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Case Report

Large Vessel Occlusion Secondary to COVID-19 Hypercoagulability in a Young Patient: A Case Report and Literature Review

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) initially most appreciated for its pulmonary symptoms, is now increasingly recognized for causing multi-organ disease and stroke in the setting of a hypercoagulable state. We report a case of 33-year-old African American woman with COVID-19 who developed acute malignant middle cerebral artery infarction due to thromboembolic occlusion of the left terminal internal carotid artery and middle cerebral artery stem. Mechanical thrombectomy was challenging and ultimately unsuccessful resulting in limited reperfusion of <67% of the affected vascular territory, and thrombectomized clot was over 50 mm in length, at least three times the average clot length. The final stroke size was estimated at 224 cubic centimeters. On admission her D-dimer level was 94,589 ng/mL (normal 0−500 ng/ml). Throughout the hospitalization D-dimer decreased but never reached normal values while fibrinogen trended upward. Hypercoagulability panel was remarkable for mildly elevated anticardiolipin IgM of 16.3 MPL/mL (normal: 0−11.0 MPL/mL). With respect to remaining stroke workup, there was no evidence of clinically significant stenosis or dissection in the proximal internal carotid artery or significant cardioembolic source including cardiomyopathy, atrial fibrillation, cardiac thrombus, cardiac tumor, valvular abnormality, aortic arch atheroma, or patent foramen ovale. She developed malignant cytotoxic cerebral edema and succumbed to complications. This case underscores the importance of recognizing hypercoagulability as a cause of severe stroke and poor outcome in young patients with COVID-19 and highlights the need for further studies to define correlation between markers of coagulopathy in patients with COVID-19 infection and outcome post stroke.

Key Words: COVID-19—SARS-CoV-2—Coagulopathy—Large vessel occlusion—Stroke—Young patient—Hypercoagulability

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the associated disease is known as the coronavirus disease 2019 (COVID-19) and was first appreciated for causing severe respiratory symptoms.[1,2] However, reports have emerged describing extrapulmonary involvement and in particular an increased risk for venous and arterial thromboembolism in the form of acute ischemic stroke.[3−5] More alarming are the reports of acute ischemic stroke in patients younger than 50 years of age with SARS-CoV-2 infection, a patient population in which ischemic strokes are relatively infrequent but

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potentially disabling.[5,6] In this case report, we describe a young patient with extensive large vessel thrombosis in the setting of PCR confirmed SARS-CoV-2 infection.

Case

A 33-year-old African American woman with a past medical history of morbid obesity and no personal or family history of thromboembolic events in first degree relatives, developed cough, fever and fatigue after exposure to a SARS-CoV-2 confirmed family member. The patient initially tried outpatient management with self-quarantine, azithromycin and promethazine dextromethorphan. On day 9 of symptoms, she developed acute right hemiparesis, global aphasia, left gaze deviation and left homonymous hemianopsia and presented to a primary stroke center as a wake-up stroke, 12.5 h after last known well. She arrived outside of the extended 9-h therapeutic window for intravenous thrombolysis and was emergently transferred to a comprehensive stroke center for thrombectomy. The National Institutes of Health Stroke Scale (NIHSS) score was 15 at 12.5 h after last known well. Alberta stroke program early CT score (ASPECTS) was 6 on arrival (Fig. 1) and a left internal carotid artery (ICA) terminus and the proximal middle cerebral artery (M1) occlusion was confirmed with a CT angiogram. CT perfusion was favorable for intervention, and she underwent a challenging mechanical thrombectomy of the terminal ICA and M1 lesions measuring over 50 mm in length utilizing a Trevo 4 × 30 stent retriever and ACE 68 aspiration catheter. After 3 passes, thrombectomy was ultimately unsuccessful resulting in limited reperfusion of <67% of the affected vascular territory with Thrombolysis in Cerebral Infarction scale (TICI) improving from 0 to 2A. The final stroke size was estimated on a non-contrast head CT at 224 cubic centimeters by the widely accepted Tada Formula of a × b × c × 1/2, where "a" and "b" indicate the perpendicular diameters of the largest area of ischemia, and "c" is the maximal diameter in the remaining third dimension

