2020

Cerebrovascular Complications of COVID-19

J. M. Katz
Zucker School of Medicine at Hofstra/Northwell, jkatz2@northwell.edu

R. B. Libman
Zucker School of Medicine at Hofstra/Northwell, RLibman@Northwell.edu

J. J. Wang
Zucker School of Medicine at Hofstra/Northwell, jwang11@northwell.edu

P. Sanelli
Zucker School of Medicine at Hofstra/Northwell, psanelli@northwell.edu

C. G. Filippi
Zucker School of Medicine at Hofstra/Northwell, cfilippi@northwell.edu

See next page for additional authors

Stroke

BRIEF REPORT

Cerebrovascular Complications of COVID-19

Jeffrey M. Katz, MD; Richard B. Libman, MD; Jason J. Wang, PhD; Pina Sanelli, MD; Christopher G. Filippi, MD; Michele Gribko, DNP; Steven V. Pacia, MD; Ruben I. Kuzniecky, MD; Souhel Najjar, MD; Salman Azhar, MD

BACKGROUND AND PURPOSE: Coronavirus disease 2019 (COVID-19) evolved quickly into a global pandemic with myriad systemic complications, including stroke. We report the largest case series to date of cerebrovascular complications of COVID-19 and compare with stroke patients without infection.

METHODS: Retrospective case series of COVID-19 patients with imaging-confirmed stroke, treated at 11 hospitals in New York, between March 14 and April 26, 2020. Demographic, clinical, laboratory, imaging, and outcome data were collected, and cases were compared with date-matched controls without COVID-19 from 1 year prior.

RESULTS: Eighty-six COVID-19–positive stroke cases were identified (mean age, 67.4 years; 44.2% women). Ischemic stroke (83.7%) and nonfocal neurological presentations (67.4%) predominated, commonly involving multivascular distributions (45.8%) with associated hemorrhage (20.8%). Compared with controls (n=499), COVID-19 was associated with in-hospital stroke onset (47.7% versus 5.0%; $P<0.001$), mortality (29.1% versus 9.0%; $P<0.001$), and Black/multiracial race (58.1% versus 36.9%; $P=0.001$). COVID-19 was the strongest independent risk factor for in-hospital stroke (odds ratio, 20.9 [95% CI, 10.4–42.2]; $P<0.001$), whereas COVID-19, older age, and intracranial hemorrhage independently predicted mortality.

CONCLUSIONS: COVID-19 is an independent risk factor for stroke in hospitalized patients and mortality, and stroke presentations are frequently atypical.

Key Words: cerebrovascular disorders ■ demography ■ odds ratio ■ pandemics ■ risk factors

In December 2019, coronavirus disease 2019 (COVID-19)—the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—first appeared as a respiratory illness in Wuhan, China.[1] Since then, it has become a global pandemic, infecting at least 15.8 million people worldwide, including >4.1 million people in the United States.[2] SARS-CoV-2 infection has protean presentations and clinical courses, ranging from asymptomatic carriers[3] to critical illness with acute respiratory distress syndrome and multiorgan failure secondary to an accentuated immune response.[4–6] Hypercoagulability may also develop, resulting in venous and arterial thromboembolic disease, including stroke.[7–12]

To date, only 13 stroke patients from China,[9] 7 patients from the United Kingdom,[10] and 37 patients from the United States[11,12] have been described in the literature. We present the largest series to date of COVID-19 patients who either presented with stroke or had cerebrovascular complications while hospitalized for COVID-19.

METHODS

This is a retrospective case series of COVID-19 patients concurrently diagnosed with stroke, admitted to 11 Northwell Health hospitals in New York City and Long Island between March 14 and April 26, 2020. Our institutional review board approved this study as minimal risk, waiving informed consent. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Inclusion required (1) confirmed SARS-CoV-2 infection by polymerase chain reaction testing of nasopharyngeal swab samples and (2) concurrent stroke diagnosis, defined as stroke

Correspondence to: Jeffrey M. Katz, MD, North Shore University Hospital, 300 Community Dr, 9 Tower, Manhasset, NY 11030. Email jkatz2@northwell.edu
This manuscript was sent to Marc Fisher, Senior Consulting Editor, for review by expert referees, editorial decision, and final disposition.
The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.031265.
For Sources of Funding and Disclosures, see page e231.

