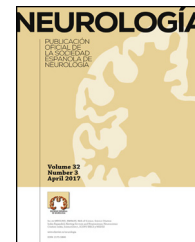




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REVIEW ARTICLE

Stroke as a complication and prognostic factor of COVID-19[☆]



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PALABRAS CLAVE

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Abstract

Introduction: Contradictory data have been reported on the incidence of stroke in patients with COVID-19 and the risk of SARS-CoV-2 infection among patients with history of stroke.

Methods: This study systematically reviews case series reporting stroke as a complication of COVID-19, and analyses the prognosis of patients with COVID-19 and history of stroke. The pathophysiological mechanisms of stroke in patients with COVID-19 are also reviewed.

Conclusions: History of stroke increases the risk of death due to COVID-19 by 3 times. Stroke currently seems not to be one of the main complications of COVID-19.

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Ictus como complicación y como factor pronóstico de COVID-19

Resumen

Introducción: Existe información contradictoria acerca de la incidencia de ictus en enfermos de COVID-19 y sobre el riesgo de los enfermos con antecedentes de ictus de padecer la pandemia.

Métodos: Revisión sistemática de la bibliografía sobre las series de casos de COVID-19 que han tenido un ictus como complicación y sobre el pronóstico de los enfermos con antecedentes de ictus que sufren COVID-19. También se han revisado los mecanismos por los que se pueden producir ictus en esta enfermedad.

Conclusiones: Tener antecedentes de ictus aumenta 3 veces el riesgo de fallecer por COVID-19. En este momento el ictus no parece una de las complicaciones principales de COVID-19.

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Introduction

Since the beginning of the COVID-19 pandemic, contradictory findings have been reported regarding the incidence of stroke in patients with the disease and the risk of SARS-CoV-2 infection among patients with history of stroke.

Methods

A systematic review analysed series of patients presenting stroke as a complication of COVID-19 and the prognosis of COVID-19 in patients with history of stroke. Pathogenesis of stroke in patients with COVID-19 is also addressed.

A systematic search was performed of the MEDLINE (PubMed search tool) and Embase® databases. The search strategy used the following Medical Subject Headings indexing terms: (cerebrovascular disorders OR stroke OR cerebral haemorrhage OR blood coagulation disorders OR myocardial infarction) AND (SARS-CoV-2 OR Coronavirus infections OR COVID-19 OR SARS virus OR Middle East Respiratory Syndrome Coronavirus). The search returned 78 articles. The following searches were also performed: "Plaque, atherosclerotic" AND "Virus diseases" (165 results); "Autopsy" AND "Coronavirus infection" (90 results). The Embase® search identified 25 articles that were not found on MEDLINE. The review was expanded by including relevant articles from the reference lists of the articles found. This review does not address other neurological complications of COVID-19, besides stroke.

Results

Before 2003, acute infection with different coronaviruses was known to cause congestion of the upper respiratory tract; these viruses are endemic, and their relationship with several chronic neurological diseases are currently under study.¹ Since then, 3 new coronaviruses have caused epidemics of respiratory syndromes with high mortality rates, which are occasionally associated with neurological complications. The 2003 epidemic was caused by the SARS-CoV virus, the 2012 epidemic by the MERS-CoV virus, and the current epidemic (COVID-19), which began in Wuhan (China) in December 2019, was caused by the novel coronavirus SARS-CoV-2. During the 2003 SARS-CoV epidemic, a series of 206 cases in Singapore included 5 cases of large-vessel stroke²; a case series from Taiwan (664 patients) included 5 cases.³ Hypercoagulability, caused either by the disease itself or by immunoglobulin treatment, was proposed as a possible cause of stroke. Autopsies performed during the 2003 epidemic revealed venous thrombosis, inflammation, and fibrinoid necrosis of small vessel walls in many organs, including the lungs, heart, and brain.⁴ The virus has been detected in the cerebrospinal fluid with polymerase chain reaction testing⁵ and in neurons and glial cells with in situ hybridisation and electron microscopy.^{6,7} During the 2012 MERS-CoV epidemic, patients with respiratory symptoms occasionally presented stroke, intracranial haemorrhage,⁸ acute disseminated encephalomyelitis, or encephalitis. As the virus was not detected in the cerebrospinal fluid or in brain tissues, neurological complications were thought to be immune-mediated.⁹

The novel coronavirus SARS-CoV-2 presents a genetic similarity of 79.5% with SARS-CoV and 96% with the bat SARS-like coronavirus.¹⁰ Similarly to other coronaviruses, it can access the nervous system via the haematogenous route or by retrograde axonal transport; the latter mechanism probably explains the frequent association with anosmia. Before entering cells, the virus binds to the ACE2 receptor,¹¹ which is present in many types of human cells.

