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COVID-19 and supra-aortic trunks disease: review of literature about critical phase and sequelae

Running title: COVID and carotid disease

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ABSTRACT

The acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the COVID-19 disease, a global pandemic. A strong association has been documented between COVID-19 and cardiovascular events, although the exact pathophysiological mechanism is still unclear. Carotid atherothrombosis and ischemic stroke represents one of the possible severe manifestations of COVID-19, as a leading cause of long-term disability and death. Different complex intertwined mechanisms seem to underlie the endothelitis which is the cause of multiple cardiovascular manifestations. To date, few case series describing COVID-19 and acute ischemic stroke caused by cervical carotid thrombosis have been published. All the patients shared common similar radiographic features, comorbidities, and biomarker profiles. The aim of this brief review is to analyze the impact of COVID-19 pandemic in the management of a Vascular Surgery Department, changing the daily vascular practice, as well as to provide practical suggestions for symptomatic carotid stenosis, while reviewing published literature.

Introduction

The acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the COVID-19 disease, a global pandemic with 176.156.662 confirmed cases of infection, including 3.815.486 deaths as reported to date from WHO data (WHO Health Emergency Dashboard, 2021, June 16th).[1]

A strong association has been documented between cardiovascular events and COVID-19 infection, even if the exact pathophysiological mechanism remains debated and needs to be clarified.[2-4] COVID-19 positive patients, both young and old, experience vascular complications, such as arterial and venous thromboembolic disease, increased by infectious and multi-organ failure status.[5] Furthermore, paradoxically, several deleterious aspects also arise for COVID-negative vascular patients. This population is subjected to an impairment of examinations and cures, caused by filling of hospitals and of operating rooms, and by the fear to get the infection coming to the hospital or to the emergency room (ER) for evaluation or treatment. This leads to more serious vascular complications at the first presentation.[6]

Carotid atherothrombosis and ischemic stroke represents one of the possible severe manifestations of COVID-19, as a leading cause of long-term disability and death.

A few case series regarding patients with COVID-19 and acute ischemic stroke caused by cervical carotid thrombosis have been described to date in literature.[7-13]

All the patients shared similar radiographic features, comorbidities, and biomarker profiles.

The aim of this review is to provide evidence of the impact of COVID-19 outbreak derived from published literature (case reports, multicenter experience, and expert opinion) on vascular surgery services and interventions for carotid artery disease, describing COVID-19-related findings, intraoperative observations, and postoperative outcomes.

Epidemiology of stroke during COVID-19 pandemic period

In the Society of Vascular and Interventional Neurology (SVIN) COVID-19 Registry, a retrospective observational cohort of 14,483 consecutive patients evaluated in the emergency department with COVID-19 across 31 hospitals in four countries, the primary outcome was the incidence rate of cerebrovascular events, including acute ischemic stroke, intracranial hemorrhages (ICH), cortical vein and sinus thrombosis (CVST). Of all the patients with laboratory-confirmed SARS-CoV-2 infection, 172 were diagnosed with an acute cerebrovascular event (1.1%). Among these, 156 had acute ischemic stroke, 28 ICH, and 3 CVST. The hospital mortality rate for SARS-CoV-2-associated complications was 38.1% for stroke, and 58.3% for ICH. After adjusting for admission site, age, baseline stroke severity and all predictors of in-hospital mortality, cryptogenic stroke mechanism ($p < 0.01$), older age ($p = 0.03$), and lower lymphocyte count at admission ($p = 0.04$) were independent predictors of mortality among patients with stroke and COVID-19. [14]

Katsanos et al. performed a meta-analysis of observational cohort studies reporting outcomes of patients with cerebrovascular events associated with SARS-CoV-2 infection. [15] Eighteen cohort studies including 67,845 patients have been identified. Among patients with SARS-CoV-2, 1.3% were hospitalized for cerebrovascular events, 1.1% for ischemic stroke, and 0.2% for hemorrhagic stroke. Compared to non-infected COVID-19 negative contemporary or historical controls, patients with SARS-CoV-2 infection had increased odds of ischemic stroke (OR = 3.58, 95% CI = 1.43–8.92) and cryptogenic stroke (OR = 3.98, 95% CI = 1.62–9.77). The higher risk of ischemic stroke in these patients seems to be related to a blood hypercoagulable state that has been linked to an immune-mediated response following SARS-CoV-2 infection. [16] In particular, patients with COVID-19 showed an increased risk of thromboembolic events, even within the first 24 hours after admission.[17]

