SARS-CoV-2 and Stroke Characteristics: A Report From the Multinational COVID-19 Stroke Study Group

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Stroke

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BACKGROUND AND PURPOSE: Stroke is reported as a consequence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in several reports. However, data are sparse regarding the details of these patients in a multinational and large scale.

METHODS: We conducted a multinational observational study on features of consecutive acute ischemic stroke, intracranial hemorrhage, and cerebral venous or sinus thrombosis among SARS-CoV-2–infected patients. We further investigated the risk of large vessel occlusion, stroke severity as measured by the National Institutes of Health Stroke Scale, and stroke subtype as measured by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria among patients with acute ischemic stroke. In addition, we explored the neuroimaging findings, features of patients who were asymptomatic for SARS-CoV-2 infection at stroke onset, and the impact of geographic regions and countries' health expenditure on outcomes.

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RESULTS: Among the 136 tertiary centers of 32 countries who participated in this study, 71 centers from 17 countries had at least 1 eligible stroke patient. Of 432 patients included, 323 (74.8%) had acute ischemic stroke, 91 (21.1%) intracranial hemorrhage, and 18 (4.2%) cerebral venous or sinus thrombosis. A total of 183 (42.4%) patients were women, 104 (24.1%) patients were <55 years of age, and 105 (24.4%) patients had no identifiable vascular risk factors. Among acute ischemic stroke patients, 44.5% (126 of 283 patients) had large vessel occlusion; 10% had small artery occlusion according to the TOAST criteria. We observed a lower median National Institutes of Health Stroke Scale (8 [3–17] versus 11 [5–17]; P=0.02) and higher rate of mechanical thrombectomy (12.4% versus 2%; P<0.001) in countries with middle-to-high health expenditure when compared with countries with lower health expenditure. Among 380 patients who had known interval onset of the SARS-CoV-2 and stroke, 144 (37.8%) were asymptomatic at the time of admission for SARS-CoV-2 infection.

CONCLUSIONS: We observed a considerably higher rate of large vessel occlusions, a much lower rate of small vessel occlusion and lacunar infarction, and a considerable number of young stroke when compared with the population studies before the pandemic. The rate of mechanical thrombectomy was significantly lower in countries with lower health expenditures.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: cerebrovascular disorders ■ intracranial hemorrhages ■ neuroimaging ■ stroke ■ venous thrombosis

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
CASCADE	Call to Action: SARS-CoV-2 and Cerebrovascular Disorders
COVID-19	coronavirus disease 2019
CVST	cerebral venous or sinus thrombosis
ICH	intracranial hemorrhage
IPH	intraparenchymal hemorrhage
IVT	intravenous thrombolysis
LVO	large vessel occlusion
NIHSS	National Institutes of Health Stroke Scale
SAH	subarachnoid hemorrhage
SVO	small-vessel occlusion
TOAST	Trial of ORG 10172 in Acute Stroke Treatment

Since the emergence of the coronavirus disease 2019 (COVID-19) pandemic, several cases of cerebrovascular events were reported among patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] Studies presented the incidence and prevalence of acute ischemic stroke (AIS), intracranial hemorrhage (ICH), and cerebral venous or sinus thrombosis (CVST) in SARS-CoV-2–infected patients.[2–6]

Many studies proposed coagulopathy as the underlying pathophysiological mechanism for the cerebrovascular events.[7,8] Small case series demonstrated a higher proportion of large vessel occlusions (LVOs),[2,9] or cryptogenic strokes,[4,10] with elevated D-dimer level, liver enzymes, and inflammatory or renal failure biomarkers among the patients who experienced SARS-CoV-2 infection.[4,5] Additionally, most of the studies noted a higher severity and mortality rate among stroke patients diagnosed with SARS-CoV-2 compared with others.[4,11,12]

To present a more comprehensive overview of stroke among patients infected with SARS-CoV-2, we devised a multinational multiple-phase study. In the first phase, we estimated the risk of stroke among the SARS-CoV-2–infected hospitalized patients. [13] In the current study, we aimed to present more details on the features and characteristics of our expanded multinational stroke cohort with prior SARS-CoV-2 infection. We further investigated the risk of LVO, stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), and stroke subtype as measured by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria in the entire cohort, as well as different geographic regions.

METHODS

Study Design

The details of the study design are available in Document I in the Data Supplement. The authors declare that all supporting data are available within the article. Additional data that support the findings of this study are available from the corresponding author upon reasonable request. This multicenter, multinational prospective and observational study was conducted and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology,[14] and Enhancing the Quality and Transparency of Health Research guidelines.[15] The study protocol was designed by the investigators at the Neuroscience Institute of Geisinger Health System, Pennsylvania, and received approval by the Institutional Review Board of Geisinger Health System and other participating institutions. Investigators from 6 continents including North America (Canada, 6 states of the United States, and Mexico), South America (Brazil), Europe (Belgium, Croatia, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Norway, Portugal, Spain, Sweden, and Switzerland), Asia (India,

Iran, Iraq, Israel, Lebanon, Singapore, South Korea, Turkey, and the United Arab Emirates), Oceania (Australia and New Zealand), and Africa (Egypt, Nigeria, and Uganda) responded to our invitation. The centers were included by nonprobability sampling, and data were included until June 10, 2020.

Participants

We included consecutive SARS-CoV-2–infected adult patients who had imaging-confirmed subsequent stroke[16]—AIS, intracerebral hemorrhage, subarachnoid hemorrhage (SAH), and CVST. The preferred diagnostic criteria for SARS-CoV-2 were defined according to the World Health Organization interim guidance.[17] Ischemic or hemorrhagic strokes were defined in the presence of a rapid onset of a neurological deficit with evidence of acute ischemic or hemorrhagic lesions on computed tomography or magnetic resonance imaging. Patients who had transient stroke-like symptoms (transient ischemic attack) without acute lesions on computed tomography or magnetic resonance imaging were not included in this study due to the high diagnostic error. [18–20]

The inclusion of the stroke patients was based on the confirmed prior infection by SARS-CoV-2 (and not symptom presentation). Patients who initially presented to the hospital with stroke-related chief complaints and asymptomatic SARS-CoV-2 infection were detected by admission tests, those who had a stroke while being hospitalized for SARS-CoV-2 infection, or patients with stroke-related admission who had confirmed prior diagnosis of SARS-CoV-2 were included in this study.

Data Element and Processing

Collaborators were asked to provide data according to a core protocol. The age, sex, vascular risk factors and comorbidities (ie, hypertension, diabetes, ischemic heart disease, atrial fibrillation, carotid stenosis, chronic kidney disease, cardiac ejection fraction <40%, active neoplasms, rheumatological diseases, smoking status, and history of transient ischemic attack or stroke), and laboratory findings (ie, the count for white blood cells, neutrophils, lymphocytes, and platelets, C-reactive protein, blood urea nitrogen, creatinine, alanine transaminase, aspartate transaminase, lactic acid dehydrogenase, fibrinogen, and D-dimer) were requested for the patients with stroke. We also obtained additional data including the onset of the stroke and SARS-CoV-2 infection diagnosis, the initiation of mechanical ventilation (if applicable), length of hospital stays, and patient disposition—defined as still in the hospital, in-hospital death, being discharged to home, acute rehabilitation service, or nursing home. The details of neurological symptoms and investigations, imaging-based localization of the lesion(s), use of antiplatelets or anticoagulants before the stroke, the NIHSS, the ICH score, administration of intravenous thrombolysis (IVT), and mechanical thrombectomy were also requested. The severity of the stroke according to NIHSS was defined as no stroke symptoms (NIHSS score, 0), minor (NIHSS score, 1–4), moderate (NIHSS score, 5–15), moderate-to-severe (NIHSS score, 16–20), and severe stroke (NIHSS score, 21–42).[21] The TOAST criteria were defined as large artery atherosclerosis, cardioembolism, small artery occlusion, other determined etiology, and undetermined etiology.[22]In addition, the lesions on diffusion-weighted imaging or computed tomography images were categorized as lacunar,[23] embolic/large vessel atherothromboembolism,[24,25] vasculitis pattern,[26] or other phenotypes (borderzone or equivocal lesions). In this study, the AISs due to LVOs are referred as occlusion of the internal carotid artery, middle cerebral artery at M1 and M2, anterior cerebral artery at A1, posterior cerebral artery at P1, intracranial vertebral artery, or basilar artery.[27] Brain imaging findings were evaluated by local radiologists with expertise in neuroimaging. To determine the interval between the infection and stroke, the onset of SARS-CoV-2 was considered as either the symptom onset or the day of taking the sample with a positive result, whichever was first. The interval was considered as zero if the infection was diagnosed at the same visit as the onset of stroke. Countries were considered as either low or middle and high health expenditure based on the World Health Organization reports.[28] The countries' annual health expenditure of above US $1000 per capita (2015–2017; Table I in the Data Supplement) and total health expenditure of above US $10 000 per capita (2010–2017; Figure I in the Data Supplement) were considered as the cutoff.

