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Community Outreach

Approach to the Patient with COVID-19-Associated Thrombosis: A Case-Based Review

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Disclosures of potential conflicts of interest may be found at the end of this article.

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Abstract. Coronavirus disease 2019 (COVID-19) is a current global pandemic caused by the novel coronavirus SARS-CoV-2. Alongside its potential to cause severe respiratory illness, studies have reported a distinct COVID-19-associated coagulopathy that is characterized by elevated D-dimer levels, hyperfibrinogenemia, mild thrombocytopenia, and slight prolongation of the prothrombin time. Studies have also reported increased rates of thromboembolism in patients with COVID-19, but variations in study methodologies, patient populations, and anticoagulation strategies make it challenging to distill implications for clinical practice. Here, we present a practical review of current literature and uses a case-based format to discuss the diagnostic approach and management of COVID-19-associated coagulopathy. ***The Oncologist*** 2020;25:e1500–e1508

Implications for Practice: Coronavirus disease 2019 (COVID-19)-associated coagulopathy is characterized by elevated D-dimer levels, hyperfibrinogenemia, and increased rates of thromboembolism. Current management guidelines are based on limited evidence from retrospective studies that should be interpreted carefully. At this time, all hospitalized patients with suspected or confirmed COVID-19 should receive coagulation test surveillance and standard doses of prophylactic anticoagulation until prospective randomized controlled trials yield definitive information in support of higher prophylactic doses.

Introduction

Beginning in December 2019, spread of the novel coronavirus SARS-CoV-2 from Wuhan, China, has led to an unprecedented global pandemic of its clinical syndrome known as coronavirus disease 2019 (COVID-19). COVID-19 exists on a spectrum of clinical severity, ranging from asymptomatic infection to severe sepsis, acute respiratory distress syndrome (ARDS), multiorgan failure, and death. Coagulation abnormalities and an increased risk of venous thromboembolism (VTE) are also associated with COVID-19, and these features have captured the attention of hematologists/oncologists. Here, we offer a pragmatic review of the COVID-19-associated coagulopathy and its management using a case-based format drawn from our experiences in caring for hospitalized patients with COVID-19.

Case Vignette Part 1: Coagulation Abnormalities in COVID-19

A 30-year-old male with no significant medical history presented to the emergency department with altered mental status and hypoxemia. His oxygen saturation was 79% despite supplemental oxygen, and initial chest imaging revealed diffuse bilateral airspace opacities. He was intubated in the emergency department. SARS-CoV-2 polymerase chain reaction testing was performed and found to be positive. A sputum culture was obtained and was later positive for *Haemophilus influenzae*. The initial prothrombin time (PT) was 14.5 seconds (normal range 11.5–14.5 seconds) with an international normalized ratio (INR) of 1.2, activated partial thromboplastin time (aPTT) was 38.4 seconds (normal range 23.8–36.6 seconds), D-dimer level was 1,986 ng/mL (normal range < 500 ng/mL), fibrinogen level was 696 mg/dL (normal range 200–400 mg/dL), and the platelet count was 219 K/μL (normal range 150–450 K/μL). He began antibiotic therapy with vancomycin and cefepime and was admitted to the intensive care unit (ICU), where he was started on VTE prophylaxis with 40 mg of enoxaparin daily.

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Table 1. ISTH scoring systems for overt DIC and SIC

Characteristic	Score	DIC range	SIC range
Platelet count, 10^9/L	2	<50	<100
	1	≥50, <100	≥100, <150
Fibrinogen degradation product/D-dimer	3	Strong increase	—
	2	Moderate increase	—
Prothrombin time, seconds	2	≥6	>1.4
	1	≥3, <6	>1.2, ≤1.4
Fibrinogen, mg/dL	1	<100	—
SOFA score	2	—	≥2
	1	—	1
Total score for DIC or SIC		≥5	≥4

Abbreviations: —, not applicable; DIC, disseminated intravascular coagulation; ISTH, International Society of Thrombosis and Hemostasis; SIC, sepsis-induced coagulation; SOFA, Sequential Organ Failure Assessment.

