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Strokes in coronavirus disease - 19

ABSTRACT

COVID- 19 can present as acute ischemic stroke (AIS) without other typical features (fever, respiratory etc.). AIS can occur at any stage of infection with the SARS- CoV- 2 virus, including the convalescent phase. Strokes in COVID- 19 usually involve large vessels and at times, multiple territories (even in the absence of atrial fibrillation). AIS in COVID- 19 occurs due to multiple interconnected pathways: abnormality of coagulation, vasculitis, cardiomyopathy, hypoxemia, and loss of cerebral auto regulation. Patients with AIS and COVID- 19 have to be managed as any acute stroke patient, but with special precautions: risk of bleeding tends to be higher in those receiving thrombolytic therapy especially in those with a raised D dimer and prevent nosocomial spread of infection. As compared to non-COVID- 19 strokes, those with COVID strokes tend to have higher mortality and worse functional outcome.

Keywords: Acute ischemic stroke (AIS), Pathophysiology, Coronavirus disease-19 (COVID-19)

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents with fever, respiratory (influenza like illness) and rarely, gastrointestinal symptoms. However, it is also known to cause neurological complications in many patients. Even early in the pandemic, thrombotic complications associated with COVID-19 were recognised including COVID-19 associated acute ischemic strokes (AIS). Of cerebrovascular complications, AIS was more common in those with COVID-19; though both intra cerebral hemorrhage and cerebral venous thrombosis were reported. Strokes can often be a presenting feature of COVID-19,[1] could occur during the hospital stay and even in the convalescent phase.[2] Siow *et al*. in their meta-analysis of 899 patients with COVID-19 and stroke noted that in 24.5% of patients; stroke was the presenting symptom of COVID-19 and they did not have fever or respiratory symptoms at presentation.[3] They raised the possibility that such patients without typical features could pose a risk for nosocomial spread of infection. Although COVID-19 associated strokes can occur even in those with mild disease, they are more common in those with severe COVID-19 disease and with pre-existing vascular risk factors (VRF).

Stroke in COVID-19, though uncommon, can lead to significant morbidity, mortality,[3,4] and prolonged stay in the hospital. The purpose of this review is to highlight the incidence of AIS in those with COVID-19, risk factors for stroke in those with COVID-19, pathophysiology, characteristics of stroke, management, and prognosis as compared to those with non COVID-19 strokes.

Rajesh Benny[1], Kishore V. Shetty[2]

[1]*Department of Neurology, Senior Consultant Neurologist, Fortis Hospital, Mulund, Mumbai, Maharashtra, India,*
[2]*Consultant Neurologist, Karuna Hospital, Mumbai, Maharashtra, India*

Corresponding Author:
Dr. Rajesh Benny, Department of Neurology, Senior Consultant Neurologist, Fortis Hospital, Mulund, Mumbai, Maharashtra, India.
E-mail: rajeshbenny@gmail.com

AIS IN COVID-19

Mao *et al*. from Wuhan reported the association of stroke in COVID-19 in April 2020.[5] Their experience suggested that stroke would occur only in those with severe COVID-19. Most of the early studies reported that stroke as a complication of COVID-19 would occur late in the disease course; usually after the first 2 weeks of infection.[5-7]

Stroke is an infrequent complication of COVID-19; incidence varies from 0.4% to 8.1%. A recent meta- analysis reported a pooled incidence of new strokes in COVID-19 patients of 1.3% (95% confidence intervals [CI]: 0.9–1.8). The authors also noted geographical variation in the incidence of strokes: incidence in Asia (3.1%; 95% CI: 1.9–5.1) was higher than in Europe (1.2%; 95% CI 0.7–1.9) and North America (1.1%; 95% CI: 0.8–1.4).[8] The incidence of strokes in those severely ill with COVID-19 was however higher at 9.8% (range 2.7–30.6%).[3]

During the first wave of the pandemic, as cities grappled with the large number of patients with respiratory illness, patients coming to emergency with acute stroke actually decreased

(COVID-19 paradox).[9-12] This paradox was observed because patients with mild stroke may have avoided seeking medical attention due to fear of exposure in overcrowded hospitals or the overwhelming burden of pandemic may have resulted in limitation of medical facilities available for those with stroke.[12]

An important question is whether COVID-19 is causally associated with stroke or is an incidental finding in those with stroke due to the large number of the patients getting affected in the community. Infection with the SARS- CoV-2 increases thrombotic complications. Considering that any infection increases the risk for stroke, compared to influenza, the likelihood of stroke was 7.6 times higher with COVID-19 infection after adjustment for age, sex, and race suggesting infection with the SARS- CoV- 2 virus to be an independent risk factor for stroke.[13] Furthermore, COVID-19 associated strokes tend to be due to large vessel occlusion (even in those without any traditional vascular risk factor) and can involve multiple territories (without an underlying malignancy or atrial fibrillation): these features indicate a causal relationship in at least these subtypes of strokes.