Not only the risk of stroke is higher in COVID-19 patients, but also the mortality rate associated with stroke. As a matter of fact, in-hospital mortality was found to be more than five-fold higher among SARS-CoV-2 stroke patients vs. non-infected contemporary or historical stroke patients (OR = 5.60, 95% CI = 3.19–9.80). [15]

Some studies presented in the literature have demonstrated that diabetes mellitus (DM) is one of the most serious comorbidities affecting stroke patients infected with SARS-CoV-2. Patients with DM have an increased risk of severe complications and stroke during infection.[18] In diabetics the principal pathophysiological mechanisms were described as a hypercoagulable state, dysregulation of glucose metabolism, and reduced Angiotensin-converting enzyme 2 expression (ACE2).[19, 20]

Coagulation and inflammatory tests results highlighted a substantial difference in coagulation profiles and acute-phase proteins, such as lower lymphocyte count, lower platelet count, and higher lactate dehydrogenase between COVID-19 stroke patients and controls. [14-21]

Another risk factor is represented by patient's neurological history. Meta-analytical studies have shown that the presence of previous neurological disease represents an independent risk predictor of mortality for any cause in hospitalized COVID-19 patients. [15] A history of stroke leads to a 3 to 5-fold increase in the risk of mortality and a 2.5-fold increase in the likelihood of serious illness and adverse outcomes in COVID-19 patients when compared with the general population. [22-24] Elderly patients and those with comorbidities are more likely to develop severe complications of COVID-19 infection and present a higher risk of thrombosis.[25, 26]

Furthermore, another important aspect during SARS-CoV-2 outbreak period is the delay of receiving thrombolytic treatment. The delay in tissue plasminogen activator (tPA) treatment administration could partially be explained by the absence of prompt symptom recognition due to social distancing or reticence regarding prompt hospital presentation matched with health care system overload and preventive measures following the pandemic situation.[27-30]

Furthermore, many patients infected with SARS-CoV-2 were diagnosed with stroke during their hospital admission, contraindicating thrombolysis treatment. Moreover, COVID-19 patients were often intubated, anticoagulated, with critical illness. Delays in imaging, due to the delay in symptom recognition during hospitalization, could be an important explanation for the deferred active treatment of stroke patients. [31-33]

Pathophysiology

Arterial thrombosis and stroke are strictly related to coronavirus infections even if in the previous outbreaks, those were more related to thrombosis of the intracranial arteries. Umapathi et al., after the 2002 severe acute respiratory syndrome (SARS) outbreak, reported five cases of stroke out of 206 patients. [34] Ischemic strokes were also reported during the Middle East respiratory syndrome (MERS-CoV) epidemic in Saudi Arabia. [35]

There is a wide evidence in the literature that some patients may respond to COVID-19 with an exuberant "cytokine storm" response. [36] Immunological studies have demonstrated that pro-inflammatory cytokines interleukin 6 (IL-6), IL-17A, and tumor necrosis factor α were elevated in most patients with poor outcomes. [37] Hypercoagulability is an important finding during an inflammatory state. Pro-inflammatory cytokines are critically involved in platelet hyperactivation and abnormal clot formation and play an important role in the downregulation of important physiological anticoagulant pathways. [38] Yaghi et al. identified, of 3556 patients hospitalized with COVID-19 infection, a total of 32 patients (0.9%) who had radiologically proven ischemic stroke and required mechanical ventilation in most cases. Cryptogenic stroke subtype was more common (65.6%) as compared with contemporary controls (30.4%; $P=0.003$) and historical controls (25.0%; $P<0.001$), possibly related to an acquired associated hypercoagulability. [39]

