# Post COVID-19 Arterial Thromboembolism: A Clear and Present Danger

Bingwen Eugene Fan, MBBS, MRCP, MMED[1,2,3,4] Christine Cheung, PhD[3,5]

[1] Department of Haematology, Tan Tock Seng Hospital, Singapore
[2] Department of Laboratory Medicine, Khoo Teck Puat Hospital, Singapore
[3] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[4] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[5] Institute of Molecular and Cell Biology, Singapore

**Address for correspondence** Bingwen Eugene Fan, MBBS, MRCP, MMED, Department of Haematology, Tan Tock Seng Hospital, 11 Jln Tan Tock Seng, Singapore 308433 (e-mail: Bingwen_Eugene_Fan@ttsh.com.sg).

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While an increased incidence of thromboembolic events and hypercoagulability during acute SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection has been well described,[1,2] arterial thrombosis post COVID-19 (coronavirus disease 2019), although uncommon, has yet to be recognized as part of the late sequelae of COVID-19 (i.e., "long COVID") by the Centers for Disease Control and Prevention (CDC) in their guidance of "Late Sequelae of COVID-19" under the Clinical Care Guidance for Healthcare Professionals about Coronavirus (COVID-19),[3] or by the National Institute for Health and Care Excellence (NICE) in recently published living guidelines on post–acute COVID-19.[4] This is, despite the emerging reports of post COVID-19 arterial thrombosis, particularly in patients without cardiovascular risk factors.[5–9]

In a preprint study[10] evaluating the incidence of neurological and psychiatric sequelae in 6 months in 236,379 post COVID-19 survivors, the authors noted an increased risk of cerebrovascular events, with higher hazard ratio in most diagnostic categories than after influenza or other respiratory infections. A high incidence of stroke was found, as high as 1:10 (or 3% in patients with first episode of stroke) in patients who had previously experienced delirium or altered mental state. Moreover, it was noted that the incidence of these complications was increased even in individuals who had not required hospitalization. In a case series on delayed arterial thrombosis post COVID-19,[5] we described four cases in young males (aged <40 years) with previous asymptomatic SARS-CoV-2 infection, and lack of preexisting cardiovascular risk factors. These patients presented with a median of 78 days from positive SARS-CoV-2 total antibody positivity to thrombotic event with catastrophic strokes, acute myocardial infarction, and acute ischemic limb. Standard thrombophilia workup (including tests for antiphospholipid syndrome, protein C, protein S, antithrombin levels, and factor V Leiden mutation) was negative, with von Willebrand factor (VWF) and D-dimer levels remaining persistently elevated weeks after their initial thrombotic event. Our observations suggest that the SARS-CoV-2 virus poses significant chronic immuno-thrombogenicity which may cumulate eventually in a major thrombotic event that occurs unexpectedly many weeks later in fit patients with mild or asymptomatic COVID-19 infection. Sustained prothrombotic changes in COVID-19 patients were found in a separate study,[11] with increased thrombin generation, decreased plasma fibrinolysis, elevated factor VIII, VWF, and plasminogen activator inhibitor-1 (PAI-1) levels on admission and 4 months after discharge, suggestive of platelet activation and ongoing intravascular coagulation. Several other case reports highlight the phenomena of post COVID-19 arterial events as well. Notably, two case reports demonstrated the development of late, lower extremity, multilevel arterial thrombosis in a 24-year-old male and a 54-year-old male, both with nonsevere COVID-19 and without previous significant medical histories.[6,7] A previously healthy 61-year-old female with COVID-19 not requiring hospitalization presented 32 days later with fatal main pulmonary artery thrombosis discovered on autopsy.[8] Although pulmonary artery thrombosis is often considered a form of venous thrombosis, as the occlusion can result from emboli arising from a deep vein thrombosis, we make a point here that (1) this will still terminate in the pulmonary arteries and not pulmonary veins and (2) that in COVID-19, pulmonary thromboses are thought to originate in the pulmonary arteries/vasculature.[12] Also, a 35-year-old male with a medical history of mild-intermittent asthma and obesity

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presented 49 days after the onset of flu-like illness not requiring hospitalization (SARS-CoV-2 antibodies were positive on day 2 of admission) with extensive thrombosis including a large left ventricle thrombus, right coronary artery thrombosis, and a middle cerebral artery thrombosis.[9] In summary, these post COVID-19 cases, most of who were young and with no evident cardiovascular risk factors, developed delayed, massive arterial thromboses.