Discussion

This patient's presentation highlights the challenge of distinguishing COVID-19-associated coagulopathy from other coagulopathies associated with critical illness such as disseminated intravascular coagulation (DIC) or sepsis-induced coagulopathy (SIC). DIC is characterized by consumptive coagulopathy and hyperfibrinolysis, leading to prolongation of PT and aPTT, thrombocytopenia, and elevations in fibrinogen-degradation products such as the D-dimer. SIC is an entity intended to capture coagulation abnormalities of patients "at risk" of developing DIC and thus exhibits similar but less severe lab abnormalities as DIC. The International Society on Thrombosis and Haemostasis (ISTH) has developed diagnostic criteria for both DIC and SIC [1], outlined in Table 1.

In COVID-19-associated coagulopathy, the most prominent coagulation abnormalities are elevated D-dimer and hyperfibrinogenemia. Mild thrombocytopenia and prolonged PT have also been reported. In an early report from Wuhan, the median fibrinogen level was elevated for all patients with COVID-19 on admission (451 mg/dL for survivors vs. 516 mg/dL for nonsurvivors, p = .149). COVID-19 nonsurvivors compared with survivors had significantly higher levels of D-dimer (2,120 ng/mL vs. 610 ng/mL in survivors), fibrinogen degradation products (7.6 μg/mL vs. 4.0 μg/mL in survivors), and PT prolongation (15.5 seconds vs. 13.6 seconds in survivors) at the time of admission [2]. Another study reported that a greater proportion of nonsurvivors compared with survivors had an elevated D-dimer >1,000 ng/mL at admission (81% vs. 24%, respectively), prolonged PT ≥16 seconds (13% vs. 1%), and thrombocytopenia <100 K/μL (20% vs. 1%) [3]. Larger subsequent series confirmed these observations. In a retrospective study of 138 patients from a Wuhan hospital, ICU patients in comparison with non-ICU patients had a significantly higher median D-dimer level (414 ng/mL vs. 166 ng/mL, respectively), a trend toward a longer PT (13.2 seconds vs. 12.9 seconds), and a trend toward lower platelet counts (142 K/μL vs. 165 K/μL) [4]. And in a series of more than 1,000 COVID-19 cases from 30 Chinese provinces, 69.4% of patients who met the composite endpoint of admission to the ICU, need for mechanical ventilation, or death had an elevated D-dimer ≥500 ng/mL compared with 44.2% of those who did not [5]. The median platelet count was 156 K/μL in patients meeting the composite endpoint versus 169 K/μL for patients who did not.

Although COVID-19-associated coagulopathy resembles DIC and SIC in its pattern of abnormal laboratory testing and association with critical illness, it is ultimately distinct. First, thrombocytopenia is infrequently present in patients with COVID-19; if present, it is not as severe as thrombocytopenia seen in DIC with typical platelet counts <50 K/μL. Second, although fibrinogen levels can fall later in hospitalization for some patients [2], COVID-19 is characterized by hyperfibrinogenemia as a response to elevated proinflammatory cytokines [3, 6], which is distinct from the hypofibrinogenemia of <100 mg/dL seen in DIC. The early report by Tang et al. showed that only a minority of nonsurviving patients had platelet counts <50 K/μL (24%) and fibrinogen <100 mg/dL (29%), in contrast to the large majority that had D-dimer >3,000 ng/mL (86%) [2]. Similarly, Zhou et al. showed that a minority of the severely ill patients had thrombocytopenia (13%) and PT prolongation (20%), in contrast to the large majority with D-dimer elevations >1,000 ng/mL (81%) [3]. Findings at our institution support these early observations from Wuhan in all patients with COVID-19, with both mean fibrinogen of 561 mg/dL and median D-dimer of 1,064 ng/mL above the upper limits of normal, yet normal platelet count and PT [7]. To summarize, COVID-19-associated coagulopathy is characterized by elevated D-dimer, hyperfibrinogenemia, lack of severe thrombocytopenia, and typically normal PT and aPTT (Table 2).