RISK FACTORS FOR STROKE IN THOSE WITH COVID-19

Strokes with COVID-19 are more common in elderly males (mean age 65.5 years) (pooled median difference for age = 4.8 years; 95% CI = 1.7–22.4).[3,8,14] Those with COVID-19 and stroke were more likely to have vascular risk factor (VRF) such as hypertension, diabetes, dyslipidemia, ischemic heart disease, smoking, chronic kidney disease and in some studies, malignancy.

Although uncommon, even young patients without risk factors can present with large vessel occlusion AIS as a presentation of COVID-19.[15,16]

AT WHAT STAGE OF INFECTION WITH THE SARS- COV- 2 VIRUS DOES STROKE OCCUR?

Initial studies reported strokes in COVID-19 to occur late in the disease course; usually in the 2nd week of infection.[5-7] There is now enough evidence of early occurrence of stroke in those with COVID-19.[3] Recent studies[1] have reported that stroke could be the initial manifestation of COVID-19 in 67% of patients. At the onset of stroke, these patients did not have fever, cough or other typical features of COVID-19. Most centers also perform a computed tomography (CT) scan of the chest to triage patients into suspected COVID-19 based on the presence of pneumonia. However, of the patients with strokes in their study;[1] 22.2% had normal CT chest results. This emphasizes that stroke can be a sole presentation of COVID-19 and adequate precautions need to be taken to prevent nosocomial spread of COVID-19 in this situation.

Another interesting finding is the occurrence of AIS even in those who are in the convalescent phase of the infection (positive nucleocapsid antibody of SARS-CoV-2 by serological tests but a negative nasal swab Reverse transcription polymerase chain reaction for the SARS- CoV- 2 virus). The median time from positive serological result to AIS was 54.5 (0–130) days. Hence, stroke can be one of the long-haul manifestation of COVID-19 especially in those who are <50 years of age. This underscores the importance of SARS-CoV-2 serological testing during the etiological workup of patients who experienced AIS in the present pandemic, especially in the absence of traditional vascular risk factors.[2]

Strokes are more common in those with severe infection.[8] However, studies have observed AIS to occur even in those with non- severe COVID-19[1,14,17] suggesting that stroke mechanisms are active from the onset of infection.

CHARACTERISTICS OF COVID-19 STROKES

COVID-19 strokes tend to be large with an average median National institute of health stroke scale (NIHSS) on admission to be 15 (range 13–18). Most (79.6%) tend to have large vessel occlusions.[7,8] Furthermore, simultaneous involvement of multiple territories was seen in 42.5% of strokes[8] (including the three-territory sign usually associated with atrial fibrillation or an occult malignancy). The mechanism of stroke was cryptogenic in the majority, followed by cardioembolic and large vessel atherosclerosis. Lacunar strokes, although infrequent (3.3%), have also been reported.[4,8]

PATHOPHYSIOLOGY OF AIS IN COVID-19

Many pathogenic mechanisms have been proposed to cause AIS in those with COVID-19. However, there is no single pathway to explain COVID-19 associated strokes. COVID-19 strokes can occur due to conventional mechanisms, infection with the SARS- CoV- 2 virus acting as a trigger,[18] or it can be due to novel pathophysiologic mechanisms specific to the infection.

Most strokes in COVID-19 tend to occur in the elderly with an underlying traditional VRF. However, in a proportion of patients, mechanisms other than the traditional VRFs are responsible. Many have elevated inflammatory markers (C reactive protein) or surrogates for systemic coagulopathy (D-dimer). This is especially seen in younger patients with stroke and in those with large vessel thrombosis without VRF.

