Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

COVID-19 and hypercoagulability in the outpatient setting

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The COVID-19 pandemic caused by the SARS-CoV-2 virus has resulted in an overwhelming surge in utilization of healthcare resources. The effect on hospitals is incontrovertible but the effect on outpatient services is less well-studied. The most common symptoms at onset of COVID-19 are fever, cough, fatigue, and headache and may mimic other common upper respiratory infections [1]. Patients with these symptoms are likely to present to outpatient providers. In most patients, symptoms will be mild to moderate, where management for mild symptoms does not require hospitalization [2]. These patients are encouraged to remain isolated with frequent follow-up with their healthcare provider to assess their respiratory status, with urgent hospitalization for respiratory distress. Factors predicting poor outcomes include older age, obesity, diabetes mellitus, and hypertension [1]. Among hospitalized patients with COVID-19, venous thromboembolism (VTE), and in particular pulmonary emboli, are commonly diagnosed [3]. Recently, evidence for D-dimer cutoff values that predict high-risk for VTE has been demonstrated and the presence of VTE has been shown to be a poor prognostic indicator in severe COVID-19 patients [4]. The extent to which the risk of hypercoagulability exists in the outpatient setting is unknown but has serious implications for outpatient and primary care providers (PCP).

In the inpatient setting, patients with severe SARS-CoV-2 infections leading to pneumonia and hypoxic respiratory failure demonstrate elevated D-dimer and fibrinogen, evidencing a hypercoagulable state [5]. The underlying pathophysiology contributing to the hypercoagulable state may be related to cytokine storm inducing endothelial damage, microvascular thrombosis, and/or to the development of prothrombotic antiphospholipid antibodies [6]. In patients with severe COVID-19, elevated D-dimer correlated positively with increased 28-day mortality [7] and current guidelines recommend therapeutic anticoagulation in the setting of elevated D-dimers, as a high incidence of VTE has been reported on prophylactic dosing [8]. The prognostic value of D-dimers and anti-coagulation benefit in mild disease remains unknown.

The pathophysiologic differences between patients with severe and mild disease is currently being studied, however patients with mild disease demonstrate decreased lymphocyte count with increases in plasma IL-6 concentrations, suggesting the presence of an activated underlying inflammatory cascade [9]. Comparable to hospitalized patients, this proinflammatory state may predispose outpatients to the development of VTE and portend a worse outcome. Prior studies have demonstrated an association between pro-inflammatory cytokines and onset of VTE [10,11]. Moreover, studies of outpatients with VTE demonstrated that about 1/5 of patients had a recent infection, suggesting the recent setting of inflammation from infection may contribute to VTE risk. It stands to reason that viral infection from COVID-19, which has demonstrated remarkable elevations in hematological markers of coagulation [12], would increase this risk further, especially as similar findings were seen in patients with severe acute respiratory syndrome (SARS), a related coronavirus [13].

Patients with acute medical illness are at elevated VTE risk for up to 90 days post-discharge [14]. Specific regimens of extended thromboprophylaxis may include betrixaban 160 mg on day 1, followed by 80 mg once daily for 35–42 days; rivaroxaban 10 mg daily for 31–39 days; or aspirin in lower-risk patients, as recommended by American Society of Hematology [14]. However, low molecular weight heparin (LMWH) may also be preferred over direct oral anticoagulants due to possible interaction with concurrent antiviral or antibiotic treatment [15]. The question of whether non-hospitalized COVID-19 patients should receive VTE prophylaxis or therapeutic anticoagulation remains to be elucidated. Similarly, the role of anti-platelet therapy in this setting has not been studied. In this time of uncertainty, providers should follow guidelines put forth by the CDC and other governing medical associations as well as integrate up-to-date data from ongoing clinical trials into daily practice. Laboratory evaluation of proinflammatory markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin as well as assessment of coagulation with D-dimer, fibrinogen, and prothrombin time (PT) in patients who test positive for SARS-CoV-2 are being used in the inpatient setting, but their prognostic utility for VTE risk in outpatients have not been studied. In the outpatient setting, as many providers follow patients through telehealth to minimize transmission, the index of suspicion for VTE in patients presenting with symptoms typical of deep-venous thrombosis or pulmonary emboli should remain high [16]. In patients

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without signs of VTE, close observation via telehealth for patients may be appropriate, as many are encouraged to self-isolate. VTE prophylactic strategies such as frequent mobilization are not known to be effective in patients with COVID-19, but may be reasonable in patients who have mild disease, are functionally able to perform instrumental activities of daily living, and are confined at home during this time. In high-risk patients, such as those with a history of malignancy or prior VTE, recent guidelines suggest the consideration of prophylactic anticoagulation with standard dosing [12,16]. Utilization of currently available risk calculators such as the Padua Prediction Score [17] can aid in the consideration of anti-coagulation therapy. While elderly patients are at greater risk for severe COVID-19, clinical judgement for further anti-coagulation for those already on anti-coagulation or anti-platelet therapy must consider bleeding risk factors [12]. Providers may also counsel patients to consider stopping pro-thrombotic medications such as selective cyclo-oxygenase-2 (COX-2) inhibitors or supplements such as vitamin K or vitamin E. Studies evaluating any benefit versus perceived harm from standard NSAIDS are ongoing.

With the global burden of COVID-19 mortality reaching over 300,000 deaths worldwide, little is known about the specific pathogenic viral features and poor outcomes in these patients. A recent prospective study of autopsy findings from consecutive deaths from COVID-19 found thromboembolic events to be a common cause of mortality, with only a small proportion of patients characterized from the outpatient setting [18]. In the case of patients with mild symptoms from coronavirus, risk factors should be integrated with laboratory data and emerging guidelines to mitigate the risks of thromboembolism. Further investigations from the outpatient setting of COVID-19 are warranted with high priority, as the global impact of optimizing risk-management in these patients extends far beyond VTE prevention alone.

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Declaration of competing interest

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