Returning to our case, the patient's elevated D-dimer, slightly prolonged PT, lack of thrombocytopenia, and elevated fibrinogen level in the context of COVID-19 are suggestive of COVID-19-associated coagulopathy. Patients admitted for newly confirmed or presumed COVID-19 infection should have coagulation testing performed at the time of admission as outlined in Table 3 [8]. Monitoring with PT testing is preferred instead of using only the INR, as the INR is not sensitive enough to reflect the mild coagulation changes in patients with COVID-19; however, the INR

Table 2. Comparison of findings in COVID-19-associated coagulopathy and DIC

Characteristic	COVID-19-associated coagulopathy	DIC
D-dimer	↑↑	↑
Fibrinogen	↑	↓
PT	↔	↑
aPTT	↔	↑
Platelets	↓	↓↓
Microvascular thrombi	Present	Present

Abbreviations: aPTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; PT, prothrombin time.

Table 3. Coagulation testing of patients with COVID-19

Recommended coagulation testing
Complete blood count
Prothrombin time
Activated partial thromboplastin time
D-dimer
Fibrinogen

Abbreviation: COVID-19, coronavirus disease 2019.

should be obtained for patients receiving a vitamin K antagonists such as warfarin.

Case Vignette Part 2: Thromboembolic Events in COVID-19

In the ICU, the patient's respiratory status slowly improved. However, on hospital day 8 he developed hypotension, tachycardia, and intermittent oxygen desaturation, raising concern for pulmonary embolism (PE). A PE-protocol computed tomography scan of the chest revealed a new right-sided subsegmental PE. Upper and lower extremity ultrasound studies did not reveal a deep venous thrombosis (DVT). At this time, the PT was 12.1 seconds with an INR of 1.0, aPTT was 45.5 seconds, D-dimer had risen to above the upper limits of detection (>4,000 ng/mL), fibrinogen remained elevated at 743 mg/dL, and platelets remained normal at 178 K/μL.

Discussion

The importance of COVID-19-associated coagulopathy became apparent after studies reported high VTE rates in patients with COVID-19. Rather than behaving like a bleeding diathesis like other coagulopathies, COVID-19 has emerged as a hypercoagulable state. Estimates of the rate of VTE in patients with COVID-19 have ranged from 11% to 69% (Table 4) [9–17]. These estimates are higher than the 7.7% VTE incidence historically observed among ICU patients [18]. One particular study showed that rates of PE are higher in ICU patients with COVID-19 (20.6%) compared with time-of-year-matched ICU patients without COVID-19 (6.1%) and a cohort of ICU patients with influenza admitted in 2019, suggesting COVID-19 may be associated with a higher VTE risk not previously seen in other respiratory viral illnesses [14]. At our institution, we reviewed rates of symptomatic VTE in 210 patients with COVID-19 and found a fourfold increase in the incidence of VTE in patients admitted to the ICU compared with the ward despite standard-dose VTE prophylaxis, with a cumulative VTE incidence of 11.5% at 14 days [7].

Differences in study methodology and clinical practice contribute to the wide range of estimated VTE rates. For instance, studies using routine DVT screening may report a higher incidence of DVT owing to the inclusion of clinically asymptomatic DVTs. In the study by Llitjos et al., the use of DVT screening was associated with a VTE rate of 69% [15]. In addition, routine thromboprophylaxis is not given to hospitalized patients in China as the prevalence of VTE in Asian populations is significantly lower than that in White patients, for instance [19, 20]. In the study by Cui et al., despite inclusion of only patients admitted to the ICU, no thromboprophylaxis was administered and the VTE incidence was 25% [11]. At our institution, although our reported 14-day cumulative incidence is lower than the 17%–23% reported by others during the same period of time [9, 13], the dose of prophylactic anticoagulation used by our institution was 25% higher. Thus, it is important when interpreting studies on COVID-19 coagulopathy to be mindful of the illness severity of the patients studied (ward admission vs. ICU admissions), the type of VTE events recorded (venous events alone vs. venous plus arterial events), the criteria for VTE testing (symptom-driven vs. surveillance screening), and the intensity of anticoagulation received at the time of the VTE (prophylactic vs. therapeutic vs. other). We have summarized these attributes of the existing literature in Table 4.