Abnormality of coagulation

Thrombosis in COVID-19 begins with activation of the innate immune system due to infection with the SARS- CoV- 2 virus (immunothrombosis).[19] COVID-19 associated vascular thrombosis starts in the pulmonary vasculature. However, when it spreads systemically it leads to COVID-19 associated coagulopathy (CAC) which is characterised by increased levels of D-dimer to above twice normal, increase in fibrinogen levels, slight prolongation of PT (1–3 s above normal) and mild thrombocytopenia.[20] As the CAC progresses to overt

disseminated intravascular coagulation (DIC); fibrinogen levels decrease, there is severe thrombocytopenia with marked prolongation of the prothrombin time (PT)/activated partial thromboplastin time (aPTT).

Viral invasion of the endothelium (through the angiotensin-converting enzyme 2 [ACE 2] receptors) triggers complement activation and the coagulation pathway, leading to microvascular thrombosis.[21] Viral infection of the endothelium activates monocytes which releases pro inflammatory cytokines such as interleukins (IL1), IL6, interferon-γ, and Tumour Necrosis Factor-α. This results in recruitment of neutrophils and activation of tissue factor (TF). TF then binds to coagulation factor VII (FVII) activating the extrinsic factor of coagulation. The viral infection of the endothelium also releases von Willebrand factor[22] which plays a role in activating platelets and amplifies the coagulation cascade. Recruitment of neutrophils leads to neutrophil extracellular trap (NET) formation which further facilitates thrombosis.[23] In addition, endogenous mechanisms of fibrinolysis are inhibited by platelet aggregation and NET formation. All these factors contribute to the development of CAC.

Patients with COVID-19 can also have a hyperinflammatory response (cytokine storm) which may also be a trigger for the pathological thrombosis in these patients[24] and causes further vascular injury.[25] The two markers of the systemic inflammatory response which are most often elevated in severe COVID-19 are C reactive protein and IL -6. Elevated C reactive protein can promote thrombosis by triggering the extrinsic pathway of coagulation.[26]

Among the various factors leading to thrombosis that have been debated/published in the literature, elevated D-dimer levels is observed to be the most common. D-dimer is a sensitive biomarker for thrombosis and can be elevated in non COVID-19 ischemic strokes[27] and many thrombotic conditions. Yaghi *et al*.[16] reported that patients with stroke and COVID-19 had high levels of D-dimer. Nearly, 50% of patients with severe COVID-19 had an elevated D-dimer and this proportion increased to nearly 100% in those who died.[28] D-dimer levels were elevated even in patients with non-severe COVID-19 who had an ischemic stroke.[1]

There have been reports of antiphospholipid antibodies (aPL) in sera of COVID-19 patients with stroke.[7,29] While aPL are often seen transiently after a viral infection, their role in the pathogenesis of thrombosis is not yet clear. A recent meta- analysis did not find increased risk of thrombosis due to elevated aPL in the early stages of infection.[30]

Vasculitis

The ACE2 receptors, to which the SARS CoV-2 binds, are expressed on the endothelial cells also. The endothelial invasion by the virus is cytotoxic and results in a lymphocytic endotheliitis.[31] This results in endothelial dysfunction and microvascular abnormality with subsequent inflammation and a procoagulant state.[32] Vessel inflammation occurs not only due to a direct viral infection of the endothelium but also because of injury by the inflammatory cytokines released during the cytokine storm.[25] In young patients without VRF's, vessel wall inflammation causing thrombosis may be one of the possible mechanisms responsible for large vessel occlusive strokes in this population.[33]

Cardiomyopathy

Cardiomyopathy and arrythmias may be caused by direct viral infection, cytokine storm,[34] hypoxia, and sympathetic overactivity.[35] Yaghi *et al*.[16] reported that those with COVID-19 strokes were more likely to have elevated troponin levels as compared with historical controls further implicating the role of myocardial injury in COVID-19 strokes. In the setting of a hypercoagulable state, these factors may predispose to intramural thrombosis and embolism.

Loss of cerebral auto regulation

Depletion of ACE2 due to viral infection of the endothelium leads to the unopposed action of ACE1, increased formation of angiotensin I and II with depletion of the neuroprotective angiotensin (1–7). This results in abnormality of the renin angiotensin system, loss of autoregulation of blood pressure, vasoconstriction, and increase in procoagulant and proinflammatory effects.[36]

Hypoxemia

Lung involvement and hypoxemia are common in those with COVID-19 and the level of hypoxemia worsens as severity of the lung infection worsens. Hypoxemia can trigger platelet activation.[37] Hypoxia can also lead to increased formation of hypoxia inducible factors (HIF-1 and HIF- 2). HIF can increase expression of TF, prevent fibrinolysis and increase the formation of NETs which in turn can lead to thrombosis by activating the extrinsic and intrinsic pathway of coagulation.[38]

CAN STROKE BE PREVENTED IN THOSE WITH COVID-19?