Stroke is available at www.ahajournals.org/journal/str

BRIEF REPORT

Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

symptom onset during COVID-19 illness or onset of COVID-19 symptoms or SARS-CoV-2 polymerase chain reaction positivity within 14 days of stroke symptom onset. Only imaging-confirmed cases were included. Historical controls without COVID-19 were comprised of all stroke patients admitted 1 year earlier, between the same dates, to the same hospitals.

Data obtained from retrospective chart review and Get With The Guidelines-Stroke and COVID-19 databases included demographic, clinical, laboratory, and outcome measures. Additional details may be found in Materials in the Data Supplement. Clinical outcome was measured by discharge disposition, including death. Case neuroimaging data including brain computed tomography or magnetic resonance imaging and angiographic findings were attained by independent neuroradiologist review.

STATISTICAL ANALYSIS

A bivariate analysis of demographic, clinical, and outcome variables comparing COVID-19 stroke patients to controls was performed using χ^2. A logistic regression model was created to determine independent risk factors for in-hospital stroke and mortality. Statistical significance was considered for $P<0.05$. All statistical analyses were done in SAS v9.4 (SAS Institute).

RESULTS

In the study period, 10 596 COVID-19 patients were hospitalized (mean [range] percent hospital admissions with COVID-19, 43.3% [29.8%–64.2%]), and of these, 86 (0.8%; mean age [range], 67.4 [25–94] years; 44.2%