Notably, the development of thrombosis is associated with the reported laboratory abnormalities of elevated procoagulant levels and D-dimer seen in COVID-19 coagulopathy, supporting the notion that COVID-19 coagulopathy is a hypercoagulable state. Patients with COVID-19 with VTE are characterized by an elevated D-dimer, with median D-dimer levels in patients with VTE ranging from 1,700 to 5,200 ng/mL [11, 15]. One study showed that D-dimer levels of >1,500 ng/mL were predictive of VTE with a sensitivity of 85% and specificity of 88.5% [11]. Another study used multivariate analysis to show that every log-transformed unit increase in D-dimer level was associated with a subdistribution hazard ratio of 1.6 for developing DVT [13]. Thrombocytopenia and prolonged PT are less commonly reported. Helms et al. showed that >66% of patients with COVID-19 ARDS had normal platelet counts and prothrombin time, no patient had a positive ISTH score for DIC (<5 points), and only 22% had a positive SIC score, in contrast to >95% of patients with elevated fibrinogen and D-dimer level [12].

What might be the pathophysiology underlying COVID-19-associated thrombosis? Inflammation likely plays a central role in an interplay with thrombosis now referred to as thromboinflammation [21]. An early study of patients with COVID-19 in Wuhan showed that the majority of patients had elevated inflammatory markers including interleukin (IL)-6 (52%), erythrocyte sedimentation rate (85%), and ferritin (63%) [22]. Higher inflammatory markers have been associated with severe disease and higher mortality. In a study of 21 patients, cases of severe COVID-19 (defined as

Table 4. Pertinent attributes of current studies reporting an increased risk of VTE in COVID-19

Study	Patient population(s)	Patients, *n*	Thromboembolic events recorded[a]	Thromboembolic testing criteria	Anticoagulation received	Median follow-up	Results
Klok et al. [10]	Patients with COVID-19 in the ICU	184	Radiographically confirmed PE/DVT Arterial events included[a]	Prompting by clinical suspicion	All received anticoagulation: - Nadroparin 2,850 IU/day - Nadroparin 5,700 IU/day - Nadroparin 5,700 IU b.i.d.	14 days	Cumulative thrombotic incidence: 49% at 14 days
Cui et al. [11]	Patients with COVID-19 in the ICU	81	Radiographically confirmed PE/DVT	Not specified	Not specified	Not specified	VTE rate: 25%
Helms et al. [12]	- Patients with COVID-19 with ARDS in the ICU - Patients without COVID-19 with ARDS in the ICU	With propensity matching: - COVID-19: 77 - Non-COVID-19: 145	Radiographically confirmed PE/DVT Arterial events included[a]	Prompting by clinical suspicion	All received anticoagulation: - >75% of patients with COVID-19 received prophylactic dosing - >70% of patients without COVID-19 received prophylactic dosing	≥7 days	Thrombotic rate with propensity matching: - COVID-19 ARDS: 11.7% - Non-COVID-19 ARDS: 4.8%
Middledorp et al. [13]	All hospitalized patients with COVID-19	198 - ICU: 75 - Ward: 123	Radiographically confirmed PE/DVT	DVT screening performed for 55 patients (38 ICU, 17 ward); otherwise, prompted by clinical suspicion	All received anticoagulation: - Ward: Nadroparin 2,850 IU/day - ICU: Nadroparin 2,850 IU/day before April, twice daily starting in April	7 days - ICU: 15 days - Ward: 4 days	VTE rate: - All VTE: 20% - Symptomatic VTE only: 13% - 14 DVTs were discovered incidentally by screening - All ICU VTE: 47% - ICU symptomatic VTE only: 28% - All ward VTE: 3.3% - Ward symptomatic VTE: 3.3%
Poissy et al. [14]	- Patients with COVID-19 in the ICU - Time-of-year matched patients without COVID-19 in the ICU in 2019 - Patients with influenza in the ICU admitted in 2019	- COVID-19: 107 - Time-of-year matched non-COVID-19: 196 - Patients with influenza: 40	Radiographically confirmed PE	Prompting by clinical suspicion	All received anticoagulation: - Proportion of patients receiving prophylactic vs. therapeutic anticoagulation was not specified	15 days	VTE rate: - Patients with COVID-19: 20.6% - Time-of-year-matched patients without COVID-19: 6.1% - Patients with influenza in 2019: 7.5%
Llitjos et al. [15]	Patients with COVID-19 in the ICU	26	Radiographically confirmed PE/DVT	DVT screening was performed for all patients; PE workup was prompted by clinical suspicion	All received anticoagulation: - 8 received prophylactic dose - 18 received therapeutic dose	Not specified	VTE rate: - Overall: 69% - Patients receiving prophylactic anticoagulation: 100% - Patients receiving therapeutic anticoagulation: 56%