She was confirmed to be SARS-CoV-2 positive. On admission her D-dimer level was 94,589 ng/mL (normal 0−500 ng/ml). After thrombectomy transiently her D-dimer peaked, while fibrinogen nadired. However, throughout the hospitalization D-dimer decreased but never reached normal values while fibrinogen trended upward (Fig. 2). Hypercoagulability panel revealed mildly elevated anticardiolipin IgM of 16.3 MPL/mL

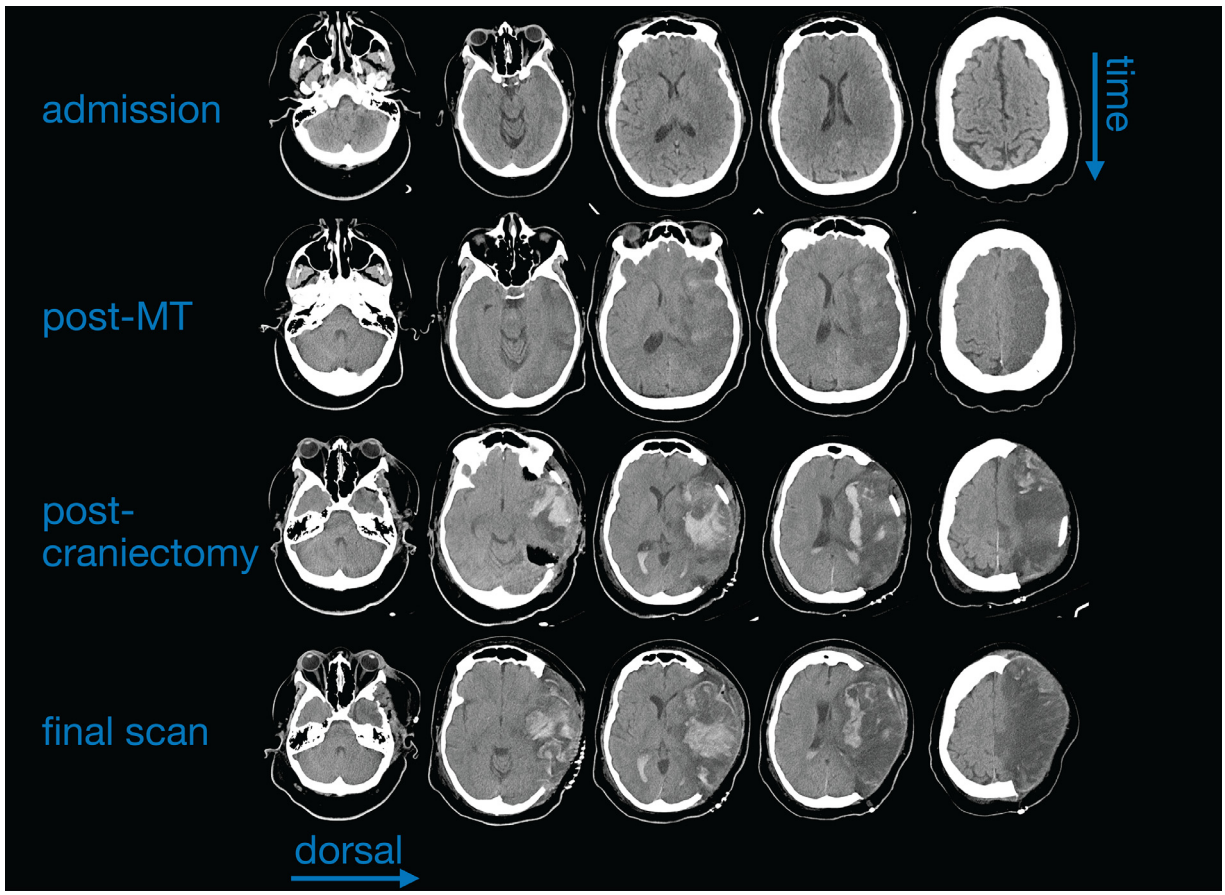
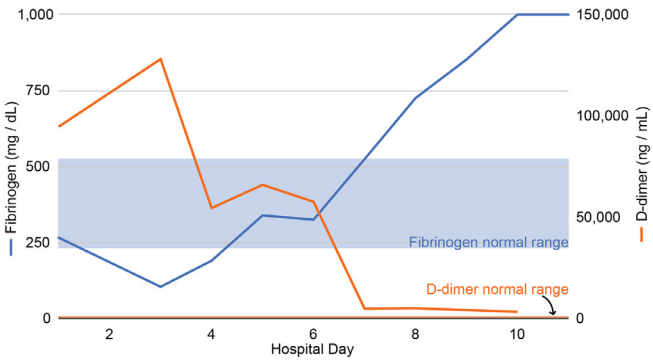