A possible mechanism still under investigation seems to be related to the capacity of SARS-CoV-2 infection to bind the viral surface spike protein to the human ACE2 receptor after activation of the spike protein by a transmembrane protease serine 2. [40] Kolikonda et al. suppose that tissue viral invasion may occur not only via ACE2, but also via nasal spreading to the olfactory bulb through the trans-synaptic route. Through the central nervous system penetration, the viral invasion of mechano- and chemoreceptors in the medulla can lead to respiratory failure, increasing mortality of patients with unstable carotid plaques. [41]

Clotting disorder has been observed in COVID-19 in more than 50% of patients with severe disease. [42] Several studies prove that elevated d-dimer concentrations and fibrin degradation products in COVID-19 patients are the most relevant alterations in coagulation parameters.[25]

A preliminary report observed peculiar histopathologic findings in the carotid arteries of COVID-19 patients with stroke. COVID-19 RNA loads in carotid arteries were found to be comparable to those observed in throat samples, together with a moderate degree of inflammation. [43] These data could suggest that SARS-CoV-2 infects and replicates into the carotid arteries: based on these findings, the authors hypothesize that after entering the bloodstream, SARS-CoV-2 infects and replicates in vascular endothelial cells, where it modulates vascular response and further migrates to organs.

Finally, the carotid body itself could be a site of SARS-CoV-2 invasion, due to local expression of its ACE2 receptor and an alternative route of nervous system invasion, through retrograde transport along the carotid sinus nerve. Peripheral arterial chemoreception is mainly mediated by the carotid body, which in turn may induce local and systemic inflammation reactions, increasing arterial chemosensitivity and sympathetic outflow. [44]

Ischemic Stroke due to carotid artery thrombosis during severe COVID-19 infection

Basically, in case of SARS-CoV-2 infection we can observe two main pathways for the development of large arteries occlusion at the carotid level: a) *acute thrombosis without signs of atherosclerosis* and b) *worsening of a pre-existing atherosclerotic stenosis*.

A retrospective study of data from the COVID-19 outbreak in Wuhan, China, showed that the incidence of stroke among hospitalized patients was approximately 5%, with the youngest being 55 years old. [3]

A report from the international COVID-19 stroke group highlights a higher proportion of large vessel occlusions, a lower rate of small vessel occlusions, lacunar infarction and a considerable number of strokes in young patients when compared with population studies performed before the pandemic. This is only partly explained by the delay of presentation of patients with mild-to-moderate stroke symptoms at medical centers. In this study, preliminary findings confirm a relatively high number of young acute ischemic stroke patients, with male predominance. [45] Esenwa et al. presented three cases of patients with COVID-19 and acute ischemic stroke due to fulminant carotid thrombosis. In their postulate, the overwhelming innate immune response to SARS-CoV-2 results not only in systemic inflammation and associated coagulopathy, but also in a local endothelitis which may destabilize a non-significant chronic atherosclerotic plaque to thrombosis. [7]

Goldberg et al described the case of a patient testing positive for SARS-CoV-2 infection, who developed pneumonia and stroke, secondary to evolution from a mild extra- and intracranial atherosclerotic disease to a high-grade stenosis at the level of internal carotid bifurcation, confirmed by arteriography. [46] They support the hypothesis that the activation of immune and inflammatory pathways could lead to plaque disruption, as a source of thrombosis.

The impact of COVID-19 pandemic in the management and outcomes of carotid artery disease in vascular surgery departments.

The unexpected spreading of the pandemic forced governments around the world to reorganize medical centers, prioritizing COVID-19 infection containment and treatment.

From a different perspective, due to the tricky situation and all the related uncertainties of the first wave of Covid-19, the patients themselves, primary care physicians, and specialists were less likely to call the practitioner, go to the ER, ask vascular referrals, or recommend interventions, respectively.