Outcome Measures

The primary outcome measures in this study were the presence versus absence of LVO, stroke severity as measured by NIHSS, and stroke subtype as measured by the TOAST criteria among the AIS patients.

We further compared the groups of the patients with AIS or intraparenchymal hemorrhage (IPH) according to their age (younger versus older than 55 years and younger versus older than 65 years),[29] sex, geographic regions (America, Europe, Asia, and the Middle East), countries' health expenditure (low versus middle and high income), imaging findings, and the interval of stroke onset and infection diagnosis (same day versus others). We did not analyze the disposition and length of stay as outcome measures since many patients were still in the acute phase or admitted in long-term acute care hospitals at the closure of our study.

Statistical Analyses and Modeling

We used descriptive statistics to summarize the data. Demographic data, comorbidities, laboratory findings, and neurological investigations were reported as medians and interquartile range, mean and SDs, and under stratified categories when possible. The equality of the variances was assessed by Leven test. Categorical variables were reported as absolute frequencies and valid percentages. The comparisons between categorical variables were conducted with the Pearson χ^2 test, while the differences among continuous variables were assessed by independent *t* test and ANOVA. A post hoc *z* test on the adjusted residuals and Cramér phi, Tukey, or Dunnett tests were used to demonstrate the degree and direction of the associations in comparison of means, while post hoc comparison of medians was conducted by the Dunn-Bonferroni approach to compare subgroups. All tests were performed using IBM SPSS Statistics, version 26,[30] and $P<0.05$ was considered statistically significant. Bonferroni correction was used for adjusting all *P* values in multiple comparisons.

RESULTS

Collaborators from 136 tertiary centers of 32 countries participated in this prospective study. Among them, 71 centers from 17 countries had at least 1 stroke patient

Table 1. The Baseline Characteristics, Comorbidities, and Laboratory Findings Among SARS-CoV-2 Infected Patients With Stroke

Parameter	AIS, n=323 (74.8%)	Intracerebral hemorrhage, n=68 (15.7%)	SAH, n=23 (5.3%)	Cerebral venous/sinus thrombosis, n=18 (4.2%)
Age, y; mean (SD)	67.2±15.2	63±16	62.6±14.1	48.9±11.5
Age, y; median (IQR)	68 (58–78)	65 (54–75)	62 (54–74)	51 (39.5–55.2)
<40, n (%)	23 (7.1)	8 (12.9)	1 (4.3)	5 (27.8)
41–64, n (%)	110 (34.1)	20 (32.3)	12 (52.2)	11 (61.1)
65–74, n (%)	77 (23.8)	13 (21)	5 (21.7)	2 (11.1)
≥75, n (%)	113 (53)	21 (33.9)	5 (21.7)	0 (0)
Sex: female, n (%)	130 (40.2)	30 (44.1)	12 (52.2)	11 (61.1)
Asymptomatic for SARS-CoV-2 infection at the time of admission, n (%)	104 (36.1)	31 (53.4)	8 (36.4)	4 (22.2)
SARS-CoV-2 to stroke interval, d; mean (SD)	5±7	5±8	3±5	3±4
SARS-CoV-2 to stroke interval, d; median (IQR)	3 (0–9)	0 (0–10.3)	1.5 (0–5.3)	4.5 (0.7–10.3)
NIHSS, median (IQR)	9 (4–17)	10 (0–19)	6 (0–16)	14 (7–17)
ICH score, median (IQR)	…	3 (2–4)	…	…
Mechanical ventilation, n (%)	238 (73.7)	31 (50)	12 (52.2)	10 (55.6)
Initiation of mechanical ventilation, d; median (IQR)	2 (1–3)	2 (1–4)	5 (1–15)	1 (1–2)
Length of hospital stay, d; mean (SD)	12±12	15±18	18±20	18±14
Length of hospital stay, d; median (IQR)	7 (4–16)	8 (3–21)	11 (4.2–31)	14 (7–30)
Disposition*				
Discharged home, n (%)	127 (42.8)	10 (17.9)	3 (15)	12 (66.7)
In-hospital mortality, n (%)	82 (27.6)	35 (62.5)	11 (55)	3 (16.7)
Still in hospital or dispositioned to subacute care, n (%)	88 (29.6)	11 (22)	6 (30)	3 (16.7)
Medications				
Prior antiplatelet therapy, n (%)	87 (28.0)	16 (28.1)	3 (14.3)	0 (0.0)
Prior anticoagulant therapy, n (%)	28 (9.0)	6 (10.5)	2 (9.5)	4 (23.5)
Region				
Middle East, n (%)	153 (47.4)	43 (63.2)	17 (73.9)	15 (83.3)
America, n (%)	6 (1.9)	0 (0.0)	0 (0.0)	2 (11.1)
Europe, n (%)	88 (27.2)	19 (27.9)	6 (26.1)	1 (5.6)
Asia, n (%)	76 (23.5)	6 (8.8)	0 (0.0)	0 (0.0)
Countries' health expenditure				
Middle to high, n (%)	170 (52.6)	26 (38.2)	5 (21.7)	2 (11.1)
Low, n (%)	153 (47.4)	42 (61.8)	18 (78.3)	16 (88.9)
Comorbidities				
Hypertension, n (%)	202 (63.1)	43 (63.2)	14 (60.9)	1 (5.6)
Diabetes, n (%)	111 (34.6)	21 (30.9)	4 (17.4)	2 (11.1)
Ischemic heart disease, n (%)	72 (24.3)	12 (17.6)	4 (21.1)	0 (0)
Atrial fibrillation, n (%)	45 (14.1)	3 (4.4)	2 (8.7)	0 (0)
Carotid stenosis, n (%)	38 (12.8)	2 (2.9)	0 (0)	0 (0)
Chronic kidney disease, n (%)	42 (13.1)	9 (13.2)	3 (13)	2 (11.1)
Cardiac ejection fraction <40%, n (%)	24 (8.1)	7 (10.3)	0 (0)	0 (0)
Active neoplasm, n (%)	21 (7.1)	4 (5.9)	1 (4.3)	0 (0)
Rheumatological disease, n (%)	5 (1.7)	0 (0)	1 (4.3)	0 (0)
Prior stroke or transient ischemic attack, n (%)	5 (1.7)	0 (0)	0 (0)	0 (0)

(*Continued*)