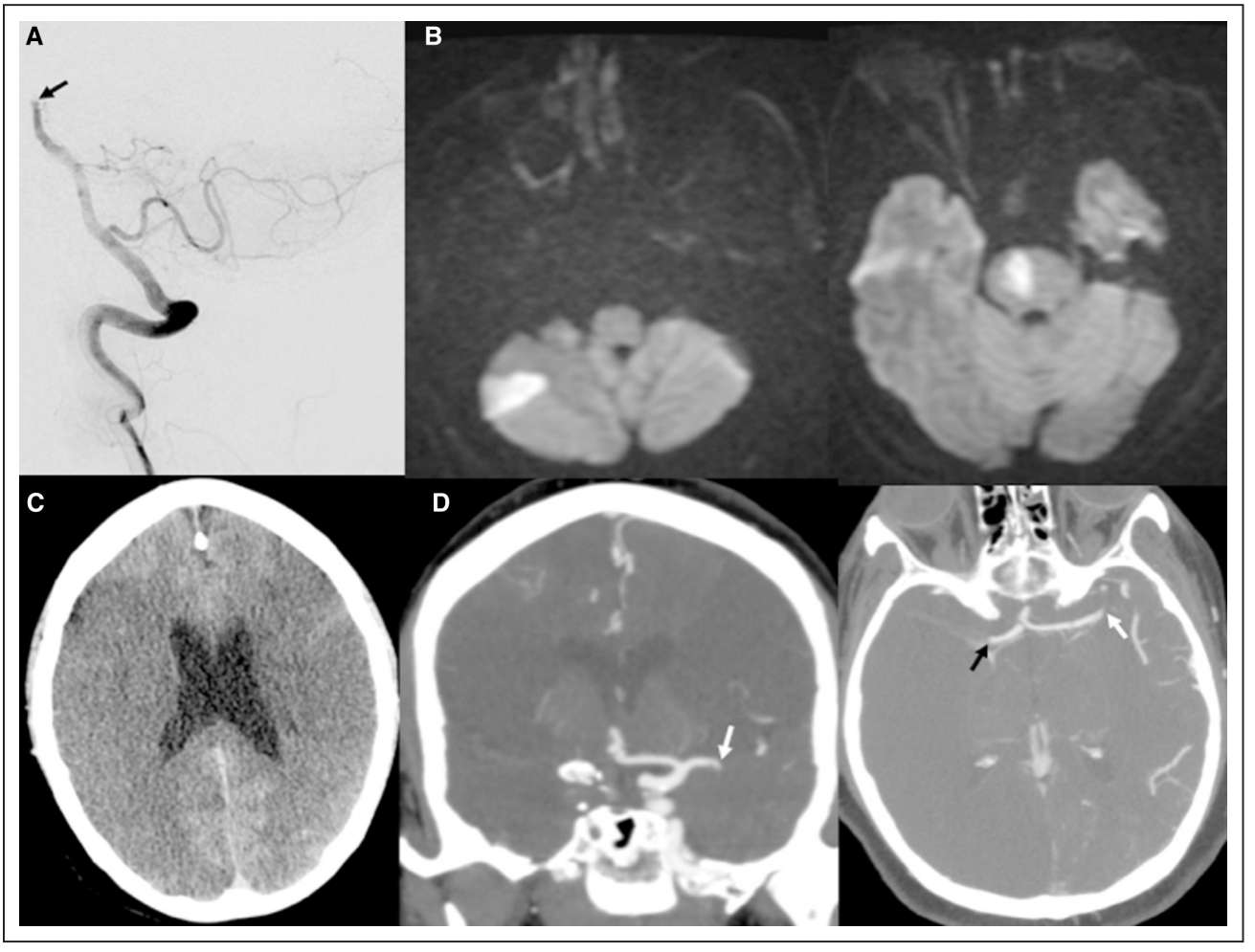

Figure. Coronavirus disease 2019 (COVID-19)–associated large vessel occlusion.
A, Angiogram displaying distal basilar artery occlusion (black arrow) in a 54-y-old man. **B**, Post-thrombectomy, magnetic resonance imaging diffusion shows right inferior cerebellar and paramedian pontine infarctions. **C**, Computed tomography (CT) head showing bilateral middle cerebral artery infarctions in a 62-y-old woman with. **D**, CT angiogram demonstrating occlusions of proximal left middle cerebral artery (white arrows) and terminal right internal carotid artery and middle cerebral artery (black arrow).

Stroke. 2020;51:e227–e231. DOI: 10.1161/STROKEAHA.120.031265

women) met inclusion with imaging-confirmed infarctions (83.7%) or exclusive intracranial hemorrhage (16.3%). In the ischemic subgroup, 20.8% had associated brain hemorrhage, including hemorrhagic transformation (n=6) and simultaneous hemorrhage and infarction (n=9). Multivascular territory infarction (45.8%) was most common. Of ischemic patients with noninvasive angiography (38.9%), 57.1% had extracranial or intracranial large vessel occlusion (Figure).

Fifty-eight patients (67.4%) presented with nonfocal deficits. Encephalopathy was the most common presenting symptom (n=41), followed by seizures, generalized weakness, falls, and dizziness. Many had substantial COVID-19 complications while hospitalized, including pneumonia (88.4%), hypoxia (69.8%), and end-organ dysfunction (67.4%), with frequent critical-care admission (51.2%) and mechanical ventilation (44.0%). Of 45 patients testing positive for COVID-19 after stroke onset, most had mild COVID-19 symptoms (n=23) or

Table 1. Bivariate Analysis Comparing Stroke Patients With and Without COVID-19

Variable	Category	COVID-19 n=86 n (%)	Control n=499 n (%)	*P* Value
Demographic and clinical				
Age, y	20–69	46 (53.5)	219 (43.9)	0.099
	≥70	40 (46.5)	280 (56.1)	
Sex	Female	38 (44.2)	234 (46.9)	0.642
Race	White	26 (30.2)	266 (53.3)	0.001
	Black	27 (31.4)	115 (23.1)	
	Asian	10 (11.6)	49 (9.8)	
	Multiracial/other	23 (26.7)	69 (13.8)	
Stroke subtype	Ischemic	72 (83.7)	397 (79.6)	0.371
	Hemorrhagic	14 (16.3)	102 (20.4)	
Stroke onset location	In hospital	41 (47.7)	25 (5.0)	<0.001
Stroke risk factors	Hypertension	63 (73.3)	369 (74.0)	0.893
	Diabetes mellitus	179 (35.9)	35 (40.7)	0.391
	Dyslipidemia	28 (32.6)	206 (41.3)	0.127
	Smoking	6 (7.0)	45 (9.0)	0.535
	Atrial fibrillation	63 (12.6)	8 (9.3)	0.384
	Past stroke or TIA	9 (10.5)	115 (23.1)	0.008
	None	15 (17.4)	66 (13.2)	0.296
Obesity	BMI ≥30 kg/m^2	27 (31.4)	136 (27.3)	0.429
Admission medication	Antithrombotic	27 (31.4)	246 (49.3)	0.002
	Antihypertensive	48 (55.8)	334 (66.9)	0.045
	Lipid lowering	36 (41.9)	233 (46.7)	0.406
Deep vein thrombosis		13 (15.1)	24 (4.8)	<0.001
Acute treatment	Intravenous r-tPA	7 (8.1)	71 (14.2)	0.125
	Thrombectomy	1 (1.2)	23 (4.6)	0.137
Vital signs and blood work				
Systolic blood pressure	≥140 mm Hg	43 (50.0)	341 (68.3)	0.001
Heart rate	≥100 bpm	34 (39.5)	70 (14.0)	<0.001
Platelets	<150 K/uL	19 (22.1)	55 (11.0)	0.004
INR	≥1.2	36 (41.9)	94 (18.8)	<0.001
Outcome				
Hospital discharge disposition	Home	25 (29.1)	228 (45.7)	<0.001
	Rehabilitation	31 (36.1)	210 (42.1)	
	Expired/hospice	30 (34.9)	61 (12.2)	
Mortality		25 (29.1)	45 (9.0)	<0.001