Collaterally, the outbreak has also deeply changed protocols and habits of surgeons, rescheduling priorities. [47] In many countries during the first spreading phase, health politics led to a new medical structure, providing "Hub/Spoke" hospitals for highly specialized medical activities. In Lombardy, the hubs guaranteed full time evaluation of all patients with known or suspected vascular surgery disease in emergency or not able to be postponed more than 30 days, and surgical treatment was reserved only to symptomatic, urgent, or emergent disease. [48]

The Vascular and Endovascular Research Network (VERN) has determined a series of online polls of vascular surgical practice worldwide to evaluate the effect of the COVID-19 pandemic on workstream. [12] A total of 249 centers have been analyzed on the impact of COVID-19 on carotid surgery practice. Only 42% of the centers were still able to follow international guidelines and have not modified practice. Nevertheless, 45% of centers showed that they were now managing most recently symptomatic patients with TIA or minor stroke with 'best medical therapy' after multidisciplinary team revision. [12] Meanwhile, merely 12% of the vascular units were able to provide carotid endarterectomy (CEA) or carotid artery stenting (CAS) to patients with worsening symptoms. [49]

Regarding CAS, Kiwan et al proposed a simplified protocol during the COVID-19 pandemic to treat symptomatic carotid stenosis within 14 days from the index episode, to minimize non-urgent inpatient admissions. Furthermore, to reduce the hospital stay, the authors proposed a radial-first approach. Admission was limited only to those with a complex medical history, without sufficient social support or who lived more than one hour from the hospital. [50]

Regarding the timing of surgery, the NIHR Global Health Research Unit of Global Surgery observed conflicting recommendations during the COVID-19 era which delayed surgery from 1 to 12 weeks. In their prospective cohort study, indications for surgery were classified as benign disease, cancer, obstetrics, or trauma, while emergency surgery was defined as surgery on an unplanned admission. They observed a significantly higher risk of 30-day mortality in patients with preoperative SARS-CoV-2 infection diagnosed within 7 weeks before surgery compared with patients who did not have pre-operative SARS-CoV-2 infection, because of post-operative complications. However, there was no significant difference in 30-day postoperative mortality rate in those patients diagnosed with SARS-CoV-2 infection >7 weeks before surgery. The authors suggested that decisions should be tailored for each patient, since the possible advantages of delaying surgery for at least 7 weeks following SARS-CoV-2 diagnosis must be balanced against the potential risks of delay. [51]

Finally, several case reports and experiences with small cohorts of patients have been reported during pandemic period.

Viguier et al first described the case of a 73-year-old man with an acute ischemic stroke, complicating a large floating thrombus within the common carotid artery in a case of SARS-CoV-2 pneumonia.[8] Gulko et al. reported two cases with acute thrombosis in the ipsilateral common carotid artery bifurcation not associated with progression of atherosclerotic disease. [9]

Regarding surgery, Singh et al. described one case of urgent CEA in a 71-year-old male patient with COVID-19 infection and who developed acute left-sided weakness in February 2020 during the Diamond Princess cruise. In this case the medical history included hypertension and inability to take the usual antiplatelet therapy. After 1 month of waiting due to staying aboard with SARS-CoV-2, CT scan confirmed pneumonia, the patient underwent CEA for the presence of a mobile intramural filling defect within a soft, homogeneous plaque of the internal carotid artery. Surgery was then carefully planned and post-operative care was optimized to ensure the maximum safety for the patient. Upon the dissection of the carotid artery, the authors realized abnormally inflamed characteristics of the vessel: the amount of perivascular inflammation required extra care in dissection and resulted in the thinning of the endarterectomized carotid wall. [10]