Fig. 1. *Serial CT images during hospitalization. Four CT studies are shown during the patient's hospitalization, with later studies being lower rows. Similar axial cuts are shown from each studies. Left is most ventral, right is dorsal.*

Lupus Anticoagulant	PT High sensitivity	PTT High sensitivity	Russell's Viper Venom Screen	RVVT Screen 1:1 mixing study	DRVV Confirmation	DRVV Confirm 1:1 mixing study	LA Ratio	Protein C	Protein S
Negative	23 (22.8 - 31.5 sec)	11.6 (9.1 - 12.1 sec)	41.6 (27.9 - 40.3 sec)	39.2 (sec)	35.2 (22.8 - 31.5 sec)	39.1 (sec)	1.1 (0.9 - 1.20)	85 (65 - 174%)	129 (65 - 132%)

MTFHR C677T	MTFHR A1298C	beta 2 glycoprotein IgG	beta 2 glycoprotein IgM	Prothrombin gene mutation	Antithrombin III	Factor V Mutation	Homocysteine	Anticardiolipin IgG	Anticardiolipin IgM
Negative	Negative	<9.4 (U/mL)	<9.4 (U/mL)	Absent	84 (83 - 128%)	Absent	5 (5 - 15 µmol/L)	2.7 (0 - 15.0 GPL/mL)	16.3 (0 - 11.0 MPL/mL)



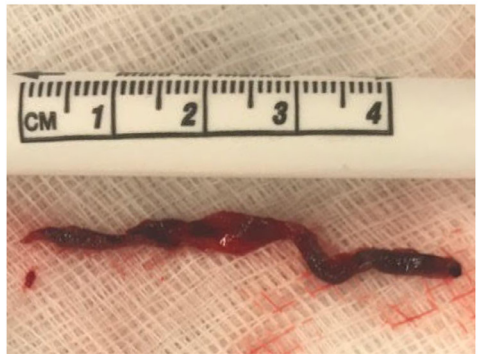


Fig. 2. *Laboratory values and thrombus post-thrombectomy. Top: Patient results from tertiary care hospital hypercoagulability panel, along with normal laboratory values are shown. Bottom left: Fibrinogen (normal 231–523 mg/dl) and D-dimer (normal 0–500 ng/ml) laboratory trends during hospitalization. Normal values shown by orange and blue shaded boxes. Bottom right: one of multiple thrombi removed during mechanical thrombectomy procedure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)*

(normal: 0–11.0 MPL/mL) with the remaining results largely unremarkable (Fig. 2). With respect to remaining stroke workup, there was no evidence of clinically significant stenosis or dissection in the proximal ICA. Cardioembolic workup only showed a prolonged QTc of 498 ms, likely secondary to her taking azithromycin and a trivially sized pericardial effusion, but showed no evidence of cardiomyopathy, atrial fibrillation, cardiac thrombus, cardiac tumors, valvular abnormalities, aortic arch atheroma, or patent foramen ovale.