Table 1. Continued

Parameter	AIS, n=323 (74.8%)	Intracerebral hemorrhage, n=68 (15.7%)	SAH, n=23 (5.3%)	Cerebral venous/sinus thrombosis, n=18 (4.2%)
Smoking, n (%)	53 (16.6)	11 (16.2)	3 (13)	0 (0)
Laboratory findings				
White blood cell count, ×109/L; mean (SD)	9.8±4.8	11.4±10.0	13.5±12.9	11.1±6.0
White blood cell count, ×109/L; median (IQR)	9 (6.8–11.2)	9.5 (7.7–12.1)	10 (8.8–12.2)	11.1 (6.7–14.8)
<4 ×109/L, n (%)	7 (2.3)	3 (5.7)	0 (0)	2 (22.2)
4–10 ×109/L, n (%)	184 (61.1)	29 (54.7)	10 (50)	4 (44.4)
10–20 ×109/L, n (%)	96 (31.9)	18 (34)	9 (45)	3 (33.3)
≥20 ×109/L, n (%)	14 (4.7)	5 (10)	1 (5)	0 (0)
Neutrophil count, ×109/L; mean (SD)	7.7±4.5	9.3±8.5	9.6±6.1	9.2±5.1
Neutrophil count, ×109/L; median (IQR)	6.8 (4.8–9.2)	7.2 (5.2–10.6)	7.3 (5.4–11)	9.4 (4.7–14.2)
<4 ×109/L, n (%)	43 (15.2)	5 (10)	1 (5)	1 (12.5)
4–10 ×109/L, n (%)	182 (64.3)	33 (66)	12 (60)	6 (75)
10–20 ×109/L, n (%)	49 (17.3)	10 (20)	6 (30)	1 (12.5)
≥20 ×109/L, n (%)	9 (3.2)	2 (4)	1 (5)	0 (0)
Lymphocyte count, ×109/L; mean (SD)	1.5±1.5	2.0±3.6	2.8±6.3	2.0±1.3
Lymphocyte, ×109/L; median (IQR)	1.3 (0.9–1.9)	1.3 (0.9–2.0)	1.3 (0.9–1.9)	1.9 (1.2–2.3)
<1 ×109/L, n (%)	93 (32.5)	21 (39.6)	6 (28.6)	1 (12.5)
1–2 ×109/L, n (%)	130 (45.5)	19 (35.8)	10 (47.6)	4 (50)
2–3 ×109/L, n (%)	41 (14.3)	9 (35.8)	3 (14.3)	2 (25)
3–4 ×109/L, n (%)	11 (3.8)	1 (1.9)	0 (0)	1 (12.5)
≥4 ×109/L, n (%)	11 (3.8)	3 (5.7)	2 (9.5)	0 (0)
Platelet count, ×109/L; mean (SD)	314.5±440.7	197.1±89.1	191.45±60.9	254.2±170.1
Platelet count, ×109/L; median (IQR)	229 (161–333.7)	178.5 (142.5–254)	183 (141–246)	237 (139–337)
<350 ×109/L, n (%)	228 (78.1)	50 (94.3)	20 (100)	8 (88.9)
350–500 ×109/L, n (%)	64 (21.9)	3 (5.7)	0 (0)	1 (11.1)
ALT, U/L; mean (SD)	63.3±86.3	50.4±66.0	67.2±78.1	120.9±231.6
ALT, U/L; median (IQR)	29.8 (10.1–90.2)	22.9 (8.0–67.7)	53 (11.6–75.2)	39 (29–107)
AST, U/L; mean (SD)	32.1±26.8	35.7±24.5	43.4±27.9	121.5±265.1
AST, U/L; median (IQR)	23.9 (14–40.5)	28.9 (20–43)	35 (21–69.8)	44 (30.5–63)
BUN, mg/dL; mean (SD)	53.1±104.2	99.9±290.8	83.1±160.6	31.9±16.3
BUN, mg/dL; median (IQR)	32 (21–50)	33.5 (21.5–51)	36 (26–60)	30 (23–37)
Creatinine, mg/dL; mean (SD)	1.5±1.7	2.2±2.6	2.57±3.12	1.46±1.21
Creatinine, mg/dL; median (IQR)	1.1 (1.1–1.5)	1.1 (0.9–1.8)	1 (0.9–2.8)	1.1 (0.9–1.6)
CRP, mg/L; mean (SD)	61±131	79±192	85±155	54±37
CRP, mg/L; median (IQR)	36 (24–57)	37 (24–54)	41 (29.5–62.5)	30 (23.5–37)
LDH, U/L; mean (SD)	604.8±1536.7	450.8±443.3	443.0±268.5	766±812.1
LDH, U/L; median (IQR)	377 (245–524)	366.5 (254.5–571)	252 (230–664)	453 (250–1115)
Fibrinogen, mg/dL; mean (SD)	463.6±989.6	706.1±418.1	…	…
Fibrinogen, mg/dL; median (IQR)	223 (3.9–490.5)	693 (303–1246)	…	…
D-dimer, ng/mL; mean (SD)	2654.8±6429.4	8668.4±16318.1	…	1080.8±1376.5
D-dimer, ng/mL; median (IQR)	1027 (551–2200)	2303 (584.5–6875)	…	…

AIS indicates acute ischemic stroke; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; ICH, intracranial hemorrhage; IQR, interquartile range; LDH, lactate dehydrogenase; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage; and SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

*Data on patients' disposition were sparse.

eligible included in this study. One center in the Middle East could not provide data by the deadline. The rest of the centers did not have stroke patients who met our inclusion criteria (Document I in the Data Supplement). We received data on 432 patients—America: 114 (26.4%), Europe: 82 (19.0%), Middle East: 228 (52.8%),

and Asia: 8 (1.9%). Among them, 203 (47.0%) patients were from countries with middle-to-high health expenditure. The mean age for the entire cohort was 65.7±15.7 years. Of 432 patients, the majority were men—249 (57.6%), $P<0.001$. A total of 144 (37.8%) of 380 patients with a known interval of stroke and infection presented to the hospital with chief complaints of stroke-related symptoms, with asymptomatic or SARS-CoV-2 infection. Among the 430 patients with complete comorbidity profiles, 105 (24.4%) patients had no identifiable vascular risk factors at the time of stroke incidence. Demographic characteristics under each stroke subtype are presented in Table 1.

Overall, 323 (74.8%) patients had AIS, 91 (21.1%) ICH, and 18 (4.2%) CVST. Among the patients with ICH (Table 2), 3 (3.3%) had simultaneous SAH and IPH without any evidence of aneurysm, and 4 (4.4%) were presented with simultaneous intraventricular hemorrhage and IPH. Isolated SAH occurred in 23 (25.3%) and isolated IPH in 61 (67%) of the patients with hemorrhagic stroke. Among 23 patients with isolated SAH, 16 (69.5%) had no evidence of aneurysm. Among the 18 patients with CVST, 5 (27.8%) had multiple cerebral sinuses and veins involvements.

The distribution of AIS subtypes according to the TOAST classification was the following: large artery atherosclerosis (33%), cardioembolism (27%), small vessel occlusion (SVO; 10%), other determined etiology (8%), and undetermined etiology (22%; Table 3). The subgroups of the patients according to the TOAST classification were different in terms of age, sex, the prevalence of LVO, imaging patterns, and need for mechanical ventilation. We observed a lower median of D-dimer among patients with large artery atherosclerosis compared with those with cardioembolic strokes (486.5 [371.5–1422.5] versus 1100.0 [955.0–2355.0] ng/mL; $P=0.04$). There were no significant differences in terms of lactate dehydrogenase or fibrinogen among the TOAST subgroups.

Of 283 AIS patients with confirmed data on the site of vascular occlusion, 126 (44.5%) had LVO (Table 4). In comparison with those without LVO, patients with LVO had higher prevalence of large artery atherosclerosis based on TOAST criteria (58.2% versus 9.6%), higher embolic/large vessel atherothromboembolism (88.4% versus 73.3%), and lower lacunar pattern (1.8% versus 17%) on imaging. Patients with LVO also had higher rates of IVT (22.2% versus 8.9%) and mechanical thrombectomy (19% versus 0%).

Table 2. Localization and Presenting Symptoms Regarding the SARS-CoV-2 Infected Patients With ICH and Cerebral Sinus and Venous Thrombosis

Localization	n (%)	Symptoms	n (%)
ICH			
SAH	23 (25.3)	Intracranial (minus subarachnoid) hemorrhage	68 (15.7)
Middle cerebral artery aneurysm	2 (8.6)	Altered level of consciousness	27 (39.7)
Posterior cerebral artery aneurysm	1 (4.3)	Limb paresis	25 (36.7)
Anterior communicating artery aneurysm	2 (8.6)	Aphasia	3 (4.4)
Basilar top aneurysm	2 (8.6)	Facial paresis	2 (2.9)
No aneurysm detected	16 (69.5)	Sensory loss	3 (2.9)
Subarachnoid and IPHs	3 (3.3)	Dysarthria	4 (2.9)
Intraventricular and IPHs	4 (4.4)	Ataxia	5 (2.9)
IPH	61 (67)	Visual field defect	1 (1.5)
Cerebellar hemorrhage	3 (7.0)	SAH	23 (25.3)
Brain stem hemorrhage	4 (9.3)	Thunderclap headache	16 (69.5)
Basal ganglia hemorrhage	19 (43.1)	Decreased level of consciousness	5 (21.7)
Thalamic hemorrhage	7 (16.3)	Cerebral herniation	1 (4.3)
Lobar hemorrhage	20 (46.5)	Seizure	1 (4.3)
Missing	17 (28.3)	Missing	21 (30.9)
Cerebral venous and sinus thrombosis			
Superior sagittal sinus	6 (33.3)	Headache	9 (50)
Sigmoid sinus	6 (33.3)	Seizure	7 (38.9)
Transverse sinus	5 (27.8)	Altered level of consciousness	5 (27.8)
Lateral sinus	3 (16.7)	Increased intracerebral pressure	2 (11.1)
Straight sinus	1 (5.6)	Concomitant ICH	2 (11.1)
Cortical veins	1 (5.6)		
Multiple sinus or venous involvement	5 (27.8)		

ICH indicates intracranial hemorrhage; IPH, intraparenchymal hemorrhage; SAH, subarachnoid hemorrhage; and SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Table 3. Neurological Findings Among Patients With Acute Ischemic Stroke