Because the disease originated in China, the only case series of COVID-19 published to date include Chinese patients.^{12–24} Of

Table 1 History of stroke in patients with COVID-19 and in the general population in China.

Guan ¹³ (N = 1099)	15 (1.4%)
Ruan ¹⁹ (N = 150)	12 (8%)
Wang ¹⁴ (N = 138)	7 (5.1%)
Lu ²⁶ (N = 12 654)*	278 (2.2%)*

* Chinese general population.

these series, only the first 4 analyse complications or causes of death; only one of these reviewed neurological manifestations and complications, including stroke. This case series¹² analyses 214 patients presenting SARS-CoV-2 infection in January and February 2020, 78 (36.4%) of whom presented one or more of the following neurological manifestations: dizziness, headache, impaired consciousness, stroke, ataxia, seizures, anosmia, visual alterations, neuropathic pain, and muscle damage. Stroke was reported in 2.8% of the total cohort, occurring in 5.7% of patients with severe respiratory infection (4 ischaemic and one haemorrhagic stroke) and 0.8% of those with less severe symptoms (one ischaemic stroke). Two of the 6 patients with stroke attended hospital due to hemiplegia and were incidentally found to have pneumonia secondary to SARS-CoV-2 infection at admission, having presented no respiratory symptoms previously. Although the median time between onset of respiratory symptoms and stroke was 10 days, stroke occurred 1–2 days after hospitalisation in most cases. Patients with severe neurological damage had higher D-dimer levels than other patients, and presented greater immunosuppression caused by the virus, demonstrated by the lower lymphocyte count.

The second issue addressed in this study is whether history of stroke increases the risk of developing COVID-19 or the severity of symptoms. One of the earliest studies, which included 99 patients admitted from 1 to 20 January 2020 in Wuhan, reported history of cardiovascular or cerebrovascular disease in 40% of patients.²⁵ Different COVID-19 case series report different percentages of patients with history of stroke (Table 1); if we combine the data from all series,^{13,14,19} the percentage of patients with history of stroke shows little difference from that reported in a previous sample of the Chinese general population (2.2%).²⁶

In all the case series studied, history of stroke was associated with poorer progression of COVID-19. In a cohort of patients from 55 hospitals, history of stroke was twice as frequent among patients classified as having severe COVID-19 than among patients with mild symptoms.¹³ In a smaller series, only one of 7 patients with history of stroke was not admitted to intensive care.¹⁴ Combined data from patient series from hospitals across China, including more than 1500 patients, shows that history of stroke is associated with a three-fold increase in the risk of death (Table 2).^{17,18}

While history of cardiovascular disease and risk factors are not the main focus of this review, we should note that, like history of stroke, they are associated with poorer prognosis of COVID-19. The largest, most recent Chinese register, which includes 72 314 patients with COVID-19, reports a mortality rate of 2.3% globally, 10.5% in patients with history of cardiovascular disease (including stroke), and 7.3% in patients with diabetes.²⁰

SARS-CoV-2 may cause stroke by several mechanisms: invasion of vessel walls, coagulation disorders, cerebral embolism secondary to myocardial damage, or destabilisation of an existing atheromatous plaque. The virus is able to invade vessel walls because endothelial cells express the ACE2 receptor, which the virus uses to enter cells; SARS-CoV-2 has been detected in the endothelium.²⁷ When it invades vessel walls, it may behave similarly to the varicella zoster virus, the most frequent viral cause of stroke, triggering inflammation and even necrosis of the walls of cerebral arteries.²⁸

Table 2 Association between history of stroke and prognosis.

Prognosis	Chen ¹⁷ N = 1590	Wang ¹⁸ N = 1550	Guan ¹³ N = 1099	Ruan ¹⁹ N = 150	Wang ¹⁴ N = 138
Death vs survival	HR: 3.1; 95% CI, 1.07–8.94	OR: 3.89; 95% CI, 1.64–9.22		7 (10%) vs 5 (6%)	
ICU vs non-ICU					6 (16.7%) vs 1 (1.0%)
Severe vs non-severe			4 (2.3%) vs 11 (1.2%)		

CI: confidence interval; HR: hazard ratio; ICU: intensive care unit; OR: odds ratio.

