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LETTER TO THE EDITOR

The underrecognized prothrombotic vascular disease of COVID-19

We have read with interest "COVID-19-associated coagulopathy and thromboembolic disease: Commentary on an interim expert guidance" recently provided by Cannegieter and Klok.[1] This commentary exemplifies the importance that venous thromboembolism (VTE) and atheroembolism may be underrepresented and a cause for increased morbidity and mortality among coronavirus disease 2019 (COVID-19) patients. COVID-19 is mainly recognized as an acute infectious disease caused by the severe acute respiratory syndrome coronavirus 2; however, COVID-19 is emerging as an underrecognized hypercoagulable endothelial vascular disease that has contributed to significant morbidity and mortality. Although similar thrombotic events have occurred during outbreaks of severe acute respiratory syndrome (SARS),[2] emerging data, reports, and commentary of the prothrombotic complications (eg, VTE and arterial complications) in patients with COVID-19 is rapidly accumulating. Recently, Cui and colleagues[3] retrospectively reported a lower-extremity VTE incidence of 25% (20/81) with a mortality of 40% (8/20) among the 81 patients diagnosed with severe COVID-19 pneumonia. Klok and colleagues[4] reported a 13% mortality rate among 184 intensive care units (ICU) patients infected with COVID-19, with 3.7% having arterial thrombotic events and 27% with VTEs confirmed by imaging despite the use of standard-dose thromboprophylaxis. Furthermore, Llitjos and colleagues[5] reported a 69% incidence of VTE events among patients with COVID-19 in the ICU. Moreover, pulmonary embolism (PE) has been reported in 23% of COVID-19-positive ICU patients while on thromboprophylaxis.[5] Although the recent data demonstrate a high incidence of thromboembolic complications, especially VTE complications, in hospitalized patients with COVID-19 in the ICU with respiratory failure, to date, the literature of VTE complications on medical wards or outpatients with COVID-19 remain sparse. Reports of strokes in the young and middle-aged have also been increasing among patients with COVID-19.[6] Similarly, large-artery cerebral thrombosis have been seen among individuals with SARS caused by coronavirus in 2004.[7] The mechanism underlying morbidity related to thrombosis in patients with COVID-19 remains unclear, but the importance of recognizing the thrombogenicity of COVID-19 is imperative, preventable, and potentially lifesaving.

Many of the emerging reports surrounding the potential causes for thrombosis, demand ischemia, or microthrombosis have evolved around elevated markers of hypercoagulability, including D-dimer, tissue factor expression, fibrinogen levels, factor VIII levels, short-activated partial thromboplastin time, platelet binding, and thrombin formation.[8] Based on well-defined clinical and laboratory parameters, a proposal for staging COVID-19 coagulopathy may provide treatment algorithms stratified into 3 stages.[9] However, reports on acquired thrombophilias, such as antiphospholipid antibody syndrome, have been limited and should be considered among patients with COVID-19 in the right clinical context, especially among those without severe coagulopathy or known VTE risk factors (eg, immobility, active cancer, chronic neurological disease with leg paresis).[10]

To address these thrombotic concerns in COVID-19, providers should obtain a detailed inquiry into constitutional or specific symptoms and consider certain laboratory and diagnostic testing that might affect treatments and outcomes. Patients with COVID-19 who develop arterial thrombosis require a thorough evaluation for a vasculitis, systemic or local infections, trauma, dissection, vasospasm, atheroembolism (eg, artery-to-artery embolism, VTE through patent foramen ovale), or vascular anomaly. Furthermore, patients with COVID-19 should be considered for testing for heparin-induced thrombocytopenia, disseminated intravascular coagulation, or for acquired thrombophilia, such as antiphospholipid antibodies (eg, lupus anticoagulant, anticardiolipin antibodies, anti-β2 glycoprotein-1 antibodies) in the right clinical context.

Currently, there are no absolute indications for routine acquired thrombophilia testing among patients with COVID-19. The role of special coagulation testing for an acquired thrombophilia must be considered in the context of the clinical presentation and should be done only if the results are likely to change medical management. Relative indications among patients with COVID-19 could include selected screening among those with an incident thrombotic event at a young age (eg, ≤40-45 years for venous thrombosis, ≤50-55 years for arterial thrombosis), recurrent thrombosis without risk factors, unprovoked thrombosis, or thrombosis in unusual vascular territories (eg, cerebral vein, portal vein, hepatic vein, mesenteric vein or artery, renal vein or artery).

Timing of acquired thrombophilia testing must be considered.[11] Acute thrombosis can transiently reduce the levels of antithrombin and proteins C and S. Furthermore, patients with COVID-19 on heparin therapy can have lower antigen levels and antithrombin activity, thereby impairing the interpretation of clot-based assays for a lupus anticoagulant. Direct oral anticoagulants may cause false-positive lupus anticoagulant testing and falsely low antithrombin activity. Direct leukocyte genomic DNA testing for the factor V Leiden and prothrombin G20210A mutations is unaffected by anticoagulation therapy and can be performed at any time.

The typical duration of anticoagulation therapy among patients with thrombosis may not apply to all patients with COVID-19 or clinical situations and warrants further study. Until further research suggests otherwise, patients with COVID-19 with an acquired thrombophilia and a first-lifetime VTE should be managed by existing guidelines.[12] Similarly, the risks and benefits of extended anticoagulation should be reassessed periodically because the risk of VTE recurrence following an incident event is unknown among patients with COVID-19, and the risk of anticoagulant-related bleeding also may vary over time.

Providers need to have an increased vigilance against possible thrombotic complications among patients with COVID-19 and appropriate laboratory and/or diagnostic testing should not be delayed so that necessary therapeutic treatments may be given to reduce and/or prevent significant morbidity and mortality.

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