Parameters	n (%)	Parameters		n (%)
Imaging pattern of ischemia		Vascular territory based on imaging*		
Embolic/large vessel atherothromboembolism	206 (80.5)	Anterior cerebral artery	Unilateral	7 (2.2)
Lacunar	26 (10.2)		Bilateral	1 (0.3)
Borderzone	23 (9.0)	Middle cerebral artery	Unilateral	181 (56)
Vasculitis	1 (0.4)		Bilateral	5 (1.5)
		Posterior cerebral artery	Unilateral	33 (10.2)
TOAST criteria			Bilateral	4 (1.2)
LAA	56 (32.9)	Posterior inferior cerebellar artery		9 (2.8)
Cardioembolism	46 (27.1)	Missing		64 (19.8)
Small artery occlusion	17 (10.0)	Symptoms at onset*		
Other determined etiology	13 (7.6)	Hemineglect		1 (0.4)
Undetermined etiology	38 (22.4)	Limb paresis	Unilateral	168 (72.4)
			Bilateral	2 (0.9)
NIHSS		Sensory loss	Unilateral	26 (11.2)
No stroke symptoms (NIHSS score, 0)	20 (7.5)		Bilateral	1 (0.4)
Minor stroke (NIHSS score, 1–4)	49 (18.4)	Visual field loss	Unilateral	14 (6.0)
Moderate stroke (NIHSS score, 5–15)	117 (43.8)		Bilateral	2 (0.9)
Moderate-to-severe stroke (NIHSS score, 16–20)	35 (13.1)	Gaze preference		13 (5.6)
Severe stroke (NIHSS score, 21–42)	46 (17.2)	Facial paresis		46 (19.8)
		Aphasia		56 (24.1)
LVO	126 (44.5)	Dysarthria		41 (17.7)
		Altered level of consciousness		57 (24.6)
Mechanical thrombectomy	24 (7.4)	Ataxia		21 (9.1)
		Seizure		7 (3.0)
IVT	44 (13.6)	Missing		91 (28.2)

IVT indicates intravenous thrombolysis; LAA, large artery atherosclerosis; LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*Due to multiple infarcts in some patients, the summation may exceed 100%.

The median of NIHSS among AIS patients was 9 (4–17; Table 1). The risk of LVO increased from 8.3% among patients with no stroke symptoms (NIHSS score, 0) to 75.6% among patients with severe stroke (NIHSS score, >21; Table 4). IVT (31.4%) and mechanical thrombectomy (25.4%) were more prevalent among patients with moderate-to-severe stroke (NIHSS score, 16–20). The need for mechanical ventilation increased from 10% among patients with no stroke symptoms to 63% among patients with severe stroke.

We observed similar rates of LVOs and IVT in various geographic regions (Tables II and III in the Data Supplement). However, the rate of mechanical thrombectomy was significantly lower in the Middle Eastern countries and countries with lower health expenditure—2.6% in the Middle East versus 21.1% in Europe ($P<0.001$) and 2% in countries with lower health expenditure versus 12.4% in countries with higher health expenditure ($P<0.001$). We also detected a higher NIHSS in countries with lower health expenditure (11.0 [5.0–17.0] versus 8.0 [3.0–17.0]; $P=0.02$). Similarly, when comparing different regions, patients in America and Europe had a lower NIHSS than those in the Middle East (7.0 [0.0–16.0] in America and 8.0 [4.0–18.0] in Europe versus 12.0 [6.0–17.0] in the Middle East; $P=0.06$).

AIS patients were grouped based on sex and age (Tables IV through VI in the Data Supplement). Of 323 patients with AIS, 59.8% were men, and 36.2% were <55 years of age. Women had a lower rate of smoking and chronic kidney disease and higher NIHSS. Patients above 55 years had a higher proportion of hypertension, atrial fibrillation, ischemic heart disease, and carotid stenosis. Patients >65 years of age also had a higher rate of cardiac ejection fraction of <40%. Patients who were asymptomatic for SARS-CoV-2 infection at the stroke onset had a higher in-hospital mortality and a higher median of D-dimer (Table VII in the Data Supplement). The subgroups of AIS patients based on neuroimaging findings were different in terms of the proportion of LVO, TOAST criteria, and NIHSS categories (Table VIII in the Data Supplement).

Table 4. Baseline Characteristics and Neuroimaging Findings Under Each Outcome Measures

Parameters	TOAST criteria					
	A: LAA, n =56 (32.9%)	B: cardioembolism, n=46 (27.1%)	C: small artery occlusion, n=17 (10.0%)	D: other determined, n=13 (7.6%)	E: undetermined, n=38 (22.4%)	*P* value
Age, y; mean (SD)	63±15	72±14 D	67±18	57±16	65±18	0.01
Sex: female, n (%)	19 (33.9)	21 (45.7)	3 (17.6)	9 (69.2) C	15 (39.5)	0.05
LVO, n (%)	46 (85.2) B, D, E	24 (53.3)	0 (0.0)	2 (18.2)	7 (20.0)	<0.001
IVT, n (%)	14 (25.0)	8 (17.4)	0 (0.0)	2 (15.4)	4 (10.5)	0.12
Mechanical thrombectomy; n (%)	10 (17.9)	10 (21.7)	0 (0.0)	1 (7.7)	2 (5.3)	0.07
NIHSS, median (IQR)	9.0 (5.0–17.0)	13.0 (8.0–20.0)	4.0 (2.0–8.0)	14.0 (6.0–18.0)	7.0 (3.0–17.0)	0.10
TOAST criteria						…
Large artery atherosclerosis, n (%)	…	…	…	…	…	
Cardioembolism, n (%)	…	…	…	…	…	
SVO, n (%)	…	…	…	…	…	
Stroke of other determined etiology, n (%)	…	…	…	…	…	
Stroke of undetermined etiology, n (%)	…	…	…	…	…	
Imaging patterns						<0.001
Embolic/large vessel atherothromboembolism, N (%)	54 (96.4) C, D	43 (93.5) C	4 (23.5)	9 (69.2)	34 (89.5) C	
Lacune, n (%)	0 (0.0)	1 (2.2)	13 (76.5) B, D, E	1 (7.7)	4 (10.5)	
Borderzone, n (%)	2 (3.6)	1 (2.2)	0 (0.0)	3 (23.1) A, B	0 (0.0)	
Vasculitis pattern, n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	
Interval between infection onset to stroke, d; median (IQR)	4.0 (1.0–10.0)	2.0 (0.0–11.0)	2.0 (0.0–6.0)	10.0 (4.0–17.0)	4.0 (0.0–12.0)	0.12
Mechanical ventilation, n (%)	22 (29.3)	10 (21.7)	4 (23.5)	9 (69.2)	11 (28.9)	0.02
Disposition*						0.12
Discharged home, n (%)	24 (42.9)	16 (34.8)	11 (64.7)	8 (61.5)	9 (24.3)	
In-hospital mortality, n (%)	14 (25.0)	13 (28.3)	3 (17.6)	2 (15.4)	9 (24.3)	
Still in hospital/subacute care, n (%)	18 (32.1)	17 (37.0)	3 (17.6)	3 (23.1)	19 (54.1)	
Length of hospital stay, d; median (IQR)	6.0 (4.0–15.0)	7.0 (5.0 –14.0)	7.0 (5.0–16.0)	20.0 (4.0–35.0)	8.0 (6.0–26.0)	0.17
Comorbidities						
Hypertension, n (%)	30 (53.6)	35 (76.1) D	10 (58.8)	4 (30.8)	25 (65.8)	0.03
Diabetes, n (%)	20 (35.7)	15 (32.6)	6 (35.3)	1 (7.7)	12 (31.6)	0.41
Ischemic heart disease, n (%)	11 (19.6)	21 (45.7) A, E	3 (17.6)	1 (7.7)	2 (5.3)	<0.001
Atrial fibrillation, n (%)	2 (3.6)	23 (50.0) A, E	4 (23.5)	1 (7.7)	1 (2.6)	<0.001
Carotid stenosis, n (%)	16 (28.6) E	6 (13.0)	1 (5.9)	0 (0.0)	2 (5.3)	0.01
Chronic kidney disease, n (%)	8 (14.3)	3 (6.5)	6 (35.3) B	1 (7.7)	3 (7.9)	0.03
Cardiac ejection fraction <40%, n (%)	5 (8.9)	8 (17.4)	1 (5.9)	1 (7.7)	5 (13.2)	0.61
Active neoplasm, n (%)	2 (3.6)	9 (19.6) A	1 (5.9)	0 (0.0)	0 (0.0)	<0.001
Rheumatological disease, n (%)	0 (0.0)	3 (6.5)	1 (5.9)	0 (0.0)	0 (0.0)	0.32
Prior stroke or transient ischemic attack, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0.48
Smoking, n (%)	11 (19.6)	5 (10.9)	2 (11.8)	0 (0.0)	4 (10.5)	0.34
Laboratory findings						
White blood cell count ×109/L, mean (SD)	10.2±5.5	10.3±4.5	9.9±2.5	11.6±8.1	8.5±3.9	0.29
Neutrophil count ×109/L, mean (SD)	8.4±4.8	7.9±4.5	8.0±2.7	9.7±7.7	6.5±3.7	0.24
Lymphocyte count ×109/L, mean (SD)	1.5±2.3	2.1±1.3	2.0±2.1	1.5±0.7	2.1±1.9	0.35
Platelet count ×109/L, mean (SD)	258.0±134.4	503.5±992.7	220.7±151.3	343.9±166.9	416.6±431.2	0.20