Chiesa et al described 20 patients with carotid stenosis at admission: symptomatic in eight cases and asymptomatic but pre-occlusive or with unstable plaque in 12 patients. The time elapsed from the onset of symptoms to definitive treatment was significantly higher in COVID-19 patients. [11] The COVID-19 Vascular sERvice (COVER), a prospective observational cohort study designed to investigate the worldwide impact of the COVID-19 pandemic on vascular surgery at both service provision and individual patient levels, reported an unexpectedly high mortality following vascular intervention during this period. Of 1,103 patients submitted to vascular or endovascular intervention, collected from 57 vascular units in 19 countries, with 71.6% elective or scheduled procedures, the overall in-hospital mortality was 11.0% (121/1103 patients). Suspected or confirmed COVID-19 infection was documented in 4.0%. Regarding carotids, the mean time from index neurological event to intervention was 26.3 ± 41.1 days. In-hospital mortality for any carotid intervention was 10.7%, (11/103) with a combined stroke or death rate of 13.6% (14 of 103). One-third of the carotid interventions (38 patients; 36.9 %) were performed for asymptomatic carotid stenosis with a 7.9% (3 patients) all-cause mortality rate. Symptomatic carotid interventions were associated with a 12.3% (8 of 68) all-cause mortality rate. [12] Wang et al., in five COVID-19 positive patients with occlusion of the large anterior cervical vessels, proposed the use of a suction aspiration after thrombolysis with rTPA and final stent deployment. They concluded that patients with COVID-19 are more likely to have worse radiographic and clinical outcomes after endovascular approach, associated with clotting in multiple locations, clot fragility, and extensive clot burden. [13]

Practical suggestions for symptomatic carotid stenosis: updated proposal carotid guidelines during the current COVID-19 pandemic

Pending the 2022 review, the Clinical practice guidelines of the European Society for Vascular Surgery (ESVS) reported current indications for carotid revascularization in symptomatic and asymptomatic patients. [52] Overall, the burden of the pandemic has revolutionized the common clinical practice all over the world.

Asymptomatic cases should not be considered as priorities and should be submitted to best medical therapy (BMT), postponing surgery with respect to symptomatic cases. In case of neurological symptoms, patient-tailored evaluation and surgery planning must be carefully developed was to reduce post-operative morbidity and mortality. To complicate the whole management, it must be underlined that during the COVID-19 pandemic period there was a significant delay between onset of symptoms, first evaluation, and undergoing carotid revascularization.

A special case is represented by the patients with symptomatic carotid stenosis and perioperative COVID-19 infection. If ESVS guidelines recommend that carotid revascularization should be performed as soon as possible from onset of symptoms, with the purpose to avoid early recurrent stroke, [52] these patients are at increased risk of death and pulmonary complication following surgery. Therefore, there is a consensus on delaying surgery after at least 7 weeks in patients who have experienced SARS-CoV-2 respiratory infection. [51]

Emerging data supported antiplatelet strategies in symptomatic patients waiting for carotid revascularization during COVID-19 outbreak. [52]

Conclusions

The COVID-19 outbreak has radically changed all medical practice. Cerebrovascular disease may be directly related with COVID-19 prothrombotic state or may be due to delays in treatments due to hospital overload or patients' fear. In this scenario, it is necessary to discriminate urgent and deferrable situations, particularly in cases of asymptomatic carotid stenosis. Further analyses are needed to describe management and outcomes of COVID-19 positive patients with intracranial or extracranial cerebrovascular disease, although published data indicate higher complications and postoperative mortality rate in infected treated patients.

Data regarding the even worsts COVID-19 second and third waves are still lacking, but preliminary unpublished reports seem to show a general better response of hospital management for vascular disease.

The lesson learned from the first wave, regarding organization of admissions, isolation and precautions in case of suspected COVID-19 illness, and selection of patients has improved the management of both elective and emergent vascular surgery.

Currently, mass vaccination should be effective in reducing viral spread and severity of SARS-CoV-2 infection, and however it will surely help the national health systems to face the pandemic in all respects. Anyway, the fear of a possible fourth wave is alarming, in particular if more contagious or deadly variants of the virus will proliferate, and as nations roll back mitigation measures. In this case all the vascular community should be now well trained to act sooner and more decisively, even in case of a new and severe outbreak, regardless of limited resources.