Although post thrombotic events are known to occur after acute viral infections such as influenza,[13,14] where up to a third of acute myocardial infarctions are preceded by an upper respiratory infection, less is known about the long-term impact on vascular health and delayed manifestation of thrombosis after recovering from COVID-19. The classic Virchow's triad for thrombosis consists of stasis, endothelial injury, and hypercoagulable state. While hypercoagulability and stasis impact primarily on acute thrombogenesis, they may play less prominent roles in delayed arterial events observed in convalescent COVID-19 patients. Vascular underpinning of post COVID-19 thrombosis has centered on endothelial dysfunction as one of the key mechanisms. This occurs likely because of prior cytotoxic effects of SARS-CoV-2 infection and overactive immune response causing prolonged vasculitis.[15] This culminates in breach of endothelial barrier integrity, exposing tissue factors and procoagulant cytokines from underlying vessels, thus triggering tissue factor driven secondary hemostasis.

Evidence for endothelial dysfunction during post COVID-19 recovery has been shown in children. Multisystem inflammatory syndrome,[16] comprising post–viral myocarditis and inflammatory vasculopathy, is attributed to prior trophism of coronavirus to endothelial cells. Children with COVID-19-associated chilblains of extremities have also been observed to show marked endothelial inflammation, with endothelial infection by SARS-CoV-2.[17] In addition, autopsy findings of COVID-19 adult patients show severe endothelial injury associated with the presence of intracellular SARS-CoV-2, cell membrane disruption, and vascular angiogenesis.[18] More recently, detailed interpretation of pathological reports has explained involvement of vascular-immune crosstalk in extensive pulmonary thrombosis, resulting in systemic microembolism which may have caused multiorgan ischemia and complications.[15] All these aforementioned events may contribute to possible persistence of endothelial dysfunction, as shown by increased numbers of circulating endothelial cells (biomarker of vascular injury) and more pronounced endothelial activation markers (ICAM-1, P-selectin) in recovered COVID-19 patients compared with healthy non-COVID-19 individuals.[19]

The rapid rise in COVID-19 infection exacerbated by more virulent variants of SARS-CoV-2 such as B.1.1.7, B.1.351, and P1/2,[20] and growing numbers of COVID-19 "long haulers," is expected to cause an increased global healthcare burden. The evidence of persistent endothelial dysfunction in post COVID-19 patients, including those with either no or minimal symptoms during initial infection, raises pressing concerns about the potential long-term cardiovascular effects. Besides arterial thromboembolism, COVID-19 survivors developing endothelial dysfunction may experience chronic cardiovascular complications such as heart failure, sudden cardiac death, arrhythmias (especially atrial fibrillation), accelerated arteriosclerosis,[21] pulmonary hypertension,[22] and arterial aneurysms.[23] Moreover, the incidence of vascular events due to endothelial dysfunction from COVID-19 in survivors is likely to be exacerbated by comorbidities such as hypertension and diabetes. Immunomodulatory therapy targeting thromboinflammation in COVID-19,[24] such as tocilizumab (anti–interleukin-6 receptor monoclonal antibodies) or the use of high-dose steroid therapy, may have benefits in reducing the inflammatory cascade in COVID-19 and endotheliitis in at-risk patients, and requires further evaluation. The efficacy and safety of prolonged thromboprophylaxis in post COVID-19 survivors is dependent on an increased understanding of the pathophysiology and mechanisms of such complications. Therefore, further systematic studies on COVID-19-associated thrombosis are necessary and results from ongoing clinical trials such as the ACTIV-4 trial (NCT04498273) evaluating prolonged thromboprophylaxis following discharge are eagerly awaited.

**Conflict of Interest**
None declared.

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