Patients with COVID-19 are at a higher risk for thrombosis (both arterial and venous) including ischemic strokes. When compared to other viral respiratory infections, patients with COVID-19 are 3 times more likely to develop thrombosis in both critically ill and non-critical hospitalised patients.[39] In patients with severe COVID disease or elevated D-dimer levels, low molecular weight heparin for thromboprophylaxis was associated with better outcome as compared to other anti-coagulants.[40] On the other hand, there are case reports of occurrence of AIS even in those receiving thromboprophylaxis.[7] COVID-19 associated coagulopathy is predominantly thrombogenic; however, in those who have severe infection, overt DIC with low platelet, prolonged PT and aPTT with decrease in fibrinogen levels can be seen.[41] The use

of anticoagulants cannot be advocated for all patients, as there is a significant risk of developing hemorrhagic complications (including ICH). Although there is insufficient data from large trials to suggest the optimal dose of anticoagulation to prevent thrombotic complications while avoiding the risk of bleeding, Gavioli *et al*.[42] have proposed a clinical algorithm for the choice and dosage of anticoagulants in hospitalized patients with COVID-19.

HOW TO MANAGE COVID-19 STROKES?

During the pandemic, many AIS patients may be detected to have associated COVID-19 at presentation. Time is of the essence during the initial evaluation and decision making in acute stroke patients. Therefore, a patient with AIS in a region where COVID-19 infection is active should be evaluated with the consideration that the patient could have COVID-19 infection. The protocols for management of AIS associated with COVID-19 would be the same as those in non COVID-19 strokes. However, there are certain considerations for strokes in those with COVID-19:

- COVID-19 patients with strokes may be more likely to have large vessel thrombotic occlusion: In addition to the prompt administering of intravenous recombinant tissue plasminogen activator in those who do not have contra indications, the presence of a large clot burden may necessitate the use of mechanical thrombectomy in some. Adequate care must be taken in the angiography suite to prevent nosocomial spread of infection especially when aerosols can be generated, for example, endotracheal intubation.
- Patients with AIS may have associated CAC and those with severe disease may also have overt DIC. This will increase the risk of ICH after intravenous thrombolytic therapy.
- The risk of contracting infection by the stroke care team.

Members of the stroke care team should take adequate precautions to prevent transmission and nosocomial spread of COVID-19. The number of doctors monitoring these patients at a given time should be as minimal as possible without compromising the care. Members of the stroke care team should maintain a distance of at least two meters, wear surgical masks, gowns and a particulate filtering facepiece respirator (N95 or equivalent) while examining these patients.

Precautions for thrombolysis in eligible COVID-19 patients with AIS

Most patients with moderate to severe COVID-19 have coagulopathy and thrombocytopenia, which often correlates with disease severity. The risk of intracranial hemorrhage is consequently higher in those who receive thrombolytic therapy. Elevated D dimer is an independent predictor of ICH and is associated with an unfavorable outcome after thrombolysis in AIS even in the non COVID-19 setting.[43] However, it is not ethically acceptable to deny these patients thrombolysis for fear of bleeding complications. To add to the problem is the non-availability of relatives who can be explained in person these treatment dilemmas. One needs to take a balanced decision after carefully considering the benefit and risk of thrombolysis. This would need a multi-disciplinary team involving the neurologist, hematologist and the critical care specialist. Where available, point of care evaluation of platelet count, D-dimer level, PT with INR and aPTT should be done to help in decision making.

COVID-19 STROKES AS COMPARED TO NON-COVID STROKES

Those with COVID-19 and strokes were more likely to be males and younger than in those with strokes but without the infection. As compared to non COVID-19 strokes; in those with COVID-19, large vessel occlusion and cryptogenic strokes were more common.[8] COVID-19 ischemic strokes tend to have a higher mortality and worse functional outcome as compared to non COVID-19 strokes.[4,8,16,44] In a recent study, parameters of stroke severity like higher NIHSS on admission, altered sensorium, poor Glasgow coma scale (GCS), need for invasive mechanical ventilation, as well as raised D- dimer and CRP levels were predictors of higher mortality in those with strokes.[1]

IS STROKE IN COVID-19 A CLINICAL PREDICTOR FOR CONVERSION TO SEVERE COVID-19 EVENTUALLY?

