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Bihemispheric ischemic strokes in patients with COVID-19

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Abstract:

BACKGROUND: There is emerging evidence that COVID-19 can trigger thrombosis because of a hypercoagulable state, including large-vessel occlusion ischemic strokes. Bihemispheric ischemic stroke is uncommon and is thought to indicate an embolic source. Here, we examine the findings and outcomes of patients with bihemispheric stroke in the setting of COVID-19.

METHODS: We performed a retrospective cohort study at a quaternary academic medical center between March 1, 2020, and April 30, 2020. We identified all patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who presented with simultaneous bihemispheric ischemic strokes.

RESULTS: Of 637 COVID-19 admissions during the 2-month period, 13 had a diagnosis of acute ischemic stroke, including 5 who developed bihemispheric cerebral infarction. Three of those 5 (60%) were female, median age was 54 (range 41–67), and all five were being managed for severe COVID-19-related pneumonia complicated by acute kidney injury and liver failure before the diagnosis of cerebral infarction was established. Five presented with elevated ferritin, lactate dehydrogenase, and interleukin-6 (IL-6) levels, and four had lymphopenia and elevated D-dimer levels. All patients underwent neuroimaging with computed tomography for persistent depressed mentation, with or without a focal neurologic deficit, demonstrating multifocal ischemic strokes with bihemispheric involvement. Outcome was poor in all patients: two were discharged to a rehabilitation facility with moderate-to-severe disability and three (60%) patients died.

CONCLUSIONS: Stroke is implicated in SARS-CoV-2 infection. Although causality cannot be established, we present the imaging and clinical findings of patients with COVID-19 and simultaneous bihemispheric ischemic strokes. Multifocal ischemic strokes with bihemispheric involvement should be considered in COVID-19 patients with severe infection and poor neurologic status and may be associated with poor outcomes.

Keywords:

Coronavirus disease 2019, embolism, ischemic stroke, neurologic complications, severe acute respiratory syndrome coronavirus 2

Introduction

The coronavirus disease 2019 (COVID-19) global outbreak commenced in Wuhan, China, in December 2019 and was designated a pandemic on March 11, 2020, by the World Health Organization.[1,2] COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is associated with several manifestations of varying degree including asymptomatic disease, mild upper respiratory tract illness, severe viral pneumonia, respiratory failure, and death with 26%–32% of patients warranting intensive care unit (ICU) admission.[3-5] Although COVID-19 predominantly causes pulmonary injury,

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there is emerging evidence on COVID-19-related neurologic complications, of which stroke has a reported incidence of 2.5%–2.8%.[6-8] Given that preexisting vascular risk factors are prevalent in COVID-19 patients, the association between stroke and COVID-19 may be unrelated; however, there is overwhelming evidence suggesting a high risk for coagulopathy and thromboembolic events in patients with COVID-19, primarily in the acute phase of the infection.[6,7,9] A recent case series reported large-vessel ischemic stroke in 5 patients with COVID-19 under the age of 50, each with minimal to no preexisting vascular risk factors and presenting with elevated markers of inflammation on laboratory testing.[10] In addition to the prevalence of stroke in COVID-19 patients, stroke is highly suggestive of severe infection and poor outcomes.[8] Ischemic stroke with bihemispheric involvement is generally indicative of an embolic source and is associated with increased death and disability.[11] Herein, we present 5 cases of acute multifocal ischemic stroke with bihemispheric involvement in the setting of COVID-19 infection.

Methods

Study population

We retrospectively reviewed 46 charts of patients with acute ischemic stroke admitted between March 1, 2020, and April 30, 2020 to Westchester Medical Center, a large quaternary medical center in Valhalla, NY. These patients were identified using our ischemic stroke database. We identified 13 charts of patients with acute ischemic stroke and concomitant COVID-19. A confirmed case of SARS-CoV-2 infection was defined by a positive result on reverse-transcriptase polymerase chain reaction assay on nasopharyngeal swab. Among the patients with acute ischemic stroke and concomitant COVID-19, we identified 5 patients with bihemispheric involvement. These patients were identified by reviewing neuroimaging with either noncontrast computed tomography (CT) of the head or magnetic resonance imaging of the brain. All radiology reports were reviewed. We defined bihemispheric stroke as acute infarcts involving both cerebral hemispheres.