Unfortunately, at 38 hours after last known well (25 hours after thrombectomy), she developed signs and symptoms of malignant cerebral edema with uncal and transtentorial herniation which was confirmed radiographically and treated with decompressive hemicraniectomy at 42 hours after last known well (29 hours after thrombectomy). Her hospital course was complicated by sepsis secondary to enterococcus and proteus isolated from blood cultures. The patient had a cardiac arrest on hospital day 11 and subsequently passed despite aggressive resuscitation.

Discussion

The relative proportion of strokes in the young (under 45 years old) has been increasing over the past few decades.[7] In this age group, African Americans and Hispanics have higher stroke rates than Caucasians.[8] In one study hematologic and vasculopathic etiologies made up 44% of strokes in young patients.[9] In the young, the most common causes are nonatherosclerotic, more often secondary to cardioembolism or arterial dissection,[10] with risk factors including oral contraceptives, smoking, migraine, drug use, infections, vasculitis, connective tissue disease, congenital and acquired thrombophilia, malignancy and pregnancy, amongst others.[7,10]

Depending on the location of occlusion, an average clot length may be 10–16 mm.[11,12] In the case of our patient, the largest thrombus retrieved was over 50 mm in length (Fig. 2), at least three times the average clot length. Although there are conflicting data,[13–15] clot length has been associated with decreased reperfusion rate and worse outcome.[16] In fact, the odds ratio for worse outcomes increases by 1.24 for every 5 mm increment over 14 mm.[16]

An independent risk factor for stroke (odds ratio 3.4–14.5[17]) is an inflammation-driven[18] hypercoagulable and vasculopathic state[19] from recent infection, especially respiratory in origin.[20–22] Higher incidence of ischemic stroke has been reported with other respiratory viruses such as influenza.[23,24] Ischemic stroke has also been observed in other coronaviruses[25] and recent data suggests COVID-19 confers a greater risk of stroke than influenza.[26]

Clinical manifestations of COVID-19 often include fatigue, fever, shortness of breath and cough, along with neurological symptoms of anosmia and hypogeusia[27]; other findings include sore throat, anorexia, myalgia, sputum production,

hemoptysis, abdominal pain, nausea and vomiting.[28] SARS-CoV-2 spike glycoprotein gains entry to cells via the angiotensin-converting enzyme 2 (ACE2), which is expressed in oral and nasal mucosa, lung, through the gastrointestinal tract, liver, kidney and the brain.[29] Notably, it is expressed in vascular (arterial and venous) endothelium throughout much of the body.[29] ACE2, part of the brain's renin angiotensin system (RAS), decreases sympathetic tone while increasing both parasympathetic tone and baroreflex sensitivity leading to a net improvement in brain blood pressure regulation.[30] ACE2 activity has been shown to increase atherosclerotic plaque stability, inhibit thrombus formation and is neuroprotective through inhibition of early phase inflammatory response during cerebral ischemic.[31] Cellular infection with SARS-CoV-2 is believed to lead to a decrease of ACE2 expression causing a net vasoconstriction, prothrombotic and proinflammatory state in the brain.[31]

Current understanding of COVID-19 suggests an extreme hypercoagulable state,[32,33] that is likely driven by a combination of inflammation[34] and brainwide RAS dysregulation.[31] Linking scientific understanding with paraclinical findings, D-dimer elevation has been shown in stroke patients with recent infection compared with stroke patients without infection.[35] In COVID-19, D-dimer elevation also appears to be an important prognostic marker[2,36] and has been observed in initial COVID-19 stroke patients.[5,6,37] Our patient's dismal outcome correlated with severely elevated D-dimer of about 95,000 ng/ml on admission. Platelet activation, impaired endothelial functioning and dehydration are also thought to play a role in strokes preceded by infection.[38] Concurrent endothelial damage in combination with a hypercoagulable state in COVID-19 disease highly favors thrombus formation.[39]