In their study, Benny *et al* noted that patients with stroke who went on to develop severe COVID-19 subsequently had the following features: presentation with altered sensorium, low GCS on admission, large vessel occlusion, multiple territory stroke, and abnormal findings on high-resolution computed tomography (HRCT) chest.[1] This was also observed in a pooled analysis where the authors noted that the presence of cerebrovascular disease was associated with a 2.5-fold increased disease severity in patients with COVID-19.[45] The present criteria for COVID-19 severity are based on oxygen saturation, HRCT chest and multi system involvement.[46] In a patient with COVID-19, the presence of a stroke indicates a multi system involvement and hence, stroke may be included as a risk factor for conversion to severe COVID-19. This needs to be confirmed by larger studies.

COVID-19 AIS: WHAT HAVE WE LEARNT TILL NOW?

All elderly patients with COVID-19 and even one VRF should be monitored carefully for the occurrence of stroke. Ischemic strokes in COVID-19 are caused by multiple but interlinked pathways. Based on current knowledge about the propensity for thrombosis in those with COVID-19, the use of LMWH for primary prevention of strokes is considered reasonable. AIS may be the presenting feature of COVID-19 and may

also occur in the early as well as convalescent stages of COVID-19. A patient with AIS and COVID-19 poses unique challenges: risk of nosocomial spread of infection, large strokes, increased chances of hemorrhage with reperfusion or anticoagulant therapy, a higher mortality and poor functional outcome. Management of each patient with COVID-19 stroke has to be individualized after carefully assessing the benefits and risks involved in the treatment.

REFERENCES

1. Benny R, Singh RK, Venkitachalam A, Lalla RS, Pandit RA, Panchal KC, *et al.* Characteristics and outcomes of 100 consecutive patients with acute stroke and COVID-19. J Neurol Sci 2021;423:117348.
2. Tu TM, Seet CY, Koh JS, Tham CH, Chiew HJ, De Leon JA, *et al.* Acute ischemic stroke during the convalescent phase of asymptomatic COVID-2019 infection in men. JAMA Netw Open 2021;4:e217498.
3. Siow I, Lee KS, Zhang JJ, Saffari SE, Ng A, Young B, *et al.* Stroke as a neurological complication of COVID-19: A systematic review and meta-analysis of incidence, outcomes and predictors. J Stroke Cerebrovasc Dis 2020;30:105549.
4. Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, *et al.* Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: The global COVID-19-19 stroke registry. Stroke 2020;51:e254-8.
5. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683-90.
6. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, *et al.* Acute cerebrovascular disease following COVID-19: A single center, retrospective, observational study. Stroke Vasc Neurol 2020;5:279-84.
7. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, *et al.* Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry 2020;91:889-91.
8. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke 2021;16:137-49.
9. Rudilosso S, Laredo C, Vera V, Vargas M, Renú A, Llull L, *et al.* Acute stroke care is at risk in the era of COVID-19: Experience at a comprehensive stroke center in Barcelona. Stroke 2020;51:1991-5.
10. Siegler JE, Heslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center. J Stroke Cerebrovasc Dis 2020;29:104953.
11. Sharma M, Lioutas VA, Madsen T, Clark J, O'Sullivan J, Elkind MS, *et al.* Decline in stroke alerts and hospitalisations during the COVID-19 pandemic. Stroke Vasc Neurol 2020;5:403-5.
12. Aguiar de Sousa D, Sandset EC, Elkind MS. The curious case of the missing strokes during the COVID-19 pandemic. Stroke 2020;51:1921-3.
13. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, *et al.* Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. JAMA Neurol 2020;77:1-7.
14. Trifan G, Goldenberg FD, Caprio FZ, Biller J, Schneck M, Khaja A, *et al.* Characteristics of a diverse cohort of stroke patients with SARS-CoV-2 and outcome by sex. J Stroke Cerebrovasc Dis 2020;29:105314.
15. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, *et al.* Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 2020;382:e60.
16. Yaghi S, Ishida K, Torres J, Grory BM, Raz E, Humbert K, *et al.* SARS-CoV-2 and stroke in a New York healthcare system. Stroke 2020;51:2002-11.
17. Ahmadi Karvigh S, Vahabizad F, Banihashemi G, Sahraian MA, Gheini MR, Eslami M, *et al.* Ischemic stroke in patients with COVID-19 disease: A report of 10 cases from Iran. Cerebrovasc Dis 2021;50:239-44.
18. South K, McCulloch L, McColl BW, Elkind MS, Allan SM, Smith CJ, *et al.* Preceding infection and risk of stroke: An old concept revived by the COVID-19 pandemic. Int J Stroke 2020;15:722-32.
19. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol 2013;13:34-45.
20. Lee SG, Fralick M, Sholzberg M. Coagulopathy associated with COVID-19. CMAJ 2020;192:E583.
21. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, *et al.* Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res 2020;220:1-13.
22. Becker RC. COVID-19 update: COVID-19 associated coagulopathy. J Thromb Thrombolysis 2020;50:54-67.
23. Zakeri A, Jadhav AP, Sullenger BA, Nimjee SM. Ischemic stroke in COVID-19 positive patients: An overview of SARS-CoV-2 and thrombotic mechanisms for the neurointerventionalist. J Neurointervent Surg 2021;13:202-6.
24. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol 2020;2:e437-45.
25. Spence JD, de Freitas GR, Pettigrew LC, Ay H, Liebeskind DS, Kase CS, *et al.* Mechanisms of stroke in COVID-19. Cerebrovasc Dis 2020;49:451-8.
26. Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. Blood 1993;82:513-20.
27. Zhang J, Song Y, Shan B, He M, Ren Q, Zeng Y, *et al.* Elevated level of D-dimer increases the risk of stroke. Oncotarget 2017;9:2208-19.
28. Guan WJ, Ni ZY, Hu Y. China medical treatment expert group for covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
29. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, *et al.* Coagulopathy and antiphospholipid antibodies in patients with covid-19. N Engl J Med 2020;382:e38.
30. Gatto M, Perricone C, Tonello M, Bistoni O, Cattelan AM, Bursi R, *et al.* Frequency and clinical correlates of antiphospholipid antibodies arising in patients with SARS-CoV-2 infection: Findings from a multicentre study on 122 cases. Clin Exp Rheumatol 2020;38:754-9.
31. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al.* Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417-8.
32. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: A marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003;23:168-75.
33. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS, *et al.* Macrothrombosis and stroke in patients with mild Covid-19 infection. J Thromb Haemost 2020;18:2031-3.
34. Cheng R, Leedy D. COVID and acute myocardial injury: The heart of the matter or an innocent bystander? Heart 2020;106:1122-4.

35. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: A review. JAMA Cardiol 2020;5:831-40.
36. Hess DC, Eldahshan W, Rutkowski E. COVID-19 related stroke. Transl Stroke Res 2020;11:322-25.
37. Cameron SJ, Mix DS, Ture SK, Schmidt RA, Mohan A, Pariser D, *et al*. Hypoxia and ischemia promote a maladaptive platelet phenotype. Arterioscler Thromb Vasc Biol 2018;38:1594-606.
38. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res 2019;181:77-83.
39. Smilowitz NR, Subashchandran V, Yuriditsky E, Horowitz JM, Reynolds HR, Hochman JS, *et al*. Thrombosis in hospitalized patients with viral respiratory infections versus COVID-19. Am Heart J 2021;231:93-5.
40. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z, *et al*. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094-9.
41. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. Crit Care 2020;24:360.
42. Gavioli EM, Sikorska G, Man A, Rana J, Vider E. Current perspectives of anticoagulation in patients with COVID-19. J Cardiovasc Pharmacol 2020;76:146-50.
43. Hsu PJ, Chen CH, Yeh SJ, Tsai LK, Tang SC, Jeng JS. High plasma D-dimer indicates unfavorable outcome of acute ischemic stroke patients receiving intravenous thrombolysis. Cerebrovasc Dis 2016;42:117-21.
44. Perry RJ, Smith CJ, Roffe C, Simister R, Narayanamoorthi S, Marigold R, *et al*, On Behalf of the SETICOS Collaborators. Characteristics and outcomes of COVID-19 associated stroke: A UK multicentre case-control study. J Neurol Neurosurg Psychiatry 2021;92:242-8.
45. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): A pooled analysis of published literature. Int J Stroke 2020;15:385-9.
46. Fujun P, Lei T, Yongshi Y, Hu P, Wang R, Hu Q, *et al*. Management and treatment of COVID-19: The Chinese experience. Can J Cardiol 2020;36:915-30.

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