Another potential mechanism by which SARS-CoV-2 may cause stroke is by interfering with coagulation. Respiratory infection with *Streptococcus pneumoniae* or influenza virus is known to increase the incidence of myocardial infarction and stroke; the influenza vaccine partially prevents the occurrence of these events.^{29,30} Cytomegalovirus can also cause venous thrombosis by damaging vessel walls or inducing antiphospholipid antibody production.³¹ Viruses can cause thrombosis by activating the immune system, which affects coagulation, platelet activation, and endothelial function.³² The general inflammatory status or “cytokine storm” that SARS-CoV-2 causes in some patients may alter coagulation, increasing D-dimer levels and procoagulant activity.^{12,33,34} Patients with D-dimer levels above 1 µg/mL are nearly 20 times more likely to die.¹⁵ Pulmonary embolism and venous thrombosis of various tissues are even more frequent than arterial thromboses.³⁵

As occurred in the 2003 SARS epidemic,³⁶ the SARS-CoV-2 virus can damage the heart, which may in turn lead to cardioembolic stroke. Acute myocardial damage, detected by presence of elevated troponin levels, was detected in 15% of patients in one series¹⁶ and in 17% in another, in which it was also associated with morbidity and mortality³⁷; in a third study, 16.7% of patients developed arrhythmic complications, with 7% presenting acute myocardial infarction.¹⁴ Seven percent of deaths were attributed to myocarditis.¹⁹

The systemic inflammation caused by SARS-CoV-2 may also cause stroke through destabilisation of atheromatous plaques, as is thought to occur during influenza epidemics. Systemic inflammation ruptures the fibrous cap of the atheroma, exposing the thrombogenic material.³⁸ This hypothesis was proposed as an explanation for acute coronary syndromes observed during the 2003 SARS-CoV epidemic.³⁹ Systemic inflammation may activate the endothelium⁴⁰ and result in failure of thrombolytic treatment for myocardial infarction.⁴¹

Finally, rates of morbidity and mortality due to stroke may present a discreet increase as a result of such indirect mechanisms as patients’ fear of attending hospital or the fact that nearly all hospital resources are occupied in caring for patients with COVID-19. This has resulted in longer cardiac and cerebrovascular reperfusion times,^{42,43} which has led professional organisations to issue recommendations on adapting the treatment of stroke^{44,45} and myocardial infarction⁴⁶ during the pandemic. Stroke incidence may also increase because of decreased monitoring of cardiovascular risk factors as a result of reduced healthcare provision⁴⁷ and lockdown measures.⁴⁸

Limitations

The findings from this review should be considered provisional: given how recently the pandemic started, few clinical series have been published; all those published studies include only Chinese patients and place little emphasis on stroke. The saturation of hospitals and limitations to patients’ mobility may have prevented patients with history of stroke from reaching hospital, distorting data on the percentage of these patients with confirmed SARS-CoV-2 infection and on mortality rates.

Conclusions

History of stroke is associated with a three-fold increase in the risk of death due to SARS-CoV-2 infection. Stroke currently seems not to be one of the main complications of COVID-19. The virus enters the brain parenchyma, endothelium, and heart, and alters coagulation, which may lead to stroke; we must therefore remain vigilant. Patients with stroke may concomitantly present SARS-CoV-2 infection, even if they have not previously shown respiratory symptoms.

Conflicts of interest

None.

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References

- Matias-Guiu J, Gomez-Pinedo U, Montero-Escribano P, Gomez-Iglesias P, Porta-Etessam J, Matias-Guiu JA. ¿Es esperable que haya cuadros neurológicos por la pandemia por SARS-CoV-2? *Neurologia*. 2020;35:170–5, <http://dx.doi.org/10.1016/j.nrl.2020.03.001>.
- Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *J Neurol*. 2004;251(10):1227–31, <http://dx.doi.org/10.1007/s00415-004-0519-8>.
- Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan*. 2005;14(3):113–9.
- Xiang-Hua Y, Le-Min W, Ai-Bin L, et al. Severe acute respiratory syndrome and venous thromboembolism in multiple organs. *Am J Respir Crit Care Med*. 2010;182(3):436–7, <http://dx.doi.org/10.1164/ajrccm.182.3.436>.
- Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis*. 2004;10(2):342–4, <http://dx.doi.org/10.3201/eid1002.030638>.
- Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. *Am J Pathol*. 2007;170(4):1136–47, <http://dx.doi.org/10.2353/ajpath.2007.061088>.
- Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med*. 2005;202(3):415–24, <http://dx.doi.org/10.1084/jem.20050828>.
- Al-Hameed FM. Spontaneous intracranial hemorrhage in a patient with Middle East respiratory syndrome