(*Continued*)

Table 4. Continued

LVO			NIHSS					
A: LVO, n =126 (44.5%)	B: other strokes, n=157 (55.5%)	*P* value	A: no stroke symptoms (NIHSS score, 0), n=20 (7.5%)	B: minor stroke (NIHSS score, 1–4), n=49 (18.4%)	C: moderate stroke (NIHSS score, 5–15), n =117 (43.8%)	D: moderate-to-severe stroke (NIHSS score, 16–20), n=35 (13.1%)	E: severe stroke (NIHSS score, 21–42), n=46 (17.2%)	*P* value
65.7±14.4	68±16.1	0.22	67±13	65±17	66±15	66±16	69±15	0.77
46 (36.5)	71 (45.2)	0.14	6 (30.0)	20 (40.8)	44 (37.6)	16 (45.7)	22 (47.8)	0.60
…	…	…	1 (8.3)	8 (17.0)	49 (44.5) B	23 (67.6) A, B	31 (75.6) A, B, C	<0.001
28 (22.2) B	14 (8.9)	0.002	0 (0.0)	2 (4.1)	25 (21.4) B	11 (31.4) B	5 (10.9)	<0.001
24 (19.0)	0 (0.0)	<0.001	0 (0.0)	1 (2.0)	8 (6.8)	9 (25.7) B, C	6 (13.0)	<0.001
15.0 (8.0–21.0)	6.0 (3.0–12.0)	<0.001	…	…	…	…	…	…
		<0.001						0.03
46 (58.2) A	8 (9.6)		1 (14.3)	9 (25.7)	30 (43.5)	5 (19.2)	11 (36.7)	
24 (30.4)	21 (25.3)		2 (28.6)	5 (14.3)	17 (24.6)	13 (50.0) B	8 (26.7)	
0 (0.0)	17 (20.5)		1 (14.3)	9 (25.7)	30 (43.5)	5 (19.2)	11 (36.7)	
2 (2.5)	9 (10.8) B		0 (0.0)	3 (8.6)	3 (4.3)	4 (15.4)	2 (6.7)	
7 (8.9)	28 (33.7) B		3 (42.9)	10 (28.6)	13 (18.8)	4 (15.4)	7 (23.3)	
		<0.001						<0.001
99 (88.4) B	99 (73.3)		4 (57.1)	31 (73.8)	85 (81.7)	24 (75.0)	39 (92.9)	
2 (1.8)	12 (17.0) B		2 (28.6)	8 (19.0)	10 (9.6)	1 (3.1)	1 (2.4)	
11 (9.8)	12 (8.9)		0 (0.0)	3 (7.1)	9 (8.7)	7 (21.9)	2 (4.8)	
0 (0.0)	1 (0.7)		1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
46 (58.2) A	8 (9.6)	<0.001	3.0 (0.0–12.0)	3.0 (0.0–10.0)	4.0 (1.0–8.0)	3.0 (0.0–10.0)	1.0 (0.0–10.0)	0.64
36 (28.6)	42 (26.8)	0.73	2 (10.0)	8 (16.3)	25 (21.4)	12 (34.3)	29 (63.0) A, B, C	<0.001
		0.24						<0.001
46 (37.7)	66 (44.6)		5 (62.5)	28 (62.2) D, E	52 (47.3) D, E	6 (17.6)	9 (20.5)	
40 (32.8)	35 (23.6)		1 (12.5)	5 (11.1)	18 (16.4)	19 (55.9) B, C	23 (52.3) B, C	
36 (29.5)	47 (31.8)		2 (25.0)	12 (26.7)	40 (36.4)	9 (26.5)	12 (27.3)	
6.0 (4.0–15.0)	8.0 (5.0–17.0)	0.10	2 (10.0)	8 (16.3)	25 (21.4)	12 (34.3)	29 (63.0) A, B, C	<0.001
79 (62.7)	106 (68.4)	0.32	14 (73.7)	34 (69.4)	78 (66.7)	23 (65.7)	29 (60.9)	0.86
45 (35.7)	56 (35.9)	0.98	9 (45.0)	13 (26.5)	41 (35.0)	13 (37.1)	16 (34.8)	0.65
40 (33.6) A	27 (18.2)	<0.001	1 (10.0)	2 (4.3)	33 (29.7) B	12 (36.4) B	11 (26.2) B	<0.001
21 (16.7)	19 (12.3)	0.29	4 (21.1)	4 (8.2)	12 (10.3)	11 (31.4) C	9 (17.4)	0.02
18 (15.1)	17 (11.5)	0.38	0 (0.0)	10 (21.7)	16 (14.4)	3 (9.1)	7 (16.7)	0.35
14 (11.1)	27 (17.4)	0.14	3 (15.8)	8 (16.3)	16 (13.7)	7 (20.0)	3 (6.5)	0.48
8.0 (6.7)	12 (8.1)	0.67	2 (20.0)	3 (6.5)	9 (8.1)	2 (6.1)	4 (9.5)	0.68
9 (7.6)	8 (5.4)	0.47	0 (0.0)	0 (0.0)	11 (9.9)	3 (9.1)	3 (7.1)	0.21
3 (2.5)	2 (1.4)	0.48	0 (0.0)	1 (2.2)	3 (2.7)	1 (3.0)	0 (0.0)	0.83
2 (1.7)	2 (1.4)	0.83	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.88
24 (19)	23 (14.8)	0.35	2 (10.5)	8 (16.3)	22 (18.8)	5 (14.3)	6 (13.0)	0.83
10.0±5.1	9.8±4.6	0.69	8.6±3.5	9.6±5.6	9.8±4.4	9.2±4.1	11.1±5.0	0.24
7.8±4.7	7.6±4.2	0.77	7.0±3.6	7.2±5.1	7.9±4.4	7.4±3.7	8.5±4.2	0.56
1.7±2.2	1.7±1.2	0.82	1.4±1.5	1.7±1.1	1.6±1.2	2.1±2.9	1.9±2.4	0.68
297.8±332.4	334.1±563.6	0.54	419.9±714.5	379.0±395.7	334.2±609.9	281.5±129.4	264.8±115.7	0.68

(*Continued*)

Table 4. Continued

Parameters	TOAST criteria					
	A: LAA, n =56 (32.9%)	B: cardioembolism, n=46 (27.1%)	C: small artery occlusion, n=17 (10.0%)	D: other determined, n=13 (7.6%)	E: undetermined, n=38 (22.4%)	*P* value
ALT, U/L; mean (SD)	63.5±78.4	35.5±53.3	51.0±60.0	44.9±75.5	66.5±81.2	0.29
AST, U/L; mean (SD)	36.5±34.4	30.3±23.0	25.4±13.9	34.7±38.3	24.3±19.1	0.26
BUN, mg/dL; mean (SD)	47.9±51.1	46.2±63.6	43.0±50.1	39.3±26.0	86.6±260.6	0.60
Creatinine, mg/dL; mean (SD)	1.3±0.8	1.1±0.3	1.6±1.4	1.3±1.2	1.4±1.2	0.43
CRP, mg/L; mean (SD)	47.0±52.0	49.0±58.0	35.0±18.0	42.0±25.0	107±325	0.37
LDH, U/L; mean (SD)	1064.6±2880.1	542.6±1114.4	371.2±202.7	474.7±472.4	321.5±185.6	0.53
Fibrinogen, mg/dL; mean (SD)	522.7±1054.0	674.7±1839.4	779.5±918.3	157.2±156.1	217.4±338.1	0.73
D-dimer, ng/mL; mean (SD)	919.6±956.4	2019.6±2694.8	820.7±593.0	1257.3±761.9	1386.8±1196.6	0.25

(*Continued*)

DISCUSSION

To our knowledge, this is to date the largest study that comprehensively presents the characteristics and stroke subtypes of stroke in SARS-CoV-2–infected patients at a multinational level. The results of our work indicated a relatively high number of young AIS patients, male predominance, asymptomatic SARS-CoV-2 infection in more than one-third of the AIS patients, a higher proportion of LVO strokes, and a low rate of small artery occlusion and lacunar infarcts. We also noted significant differences regarding the TOAST criteria in both regional and health expenditure subgroups, as well as higher NIHSS among countries with lower health expenditure.

