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Diagnosis, Management, and Pathophysiology of Arterial and Venous Thrombosis in COVID-19

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with arterial and venous thrombotic complications. In a US registry of patients with coronavirus disease 2019 (COVID-19), thrombotic complications occurred in 2.6% of 229 noncritically ill hospitalized patients and in 35.3% of 170 hospitalized critically ill patients.[1]

Supplemental content

The risk of thromboembolism in SARS-CoV-2 infection in nonhospitalized patients is unknown. Thrombotic complications include myocardial infarction (MI), ischemic stroke, and venous thromboembolism (VTE). Autopsy findings of microthrombi in multiple organ systems, including the lungs, heart, and kidneys, suggest that thrombosis may contribute to multisystem organ dysfunction in severe COVID-19.[2]

Although the pathophysiology is not fully defined, prothrombotic abnormalities have been identified in patients with COVID-19. In a study of 19 critically ill patients with COVID-19, elevated levels of the following markers of hypercoagulability were identified: D-dimer in 100% of participants, fibrinogen in 74% of participants, and factor VIII in 100% of participants.[3] Antiphospholipid antibodies were detected in 53% of participants, and decreased protein C, protein S, and antithrombin levels were detected in all participants.[3] Coagulation abnormalities were associated with stroke, peripheral arterial ischemia, and VTE.[3] A study of 115 patients with COVID-19 (71 with nonsevere and 44 with severe disease) documented the presence of SARS-CoV-2 RNA in platelets and high platelet-associated cytokine levels.[4] In this study, platelet aggregation occurred at lower than expected thrombin concentrations.[4] Histopathology from 38 autopsies of patients with COVID-19 demonstrated microvascular thrombi, neutrophil extracellular traps (networks of extracellular neutrophil-derived DNA), and neutrophil-platelet aggregates.[5] In vitro assays performed on peripheral blood samples in 3 patients with COVID-19 documented excessive platelet and neutrophil activation, assessed by degranulation and integrin IIb-IIIa activation and immunofluorescence, compared with samples from 5 healthy control patients.[5]

Direct viral infection of endothelial cells with dense perivascular T-cell infiltration along with aberrant macrophage activation, endothelial and inflammatory cell death, thrombotic microangiopathy, and angiogenesis further distinguish COVID-19 histopathologically from other respiratory viruses.[6] The pathophysiology of thromboembolism in COVID-19 compared with non–COVID-19 disorders may be more platelet-dependent and related to viral-mediated endothelial inflammation, in addition to hypercoagulability associated with increased concentrations of coagulation factors, acquired antiphospholipid antibodies, and decreased concentrations of endogenous anticoagulant proteins.

More severe systemic inflammation and respiratory compromise in COVID-19 are associated with a higher prevalence of thrombotic complications. Among 388 patients hospitalized with COVID-19 (16% were critically ill), despite low-molecular-weight heparin (LMWH) thromboprophylaxis in all patients in the intensive care unit and in 75% of those not in intensive care, symptomatic VTE occurred in 4.4% of patients, ischemic stroke in 2.5%, and MI in 1.1%.[7]

Table. Current Guideline Recommendations for Venous Thromboembolism Prevention in Hospitalized Patients With Coronavirus Disease 2019

Patient/setting	Recommendation	
	American College of Chest Physicians	International Society on Thrombosis and Hemostasis
Critically ill	Prophylactic-dose LMWH	Prophylactic-dose LMWH; half-therapeutic-dose LMWH can be considered if patient is high risk
Non-critically ill	Prophylactic-dose LMWH or fondaparinux	Prophylactic-dose LMWH
After discharge	Extended prophylaxis not recommended	LMWH/DOAC for up to 30 d can be considered if high thrombosis risk and low bleeding risk
Nonhospitalized	Routine prophylaxis not recommended	Routine prophylaxis not recommended

Abbreviations: DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin.

The extent to which SARS-CoV-2 increases the risk of thromboembolism is unclear. A UK-based study of 1877 hospital discharges related to COVID-19 and 18 159 related to non–COVID-19 medical illness did not differ in rates of hospital-associated VTE (4.8/1000 vs 3.1/1000; odds ratio, 1.6 [95% CI, 0.77-3.1]; $P = .20$).[8] The high rate of VTE in COVID-19 may be less specific to the virus and predominantly due to the overall illness severity and complications.