Early reports from China described cerebrovascular disease in about 5% of patients with severe COVID-19 disease, with strokes occurring almost two weeks after initial diagnosis.[37,40] Chinese populations are estimated to have between 0.1 and 0.7 fold risk for venous thromboembolism (VTE) relative to caucasians.[41–43] As the virus spread across the globe, more recently emergent large vessel occlusion (ELVO) has been reported in non-Chinese patients with COVID-19.[5,6] As an African American, our patient's ethnicity put her at the greatest risk, 1.2−1.4 fold risk of Caucasians, for VTE.[32,43,44]

Our patient also had mildly elevated IgM anticardiolipin antibodies, possibly contributing to her hypercoagulable state.[45] In one study, isolated IgM anticardiolipin antibodies made up 14% of patients with antiphospholipid syndrome and having an isolated IgM antiphospholipid syndrome conferred a stroke odds ratio of 3.8.[46] In women, elevated anticardiolipin antibodies are significant for increased risk of stroke.[47] Our patient did not have prior diagnosis of antiphospholipid syndrome, nor did she yet meet criteria for formal diagnosis, which requires two studies separated by a 12 week interval;[48] however, acute infections can lead to short-term increases in anticardiolipin antibodies.[49,50] Elevated anticardiolipin antibodies have also been observed in patients with thrombotic strokes,[51] including young patients[50] and in patients with infection-associated strokes.[35] Although, it is yet to be determined if elevations are pathogenic or indirect.[22,50,52] Elevated IgA anticardiolipin antibodies have been reported in COVID-19 patients with clinically significant coagulopathies.[53] Transient increases in anticardiolipin antibodies could be a mechanism for COVID-19-associated hypercoagulability and may have played a role in this case; however, anticardiolipin antibody levels have not been reported in recent COVID-19 stroke case series.[5,6]

It is imperative that physicians take into consideration the ELVO risk in young patients with COVID-19. Some have suggested prophylactic anticoagulation doses in COVID-19 outpatients,[54] but current NIH guidelines do not support initiating anticoagulation or antiplatelet therapy in VTE prevention of non-hospitalized patients without other risk factors.[55] Patients already on anticoagulation or antiplatelet therapies should be maintained on their current therapy when they are diagnosed with COVID-19.[55] Hospitalized patients with COVID-19 should receive standard VTE-prophylaxis similarly to patients hospitalized without COVID-19.[55] Post-hospitalized COVID-19 patients at VTE risk or presumed to have hospital-associated VTE should receive a full three month course of therapeutic anticoagulation.[56]

This case underscores the importance of recognizing hypercoagulability as a cause of severe stroke in young patients with COVID-19, particularly of African American descent, and of assessing and trending markers of coagulopathy, such as D-dimer, fibrinogen and anti-cardiolipin antibodies. Further studies are needed to define specific correlation between markers of coagulopathy in patients with COVID-19 infection and outcome post stroke.

Disclosure

The authors report no disclosures related to this manuscript.

Informed consent

Unfortunately the patient passed. The family gave verbal consent for the patient's case to be published.