Regarding the characteristics of patients with AIS, 44.5% (126 of 283 patients) had LVOs, without any age or sex predominance. This rate is comparable to a similar report from New York on stroke patients with SARS-CoV-2 infection.[31] In general, LVOs accounted for 24% to 46% of AIS worldwide.[32] If the definition of the LVOs is limited to internal carotid artery, middle cerebral artery (M1 and M2), anterior cerebral artery (A1), posterior cerebral artery (P1), intracranial vertebral artery, and basilar artery, similar to our study, the risk of LVO drops to 24% to 38%.[33,34] Considering this definition, we observed a considerably higher rate of LVOs among our patients. In our study, 13.6% of AIS patients received IVT and 7.4% underwent mechanical thrombectomy. These rates are similar to the multinational study on 174 AIS SARS-CoV-2–infected patients (12.7% IVT, 6.9% IVT and thrombectomy, and 5.2% mechanical thrombectomy).[35]

Based on the TOAST classification, large artery atherosclerosis accounts for 33% of strokes in our study, which is higher than reports from worldwide population-based studies (19%–23%).[36,37] SVO accounted for stroke etiology in 10% of our patients, and analysis of neuroimaging patterns showed 10.2% lacunar infarcts. These rates are lower than worldwide population-based studies—21% to 44% SVO[37,38] and 21% to 30% lacunar infarcts.[39,40] In Europe, SVO was present among 4.1% of patients in this study versus 12% to 31% of stroke patients in previous population studies.[41–47] Lacunar infarcts were detected in 9.3% of our AIS patients versus 14% to 31% of other population studies.[43,48–50] In the North and South America, these rates were 5.3% versus 15% to 18%[37,51] for SVO, and 9.1% versus 13% to 18% for lacunar infarcts.[37,40] Similarly, in the Middle Eastern countries, we observed 18.3% SVO versus 20% to 25% in previous reports[52–55] and 11.3% lacunar infarcts versus 19% to 26% in the previous population studies.[55–57]

Higher rates of LVO and large artery atherosclerosis strokes and lower rates of SVO and lacunar infarcts among patients in our study may present a predilection of the virus for inducing a certain type of stroke. Similar to our findings, other reports on SARS-CoV-2–infected stroke patients suggested a lower rate of SVO and lacunar infarct and a higher risk of LVO strokes among infected patients with SARS-CoV-2.[58–60] However, lacunar infarctions and SVO are more likely to produce milder deficits.[39,61–63] During the COVID-19 pandemic, patients with mild-to-moderate stroke symptoms were less likely to present at medical centers.[4,59] In addition, less severe stroke symptoms, mostly in critically ill patients or overwhelmed health centers, were more likely to be underdiagnosed. Our observation of a higher median NIHSS in countries with lower health expenditure and those in Middle Eastern countries may reflect a lower capacity of these centers for the diagnosis of mild stroke patients in the pandemic. It may also indicate that patients with mild stroke symptoms refused to present to the hospitals. In addition, we realized similar rates of LVOs and IVT in various geographic regions but a considerably lower rate of thrombectomy in countries with lower health expenditures. This observation may highlight a care disparity among countries. Future studies such as CASCADE[64] (Call to Action: SARS-CoV-2 and Cerebrovascular Disorders) are required to shed light on changes

Table 4. Continued

LVO			NIHSS					
A: LVO, n =126 (44.5%)	B: other strokes, n=157 (55.5%)	*P* value	A: no stroke symptoms (NIHSS score, 0), n=20 (7.5%)	B: minor stroke (NIHSS score, 1–4), n=49 (18.4%)	C: moderate stroke (NIHSS score, 5–15), n =117 (43.8%)	D: moderate-to-severe stroke (NIHSS score, 16–20), n=35 (13.1%)	E: severe stroke (NIHSS score, 21–42), n=46 (17.2%)	*P* value
62.9±66.5	55.5±78.6	0.43	105.6±177.7	34.5±45.9	63.9±80.3	58.0±84.3	50.1±51.2	0.04
31.5±28.1	31.6±24.0	0.98	30.9±22.3	23.6±20.2	33.1±26.2	28.1±23.7	41.5±32.7	0.02
46.6±55.9	56.6±141.5	0.49	61.3±50.5	50.0±66.8	46.5±45.6	33.9±20.8	39.5±39.0	0.32
1.3±0.9	1.5±1.4	0.27	1.5±1.2	1.0±0.3	1.5±1.3	1.2±0.9	1.6±1.1	0.05
47.4±54.8	71.3±183.8	0.17	57.0±41.0	46.0±52.0	50.0±51.0	45.0±31.0	47.0±40.0	0.91
824.1±2308.0	470.9±801.3	0.26	531.6±254.9	551.9±1136.0	457.2±707.3	511.9±412.3	1119.4±3301.0	0.57
612.9±1468.5	346.3±540.8	0.33	509.3±196.3	409.1±740.9	575.3±1556.1	133.9±149.3	465.0±298.2	0.88
1909.8±2877.1	2825.8±7596.3	0.43	7020.9±11983.6	1025.6±1087.5	3277.8±9087.7	1757.3±952.1	2033.5±3027.9	0.08

The capital letters indicate a significant post hoc *P* value for comparison of subgroups. ALT indicates alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; ICH, intracranial hemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; LAA, large artery atherosclerosis; LDH, lactate dehydrogenase; LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; SVO, small vessel occlusion; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*Data on patients' disposition were sparse.

in stroke care protocols and hospitalization rate during the pandemic and compare it to the available infrastructure in each region.

Of notice, our study results showed a considerable number of young strokes. Although the definition of young stroke is debatable, the majority of the studies considered 50 or 55 years as the cutoff.[65] We realized that 36% of the AIS patients in our study were <55 years of age and 46% were <65 years of age (Tables V and VI in the Data Supplement). These proportions are considerably higher than the population-based reports before the pandemic (12.9%–20.7%).[66,67] The median age of AIS patients in our study was 68 (58–78) years. A case series from New York on 32 AIS patients with SARS-CoV-2 showed a median of 63 years for these patients. This finding was significantly lower than AIS patients without SARS-CoV-2 in the same study and same interval (median, 70 years) or the historical cohort of AIS patients presented to the same center in 2019 (median, 68.5 years).[31] A multinational study on 174 AIS patients with SARS-CoV-2 infection reported a median age of 71 years.[35]

Regarding cerebral venous sinus thrombosis and ICH, we had 18 stroke patients with CVST; the average age of patients was 49 years, 78% were <55 years of age, and >60% were women. Classically CVST is considered to occur in young adults, with the predilection of women.[68] However, the sex ratio varies widely—44.7% to 83.4% in women.[69] A systematic review on the sex ratio of 23 638 patients with CVST demonstrated an increasing trend among women (54.8% before 1981 to 69.8% after 2001), likely due to increased use of oral contraceptives.[70] Even though CVST patients in our study were younger than patients with other stroke subtypes, they were older than previously reported CVST patients without SARS-CoV-2 infection.[69–74] In addition, only 27.8% of the patients in our study had multiple sinus or venous involvement, which is considerably lower than previous reports in non–SARS-CoV-2–infected patients.[69,73,75] One reason might be the severe condition of the patients with multiple CVSTs that prevent the proper diagnosis of these patients.

Our study reported 91 patients with ICH. Among the patients with SAH (23), no aneurysm was detected in 69.5% of patients, which is higher than the reported 15% (5%–34%) spontaneous SAH among patients without SARS-CoV-2 infection.[76] We observed that 27.9% of IPH patients had no vascular risk factors or comorbidities. These patients had higher ICH score and younger age in comparison with other patients with IPH.

This work has several limitations. Despite that we included centers from multiple countries and presented a comprehensive panel of patients' characteristics, some of the specific laboratory parameters related to rare stroke causes (eg, antiphospholipid antibodies) were not included in this study. The collaborators tried to identify SARS-CoV-2 patients who presented with stroke as the first and only symptom, but the difficulty in measuring all symptoms related to COVID-19 (such as fatigue, anosmia, and ageusia) should be taken into consideration. In addition, not all the stroke patients in this study had a final disposition outcome, which limited our conclusion about in-hospital mortality. Although attempts were made to minimize the selection bias by including patients from different ethnicities, ecological conditions, and health care systems, this study may suffer from selection bias and low power in some subgroups. The authors attempt to assess the quality of data by Risk of Bias in Exposure Studies tool[13]; however, heterogeneity may exist among data obtained from multiple settings

and multiple countries. Further studies that include a control population are warranted.

CONCLUSIONS

In conclusion, we observed a considerably higher rate of LVOs and a much lower rate of SVO and lacunar infarction when compared with the prior population studies. We also observed a relatively high number of young stroke and a high number of asymptomatic SARS-CoV-2 patients at stroke onset. The rate of mechanical thrombectomy was significantly lower in countries with lower health expenditures.