BMI indicates body mass index; COVID-19, coronavirus disease 2019; INR, international normalized ratio; r-tPA, recombinant tissue-type plasminogen activator; and TIA, transient ischemic attack.

BRIEF REPORT

were asymptomatic (n=13). Stroke onset during hospitalization for COVID-19 occurred in 41 patients (47.7%). The majority of these were diagnosed by brain imaging for encephalopathy (n=23), while only 9 had sudden-onset focal deficits.

Table 1 compares demographic, clinical, laboratory, and outcome variables of COVID-19 stroke patients and controls (n=499). No significant differences were found in terms of age or sex. Black and multiracial minorities were significantly more common in the COVID-19 cohort (58.1% versus 36.9%; *P*=0.001). COVID-19 patients were significantly more likely to have stroke while hospitalized (47.7% versus 5.0%; *P*<0.001) and had significantly less frequent cerebrovascular history (10.5% versus 23.1%; *P*=0.008) and preadmission antithrombotic and antihypertensive use. More frequent admission tachycardia, thrombocytopenia, international normalized ratio elevation, and deep vein thrombosis were observed in COVID-19 patients. COVID-19 patients were significantly more likely to die (*P*<0.001), with 29.1% all-cause mortality.

Multivariable logistic regression results are presented in Table 2. COVID-19 was the strongest independent predictor of stroke in hospitalized patients. Other risk factors included male sex and deep vein thrombosis. Cerebrovascular history predicted decreased in-hospital stroke risk. COVID-19, age ≥70 years, atrial fibrillation, and any intracranial hemorrhage, including hemorrhagic transformation, were independent risk factors for mortality.

DISCUSSION

A major finding of our study was the frequency of in-hospital stroke onset, accounting for 48% of the COVID-19 cohort compared with 5% of controls. As COVID-19 was the strongest independent predictor of in-hospital stroke onset, a causal association between COVID-19 and stroke is suggested and further supported by the absence of cerebrovascular history and evidence of coagulopathy specific to COVID-19 stroke patients. This high in-hospital stroke rate was found by others[12] and may reflect the acuity of COVID-19 patients hospitalized during the pandemic peak.

A significant racial disparity was noted with Black and multiracial minorities being the majority (58%) of the COVID-19 stroke cohort. In a consecutive series of 5700 COVID-19 patients hospitalized in the same system, 52% were Black/multiracial.[4] Therefore, this overrepresentation may result from the higher prevalence of COVID-19 in these populations. Inequalities in risk factor modification, healthcare access, socioeconomics, diet, and genetic predilections may also contribute.

The majority of COVID-19 patients presented with nonfocal deficits (67.4%), predominantly encephalopathy, ranging from confusion to coma. In previous studies, stroke chameleons accounted for up to 22% of stroke patients, and altered mental status is the most common admitting diagnosis.[13] COVID-19 patients were also more likely to die, with 29% in-hospital mortality. Although not directly comparable given the methodological differences between studies, this rate is higher than the 21% COVID-19 mortality rate separately reported by our health system.[4] COVID-19 was the strongest independent risk factor for mortality. While we were unable to differentiate stroke-specific mortality from the independent lethality of COVID-19, our excess mortality reflects an even worse prognosis for COVID-19–associated stroke.

Our study has several strengths and limitations. Numerous factors likely resulted in undercounting the COVID-19 stroke population. While inclusion of only patients with imaging-confirmed stroke is a strength, many potential stroke patients with normal initial brain imaging did not undergo repeat imaging and were not included. In addition, SARS-CoV-2 polymerase chain reaction–negative stroke patients with other biomarkers suggesting infection were excluded. Given the false negative rate of COVID-19 testing,[14] the true burden of