(continued)

Table 4. (continued)

Study	Patient population(s)	Patients, *n*	Thromboembolic events recorded[a]	Thromboembolic testing criteria	Anticoagulation received	Median follow-up	Results
Paranjpe et al. [36]	All hospitalized patients with COVID-19	2,773	Not specified	Not specified	28% received anticoagulation, dose not specified	Not specified	In-hospital mortality: - Received anticoagulation: 22.5%, median survival 21 days - Did not receive anticoagulation: 22.8%, median survival 14 days In-hospital mortality of subset requiring ventilation: - Received anticoagulation: 29.1%, median survival 21 days - Did not receive anticoagulation: 62.7%, median survival 9 days
Lodigiani et al. [17]	All hospitalized patients with COVID-19	388 patients, - ICU: 62 - Ward: 326	Radiographically confirmed PE/DVT Arterial events included[a]	Prompting by clinical suspicion	ICU: - 60 received prophylactic LMWH - 2 received therapeutic LMWH Ward: - 133 received prophylactic LMWH - 67 received intermediate LMWH - 74 received therapeutic LMWH	10 days - ICU: 12 days - Ward: 4 days	Thrombotic rate: - Overall: 7.7% - Ward: 6.4% - ICU: 16.7%
Al-Samkari et al. [16]	All hospitalized patients with COVID-19	400 - Noncritically ill: 256 - Critically ill: 144	Radiographically confirmed and presumed DVT/PE Arterial events included[a]	Prompting by clinical suspicion	Patients received standard-dose prophylactic anticoagulation, details in supplemental data not available at time of review	10 days	Radiographically confirmed and presumed VTE rate: - Overall: 6.0% - Noncritically ill: 3.5% - Critically ill: 10.4% Arterial thrombotic rate: - Overall: 2.8% - Noncritically ill: 1.2% - Critically ill: 5.6%

[a]Arterial events include ischemic stroke, myocardial infarction, and arterial embolisms.

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DVT, deep venous thrombosis; ICU, intensive care unit; IU, international unit; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism.

hypoxemia, respiratory rate > 30/minute, or requiring supplemental oxygen) exhibited higher levels of IL-2R, IL-6, IL-10, and tumor necrosis factor alpha compared with moderate COVID-19 cases [6]. The larger study by Zhou et al. showed that COVID-19 nonsurvivors were associated with higher levels of ferritin, IL-6, and procalcitonin levels than surviving patients [3]. Cummings et al. showed that a 10% increase in either IL-6 or D-dimer was associated with a 10% increase in the hazard ratio for in-hospital mortality for critically ill patients with COVID-19 [23]. Importantly, an observational study of 19 patients with COVID-19 with ARDS found that fibrinogen levels were significantly associated with IL-6 values (R^2 = 0.506, p = .003) [24], confirming an association between thrombosis and inflammation in COVID-19.

