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Review

COVID-19 and Its Implications for Thrombosis

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COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis. Reported findings indicate that immunosuppression, endothelial activation, and direct viral-mediated tissue damage rather than hyperinflammation-related injury mediates COVID-19 induced organ dysfunction. If direct infection drives injury, the vascular tissue is expected to be quite susceptible as it highly expresses angiotensin converting enzyme-2 (ACE-2), which is essential for coronavirus uptake. Viral injury, disordered cytokine release, and damage-associated molecular patterns (DAMPs) induce localized microvascular inflammation, which triggers endothelial activation, leading to vasodilation and pro-thrombotic conditions.[1-3] It has been shown that lymphocytes express the ACE-2 receptor on their surfaces thus, SARS-CoV-2 may directly infect those cells and ultimately lead to their lysis. Furthermore, the cytokine storm is characterized by markedly increased levels of interleukins and TNF –alpha, which may promote lymphocyte apoptosis.[2] Apoptosis mediates lymphocyte depletion and inhibitory effects of lactic acid on lymphocyte proliferation.[3]

Coagulation disorders are relatively frequently encountered among COVID-19 patients, especially among those with severe disease. The venous thromboembolism (VTE) risk in hospitalized COVID-19 patients is an emerging issue. The rate of symptomatic VTE in acutely ill hospitalized medical patients gets as high as 10%.[4] Thrombotic complications were first reported from intensive care units (ICU) in China and the Netherlands in up to 30% of patients. There is also emerging evidence of thrombosis in intravenous catheters and extracorporeal circuits, and arterial vascular occlusive events, including acute myocardial infarction, acute limb ischemia, and stroke, in severely affected people in studies from the USA, Italy, and France.[3]

COVID-19 associated coagulopathy is marked by elevated D-dimer and fibrinogen levels, with minor abnormalities in prothrombin time, activated partial thromboplastin time, and platelet counts in the initial stage of infection.[3,5] In a multicenter retrospective study during the

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first two months of the epidemic in China, 260 of 560 patients (46.4%) with laboratory-confirmed COVID-19 infection had elevated D-dimer (<0.5 mg/L), whereas, the elevation was more pronounced among severe cases (59.6% vs. 43.2% for mild ones).[4] In COVID-19, the typical findings include high fibrinogen and high Factor VIII activity, suggesting that significant consumption of coagulation factors is not occurring. In contrast, acute decompensated disseminated intravascular coagulation is associated with low fibrinogen due to consumption of clotting factors.[6]

Although older age and comorbidity such as cardiovascular disease confer a higher risk for severe disease, young and otherwise healthy patients are also at risk for complications.[7] Prolonged immobilization during illness, dehydration, acute inflammatory state, presence of other cardiovascular risk factors, previous history of VTE, and classical hereditary thrombophilia, such as heterozygous Factor V Leiden mutation are common comorbidities in hospitalized COVID-19 patients, which potentially increase VTE risk.[4]

Tang et al.[7] assessed 183 patients with COVID-19, 21 (11.5%) of whom died. Among the notable differences between patients who died and those who survived were increased levels of D-dimer and fibrin degradation products (~3.5 and ~1.9 fold, respectively) and prothrombin time prolongation (by 14%). A recent study from China reported that 40% of hospitalized patients with COVID-19 were at high risk of VTE.[7]

In sepsis, thrombocytopenia is usually more profound, and D-dimer concentrations do not reach the high values seen in patients with COVID-19.[6] In critically ill patients, the incidence of thromboembolic complications in patients with COVID-19 is 35-45%.[8-13]

An autopsy study revealed deep venous thrombosis in 7 of 12 patients (58%) in whom VTE was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients.[14] Autopsy studies of patients who died due to COVID-19 have shown high rates of microvascular and macrovascular thromboses, especially in the pulmonary circulation. A post-mortem series of seven patients from Germany showed that alveolar-capillary microthrombi were nine-fold common in people who died of COVID-19 than in those who died of influenza.[3]

There are variations in prophylaxis regimens, and these variations thromboprophylaxis regimens and screening schedules may help explain this variation in event rates across published studies. When we look at the studies regarding the dose and duration of heparin administration, we see the following: COVID-19 infected patients, whether hospitalized or ambulators, are at high risk for VTE an early and prolonged pharmacological thromboprophylaxis with low molecular weight heparin ((LMWH) is highly recommended. Although no data specific to COVID-19 exist, it is reasonable to employ individualized risk stratification for thrombotic and hemorrhagic complications, followed by consideration of extended prophylaxis (for up to 45 days) for patients with an elevated risk of VTE. Recently published interim consensus-based guidelines for the prevention and management of thrombotic disease in patients with COVID-19 recommended routine risk assessment for VTE for all hospitalized patients with COVID-19. Standard dose pharmacological prophylaxis should be considered in the absence of absolute contraindications in such patients. Empiric use of higher than routine prophylactic dose or therapeutic dose anticoagulation in patients admitted to the ICU in the absence of proven thromboses has also been implemented in some institutions. This is an area of ongoing intense discussions among experts, particularly for those patients who exhibit marked COVID-19 associated coagulopathy.[3,11,15-17] There is currently not sufficient evidence to recommended such a strategy.

The World Health Organization interim guidance statement recommends prophylactic daily LMWHs or twice-daily subcutaneous unfractionated heparin (UFH).[7] Parenteral anticoagulants (such as LMWH or UFH) are preferred to oral anticoagulants in the inpatient setting, given their short half-life and the presence of ready availability of reversal agents, due to the possibility of drug-drug interactions when they are taken with antiviral treatments (such as ritonavir) and antibiotics (such as azithromycin).[3] However, the existing evidence, including studies on thrombotic complications, is very limited and derived primarily from small and retrospective analysis.[18,19] The pathogenesis of hypercoagulability in COVID-19 is incomplete.

We believe that more and more quality data are needed to learn the relationship between COVID-19 and thrombosis.

Conflict of Interest

All authors declare that they have no confict of interest.

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