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References

1. WHO Timeline - COVID-19 [online]. Accessed at: https://www.who.int/news-room/detail/08-04-2020-who-timeline—covid-19. Accessed April 14, 2020.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in

Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062. Accessed at: http://dx.doi.org/10.1016/S0140-6736(20)30566-3.
3. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res Epub 2020. Accessed at: http://dx.doi.org/10.1016/j.thromres.2020.04.013.
4. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost Epub 2020. Accessed at: http://dx.doi.org/10.1111/jth.14830.
5. Avula A, Nalleballe K, Narula N, et al. COVID-19 presenting as stroke. Brain Behav Immun 2020. Accessed at: http://www.sciencedirect.com/science/article/pii/S0889159120306851.
6. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med 2020. Accessed at: http://dx.doi.org/10.1056/NEJMc2009787.
7. Hathidara MY, Saini V, Malik AM. Stroke in the young: a global update. Curr Neurol Neurosci Rep 2019;19:91.. Accessed at: http://dx.doi.org/10.1007/s11910-019-1004-1.
8. Chong JY, Sacco RL. Epidemiology of stroke in young adults: race/ethnic differences. J Thromb Thrombolysis 2005;20:77-83. Accessed at: http://dx.doi.org/10.1007/s11239-005-3201-9.
9. Varona JF, Guerra JM, Bermejo F, Molina JA, Gomez de la Cámara A. Causes of ischemic stroke in young adults, and evolution of the etiological diagnosis over the long term. Eur Neurol 2007;57:212-218. Accessed at: http://dx.doi.org/10.1159/000099161.
10. Ferro JM, Massaro AR, Mas J-L. Aetiological diagnosis of ischaemic stroke in young adults. Lancet Neurol 2010;9:1085-1096. Accessed at: http://dx.doi.org/10.1016/S1474-4422(10)70251-9.
11. Bhogal P, Bücke P, Ganslandt O, Bäzner H, Henkes H, Aguilar Pérez M. Mechanical thrombectomy in patients with M1 occlusion and NIHSS score ≤5: a single-centre experience. BMJ 2016:165-171. Accessed at: http://dx.doi.org/10.1136/svn-2016-000052.
12. Behrens L, Möhlenbruch M, Stampfl S, et al. Effect of thrombus size on recanalization by bridging intravenous thrombolysis. Eur J Neurol 2014;21:1406-1410. Accessed at: http://dx.doi.org/10.1111/ene.12509.
13. Seker F, Pfaff J, Wolf M, et al. Impact of thrombus length on recanalization and clinical outcome following mechanical thrombectomy in acute ischemic stroke. J Neurointerv Surg 2017;9:937-939. Accessed at: http://dx.doi.org/10.1136/neurintsurg-2016-012591.
14. Shu L, Riedel C, Meyne J, Jansen O, Jensen-Kondering U. Successful recanalization in acute basilar artery occlusion treated with endovascular therapy is independent of thrombus length. J Neurointerv Surg 2017;9:1047-1052. Accessed at: http://dx.doi.org/10.1136/neurintsurg-2016-012634.
15. Gralla J, Burkhardt M, Schroth G, et al. Occlusion length is a crucial determinant of efficiency and complication rate in thrombectomy for acute ischemic stroke. AJNR Am J Neuroradiol 2008;29:247-252. Accessed at: http://dx.doi.org/10.3174/ajnr.A0790.