One hallmark of thromboinflammation is the disruption of endothelial cells and their antithrombotic and anti-inflammatory functions, referred to as endotheliopathy [21]. SARS-CoV-2 enters host cells by engaging the angiotensin-converting enzyme 2 surface receptor that is expressed on various tissue types such as lung, cardiac, and kidney. SARS-CoV-2 is also expressed on endothelial cells. One study used electron microscopy to visualize viral inclusion bodies, mononuclear and neutrophilic infiltrates, and apoptotic bodies among endothelial cells of blood vessels in multiple sites, providing evidence of direct viral infection of the endothelium and associated endothelitis [25]. A detailed autopsy series of seven lungs from patients infected with SARS-CoV-2 also identified perivascular lymphocytic infiltration and diffuse alveolar damage [26]. The study reported three major features of COVID-19-associated endotheliopathy: endothelitis manifesting as prominent fibrin deposits and interstitial edema; intussusceptive angiogenesis, a pattern of alveolar vessel growth previously described in patients with influenza; and, notably, diffuse microangiopathy with microvascular thrombosis [26].

Both macrovascular and microvascular thromboemboli have been described in COVID-19. Among macrovascular events, DVTs and PEs are most commonly reported, although rare arterial events are noteworthy. A case series reported acute ischemic stroke in five patients with COVID-19, all younger than 50 years of age [27], and in a retrospective series of 214 patients from Wuhan, a significantly higher proportion of patients with severe infections (defined using the American Thoracic Society guidelines for grading community-acquired pneumonia severity) exhibited acute stroke and cerebrovascular disease compared with nonsevere patients (5.7% vs. 0.8%) [28]. Microvascular thrombosis, likely a result of endotheliopathy as discussed above, has been described in several autopsy series. Studies have noted small vessel thrombi at the peripheral lung parenchyma and within alveolar capillaries [26, 29], and even in the prostatic venous plexus in 6 out of 9 male patients examined [30].

Case Vignette Part 3: Management of COVID-19-Associated VTE

An intravenous infusion of therapeutic-dose unfractionated heparin was started at a dose targeting aPTT of 60–80 seconds per hospital guidelines for the treatment of the patient's newly diagnosed PE. His respiratory status improved, and he was extubated on hospital day 16, transitioned to subcutaneous enoxaparin 1 mg/kg twice daily, and transferred from the ICU to the ward. At the time of transfer, the PT remained normal at 13.3 seconds with an INR of 1.0, aPTT was 56.4 seconds (on enoxaparin), the D-dimer had decreased to 2,806 ng/mL, and the fibrinogen remained elevated at 591 mg/dL. He completed a 10-day course of antibiotics for respiratory *H. influenzae* infection and was discharged on hospital day 20 to a rehabilitation facility. Enoxaparin was transitioned to apixaban at the time of discharge to complete 3 months of therapeutic-dose anticoagulation for the PE.