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REFERENCES

1. World Health Organization Coronavirus WHO Health Emergency Dashboard (COVID-19), [cited 2021 June 16th]. Available from: https://covid19.who.int/
2. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. Coronavirus disease 2019 (Covid-19) and cardiovascular disease. Circulation 2020;141:1648-1655.
3. 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.
4. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. J Neurointerv Surg 2020;12:648-653.
5. Bellosta R, Piffaretti G, Bonardelli S, et al. Regional Survey in Lombardy, Northern Italy, on Vascular Surgery Intervention Outcomes During The COVID-19 Pandemic. Eur J Vasc Endovasc Surg. 2021;61(4):688-697.
6. Perini P, Nabulsi B, Massoni CB, Azzarone M, Freyrie A. Acute limb ischaemia in two young, non-atherosclerotic patients with COVID-19. Lancet. 2020;395(10236):1546.
7. Esenwa C, Cheng NT, Lipsitz E, Hsu K, Zampolin R, Gersten A et al. COVID-19-associated carotid atherothrombosis and stroke AJNR AM J Neuroradiol. 2020;41:1993-1995.
8. Viguier A, Delamarre L, Duplantier J, Olivot J, Bonneville F. Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. J Neuroradiol. 2020;47:393–394.
9. Gulko E, Gomes W, Ali S, Al-Mufti F, Mehta H. Acute Common Carotid Artery Bifurcation Thrombus: An Emerging Pattern of Acute Strokes in Patients with COVID-19? AJNR Am J Neuroradiol. 2020;41:E65-E66.
10. Singh T, Lee A, Vo R, Ali SF, Cheon BM, Josephson MB et al. Urgent carotid endarterectomy in a COVID-19 patient: standard approach with some adjustments. Vascular Disease Management 2020;17:E104–09.
11. Chiesa R, Kahlberg A, Rinaldi E, Mascia D. Emergency management of the COVID-19 pandemic in a vascular surgery department of a large metropolitan hospital in Italy. Preparation, escalation, de-escalation, and normal activity. J Card Surg. 2021;36:1632-1636.
12. Benson RA, Nandhra S, The Vascular and Endovascular Research Network (VERN) COVID-19 Vascular Service (COVER) Tier 2 Study. Outcomes of vascular and endovascular interventions performed during the Coronavirus disease 2019 (COVID-19) Pandemic. Ann Surg. 2021;273:630-635.
13. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. J Neurointerv Surg. 2020;12:648-653.
14. Siegler JE, Cardona P, Arenillas JF, Talavera B, Guillen AN, Chavarría-Miranda A, et al. Cerebrovascular events and outcomes in hospitalized patients with COVID-19: the SVIN COVID-19 multinational registry. Int J Stroke. 2021;16(4):437-447.
15. Katsanos AH, Palaiodimou L, Zand R, Yaghi S, Kamel H, Navi BB, et al. The impact of SARS-CoV-2 on stroke epidemiology and care: a meta-analysis. Ann Neurol. 2021;89(2):380-388.
16. Valderrama EV, Humbert K, Lord A, Frontera J, Yaghi S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. Stroke 2020;51:e124–e127.
17. 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 stroke registry. Stroke 2020;51:e254–e258.
18. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020;8:546–550.
19. Zaki N, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: a systematic review. Diabetes Metab Syndr 2020;14:1133–1142.

20. Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. Diabetes Res Clin Pract 2020;162:108132.
21. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy. Italy. Neurology 2020;95:e910–e920.
22. Trejo-Gabriel-Galán JM. Stroke as a complication and prognostic factor of COVID-19. Ictus como complicación y como factor pronóstico de COVID-19. Neurologia 2020;35:318–322.
23. 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;15:385–389.
24. Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19-systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis 2020;29:104949.
25. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–513.
26. Guan WJ, Ni ZY, Hu Y, Liang W, Ou C, He J, et al. China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–1720.
27. Uchino K, Kolikonda MK, Brown D, Kovi S, Collins D, Kawaja Z, et al. Decline in stroke presentations during COVID-19 surge. Stroke 2020;51:2544–2547.
28. Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral effect of Covid-19 on stroke evaluation in the United States. N Engl J Med 2020;383:400–401.
29. Zhao J, Li H, Kung D, Fisher M, Shen Y, Liu R. Impact of the COVID-19 epidemic on stroke care and potential solutions. Stroke 2020;51:1996–2001.
30. Katsanos AH, de Sa Boasquevisque D, Al-Qarni MA, Shawawrah M, McNicoll-Whiteman R, Gould L, et al. In-hospital delays for acute stroke treatment delivery during the COVID-19 pandemic. Can J Neurol Sci. 2021;48:59-65.
31. Nguyen TN, Abdalkader M, Jovin TG, Nogueira RG, Jadhav AP, Haussen DC, et al. Mechanical thrombectomy in the era of the COVID-19 pandemic: emergency preparedness for neuroscience teams: a guidance statement from the Society of Vascular and Interventional Neurology. Stroke 2020;51:1896–1901.
32. Qureshi AI, Abd-Allah F, Al-Senani F, Aytac E, Borhani-Haghighi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. Int J Stroke 2020;15:540–554.
33. Leira EC, Russman AN, Biller J, Brown DL, Bushnell CD, Caso V, et al. Preserving stroke care during the COVID-19 pandemic: potential issues and solutions. Neurology 2020;95:124–133.
34. Umapathi T, Kor AC, Venketasubramanian N, Lim CC, Pang BC, Yeo TT, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol. 2004;251:1227–1231.
35. Arabi YM, Harthi A, Hussein J, Bouchama A, Johani S, Hajeer AH, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection 2015;43:495–501.
36. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63(3):364–374.
37. Gralinski LE, Sheahan TP, Morrison TE, Menachery VD, Jensen K, Leist SR, et al. Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. mBio. 2018;9(5):e01753-18.
38. Dosquet C, Weill D, Wautier JL. Cytokines and thrombosis. J Cardiovasc Pharmacol. 1995;25(suppl 2):S13–S19.
39. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS2-CoV-2 and stroke in a New York healthcare system. Stroke. 2020; 51:2002–2011.

40. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.e8.
41. Kolikonda MK, Jandrasupalli KK, Lippmann S. Association of Coronavirus Disease 2019 and Stroke: A Rising Concern. Neuroepidemiology. 2020;54:370-374.
42. 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(10229):1054–1062.
43. Pfefferle S, Günther T, Puelles, VG, Heinrich F, Nörz D, Czech-Sioli M, et al. SARS-CoV-2 infects carotid arteries: implications for vascular disease and organ injury in COVID-19. BioxRIV 2020. [Epub ahead of print].
44. Porzionato A, Emmi A, Stocco E, Barbon S, Boscolo-Berto R, Macchi V, et al. The potential role of the carotid body in COVID-19. Am J Physiol Lung Cell Mol Physiol. 2020 Oct 1;319:L620-L626.
45. Shahjouei S, Tsivgoulis G, Farahmand G, Koza E, Mowla A, Vafaei Sadr A et al. SARS-CoV-2 and Stroke Characteristics: A report from the multinational COVID-19 Stroke Study Group. Stroke. 2021;52:e117-e130.
46. Goldberg MF, Goldberg MF, Cerejo R, Tayal AH. Cerebrovascular Disease in COVID-19. AJNR Am J Neuroradiol. 2020;41:1170-1172.
47. Bissacco D, Grassi V, Lomazzi C, Domanin M, Bellosta R, Piffaretti G, et al. Is there a vascular side of the story? Vascular consequences during COVID-19 outbreak in Lombardy, Italy. J Card Surg. 2021;36(5):1677-1682.
48. Bellosta R, Bissacco D, Rossi G, Pirrelli S, Lanza G, Frigerio D, et al. Differences in hub and spoke vascular units practice during the novel Coronavirus-19 (COVID-19) outbreak in Lombardy, Italy. J Cardiovasc Surg (Torino). 2021;62(1):71-78.
49. Naylor AR, McCabe DJH. New Data and the Covid-19 Pandemic mandate a rethink of antiplatelet strategies in patients with TIA or minor stroke associated with atherosclerotic carotid stenosis. Eur J Vasc Endovasc Surg. 2020;59:861-865.
50. Kiwan R, Jukes A, Mayich M, Boulton M, Sharma M, Pelz D, et al. A protocol for carotid artery stenting in covid times: a single Canadian centre experience. Can J Neurol Sci. 2021;5:1-12.
51. COVIDSurg Collaborative; GlobalSurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia. 2021;76:748-758.
52. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, et al. Management of atherosclerotic carotid and vertebral artery disease: 2017 Clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018;55:3-81.