Although multiple trials testing interventions to prevent thrombotic complications in COVID-19 are underway, current clinical guidelines have relied on previous studies of VTE prophylaxis in acute non–COVID-19 medical illness. Pending completion of ongoing trials, guidelines for COVID-19 are derived from recommendations in medically ill populations (**Table**). Whether these guidelines are optimal for COVID-19–related thrombosis remains unclear. Guidelines from the American College of Chest Physicians (ACCP) suggest prophylaxis with LMWH or fondaparinux instead of unfractionated heparin or direct oral anticoagulants (DOACs) for all hospitalized patients with COVID-19 in the absence of contraindications, such as active bleeding.[9] Once-daily injectable LMWH, 40 mg, and fondaparinux, 2.5 mg, are preferred to unfractionated heparin (2-3 times per day), because the former options limit clinician exposure to infected patients. These drugs are preferred to DOACs because of drug-drug interactions with antiviral agents. Although double-dose or therapeutic-dose LMWHs have been proposed, given the high VTE incidence despite standard thromboprophylaxis in critically ill patients with COVID-19, the ACCP suggests standard-dose LWMH based on the absence of clinical trial data.[9] Guidance from

the International Society on Thrombosis and Hemostasis (ISTH) suggests that half–therapeutic-dose LMWH (1 mg/kg daily) can be considered for prophylaxis in high-risk patients with COVID-19, and that a 50% higher dose be considered in patients with obesity; however, optimal prophylactic therapy remains unclear.[10] Full-dose antithrombotic therapy as prophylaxis for high-risk patients with COVID-19 is being evaluated in clinical trials (eTable in the Supplement). Although the pathophysiology of thromboembolism in COVID-19 involves platelet hyperreactivity, evaluation of antiplatelet therapy for prophylaxis is ongoing.

The risk of VTE persists after discharge in high-risk patients hospitalized for COVID-19.[10] However, the ACCP does not recommend postdischarge thromboprophylaxis.[9] In contrast, the ISTH recommends postdischarge thromboprophylaxis with LMWH or a DOAC for all high-risk hospitalized patients with COVID-19 who have a low risk of bleeding.[10] High-risk features in COVID-19 include older than 65 years, critical illness, cancer, prior VTE, thrombophilia, severe immobility, and elevated D-dimer (>2 times the upper limit of normal).[10] The ISTH suggests a duration of 14 to 30 days for postdischarge thromboprophylaxis, although optimal duration remains unclear. Thromboprophylaxis for patients who do not require hospitalization is not currently recommended.

Diagnosis of thromboembolic complications, such as pulmonary embolism and MI, should use methods validated for patients without COVID-19. Given no evidence of benefit, surveillance ultrasonography for VTE is not recommended.[9,10] Patients with COVID-19 diagnosed with arterial or venous thrombosis should be treated according to guidelines, recognizing the practical advantages of LMWH in the inpatient setting and of DOACs in the outpatient setting.[10] At this time, neither the ISTH nor ACCP recommend measuring D-dimer to screen for VTE or for determining intensity of prophylaxis or treatment.[9,10]

Conclusions

Arterial and venous thrombosis are common in COVID-19, especially in critically ill patients. Thromboprophylaxis should be considered for all hospitalized patients with COVID-19 in the absence of contraindications. Ongoing investigation will determine optimal preventive regimens in COVID-19 in the intensive care unit, at hospital discharge, and in nonhospitalized patients at high-risk for thrombosis.

ARTICLE INFORMATION

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REFERENCES

1. Piazza G, Campia U, Hurwitz S, et al. Registry of arterial and venous thromboembolic complications in patients with COVID-19. *J Am Coll Cardiol*. 2020;76(18):2060-2072. doi:10.1016/j.jacc.2020.08.070

2. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med*. 2020;8(7):681-686. doi:10.1016/S2213-2600(20)30243-5

3. Zhang Y, Cao W, Jiang W, et al. Profile of natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients. *J Thromb Thrombolysis*. 2020;50(3):580-586. doi:10.1007/s11239-020-02182-9

4. Zaid Y, Puhm F, Allaeys I, et al. Platelets can associate with SARS-Cov-2 RNA and are hyperactivated in COVID-19. *Circ Res*. 2020. doi:10.1161/CIRCRESAHA.120.317703

5. Nicolai L, Leunig A, Brambs S, et al. Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. *Circulation*. 2020;142(12):1176-1189. doi:10.1161/CIRCULATIONAHA.120.048488

6. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383(2):120-128. doi:10.1056/NEJMoa2015432

7. Lodigiani C, Iapichino G, Carenzo L, et al; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9-14. doi:10.1016/j.thromres.2020.04.024

8. Roberts LN, Whyte MB, Georgiou L, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. *Blood*. 2020;136(11):1347-1350. doi:10.1182/blood.2020008086

9. Moores LK, Tritschler T, Brosnahan S, et al Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report. *Chest*. 2020;158:1143-1163. doi:10.1016/j.chest.2020.05.559

10. Spyropoulos AC, Levy JH, Ageno W, et al; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18(8):1859-1865. doi:10.1111/jth.14929