Table 2. Independent Risk Factors for In-Hospital Stroke and Mortality

	In-Hospital Stroke		Mortality	
Parameter	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
COVID-19	20.9 (10.4–42.0)	<0.001	3.3 (1.8–6.1)	<0.001
Age ≥70 y	1.2 (0.6–2.4)	0.557	2.4 (1.3–4.5)	0.007
Sex, male	2.2 (1.1–4.3)	0.028	1.2 (0.7–2.2)	0.456
Black race	0.6 (0.3–1.6)	0.333	0.6 (0.3–1.4)	0.276
ICH	0.8 (0.4–1.8)	0.637	2.1 (1.2–3.8)	0.013
DVT	5.4 (2.0–14.5)	0.001	1.7 (0.7–4.3)	0.240
Atrial fibrillation	0.3 (0.1–1.1)	0.075	2.4 (1.1–5.5)	0.038
Obesity	1.8 (0.9–3.6)	0.096	0.7 (0.4–1.5)	0.379
Past stroke or transient ischemic attack	0.3 (0.1–0.8)	0.026	0.5 (0.2–1.2)	0.101

ICH includes hemorrhagic transformation. COVID-19 indicates coronavirus disease 2019; DVT, deep vein thrombosis; and ICH, intracranial hemorrhage.

COVID-19–related cerebrovascular complications may be underestimated. Nevertheless, our overall COVID-19 stroke rate of 0.8% is similar to the 0.9% rate reported by others.[12] By including historical controls, we were able to demonstrate that COVID-19 is an independent risk factor for stroke, specifically in-hospital onset, and avoided contaminating our control group with false negative COVID-19 patients (see the Data Supplement for details). Yet, by not including a contemporaneous comparison group, we were unable to control for differences in health access and hospital staffing during the pandemic. To our knowledge, ours is the largest series to date of COVID-19 stroke patients and includes outcome for all patients.

In conclusion, COVID-19 is a strong independent risk factor for stroke in hospitalized patients, and stroke in COVID-19 portends increased mortality. COVID-19–related stroke is more frequent among racial minorities, and presentations are often atypical, without focal deficits, in multivascular territories, and with concomitant hemorrhages. Recognition is, therefore, critical, since prompt diagnosis may impact management.

ARTICLE INFORMATION

Received June 2, 2020; final revision received July 3, 2020; accepted July 16, 2020.

Affiliations

Departments of Neurology (J.M.K., R.B.L., M.G., S.V.P., R.I.K., S.N., S.A.) and Radiology (J.M.K, P.S., C.G.F), Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY. Feinstein Institute for Medical Research at Northwell Health, Manhasset, NY (J.J.W.).

Sources of Funding

None.

Disclosures

None.

Supplemental Materials

Additional Methods and Discussion

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727–733. doi: 10.1056/NEJMoa2001017
2. COVID-19 dashboard by the Center for Systems Science and Engineering at Johns Hopkins University. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html - /bda7594740fd40299423467b48e9ecf6. Accessed July 25, 2020.
3. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill*. 2020;25:2000180. doi: 10.2807/1560-7917.ES.2020.25.10.2000180
4. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; Northwell COVID-19 Research Team. Presenting characteristics, comorbidities and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052–2059. doi: 10.1001/jama.2020.6775
5. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, 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;8:475–481. doi: 10.1016/S2213-2600(20)30079-5
6. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033–1034. doi: 10.1016/S0140-6736(20)30628-0
7. 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;18:844–847. doi: 10.1111/jth.14768
8. Cao W, Li T. COVID-19: towards understanding of pathogenesis. *Cell Res*. 2020;30:367–369. doi: 10.1038/s41422-020-0327-4
9. Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, Hong C, Chen S, Wang Y, Wang H, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Lancet*. 2020. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=355002510. Accessed April 30, 2020.
10. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, Humpries F, Jäger HR, Losseff NA, Perry RJ, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. 2020;91:889–891. doi: 10.1136/jnnp-2020-323586
11. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med*. 2020;382:e60. doi: 10.1056/NEJMc2009787
12. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, Henninger N, Trivedi T, Lillemoe K, Alam S, et al. SARS-CoV-2 and stroke in a New York Healthcare System. *Stroke*. 2020;51:2002–2011. doi: 10.1161/STROKEAHA.120.030335
13. Arch AE, Weisman DC, Coca S, Nystrom KV, Wira CR III, Schindler JL. Missed ischemic stroke diagnosis in the emergency department by emergency medicine and neurology services. *Stroke*. 2016;47:668–673. doi: 10.1161/STROKEAHA.115.010613
14. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology*. 2020;296:e32–e40. doi: 10.1148/radiol.2020200642