- corona virus. *Saudi Med J*. 2017;38(2):196–200, <http://dx.doi.org/10.15537/smj.2017.2.16255>.
9. Talbot PJ, Arnold D, Antel JP. Virus-induced autoimmune reactions in the CNS. *Curr Top Microbiol Immunol*. 2001;253:247–71, http://dx.doi.org/10.1007/978-3-662-10356-2_12.
 10. Wu A, Peng Y, Huang B, et al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. *Cell Host Microbe*. 2020;27(3):325–8, <http://dx.doi.org/10.1016/j.chom.2020.02.001>.
 11. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. *bioRxiv*. 2020, <http://dx.doi.org/10.1101/2020.01.26.919985> [consultada el 26/04/2020].
 12. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China [publicado en línea, previamente a edición impresa, 2020 Apr 10]. *JAMA Neurol*. 2020:e201127, <http://dx.doi.org/10.1001/jamaneurol.2020.1127>.
 13. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382:1708–20, <http://dx.doi.org/10.1056/NEJMoa2002032>.
 14. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020:e201585, <http://dx.doi.org/10.1001/jama.2020.1585>.
 15. 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):1054–62, [http://dx.doi.org/10.1016/S0140-6736\(20\)30566-3](http://dx.doi.org/10.1016/S0140-6736(20)30566-3).
 16. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506, [http://dx.doi.org/10.1016/S0140-6736\(20\)30183-5](http://dx.doi.org/10.1016/S0140-6736(20)30183-5).
 17. Chen R, Liang W, Jiang M, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. *Chest*. 2020;S0012-3692(20):30710–8, <http://dx.doi.org/10.1016/j.chest.2020.04.010>.
 18. Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. *Circulation*. 2017;135(8):759–71, <http://dx.doi.org/10.1161/CIRCULATIONAHA.116.025250>.
 19. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846–8, <http://dx.doi.org/10.1007/s00134-020-05991-x>.
 20. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020:e200994, <http://dx.doi.org/10.1001/jamainternmed.2020.0994>.
 21. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–13, [http://dx.doi.org/10.1016/S0140-6736\(20\)30211-7](http://dx.doi.org/10.1016/S0140-6736(20)30211-7).
 22. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)*. 2020;133:1025–31, <http://dx.doi.org/10.1097/CM9.0000000000000744>.
 23. Chang D, Lin M, Wei L, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. *JAMA*. 2020;323(11):1092–3, <http://dx.doi.org/10.1001/jama.2020.1623>.
 24. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8:475–81, [http://dx.doi.org/10.1016/S2213-2600\(20\)30079-5](http://dx.doi.org/10.1016/S2213-2600(20)30079-5).
 25. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–13, [http://dx.doi.org/10.1016/S0140-6736\(20\)30211-7](http://dx.doi.org/10.1016/S0140-6736(20)30211-7).
 26. Lu Y, Wang P, Zhou T, et al. Comparison of prevalence, awareness, treatment, and control of cardiovascular risk factors in China and the United States. *J Am Heart Assoc*. 2018;7(3):e007462, <http://dx.doi.org/10.1161/JAHA.117.007462>. Published 2018 Jan 26.
 27. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2). *J Med Virol*. 2020, <http://dx.doi.org/10.1002/jmv.25915>.
 28. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol*. 2009;8(8):731–40, [http://dx.doi.org/10.1016/S1474-4422\(09\)70134-6](http://dx.doi.org/10.1016/S1474-4422(09)70134-6).
 29. Barnes M, Heywood AE, Mahimbo A, Rahman B, Newall AT, Macintyre CR. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. *Heart*. 2015;101(21):1738–47, <http://dx.doi.org/10.1136/heartjnl-2015-307691>.
 30. Chiang MH, Wu HH, Shih CJ, Chen YT, Kuo SC, Chen YTL. Association between influenza vaccination and reduced risks of major adverse cardiovascular events in elderly patients. *Am Heart J*. 2017;193:1–7, <http://dx.doi.org/10.1016/j.ahj.2017.07.020>.
 31. Delbos V, Abgueguen P, Chennebault JM, Fanello S, Pichard E. Acute cytomegalovirus infection and venous thrombosis: role of antiphospholipid antibodies. *J Infect*. 2007;54(1):e47–50, <http://dx.doi.org/10.1016/j.jinf.2006.03.031>.
 32. Elkind MS. Why now? Moving from stroke risk factors to stroke triggers. *Curr Opin Neurol*. 2007;20(1):51–7, <http://dx.doi.org/10.1097/WCO.0b013e328012da75>.
 33. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506, [http://dx.doi.org/10.1016/S0140-6736\(20\)30183-5](http://dx.doi.org/10.1016/S0140-6736(20)30183-5).
 34. 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(4):844–7, <http://dx.doi.org/10.1111/jth.14768>.
 35. Klok FA, Kruij MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;S0049-3848(20):30120–1, <http://dx.doi.org/10.1016/j.thromres.2020.04.013>.
 36. Halhogbani T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. *Ann Saudi Med*. 2016;36:78–80.
 37. 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):1054–62, [http://dx.doi.org/10.1016/S0140-6736\(20\)30566-3](http://dx.doi.org/10.1016/S0140-6736(20)30566-3).
 38. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect Dis*. 2010;10(2):83–92, [http://dx.doi.org/10.1016/S1473-3099\(09\)70331-7](http://dx.doi.org/10.1016/S1473-3099(09)70331-7).
 39. Tsui KL, Leung TC, Yam LY, et al. Coronary plaque instability in severe acute respiratory syndrome. *Int J Cardiol*. 2005;99(3):471–2, <http://dx.doi.org/10.1016/j.ijcard.2003.11.052>.
 40. Murphy RT, Foley JB, Crean P, Walsh MJ. Reciprocal activation of leukocyte-endothelial adhesion molecules in acute

