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EDITORIAL COMMENT

Thrombosis and Thromboembolism Related to COVID-19

Increase the Level of Awareness, Lower the Threshold of Suspicion, and Keep Following the Guidelines*

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This issue of *JACC: Case Reports* features 3 papers (1–3), highlighting the challenges related to clinical suspicion, diagnosis, and management of acute pulmonary embolism in patients with coronavirus disease-2019 (COVID-19). The interesting cases reported in these papers provide an opportunity for a brief review of the current state of knowledge on the association between COVID-19 and thrombosis, and of the implications of recently generated data for clinical practice.

The clinical spectrum of COVID-19 is very broad. Many patients will experience no or only minor, nonspecific symptoms, but in a minority of cases, severe disease may develop (4,5), progressing from pneumonia to the acute respiratory distress syndrome and ultimately shock with multiorgan failure (5–8). It is currently accepted that the cytokine storm following the viral infection elicits an acute systemic inflammatory response and diffuse endothelial damage; these changes are accentuated by hypoxia and immobilization and may, especially if they occur against the background of underlying risk factors for thrombosis or serious comorbidity, result in potentially life-threatening venous or arterial thrombosis (9,10).

Hemostatic laboratory abnormalities, including marked elevations of D-dimer and fibrinogen levels, are frequently observed in patients with COVID-19, and they have been associated with an unfavorable in-hospital outcome since the beginning of the epidemic (5,6,11,12). In parallel, physicians involved in the care of patients with COVID-19 repeatedly emphasize that they have been observing an "unusually large' number of patients with acute pulmonary embolism or deep vein thrombosis over the past few months. Images shown in previously published case reports (13), and those in the present issue of *JACC: Case Reports*, appear to confirm this association. But how frequently do thrombotic events really occur in patients with COVID-19? In this regard, it must be emphasized that no robust data are available to this date, and no published study was designed to prospectively screen hospitalized patients with COVID-19 for the presence of thrombosis. Instead, existing evidence is mostly based on retrospective analysis of medical records, including small numbers of patients and centers; these reports did not consistently document which findings prompted the treating physicians to search for thrombosis, and it was not clear in all studies if and for how long the patients had received thromboprophylaxis. Keeping these important limitations in mind, the reported prevalence rate of venous thromboembolism among hospitalized patients with COVID-19 was in the range of 20% to 36% (14–17), or even higher (18). Arterial thrombosis or thromboembolism appeared to be

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approximately 10 times less frequent (15,16). Importantly, a substantial proportion of the thrombotic events were diagnosed very early during the hospital stay, suggesting that they had already occurred before admission (15).

In view of the previously mentioned (preliminary) findings, and although it cannot yet be concluded with safety that the thrombosis risk among patients with severe COVID-19 is substantially higher than that of patients with severe infection caused by other bacterial or viral pathogens (19,20), thrombotic events are very likely to be a key aspect of COVID-19-associated morbidity and mortality (21). It is therefore now necessary to make a step forward, moving from individual or small-cohort observations to systematic large-scale data collection on COVID-19 and thrombosis. Randomized controlled trials, or single-arm prospective management studies screening for thrombosis and thromboembolism among all-comers with COVID-19 in the hospital setting, appear unfeasible at the present stage. Obvious reasons for that include: 1) the logistical challenge for emergency and radiology departments related to performing diagnostic imaging tests, such as computed tomography coronary angiography, as part of study protocols during the wave of an epidemic; and 2) competition with interventional trials testing novel therapeutic agents and strategies against the virus. Consequently, the best possible approach to obtaining higher-quality data appears to consist of joining forces to perform large multicenter observational studies of consecutive patients with COVID-19 and thrombosis. Even if the search for arterial or venous thrombotic events cannot be dictated by the study protocol itself in such studies, it can nevertheless be "standardized," following recent international statements and recommendations (4,22,23).

In the meantime, it is advisable to adhere to some important principles and standards for the prevention, diagnosis, and management of thrombosis associated with COVID-19 in clinical practice:

1. **Thromboprophylaxis.** Recommendations on prophylactic anticoagulation should be followed in all hospitalized patients with COVID-19, as emphasized in an interim report by the International Society on Thrombosis and Haemostasis (23) and other expert consensus documents (4,21). Standard prophylactic doses of low molecular weight or unfractionated heparin should be used. Some experts and societies go even further by mentioning that higher, "intermediate" doses of low-molecular-weight heparin may be considered on an individual basis in patients with multiple or strong risk factors for venous thromboembolism (24), although this remains a purely empirical approach.
2. **Awareness and suspicion of thrombosis.** Regardless of the "true" prevalence of thrombosis in COVID-19, the level of thrombosis awareness should be kept high, and the threshold for clinically suspecting venous thromboembolism should be low in these patients. Unexpected respiratory worsening, new or unexplained tachycardia, a fall in blood pressure not attributable to tachyarrhythmia, hypovolemia or sepsis, new-onset electrocardiographic changes suggestive of pulmonary embolism, and signs of deep vein thrombosis of the extremities all should trigger a suspicion of pulmonary embolism (22). The high level of suspicion should also extend to stroke and other arterial thrombotic events, as highlighted in previous reports (15,16).
3. **Alternative or contributing causes of thrombosis.** In the context of suspected or confirmed thrombosis in a patient with COVID-19, the possibility of heparin-induced thrombocytopenia should also be kept in mind, especially in patients with severe disease, and the recommendations regarding patient monitoring and implementation of the 4Ts score for diagnosis should be followed (25). Despite this concern, low-molecular-weight (or unfractionated) heparin remains the first-line prophylactic or therapeutic anticoagulant for hospitalized patients with COVID-19. This is based on the preference for parenteral medication in the acute phase of (any) severe illness with the risk of rapid decompensation, and on the concerns about possible interactions between direct oral anticoagulants and some of the antiviral agents currently under investigation (21).
4. **Diagnosis and treatment of pulmonary embolism.** It is important to emphasize that current guideline recommendations on the diagnosis and treatment of acute pulmonary embolism must be followed (26). This principle applies to the entire management spectrum, from standardized diagnostic algorithms to risk assessment and risk-adjusted anticoagulation, and (if needed) reperfusion treatment in the acute phase. The need to rationalize the deployment of resources and personnel, and the adherence to isolation precautions when considering diagnostic (computed tomography pulmonary angiography, but also bedside echocardiography) or therapeutic procedures (e.g., catheter-directed interventions) should certainly be taken into account in local

clinical protocols. On the other hand, deviations from guidelines such as those mentioned in Marginean et al. (2) should remain the exception, and their rationale should be justified and documented in each case.

Finally, a word of caution is warranted regarding the widespread uncontrolled use of (presumed) novel antithrombotic or antiviral therapies, with hydroxychloroquine being a prominent example. The hypothesis that hydroxychloroquine may exert antithrombotic benefits in patients with COVID-19, including inhibition of the thrombogenic effects of antiphospholipid antibodies, is under investigation. In the meantime, the empirical use of hydroxychloroquine, with or without azithromycin, in clinical practice should be discouraged, considering, among others, the high rate of QT interval prolongation and the risk for life-threatening arrhythmias such as torsade de pointes (27,28).

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