Discussion

Radiographically confirmed VTE or a high clinical suspicion for VTE in patients with COVID-19 should prompt treatment with therapeutic doses of anticoagulation just as one would for VTE diagnosed in other clinical contexts [31–33]. Full anticoagulation should also be given for other typical indications such as atrial fibrillation or a prosthetic mechanical valve. Some patients with COVID-19 have a prolonged baseline aPTT due to lupus anticoagulant or other reasons [34]; in these patients, unfractionated heparin should be monitored with anti–factor Xa levels [8]. Hyperinflammatory conditions can lead to heparin resistance; higher-than-usual heparin doses may be required for patients with COVID-19 to achieve therapeutic aPTT as the aPTT is based on in vitro clot formation; results are dependent on coagulation factor levels. The anti-Xa level measures heparin concentration, which may be a better monitoring strategy in patients with high levels of procoagulant proteins or elevated baseline aPTT. Management of bleeding complications is similar to other clinical contexts, involving prompt cessation of anticoagulation based on severity of bleeding, reversal of the anticoagulating agent if necessary and possible, rechallenge with the same or reduced-dose anticoagulation when the bleeding is felt to be controlled and/or the risk of rebleeding is reduced, and close monitoring for rebleeding episodes.

Given the higher VTE rates in patients with COVID-19, whether COVID-19-associated VTE can be prevented with more effective thromboprophylaxis is a pressing question. Addressing this has been challenging. To date, no data from prospective randomized data investigating prophylactic anticoagulation strategies are available; evidence at this time is instead limited to retrospective studies with mixed findings. One early study showed that the use of prophylactic doses (primarily enoxaparin 40–60 mg/day) of low-molecular-weight heparin (LMWH) was associated with lower 28-day mortality rates in the subset of patients with a SIC score ≥ 4 (40.0% mortality in heparin users vs. 64.2% in nonusers) and in the subset of patients with a D-dimer >6 times the upper limit of normal (32.8% mortality in heparin users vs. 52.4% in nonusers) [35]. In a larger study of more than 2,700 patients with COVID-19 in New York, the median survival was longer for patients who received treatment-dosed anticoagulation compared with patients who did not (21 days vs. 14 days, respectively) [36]. In the subset of patients requiring mechanical ventilation,

Table 5. Current societal guidelines for the management of COVID-19-associated VTE

	ASH [8]	ACC [41]	CHEST [40]	ISTH [42]	WHO [43]	NIH [39]
Recommended dose for VTE prophylaxis	Standard prophylactic dose[a] Intermediate or full dose should be investigated as part of a clinical trial					
Recommended agent for VTE prophylaxis	LMWH preferred over UFH to limit staff exposure					
Recommended treatment of documented VTE	Therapeutic dose anticoagulation, adjusted for renal function, age, and weigh as appropriate					
Recommendation for post–hospital discharge VTE prophylaxis	Reasonable to consider using a regulatory-approved regimen (e.g., betrixaban 160 mg on day 1, followed by 80 mg once daily for 35–42 days; or rivaroxaban 10 mg daily for 31–39 days	Reasonable to consider extended prophylaxis up to 45 days based on individual risk stratification using a validated risk score (e.g., IMPROVE score with D-dimer [44])	Extended prophylaxis after hospital discharge is not recommended at this time owing to currently unknown postdischarge VTE and major bleeding rates in patients with COVID-19	Reasonable to consider extended prophylaxis with LMWH or a DOAC for 2–6 weeks for key VTE risk factors such as older age, stay in the ICU, cancer, immobility, or IMPROVE score of 4 or more	None provided	Reasonable to consider for patients at low risk for bleeding and high risk for VTE as per protocols for patients without COVID-19

[a]Thirty percent of ACC authors favored intermediate dose and 5% favored therapeutic dose for prophylaxis. Fifty percent of ISTH authors favored intermediate-dose prophylaxis.

Abbreviations: ACC, American College of Cardiology; ASH, American Society of Hematology; COVID-19, coronavirus disease 2019; DOAC, direct oral anticoagulant; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; NIH, National Institutes of Health; UFH, unfractionated heparin; VTE, venous thromboembolism; WHO, World Health Organization.

therapeutic anticoagulation was associated with lower in-hospital mortality compared with no anticoagulation (29.1% vs. 62.7%, respectively). However, this study has serious limitations including the unknown illness severity of its patients, unknown indications for anticoagulation, and unknown criteria for VTE testing. A rigorous study using propensity score matching compared outcomes of 139 patients who received anticoagulation with 417 who did not and found no statistically significant difference in survival between the two groups [37]. However, the dose of anticoagulation received (e.g., prophylactic vs. therapeutic) was not specified [37].

