

SARS-CoV-2 and Stroke Characteristics

A Report From the Multinational COVID-19 Stroke Study Group

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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 stroke¹⁶—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 \$10000 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, ×10 ⁹ /L; mean (SD)	9.8±4.8	11.4±10.0	13.5±12.9	11.1±6.0
White blood cell count, ×10 ⁹ /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 ×10 ⁹ /L, n (%)	7 (2.3)	3 (5.7)	0 (0)	2 (22.2)
4–10 ×10 ⁹ /L, n (%)	184 (61.1)	29 (54.7)	10 (50)	4 (44.4)
10–20 ×10 ⁹ /L, n (%)	96 (31.9)	18 (34)	9 (45)	3 (33.3)
≥20 ×10 ⁹ /L, n (%)	14 (4.7)	5 (10)	1 (5)	0 (0)
Neutrophil count, ×10 ⁹ /L; mean (SD)	7.7±4.5	9.3±8.5	9.6±6.1	9.2±5.1
Neutrophil count, ×10 ⁹ /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 ×10 ⁹ /L, n (%)	43 (15.2)	5 (10)	1 (5)	1 (12.5)
4–10 ×10 ⁹ /L, n (%)	182 (64.3)	33 (66)	12 (60)	6 (75)
10–20 ×10 ⁹ /L, n (%)	49 (17.3)	10 (20)	6 (30)	1 (12.5)
≥20 ×10 ⁹ /L, n (%)	9 (3.2)	2 (4)	1 (5)	0 (0)
Lymphocyte count, ×10 ⁹ /L; mean (SD)	1.5±1.5	2.0±3.6	2.8±6.3	2.0±1.3
Lymphocyte, ×10 ⁹ /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 ×10 ⁹ /L, n (%)	93 (32.5)	21 (39.6)	6 (28.6)	1 (12.5)
1–2 ×10 ⁹ /L, n (%)	130 (45.5)	19 (35.8)	10 (47.6)	4 (50)
2–3 ×10 ⁹ /L, n (%)	41 (14.3)	9 (35.8)	3 (14.3)	2 (25)
3–4 ×10 ⁹ /L, n (%)	11 (3.8)	1 (1.9)	0 (0)	1 (12.5)
≥4 ×10 ⁹ /L, n (%)	11 (3.8)	3 (5.7)	2 (9.5)	0 (0)
Platelet count, ×10 ⁹ /L; mean (SD)	314.5±440.7	197.1±89.1	191.45±60.9	254.2±170.1
Platelet count, ×10 ⁹ /L; median (IQR)	229 (161–333.7)	178.5 (142.5–254)	183 (141–246)	237 (139–337)
<350 ×10 ⁹ /L, n (%)	228 (78.1)	50 (94.3)	20 (100)	8 (88.9)
350–500 ×10 ⁹ /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					P value
	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%)	
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 ×10 ⁹ /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 ×10 ⁹ /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 ×10 ⁹ /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 ×10 ⁹ /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)

ORIGINAL CONTRIBUTION

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

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Table 4. Continued

Parameters	TOAST criteria					P value
	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%)	
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 CASCADE⁶⁴ (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 tool¹³; 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

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