parenteral anticoagulation (rather than prophylactic dosing) may confer benefit to prevent and/or treat (microvascular) thrombosis			VTE treatment according to general guidelines
ACS	To determine the incidence and predictors of type I acute myocardial infarction in patients with COVID-19, and to compare their process measures and outcomes with non-infected patients	To determine the incidence and predictors of type I acute myocardial infarction in patients with COVID-19, and to compare their process measures and outcomes with noninfected patients	To determine the incidence and predictors of type I acute myocardial infarction in patients with COVID-19, and to compare their process measures and outcomes with noninfected patients			

Note: Adapted from Bikdeli et al.¹

Abbreviations: ACS, acute coronary syndrome; COVID-19, coronavirus disease 2019; CTPA, computed tomography pulmonary angiography; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; ICU, intensive care unit; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VTE, venous thromboembolism.

management or early discharge for acute VTE and for low-risk ACS should be instituted when possible. Use of telemedicine in place of in-person office visits is a strategy to minimize physical exposure.

For patients receiving vitamin K antagonists, as quarantine measures become more severe, changes in diet and vitamin K intake may affect INR values. Furthermore, frequent INR monitoring may pose logistical challenges, and considerations should be given to potential alternatives, including using extended INR testing intervals (if prior INRs have been stable), home-based INR checks,

drive-through INR checks, or switching to a direct oral anticoagulant or LMWHs when clinically appropriate.

4 | FUTURE DIRECTIONS AND CONCLUSIONS

The JACC review on this new disease comprehensively summarizes interim clinical guidance (Table 6 in Bikdeli et al¹) and critical knowledge gaps that urgently need answering (Table 1). Since COVID-19

first occurred just 4 months ago, the existing evidence, including data on thrombotic complications, is limited and derived primarily from small and retrospective analyses. At this stage, the demand for information may override general scientific principles, leading to false conclusions and even harmful consequences.²⁴ More refined and high-quality study results are needed, and funding agencies, professional societies, patients, clinicians, and investigators should work collaboratively.

The variability in preventive measures, testing strategies, diagnostic test availability, access to care, and treatment strategies, as well as variability in outcome reporting for COVID-19, may be a challenge for clinical research in terms of comparability and generalizability. On the other hand, it also offers opportunities: comparison of treatment or prophylaxis management schemes that differ per center may offer an alternative for randomized clinical trials (RCTs) under certain conditions (pseudo-randomization or instrumental variable analysis). It is promising that several initiatives for registries and other research initiatives are already up and running with support from regulatory bodies such as the US Food and Drug Administration being more flexible on performing RCTs on this disease.

Professional societies have an important role in knowledge generation and dissemination for various aspects of COVID-19, as well as leading by example, such as converting a physical conference into a virtual one. The role of scientific journals is also highly important, as they should make study results available as widely and fast as possible, while at the same time applying critical peer review to ensure that published results are reliable and valid. *RPTH* is particularly engaged as it combines open access publication with rapid turnaround time, while always keeping up high-quality standards.

RELATIONSHIP DISCLOSURE

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