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Supplemental Materials

Online Document I
Online Figure I
Online Tables I–VIII

REFERENCES

1. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77:683–690. doi: 10.1001/jamaneurol.2020.1127
2. 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
3. Sweid A, Hammoud B, Weinberg JH, Oneissi M, Raz E, Shapiro M, DePrince M, Tjoumakaris S, Gooch MR, Herial NA, et al. Letter: thrombotic neurovascular disease in COVID-19 patients. *Neurosurgery*. 2020;87:E400–E406. doi: 10.1093/neuros/nyaa254
4. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, Henninger N, Trivedi T, Lillemoe K, Alam S, et al. SARS2-CoV-2 and stroke in a new york healthcare system. *Stroke*. 2020;120:1–10.
5. Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, Vogrig A. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol*. 2020;267:2185–2192. doi: 10.1007/s00415-020-09885-2
6. D'Anna L, Kwan J, Brown Z, Halse O, Jamil S, Kalladka D, Venter M, Banerjee S. Characteristics and clinical course of Covid-19 patients admitted with acute stroke. *J Neurol*. 2020;267:3161–3165. doi: 10.1007/s00415-020-10012-4
7. Barrios-López JM, Rego-García I, Muñoz Martínez C, Romero-Fábrega JC, Rivero Rodríguez M, Ruiz Giménez JA, Escamilla-Sevilla F, Mínguez-Castellanos A, Fernández Pérez MD. Ischaemic stroke and SARS-CoV-2 infection: a causal or incidental association? *Neurologia*. 2020;35:295–302. doi: 10.1016/j.nrl.2020.05.002
8. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145–147. doi: 10.1016/j.thromres.2020.04.013
9. Escalard S, Maïer B, Redjem H, Delvoye F, Hébert S, Smajda S, Ciccio G, Desilles J-P, Mazighi M, Blanc R, et al. Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19. *Stroke*. 2020;120:1–4.
10. 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. doi: 10.1161/STROKEAHA.120.030153
11. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, Wang D, Mao L, Jin H, Hu B. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. 2020;5:279–284. doi: 10.1136/svn-2020-000431
12. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, Glaser A, Elsayegh D. COVID-19 presenting as stroke. *Brain Behav Immun*. 2020;87:115–119. doi: 10.1016/j.bbi.2020.04.077
13. Shahjouei S, Naderi S, Li J, Khan A, Chaudhary D, Farahmand G, Male S, Griessenauer C, Sabra M, Mondello S, et al. Risk of stroke in hospitalized SARS-CoV-2 infected patients: a multinational study. *EBioMedicine*. 2020;59:102939. doi: 10.1016/j.ebiom.2020.102939
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499. doi: 10.1016/j.ijsu.2014.07.013
15. Equator Network. Enhancing the QUAlity and Transparency Of health Research [Internet]. Univ. Oxford. 2019;https://www.equator-network.org
16. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, et al; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064–2089. doi: 10.1161/STR.0b013e318296aeca
17. WHO. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases. *Interim Guid*. 2020:1–7.
18. Prabhakaran S, Silver AJ, Warrior L, McClenathan B, Lee VH. Misdiagnosis of transient ischemic attacks in the emergency room. *Cerebrovasc Dis*. 2008;26:630–635. doi: 10.1159/000166839
19. Sadighi A, Stanciu A, Banciu M, Abedi V, Andary NE, Holland N, Zand R. Rate and associated factors of transient ischemic attack misdiagnosis. *eNeurologicalSci*. 2019;15:100193. doi: 10.1016/j.ensci.2019.100193
20. Nadarajan V, Perry RJ, Johnson J, Werring DJ. Transient ischaemic attacks: mimics and chameleons. *Pract Neurol*. 2014;14:23–31. doi: 10.1136/practneurol-2013-000782
21. Ver Hage A. The NIH stroke scale: a window into neurological status. *Com Nurs. Spectr*. 2011;24:44–49.
22. Adams H, Bendixen B, Kappelle L, Biller J, Love B, Gordon D, Marsh E. Classification of subtype of acute ischemic stroke. *Stroke*. 1993;23:35–41.
23. Potter GM, Marlborough FJ, Wardlaw JM. Wide variation in definition, detection, and description of lacunar lesions on imaging. *Stroke*. 2011;42:359–366. doi: 10.1161/STROKEAHA.110.594754
24. Wessels T, Röttger C, Jauss M, Kaps M, Traupe H, Stolz E. Identification of embolic stroke patterns by diffusion-weighted MRI in clinically defined lacunar stroke syndromes. *Stroke*. 2005;36:757–761. doi: 10.1161/01.STR.0000158908.48022.d7
25. Bang OY, Ovbiagele B, Liebeskind DS, Restrepo L, Yoon SR, Saver JL. Clinical determinants of infarct pattern subtypes in large vessel atherosclerotic stroke. *J Neurol*. 2009;256:591–599. doi: 10.1007/s00415-009-0125-x
26. Abdel Razek AA, Alvarez H, Bagg S, Refaat S, Castillo M. Imaging spectrum of CNS vasculitis. *Radiographics*. 2014;34:873–894. doi: 10.1148/rg.344135028
27. Waqas M, Mokin M, Primiani CT, Gong AD, Rai HH, Chin F, Rai AT, Levy EI, Siddiqui AH. Large vessel occlusion in acute ischemic stroke patients: a dual-center estimate based on a broad definition of occlusion site. *J Stroke Cerebrovasc Dis*. 2020;29:104504. doi: 10.1016/j.jstrokecerebrovasdis.2019.104504
28. Global Health Expenditure Database [Internet]. [cited 2020 Jun 30]. https://apps.who.int/nha/database/Select/Indicators/en
29. Putaala J. Young stroke. *Helsinki Univ*. 2016;1:1–15.
30. IBM. Downloading IBM SPSS Statistics 26. *Ibm*. 2020.
31. Yaghi S, Ishida K, Torres J, Grory B Mac, Raz E, Humbert K, Henninger N, Trivedi T, Lillemoe K, Alam S, et al. SARS2-CoV-2 and stroke in a New York healthcare system. *Stroke*. 2020;120:1–10.
32. Rennert RC, Wali AR, Steinberg JA, Santiago-Dieppa DR, Olson SE, Pannell JS, Khalessi AA. Epidemiology, natural history, and clinical presentation of large vessel ischemic stroke. *Neurosurgery*. 2019;85(suppl_1):S4–S8. doi: 10.1093/neuros/nyz042
33. Malhotra K, Gornbein J, Saver JL. Ischemic strokes due to large-vessel occlusions contribute disproportionately to stroke-related dependence and death: a review. *Front Neurol*. 2017;8:651. doi: 10.3389/fneur.2017.00651
34. Dozois A, Hampton L, Kingston CW, Lambert G, Porcelli TJ, Sorenson D, Templin M, VonCannon S, Asimos AW. PLUMBER Study (prevalence of large vessel occlusion strokes in mecklenburg county emergency response). *Stroke*. 2017;48:3397–3399. doi: 10.1161/STROKEAHA.117.018925
35. Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, Calleja P, Ostos F, González-Ortega G, Fuentes B, 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. doi: 10.1161/STROKEAHA.120.031208
36. Ornello R, Degan D, Tiseo C, Di Carmine C, Perciballi L, Pistoia F, Carolei A, Sacco S. Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes: a systematic review and meta-analysis. *Stroke*. 2018;49:814–819. doi: 10.1161/STROKEAHA.117.020031
37. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, et al; INTERSTROKE Investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376:112–123. doi: 10.1016/S0140-6736(10)60834-3
38. Al-Rukn S, Mazya M, Akhtar N, Hashim H, Mansouri B, Faouzi B, Aref H, et al. Stroke in the Middle-East and North Africa: a 2-year prospective observational study of stroke characteristics in the region—results from the Safe Implementation of Treatments in Stroke (SITS)–Middle-East and North African (MENA). *Int J Stroke*. 2019;14:715–722.