Data collection

Demographic data, preexisting vascular risk factors (for example, hypertension, diabetes mellitus, hyperlipidemia, cardiac disease, peripheral vascular disease, obesity, and habitual smoking), initial COVID-19 symptoms, neurologic symptoms warranting brain imaging, laboratory values, and neuroimaging modality and results for stroke diagnosis were recorded retrospectively. We looked at outcomes including discharge location and discharge disability score as measured via the modified Rankin scale (mRS). The mRS is a general assessment of function in which a score of 0 indicates no symptoms and a score of 5 indicates severe disability), and mortality.

Clinical management

All patients with COVID-19 admitted to our center are graded based on disease severity and assessed for risk for progression. COVID-19 disease severity ranges from asymptomatic to critical illness, with critical illness defined as acute hypoxic respiratory failure with shock and/or multiorgan failure. High risk for progression is defined by having any of the following: absolute lymphocyte count <0.8, lactate dehydrogenase (LDH) >250, C-reactive protein >1, ferritin >300, creatine phosphokinase > twice the normal limit, D-dimer >1, and positive troponin level. All patients with bihemispheric stroke and concomitant COVID-19 admitted to our center within the study period were critically ill and managed in an ICU. At our institution, infectious disease (ID) consultations are obtained for all critically ill COVID-19 patients for antiviral and adjunctive therapy recommendations. Prophylactic anticoagulation for venous thromboembolism (VTE) prevention is initiated in all COVID-19 patients unless otherwise contraindicated. Management of ischemic stroke was determined by patient-specific variables and are described in the results below.

Ethical approval

The research received IRB approval from the New York Medical College Institutional Review Board (IRB#14130). Due to the retrospective nature of the chart review, written informed consent was waived for this study.

Results

We provided care for 637 patients with COVID-19 infection between March 1, 2020, and April 30, 2020. During this time, patients with acute ischemic stroke were diagnosed, 13 of whom had associated COVID-19 infection. Of these 13 COVID-19 patients with acute ischemic stroke, five with bihemispheric ischemic strokes were identified [Table 1]. Three were females and the median age was 54 (range 41–67) years. Four patients had preexisting vascular risk factors. All five patients were managed for severe COVID-19-related pneumonia warranting critical care support after presenting with varying combinations of fever, cough, dyspnea, and fatigue. All five patients required mechanical ventilation. All five developed lymphopenia, leukocytosis, and progressive thrombocytopenia, all had elevated serum ferritin, LDH, d-dimer, and interleukin-6 (IL-6) levels, all experienced acute kidney injury and transaminitis, and four developed hyperfibrinogenemia. All five patients underwent neuroimaging with CT for persistently depressed mentation despite discontinuation of sedating agents for a median of 16 (range 5–27) days

Table 1: Clinical Characteristics of 5 patients with coronavirus disease 2019 and bihemispheric ischemic strokes