In the absence of randomized clinical trials, the optimal dose of prophylactic anticoagulation to prevent thrombosis in COVID-19 is not known and is the subject of global debate. Given reports of increased thrombotic rates in ICU patients, many centers believe that the current standard dose of anticoagulation for thromboprophylaxis is insufficient for critically ill patients with COVID-19 and have moved to increasing the dose of anticoagulation in their ICU patients [8–10, 13]. Some have adopted risk-adapted strategies, using various D-dimer thresholds and other combinations of clinical factors to determine the dose of anticoagulation for thromboprophylaxis [38]. At our institution, a cumulative VTE incidence of 11.5% in ICU patients treated with standard-dose thromboprophylaxis prompted us to investigate the potential benefit of intermediate-dosed thromboprophylaxis in all ICU patients, but outcomes of this dose escalation remain to be seen. Off-label use of tissue plasminogen activator (tPA) has also been studied in a small case series of three mechanically ventilated patients treated with a 25-mg tPA infusion followed by a second 25-mg infusion 22 hours later. Treatment resulted in a transient improvement in respiratory status (as reflected by the ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2), or the P/F ratio) in two patients and a durable response in one.

Society Guidance for Anticoagulation

Experts associated with societies involved with thrombosis and hemostasis have sought to provide guidance about anticoagulation for patients with COVID-19 [8, 39–43] (Table 5). Most societies endorse the use of standard anticoagulation doses for VTE prophylaxis in the absence of randomized controlled trial data supporting higher dose. Some societies have disclosed the dissenting votes regarding this recommendation, which were 35% for the American College of Cardiology panel and 50% for the International Society on Thrombosis and Hemostasis scientific committee. All societies agree that every center should make efforts to participate in randomized clinical trials that are now available to address the question of optimal anticoagulation dosing for preventing thrombosis in patients with COVID-19. Information on current clinical trials is available at clinicaltrials.gov/. Other important society recommendations include a preference for LMWH products for thromboprophylaxis rather than unfractionated heparin to minimize staff exposure.

There are currently insufficient data to support extended thromboprophylaxis for all patients after discharge, although this may be reasonable based on individual risk stratification

[44]. There is also no evidence at this time to support the use of antiplatelet agents for the prevention or treatment of thrombosis in patients with COVID-19, although many clinical trials are in progress to address these questions. Experimental therapies for COVID-19 such as the anti-C5 complement protein monoclonal antibody (mAb) eculizumab and the anti-IL-6 mAb tocilizumab may reduce thromboinflammation, but the use of such agents and the impact on disease course and risk of thrombotic events is unknown. Clinical trials for the use of eculizumab, tocilizumab, and other similar anti-inflammatory agents are ongoing (e.g., NCT04288713 and NCT04320615).

Conclusion

The hallmarks of COVID-19-associated coagulopathy at presentation are increased D-dimer and elevated fibrinogen with normal PT, aPTT, and platelet count. Clinicians should assess the platelet count, PT, aPTT, D-dimer, and fibrinogen levels in all suspected or confirmed hospitalized cases of COVID-19. An increased risk of VTE is seen in patients with COVID-19. This is due in part to the thromboinflammation and endotheliopathy that develop as a result of the inflammatory response to SARS-CoV-2 and direct viral infection of many cell types, resulting in macro- and microvascular thrombosis. Standard doses of prophylactic thromboprophylaxis should be considered for all hospitalized patients with COVID-19. Whether a higher dose of prophylactic anticoagulation may be more effective is currently not known, and data from prospective randomized controlled trials are eagerly anticipated.

Author Contributions

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Provision of study material or patients: Evan C. Chen, Rebecca L. Zon, Jean M. Connors
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Disclosures

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