- coronary syndromes. *Int J Cardiol.* 2003;90(2-3):247–52, [http://dx.doi.org/10.1016/s0167-5273\(02\)00557-0](http://dx.doi.org/10.1016/s0167-5273(02)00557-0).
41. Murphy RT, Foley JB, Mulvihill N, Crean P, Walsh MJ. Endothelial inflammation and thrombolysis resistance in acute myocardial infarction. *Int J Cardiol.* 2002;83(3):227–31, [http://dx.doi.org/10.1016/s0167-5273\(02\)00056-6](http://dx.doi.org/10.1016/s0167-5273(02)00056-6).
42. Baracchini C, Pieroni A, Viaro F, et al. Acute stroke management pathway during Coronavirus-19 pandemic [publicado en línea previamente a edición impresa, 2020 Apr 9]. *Neurol Sci.* 2020:1–3, <http://dx.doi.org/10.1007/s10072-020-04375-9>.
43. Tam CF, Cheung KS, Lam S, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on ST-segment-elevation myocardial infarction care in Hong Kong, China. *Circ Cardiovasc Qual Outcomes.* 2020;13(4):e006631, <http://dx.doi.org/10.1161/CIRCOUTCOMES.120.006631>.
44. From the American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Canadian Interventional Radiology Association (CIRA), Congress of Neurological Surgeons (CNS), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organization (ESO), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), and World Stroke Organization (WSO), Sacks D, Baxter B, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. *Int J Stroke.* 2018;13(6):612–32, <http://dx.doi.org/10.1177/1747493018778713>.
45. Rodríguez-Pardo J, Fuentes B, de Leciñana MA, Campollo J, Castaño PC, Ruiz JC, et al. Atención al ictus agudo durante la pandemia por COVID-19. Recomendaciones Plan Ictus Madrid, Neurología. 2020, <http://dx.doi.org/10.1016/j.nrl.2020.04.008> (En prensa).
46. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. *J Am Coll Cardiol.* 2020;75(18):2352–71, <http://dx.doi.org/10.1016/j.jacc.2020.03.031>, 34637-4.
47. Ghosal S, Sinha B, Majumder M, Misra A. Estimation of effects of nationwide lockdown for containing coronavirus infection on worsening of glycosylated haemoglobin and increase in diabetes-related complications: a simulation model using multivariate regression analysis. *Diabetes Metab Syndr.* 2020;14(4):319–23, <http://dx.doi.org/10.1016/j.dsx.2020.03.014>.
48. Valtorta NK, Kanaan M, Gilbody S, Hanratty B. Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing. *Eur J Prev Cardiol.* 2018;25(13):1387–96, <http://dx.doi.org/10.1177/2047487318792696>.