Variable	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	41	67	67	47	52
Sex	Female	Male	Female	Female	Male
Preexisting stroke risk factors	None	Hyperlipidemia DM type 2	Hypertension DM type 2	DM type 2 morbid obesity	Hyperlipidemia DM, CAD, PVD morbid obesity
COVID-19 symptoms on admission	Fever, cough, dyspnea	Fever, cough, dyspnea	Dyspnea, fatigue	Fever, dyspnea	Fever, cough, dyspnea
Reason for neuroimaging	Depressed LOC, left hemiparesis	Depressed LOC	Depressed LOC, diminished brainstem reflexes	Depressed LOC	Depressed LOC, diminished brainstem reflexes
NIHSS#	22	29	35	23	28
Imaging modality	CT/CTA	C/CTA	CT	CT	CT
Time from admission to imaging (days)	9	18	5	27	15
Ventilatory support	Mechanical ventilation	Mechanical ventilation	Mechanical ventilation	Mechanical ventilation	Mechanical ventilation
Stroke etiology	Disseminated intravascular coagulation	Atrial fibrillation	Presumed hypercoagulable state	Presumed hypercoagulable state	Atrial fibrillation
Treatment for stroke	Heparin infusion followed by aspirin 81 mg daily	Eliquis 5 mg twice daily	Heparin infusion followed by aspirin 81 mg daily	Heparin infusion	Heparin infusion
White cell count (k/mm^3)					
Initial	21.3	7.4	11.4	8.6	10.6
Peak	51.3	30.4	34.3	23.0	31.1
Lymphocyte count (%)					
Initial	2.5	8.6	6.0	30.0	4.7
Trough	0.0	0.0	3.0	4.0	3.5
Platelet count (k/mm^3)					
Initial	216	103	406	133	257
Trough	27	23	258	4	124
PT (s)					
Initial	12.6	10.5	10.7	11.0	10.4
Peak	15.0	26.6	12.0	>143.7	12.1
PTT (s)					
Initial	36.7	29.0	30.7	25.8	28.9
Peak	83.2	72.3	>133.6	>133.6	89.6
D-dimer (mg/L-FEU)					
Initial	0.54	1.62	3.68	6.35	19.17
Peak	>35.20	>35.20	>35.20	>35.20	>35.20
Fibrinogen (mg/dL)					
Initial	NT	NT	NT	322	641
Peak	280	624	>960	871	798
Ferritin (µg/L)					
Initial	261.5	903.7	750.5	216.4	3082.2
Peak	2454.1	5200.5	>40,000.0	34,563.2	3082.2
LDH (U/L)					
Initial	296	502	579	380	726
Peak	6127	1857	5143	2373	774
Creatinine (mg/dL)					
Initial	0.51	1.16	1.06	0.79	8.31
Peak	6.99	7.74	3.05	1.56	15.81
Dialysis	Yes	Yes	No	No	Yes
AST/ALT (U/L)					
Initial	89/59	63/44	43/29	51/79	273/442
Peak	589/246	106/106	2400/1934	1028/795	273/442

Contd...

Table 1: Contd...

Variable	Case 1	Case 2	Case 3	Case 4	Case 5
IL-6 (pg/mL)	7.7	34	12.8	109	107
Outcome status	Discharged to rehabilitation facility (mRs 4)	Discharged to rehabilitation facility (mRs 5)	Death	Death	Death

Basic Skills in Interpreting Laboratory Data, 6th ed. Bethesda, MD: American Society of Health-System Pharmacists, 2017; and DiPiro JT, Talbert RL, Yee GC, *et al*., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill, 2017.[7] *Reference ranges: White cell count: 4.5-10.8 k/mm^3, lymphocyte count: 18%-53%, platelet count: 160-410 k/mm^3, PT: 9.8-12.0 s, PTT: 25.0-32.0 s, D-dimer: <0.59 mg/L-FEU, fibrinogen: 180-400 mg/dL, ferritin: 9.0-120.0 µg/L, LDH: 125-220 U/L, creatinine: 0.57-1.11 mg/dL, AST (SGOT): 4-35 U/L, ALT (SGPT): 6-55 U/L, IL-6: ≤1.8 pg/mL. #NIHSS ranges from 0 to 42, with higher numbers indicating more severe stroke. NIHSS: National Institutes of Health Stroke Scale, CT: Computed tomography, CTA: CT angiography, LOC: Level of consciousness, DM: Diabetes mellitus, CAD: Coronary artery disease, PVD: Peripheral vascular disease, AST: Aspartate transaminase, ALT: Alanine aminotransferase, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic-oxalacetic transaminase, PTT: Partial thromboplastin time, PT: Prothrombin time, IL-6: Interlukin-6, mRS: Modified Rankin Scale, LDH: Lactate dehydrogenase, COVID-19: Coronavirus disease 2019, NT: Not taken