16. Yoo AJ, Khatri P, Mocco J, et al. Impact of thrombus length on outcomes after intra-arterial aspiration thrombectomy in the therapy trial. Stroke 2017;48:1895-1900. Accessed at: http://dx.doi.org/10.1161/STROKEAHA.116.016253.
17. Brainin M, Tabernig S, Heiss W-D. Textbook of Stroke Medicine. Cambridge University Press; 2014. Accessed at: https://play.google.com/store/books/details?id=wU5CBAAAQBAJ.
18. Esenwa CC, Elkind MS. Inflammatory risk factors, biomarkers and associated therapy in ischaemic stroke. Nat Rev Neurol 2016;12:594-604. Accessed at: http://dx.doi.org/10.1038/nrneurol.2016.125.
19. Jillella DV, Wisco DR. Infectious causes of stroke. Curr Opin Infect Dis 2019;32:285-292. Accessed at: http://dx.doi.org/10.1097/QCO.0000000000000547.
20. Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. Nat Rev Neurol 2010;6:681-694. Accessed at: http://dx.doi.org/10.1038/nrneurol.2010.163.
21. Roquer J, Cuadrado-Godia E, Giralt-Steinthauer E, et al. Previous infection and stroke: a prospective study. Cerebrovasc Dis 2012;33:310-315. Accessed at: http://dx.doi.org/10.1159/000335306.
22. Paganini-Hill A, Lozano E, Fischberg G, et al. Infection and Risk of Ischemic Stroke. Stroke 2003;34:452-457. American Heart Association. Accessed at: https://doi.org/10.1161/01.STR.0000053451.28410.98.
23. Rubinson L, Mutter R, Viboud C, et al. Impact of the fall 2009 influenza A(H1N1)pdm09 pandemic on US hospitals. Med Care 2013;51:259-265. Accessed at: http://dx.doi.org/10.1097/MLR.0b013e31827da8ea.
24. Boehme AK, Luna J, Kulick ER, Kamel H, Elkind MSV. Influenza-Like Illness as a Trigger for Ischemic Stroke. Annals of Clinical and Translational Neurology, 5. Wiley Online Library; 2018. p. 456-463. https://onlinelibrary.wiley.com/doi/abs/10.1002/acn3.545.
25. Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol 2004;251:1227-1231. Accessed at: http://dx.doi.org/10.1007/s00415-004-0519-8.
26. Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with Coronavirus Disease 2019 (COVID-19) vs patients with influenza. JAMA Neurol. Epub 2020. Accessed at: http://dx.doi.org/10.1001/jamaneurol.2020.2730.
27. Zu ZY, Jiang MD, Xu PP, et al. Coronavirus disease 2019 (COVID-19): a perspective from China. Radiology 2020:200490. Feb 21. Accessed at: http://dx.doi.org/10.1148/radiol.2020200490.
28. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1295. Accessed at: http://dx.doi.org/10.1136/bmj.m1295.
29. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203:631-637. Accessed at: http://dx.doi.org/10.1002/path.1570.
30. Feng Y, Xia H, Santos RA, Speth R, Lazartigues E. Angiotensin-converting enzyme 2: a new target for neurogenic hypertension. Exp Physiol 2010;95:601-606. Accessed at: http://dx.doi.org/10.1113/expphysiol.2009.047407.
31. Divani AA, Andalib S, Di Napoli M, et al. Coronavirus Disease 2019 and stroke: clinical manifestations and pathophysiological insights. J Stroke Cerebrovasc Dis 2020;29:104941. Accessed at: http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2020.104941.

32. Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID-19 Coagulopathy in Caucasian patients. Br J Haematol 2020. Epub Apr 24. Accessed at: http://dx.doi.org/10.1111/bjh.16749.
33. Sellers SA, Hagan RS, Hayden FG, Fischer WA. The Hidden Burden of Influenza: a Review of the Extra-Pulmonary Complications of Influenza Infection. Influenza Other Respi Viruses, 11. Wiley Online Library; 2017. p. 372-393. https://onlinelibrary.wiley.com/doi/abs/10.1111/irv.12470.
34. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect 2020;80:607-613. Accessed at: http://dx.doi.org/10.1016/j.jinf.2020.03.037.
35. Ameriso SF, Wong VL, Jr QFP, Fisher M. Immunohematologic characteristics of infection-associated cerebral infarction. Stroke 1991;22:1004-1009. Accessed at: http://dx.doi.org/10.1161/01.str.22.8.1004.
36. 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. 2020:844-847. Accessed at: http://dx.doi.org/10.1111/jth.14768.
37. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020. Epub Apr 10. Accessed at: http://dx.doi.org/10.1001/jamaneurol.2020.1127.
38. Cowan Logan T, Alvaro A, Pankow James S, et al. Hospitalized infection as a trigger for acute ischemic stroke. Stroke 2016;47:1612-1617. American Heart AssociationAccessed at: https://doi.org/10.1161/STROKEAHA.116.012890.
39. Kumar DR, Hanlin E, Glurich I, Mazza JJ, Yale SH. Virchow's contribution to the understanding of thrombosis and cellular biology. Clin Med Res 2010;8:168-172. Accessed at: http://dx.doi.org/10.3121/cmr.2009.866.
40. Li Y, Wang M, Zhou Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Epub 2020. Accessed at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3550025.
41. Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID-19 Coagulopathy in Caucasian patients. Br J Haematol 2020. Epub Apr 24. Accessed at: http://dx.doi.org/10.1111/bjh.16749.
42. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res 2009;123(Suppl 4):S11-S17. Accessed at: http://dx.doi.org/10.1016/S0049-3848(09)70136-7.
43. Roberts LN, Patel RK, Arya R. Venous thromboembolism and ethnicity. Br J Haematol 2009;146:369-383. Accessed at: http://dx.doi.org/10.1111/j.1365-2141.2009.07786.x.
44. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res 2009;123(Suppl 4):S11-S17. Accessed at: http://dx.doi.org/10.1016/S0049-3848(09)70136-7.
45. Willis R, Pierangeli SS. Pathophysiology of the antiphospholipid antibody syndrome. Auto Immun Highlights 2011;2:35-52. Accessed at: http://dx.doi.org/10.1007/s13317-011-0017-9.
46. Urbanski G, Yelnik CM, Maillard H, et al. Antiphospholipid syndrome with isolated isotype M anticardiolipin and/or Anti-B2GPI antibody is associated with stroke. Stroke 2018;49:2770-2772. Accessed at: http://dx.doi.org/10.1161/STROKEAHA.118.023021.
47. Vallabh J, A. WP, Kase CS, et al. Anticardiolipin antibodies and risk of ischemic stroke and transient ischemic attack. Stroke 2004;35:736-741. American Heart AssociationAccessed at: https://doi.org/10.1161/01.STR.0000117575.48205.2D.
48. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295-306. Accessed at: http://dx.doi.org/10.1111/j.1538-7836.2006.01753.x.
49. Vaarala O, Palosuo T, Kleemola M, Aho K. Anticardiolipin response in acute infections. Clin Immunol Immunopathol 1986;41:8-15. Accessed at: http://dx.doi.org/10.1016/0090-1229(86)90046-2.
50. Syrjänen J, Vaarala O, Iivanainen M, Palosuo T, Valtonen VV, Aho K. Anticardiolipin response and its association with infections in young and middle-aged patients with cerebral infarction. Acta Neurol Scand 1988;78:381-386. Accessed at: http://dx.doi.org/10.1111/j.1600-0404.1988.tb03673.x.
51. Barbut D, Borer JS, Caronna J, Wallerson D, Asherson R, Gharavi A. Stroke in patients with isolated IgM anticardiolipin antibody. J Stroke Cerebrovasc Dis 1994;4:18-22. Accessed at: http://dx.doi.org/10.1016/S1052-3057(10)80141-7.
52. Asherson RA, Cervera R. Antiphospholipid antibodies and infections. Ann Rheum Dis 2003;62:388-393. Accessed at: http://dx.doi.org/10.1136/ard.62.5.388.
53. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38. Accessed at: http://dx.doi.org/10.1056/NEJMc2007575.
54. Vitali C, Minniti A, Caporali R, Del Papa N. Occurrence of pulmonary embolism in a patient with mild clinical expression of COVID-19. Thromb Res 2020;192:21-22. Accessed at: http://dx.doi.org/10.1016/j.thromres.2020.05.002.
55. Antithrombotic therapy | Coronavirus Disease COVID-19 [online]. COVID-19 Treatment Guidelines. Accessed at:: https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/. Accessed July29, 2020.
56. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis 2020;50:72-81. Accessed at: http://dx.doi.org/10.1007/s11239-020-02138-z.