39. M P, L N, P D, B L. Outcomes from ischemic stroke subtypes classified by the Oxfordshire Community Stroke Project: a systematic review. *Eur J Phys Rehabil Med*. 2011;47:19–23.
40. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, et al; INTERSTROKE Investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*. 2016;388:761–775. doi: 10.1016/S0140-6736(16)30506-2
41. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, Rothwell PM; Oxford Vascular Study. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol*. 2015;14:903–913. doi: 10.1016/S1474-4422(15)00132-5
42. Yesilot Barlas N, Putaala J, Waje-Andreassen U, Vassilopoulou S, Nardi K, Odier C, Hofgart G, Engelter S, Burow A, Mihalka L, et al. Etiology of first-ever ischaemic stroke in European young adults: the 15 cities young stroke study. *Eur J Neurol*. 2013;20:1431–1439. doi: 10.1111/ene.12228
43. Ihle-Hansen H, Thommessen B, Wyller TB, Engedal K, Fure B. Risk factors for and incidence of subtypes of ischemic stroke. *Funct Neurol*. 2012;27:35–40.
44. Hauer AJ, Ruigrok YM, Algra A, van Dijk EJ, Koudstaal PJ, Luijckx G-J, Nederkoorn PJ, van Oostenbrugge RJ, Visser MC, Wermer MJ, et al. Age-specific vascular risk factor profiles according to stroke subtype. *J Am Heart Assoc*. 2017;6:e005090.
45. Carrera E, Maeder-Ingvar M, Rossetti AO, Devuyst G, Bogousslavsky J; Lausanne Stroke Registry. Trends in risk factors, patterns and causes in hospitalized strokes over 25 years: the Lausanne Stroke Registry. *Cerebrovasc Dis*. 2007;24:97–103. doi: 10.1159/000103123
46. Grau AJ, Weimar C, Buggle F, Heinrich A, Goertler M, Neumaier S, Glahn J, Brandt T, Hacke W, Diener HC. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. *Stroke*. 2001;32:2559–2566. doi: 10.1161/hs1101.098524
47. Wafa HA, Wolfe CDA, Rudd A, Wang Y. Long-term trends in incidence and risk factors for ischaemic stroke subtypes: prospective population study of the South London Stroke Register. *PLoS Med*. 2018;15:e1002669. doi: 10.1371/journal.pmed.1002669
48. Czlonkowska A, Ryglewicz D, Weissbein T, Baranska-Gieruszczak M, Hier DB. A prospective community-based study of stroke in Warsaw, Poland. *Stroke*. 1994;25:547–551. doi: 10.1161/01.str.25.3.547
49. Alzamora MT, Sorribes M, Heras A, Vila N, Vicheto M, Forés R, Sánchez-Ojanguren J, Sancho A, Pera G; "ISISCOG Study Group". Ischemic stroke incidence in Santa Coloma de Gramenet (ISISCOG), Spain. A community-based study. *BMC Neurol*. 2008;8:5. doi: 10.1186/1471-2377-8-5
50. Di Carlo A, Lamassa M, Baldereschi M, Pracucci G, Consoli D, Wolfe CD, Giroud M, Rudd A, Burger I, Ghetti A, et al; European BIOMED Study of Stroke Care Group. Risk factors and outcome of subtypes of ischemic stroke. Data from a multicenter multinational hospital-based registry. The European Community Stroke Project. *J Neurol Sci*. 2006;244:143–150. doi: 10.1016/j.jns.2006.01.016
51. Porcello Marrone LC, Diogo LP, de Oliveira FM, Trentin S, Scalco RS, de Almeida AG, Gutierres Ldel C, Marrone AC, da Costa JC. Risk factors among stroke subtypes in Brazil. *J Stroke Cerebrovasc Dis*. 2013;22:32–35. doi: 10.1016/j.jstrokecerebrovasdis.2011.05.022
52. Saber H, Thrift AG, Kapral MK, Shoamanesh A, Amiri A, Farzadfard MT, Behrouz R, Azarpazhooh MR. Incidence, recurrence, and long-term survival of ischemic stroke subtypes: a population-based study in the Middle East. *Int J Stroke*. 2017;12:835–843. doi: 10.1177/1747493016684843
53. Khorvash F, Khalili M, Rezvani Habibabadi R, Sarafzadegan N, Givi M, Roohafza H, Yadgarfar G, Dehghani L, Taheri M, Saadatnia M. Comparison of acute ischemic stroke evaluation and the etiologic subtypes between university and nonuniversity hospitals in Isfahan, Iran. *Int J Stroke*. 2019;14:613–619. doi: 10.1177/1747493019828648
54. Senel GB, Elmali AD, Mehrvar K, Farhoudi M, Aboutalebi M, Rezaei M, Ince B. A survey from Turkey and Iran on comparison of risk factors and etiology in ischemic stroke. *Iran J Neurol*. 2019;18:176–178.
55. Lutski M, Zucker I, Shohat T, Tanne D. Characteristics and outcomes of young patients with first-ever ischemic stroke compared to older patients: the National Acute Stroke ISraeli Registry. *Front Neurol*. 2017;8:421. doi: 10.3389/fneur.2017.00421
56. Kumral E, Özkaya B, Sagduyu A, Şirin H, Vardarli E, Pehliva M. The ege stroke registry: a hospital-based study in the aegean region, Izmir, Turkey. *Cerebrovasc Dis*. 1998;8:278–288. doi: 10.1159/000015866
57. Ghandehari K, Izadi-Mood Z. Khorasan stroke registry: analysis of 1392 stroke patients. *Arch Iran Med*. 2007;10:327–334. doi: 07103/AIM.009
58. 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
59. Jain R. Evolving neuroimaging findings during COVID-19. *Am. J. Neuroradiol*. 2020;41:1–2.
60. Siegler JE, Heslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center: cover title: falling stroke rates during COVID-19. *J Stroke Cerebrovasc Dis*. 2020;29:104953.
61. Favate AS, Younger DS. Epidemiology of ischemic stroke. *Neurol Clin*. 2016;34:967–980. doi: 10.1016/j.ncl.2016.06.013
62. Wilterdink JL, Bendixen B, Adams HP Jr, Woolson RF, Clarke WR, Hansen MD. Effect of prior aspirin use on stroke severity in the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Stroke*. 2001;32:2836–2840. doi: 10.1161/hs1201.099384
63. Pittock SJ, Meldrum D, Hardiman O, Thornton J, Brennan P, Moroney JT. The Oxfordshire Community Stroke Project classification: correlation with imaging, associated complications, and prediction of outcome in acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2003;12:1–7. doi: 10.1053/jscd.2003.7
64. Abootalebi S, Aertker BM, Andalibi MS, Asdaghi N, Aykac O, Azarpazhooh MR, Bahit MC, Barlinn K, Basri H, Shahripour RB, et al. Call to Action: SARS-CoV-2 and Cerebrovascular Disorders (CASCADE). *J Stroke Cerebrovasc Dis*. 2020;29:104938. doi: 10.1016/j.jstrokecerebrovasdis.2020.104938
65. F. C. Defining young stroke. *YoungStroke Inc*. [Internet]. 2017;1–15. http://youngstroke.org/wp-content/definingyoungstroke
66. Cabral NL, Freire AT, Conforto AB, Dos Santos N, Reis FI, Nagel V, Guesser VV, Safanelli J, Longo AL. Increase of stroke incidence in young adults in a middle-income country: a 10-year population-based study. *Stroke*. 2017;48:2925–2930. doi: 10.1161/STROKEAHA.117.018531
67. Kissela BM, J.C. K, Alwell K, Moomaw JC, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, Rosa FDLRL, et al. Age at stroke. *Neurol 1781-1787*. 2012;79:1781–1787.
68. Luo Y, Tian X, Wang X. Diagnosis and Treatment of cerebral venous thrombosis: a review. *Front Aging Neurosci*. 2018;10:2. doi: 10.3389/fnagi.2018.00002
69. Gunes HN, Cokal BG, Guler SK, Yoldas TK, Malkan UY, Demircan CS, Yon MI, Yoldas Z, Gunes G, Haznedaroglu IC. Clinical associations, biological risk factors and outcomes of cerebral venous sinus thrombosis. *J Int Med Res*. 2016;44:1454–1461. doi: 10.1177/0300060516664807
70. Zuurbier SM, Middeldorp S, Stam J, Coutinho JM. Sex differences in cerebral venous thrombosis: a systematic analysis of a shift over time. *Int J Stroke*. 2016;11:164–170. doi: 10.1177/1747493015620708
71. Dentali F, Poli D, Scoditti U, Di Minno MN, De Stefano V, Stefano VD, Siragusa S, Kostal M, Palareti G, Sartori MT, et al; Cerebral Vein Thrombosis International Study Investigators. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. *J Thromb Haemost*. 2012;10:1297–1302. doi: 10.1111/j.1538-7836.2012.04774.x
72. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: a cross-sectional study. *Stroke*. 2012;43:3375–3377. doi: 10.1161/STROKEAHA.112.671453
73. Sidhom Y, Mansour M, Messelmani M, Derbali H, Fekih-Mrissa N, Zaouali J, Mrissa R. Cerebral venous thrombosis: clinical features, risk factors, and long-term outcome in a Tunisian cohort. *J Stroke Cerebrovasc Dis*. 2014;23:1291–1295. doi: 10.1016/j.jstrokecerebrovasdis.2013.10.025
74. Ferro JM, Aguiar de Sousa D. Cerebral venous thrombosis: an update. *Curr Neurol Neurosci Rep*. 2019;19:74. doi: 10.1007/s11910-019-0988-x
75. Sassi SB, Touati N, Baccouche H, Drissi C, Romdhane NB, Hentati F. Cerebral venous thrombosis: a Tunisian Monocenter Study on 160 patients. *Clin Appl Thromb Hemost*. 2017;23:1005–1009. doi: 10.1177/1076029616665168
76. Kim YW, Lawson MF, Hoh BL. Nonaneurysmal subarachnoid hemorrhage: an update. *Curr Atheroscler Rep*. 2012;14:328–334. doi: 10.1007/s11883-012-0256-x