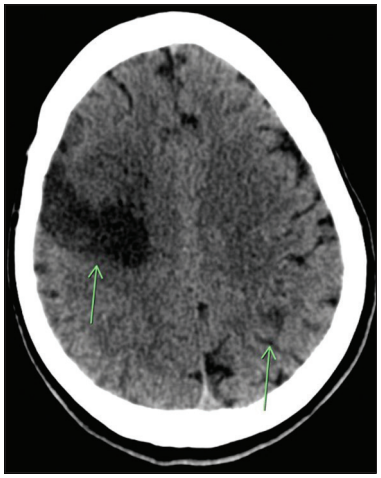

Figure 1: Computed tomography brain noncontrast of case 1 demonstrating small to moderately sized infarct within the right frontal lobe and small infarct within the left parietal vertex (green arrows)

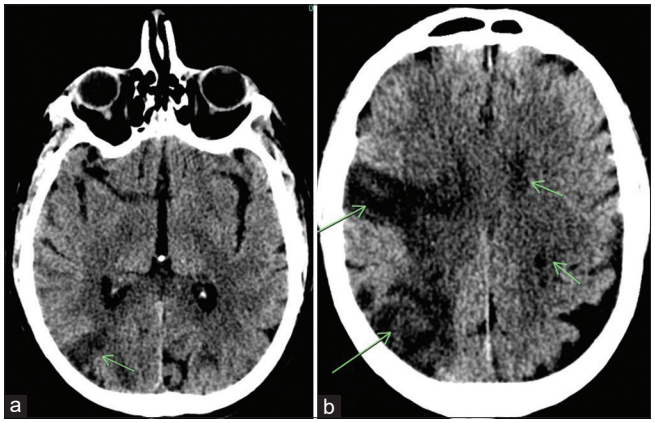

Figure 2: Computed tomography brain noncontrast of case 2 demonstrating (a) infarct within the right occipital lobe, (b) moderate to large infarcts within the right frontal and parietal lobes and small infarcts within the left frontoparietal centrum semiovale white matter. (Infarcts demonstrated by green arrows)

after admission. Neuroimaging revealed multifocal acute-to-subacute ischemic strokes with bihemispheric involvement [Figures 1-5]. All the infarcts were territorial and appeared to be embolic except for patient 4, who developed a combination of branch occlusions and bilateral capsular penetrator infarcts. CTA was completed in two patients and did not demonstrate a large-vessel occlusion or severe vessel stenosis. All patients were ineligible for acute thrombolysis or endovascular intervention as they presented outside of the therapeutic time window for acute stroke intervention. Outcome was poor in all patients. Two patients were discharged to rehabilitation facilities (1 acute and 1 subacute) with mRs scores of 4 and 5, respectively. Three patients died, of whom two patients with do-not-resuscitate code status died from cardiopulmonary arrest and one patient was declared brain dead.

Discussion

We report 5 cases of patients hospitalized for primary SARS-CoV-2 infection and discovered multifocal ischemic strokes with bihemispheric involvement during their hospital course. All patients warranted critical care support for severe COVID-19-related pneumonia with evidence of multiorgan failure. All patients underwent neuroimaging with CT primarily for persistent depressed mentation despite discontinuation or tapering of sedation, plus or minus focal neurologic deficits. The average time from admission to CT was 15 days. CT demonstrated multifocal ischemic strokes with bihemispheric in all patients, likely contributing to poor clinical status. All patients were under 70 years of age, and although they had vascular risk factors, they all had severe COVID-19 infection with significant elevations in D-dimer, ferritin, and IL-6 suggestive of hyperinflammation response. All patients had poor outcomes with death or severe disability. There are emerging data on COVID-19-related neurologic complications and its implication of severe disease and poor outcomes. A recent case series of patients with COVID-19 in Wuhan, China, reported an incidence of stroke of 5.7% in severe infection versus 0.8% in nonsevere infection.[8] It is known that systemic inflammatory processes impact patient susceptibility for stroke and that patients with stroke and systemic inflammation typically have poorer outcomes given exacerbation of cerebral damage through interleukin (IL) and neutrophil-dependent mechanisms.[12-14]

The incidence of bihemispheric involvement in patients with acute ischemic stroke is 1.4%–6.1% and bihemispheric

strokes are associated with poorer outcomes.[11,15-18] We found bihemispheric involvement in 5 (38%) patients with acute ischemic stroke and concomitant COVID-19, which is higher than reported. Outcomes in our study group were similar with increased death and disability. Given involvement of multiple vascular distributions, a central embolic source typically involving the heart, aorta, or a hypercoagulable state should be considered. The underlying mechanism for cerebral ischemia in COVID-19 patients is unclear. The relationship between stroke and COVID-19 may be coincidental, given the prevalence of traditional vascular risk factors within this population.[9] Nevertheless, there are significant data demonstrating high risk for coagulopathy and venous and arterial thromboembolic complications in patients with COVID-19.[6,7] Patients with COVID-19 are reported to have abnormal coagulation represented by higher D-dimer and fibrin degradation product levels, suggestive of recent, or acute clot development.[19] In one study, an 18-fold increase in odds of death was noted in patients with COVID-19 and admission D-dimer levels >1 μg/L.[4]

Transient causes of thromboembolism associated with critical illness may play a role in the mechanism of cerebral ischemia in COVID-19 patients. Multiple infarcts, significant coagulopathy and antiphospholipid antibodies (aPL), primarily anticardiolipin immunoglobulin (Ig) A and beta-2 glycoprotein IgM and IgG, have been described in patients with COVID-19 in China.[20] Lupus anticoagulant and prolonged aPTT have also been reported in hospitalized patients with COVID-19.[21,22] It is known that aPL antibodies can transiently arise in patients with various viral illnesses and that in some cases the presence of aPL antibodies is associated with thrombosis.[23] However, the difficulty remains differentiating from other causes of multiple thrombotic events in critically ill patients, such as disseminated intravascular coagulation, which was reported in 71.4% of nonsurvivors in the late stages of COVID-19 pneumonia.[19] Furthermore, arrhythmias such as atrial fibrillation is prevalent in acute illness and is associated with thromboembolism.[24]

Vasculopathy due to direct vascular endothelial injury is another proposed mechanism of cerebral ischemia in patients with COVID-19. It is known that SARS-CoV-2 infects cells by the binding of COVID-19 virus spike with angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in multiple organs and endothelial cells.[25] Postmortem analysis in patients with COVID-19 have reported direct viral infection of the endothelial cells and accumulation of inflammatory cells from host inflammatory response leading to diffuse endothelial dysfunction and cell death.[26] Endothelial dysfunction results in vasoconstriction and subsequent ischemia, and procoagulant state.[27] Furthermore, patients with preexisting atherosclerotic disease may be prone to plaque disruption and thrombosis due to activation of immune and inflammatory pathways.[28]

Cytokine storm as a hyperinflammatory response secondary to COVID-19 has been examined as a cause of critical illness in this patient population, implicated in: Acute respiratory distress syndrome, ischemic stroke, myocardial infarction, and more.[29,30] Patients who died from severe infection were found to have higher levels of cytokine storm markers as well as evidence of systematic binding of the SARS-CoV-2 S protein to endothelial cells of the body.[3,31] While the damage of healthy cells is usually initially isolated to the lungs, it often spreads to other organs including the vasculature and the brain. COVID-19 patients have higher risk of hypercoagulability and arteriovenous thrombosis.[32,33]

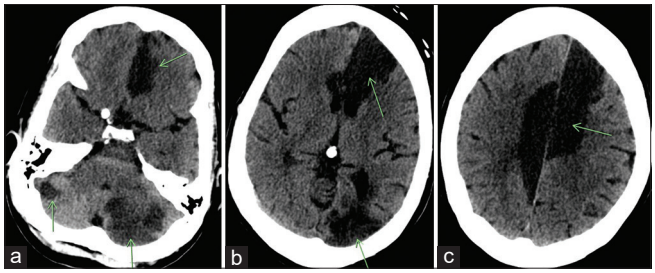

Figure 3: Computed tomography brain noncontrast of case 3 demonstrating (a) infarcts within the bilateral cerebellum and left paramedian inferior frontal lobe (green arrow), (b) infarcts within the left paramedian frontal lobe and left occipital lobe, (c) and infarcts within the bilateral paramedian frontal lobes (Green arrow)

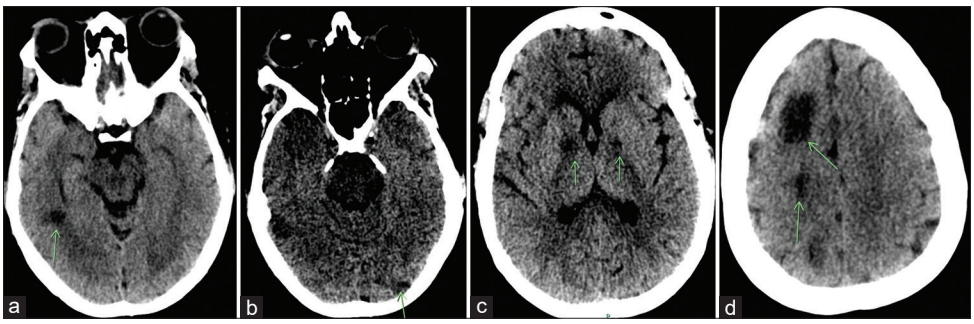

Figure 4: Computed tomography brain noncontrast of case 4 demonstrating (a) small infarct within the right temporal lobe, (b) small infarct within the left occipital lobe, (c) small infarcts within the bilateral internal capsule, (d) and infarcts within the right frontal and parietal lobes (Infarcts demonstrated by green arrow)

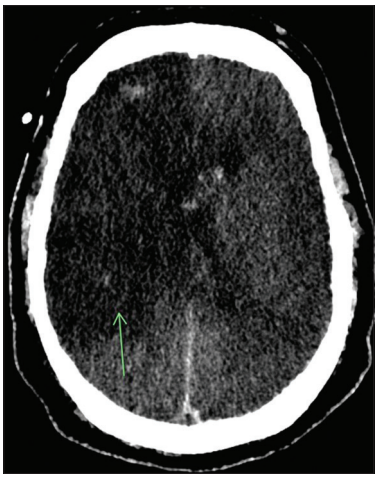

Figure 5: Computed tomography brain noncontrast of case 5 demonstrating extensive infarcts within the right anterior cerebral artery, right middle cerebral artery (MCA), left MCA, and the bilateral posterior cerebral artery territories (Infarct illustrated by green arrow)

As in our present study, patients with COVID-19 and stroke have been found to have elevated acute phase reactants including D-dimer, which were correlated with negative outcome.[29,34]

Given proposed mechanisms of cerebral ischemia in patients with COVID-19, management goals may include early treatment to minimize viral replication, stabilize endothelium and decrease clot formation, especially in patients who carry risk factors for severe infection and adverse outcomes. Anti-inflammatory anticytokine agents, medications that target ACE2 and its ligand-COVID-19 spike protein, statins and anticoagulants may be beneficial but warrant further studies including clinical trials.[35-40]

Limitations of the present study include small sample size and involvement of a single center. Though one can examine the associated clinical and imaging findings in this cohort, this prevents the establishment of causality between COVID-19 and bihemispheric stroke. The number of patients with ischemic stroke in the setting of COVID-19 may be underestimated, as some patients were hemodynamically unstable and therefore could not safely undergo neuroimaging. Furthermore, some patients may have received paralytics confounding the neurological examination resulting in delay to diagnosis of stroke.

Conclusions

Neurologic complications including stroke is implicated in SARS-CoV-2 infection. Multifocal ischemic stroke with bihemispheric involvement should be considered in COVID-19 patients with severe infection and poor neurologic status and may be associated with poor outcomes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. **Hui** DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, *et al.* The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health – The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020;91:264-6.
2. Mahase E. COVID-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. BMJ 2020;368:m1036.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054-62.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
6. Klok FA, Kruip MJ, van der Meer NJ, Arbous MS, Gommers D, Kant KM, *et al.* Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res 2020;191:148-50.
7. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, *et al.* Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9-14.
8. 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.
9. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al.* Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. Int J Infect Dis 2020;94:91-5.
10. 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.
11. Bogousslavsky J, Bernasconi A, Kumral E. Acute multiple infarction involving the anterior circulation. Arch Neurol 1996;53:50-7.
12. Emsley HC, Hopkins SJ. Acute ischaemic stroke and infection: Recent and emerging concepts. Lancet Neurol 2008;7:341-53.
13. McColl BW, Allan SM, Rothwell NJ. Systemic infection, inflammation and acute ischemic stroke. Neuroscience 2009;158:1049-61.
14. McColl BW, Rothwell NJ, Allan SM. Systemic inflammatory stimulus potentiates the acute phase and CXC chemokine responses to experimental stroke and exacerbates brain damage via interleukin-1- and neutrophil-dependent mechanisms. J Neurosci 2007;27:4403-12.
15. Altieri M, Metz RJ, Müller C, Maeder P, Meuli R, Bogousslavsky J. Multiple brain infarcts: Clinical and neuroimaging patterns using diffusion-weighted magnetic resonance. Eur Neurol 1999;42:76-82.
16. Baird AE, Lövblad KO, Schlaug G, Edelman RR, Warach S. Multiple acute stroke syndrome: Marker of embolic disease? Neurology 2000;54:674-8.
17. Roh JK, Kang DW, Lee SH, Yoon BW, Chang KH. Significance of

acute multiple brain infarction on diffusion-weighted imaging. Stroke 2000;31:688-94.
18. Saito K, Moriwaki H, Oe H, Miyashita K, Nagatsuka K, Ueno S, *et al.* Mechanisms of bihemispheric brain infarctions in the anterior circulation on diffusion-weighted images. AJNR Am J Neuroradiol 2005;26:809-14.
19. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-7.
20. 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.
21. Bowles L, Platton S, Yartey N, Dave M, Lee K, Hart DP, *et al.* Lupus anticoagulant and abnormal coagulation tests in patients with COVID-19. N Engl J Med 2020;383:288-90.
22. Harzallah I, Debliquis A, Drénou B. Frequency of lupus anticoagulant in COVID-19 patients. J Thromb Haemost 2020;18:2778.
23. Uthman IW, Gharavi AE. Viral infections and antiphospholipid antibodies. Semin Arthritis Rheum 2002;31:256-63.
24. Clayton B, Ball S, Read J, Waddy S. Risk of thromboembolism in patients developing critical illness-associated atrial fibrillation. Clin Med (Lond) 2018;18:282-7.
25. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, *et al.* Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;111:2605-10.
26. 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.
27. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: A marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003;23:168-75.
28. Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, *et al.* Inflammation, immunity, and infection in atherothrombosis: JACC review topic of the week. J Am Coll Cardiol 2018;72:2071-81.
29. Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, *et al.* Cytokine Storm in COVID-19 – Immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM consortium position paper. Front Immunol 2020;11:1648.
30. Vaninov N. In the eye of the COVID-19 cytokine storm. Nat Rev Immunol 2020;20:277.
31. Katsiki N, Banach M, Mikhailidis DP. Lipid-lowering therapy and renin-angiotensin-aldosterone system inhibitors in the era of the COVID-19 pandemic. Arch Med Sci 2020;16:485-9.
32. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, *et al.* Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 2020;11:827.
33. Kennedy RH, Silver R. Neuroimmune signaling: Cytokines and the CNS. In: Pfaff DW, Volkow ND, editors. Neuroscience in the 21st Century. New York, NY: Springer; 2016. p. 1-41. [doi: 10.1007/978-1-4614-6434-1_174-1].
34. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094-9.
35. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, *et al.* Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet 2020;395:1407-9.
36. Liu M, Wang T, Zhou Y, Zhao Y, Zhang Y, Li J. Potential role of ACE2 in coronavirus disease 2019 (COVID-19) prevention and management. J Transl Int Med 2020;8:9-19.
37. Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, *et al.* Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect 2020;9:757-60.
38. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, *et al.* Renin-angiotensin-aldosterone system inhibitors and risk of COVID-19. N Engl J Med 2020;382:2441-8.
39. Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. N Engl J Med 1995;332:488-93.
40. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, *et al.* ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18:1023-6.