



Effect of Asymptomatic and Symptomatic COVID-19 on Acute Ischemic Stroke Revascularization Outcomes

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BACKGROUND: The association of COVID-19 with higher bleeding risk and worse outcomes in acute ischemic stroke (AIS) undergoing revascularization may be related to the presence of infection symptoms. We aimed to assess the safety and outcomes of revascularization treatments in patients with AIS with asymptomatic COVID-19 (AS-COVID) or symptomatic COVID-19 (S-COVID).

METHODS: We conducted an international multicenter retrospective cohort study of consecutive AIS tested for SARS-CoV-2, receiving intravenous thrombolysis and endovascular treatment between 2020 and 2021. We compared COVID-negative controls, AS-COVID, and S-COVID using multivariable regression. We assessed symptomatic intracranial hemorrhage (symptomatic intracerebral hemorrhage), mortality, and 3-month disability (modified Rankin Scale score).

RESULTS: Among 15 124 patients from 105 centers (median age, 71 years; 49% men; 39% treated with intravenous thrombolysis only; and 61% with endovascular treatment±intravenous thrombolysis), 849 (5.6%) had COVID-19, of whom 395 (46%) were asymptomatic and 454 (54%) symptomatic. Compared with controls, both patients with AS-COVID and S-COVID had higher symptomatic intracerebral hemorrhage rates (COVID-controls, 5%; AS-COVID, 7.6%; S-COVID, 9.4%; adjusted odds ratio [aOR], 1.43 [95% CI, 1.03–1.99]; aOR, 1.63 [95% CI, 1.14–2.32], respectively). Only in patients with symptomatic infections, we observed a significant increase in mortality at 24 hours (COVID-controls, 1.3%; S-COVID, 4.8%; aOR, 2.97 [95% CI, 1.76–5.03]) and 3 months (COVID-controls, 19.5%; S-COVID, 40%; aOR, 2.64 [95% CI, 2.06–3.37]). Patients with COVID-19 had worse 3-month disability regardless of disease symptoms although disability was affected to a greater extent in symptomatic patients (aOR for worse modified Rankin Scale score shift: AS-COVID, 1.25 [95% CI, 1.03–1.51]; S-COVID, 2.10 [95% CI, 1.75–2.53]). S-COVID had lower successful recanalization (74.9% versus 85.6%; $P<0.001$), first pass recanalization (20.3% versus 28.3%; $P=0.005$), and a higher number of passes.

CONCLUSIONS: In AIS undergoing revascularization treatments, both AS-COVID and S-COVID influence the risk of intracranial bleeding and worse clinical outcomes. The magnitude of this effect is more pronounced in symptomatic infections, which also present less favorable recanalization outcomes. These findings emphasize the impact of SARS-CoV-2 infection on the prognosis of revascularized AIS independent of symptom status.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT04895462.

GRAPHIC ABSTRACT: A [graphic abstract](#) is available for this article.

Key Words: endothelial cells ■ ischemic stroke ■ renin-angiotensin system ■ SARS-CoV-2 ■ thrombosis

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†A list of Global COVID-19 Stroke Registry participants is given in the Appendix.

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Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
aOR	adjusted odds ratio
AS-COVID	asymptomatic COVID-19
EVT	endovascular treatment
IVT	intravenous thrombolysis
mRS	modified Rankin Scale
PCR	polymerase chain reaction
S-COVID	symptomatic COVID-19
SICH	symptomatic intracerebral hemorrhage
SSAH	symptomatic subarachnoid hemorrhage

SARS-CoV-2 infection is associated with a high incidence of thrombotic and cerebrovascular complications.^{1–3}

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The pathogenesis of this prothrombotic state is mediated by several mechanisms, including direct viral invasion of endothelial cells, immune-mediated thrombosis and hypercoagulopathy, activation of the alternative renin-angiotensin system pathway, and, for cerebrovascular complications, viral-mediated damage to the neurovascular unit.^{4–6}

Previous studies showed that patients with acute ischemic stroke (AIS) and COVID-19 have a worse functional outcome than those without SARS-CoV-2 infection.^{7–12} Similarly, our previous analysis of the Global COVID-19 Stroke Registry showed that patients with AIS and COVID-19 receiving intravenous thrombolysis (IVT) and endovascular treatment (EVT) had higher rates of cerebral bleeding and worse short-term and 3-month outcomes compared with contemporary AIS controls without COVID-19.¹³

Currently, it is unknown whether the higher rates of bleeding complications and worse outcomes after AIS with revascularization treatment are related to the presence of symptoms of COVID-19 infection.

Here, we aimed to assess the safety, clinical, and technical outcomes of revascularization treatment in patients with AIS and asymptomatic COVID-19 (AS-COVID) or symptomatic COVID-19 (S-COVID) in a multicenter, international cohort by comparing with a contemporary control group of patients with no COVID-19 with AIS from the same centers.

METHODS

Data Availability

The raw, anonymized data of this study are available from the corresponding author upon reasonable request and after signing a data transfer and user agreement.

Study Design, Patient Selection, and Study Variables

This retrospective, international, cohort study was conducted on the Global COVID-19 Stroke Registry.¹³ The registry included consecutive patients with AIS receiving IVT and EVT up to 24 hours from the last time seen well. Patients were treated according to stroke guidelines or the local practice of each center. Each participating center included at least 1 patient with COVID-19 and AIS treated with IVT and EVT. The inclusion period of the registry was March 1, 2020, to June 30, 2021.

Patients with COVID-19 were defined as (1) patients with community-acquired SARS-CoV-2 infection confirmed by a positive polymerase chain reaction (PCR) or antigen test, independent of the presence of COVID-19–related symptoms; (2) patients hospitalized due to COVID-19 with an in-hospital stroke; and (3) patients with COVID-19–compatible symptoms before revascularization treatment with positive PCR or antigen test within the first 7 days after treatment. The control group of COVID-19–negative patients included patients without COVID-19–compatible symptoms and with a negative PCR or antigen test within the first 7 days after revascularization treatment.

The registry had the following exclusion criteria: (1) patient without a PCR or antigen test within the first 7 days after treatment; (2) patient with nosocomial SARS-CoV-2 infection after receiving revascularization treatment, defined as PCR or antigen tests becoming positive >7 days after treatment¹⁴; (3) patient with a suspected/probable case of SARS-CoV-2 infection according to the World Health Organization definition¹⁵; (4) patient with symptomatic SARS-CoV-2 infection with symptom resolution >7 days before revascularization treatment; and (5) patient with asymptomatic SARS-CoV-2 infection with revascularization treatment performed >10 days after the first positive test for SARS-CoV-2.

For this study, among patients who were originally included in the Global COVID-19 Stroke Registry, we further excluded patients with COVID-19 without information on the presence or absence of symptoms related to the infection.

Each center was required to indicate whether patients exhibited symptoms of COVID-19 at the time of stroke onset or within 7 days prior, following the case definitions provided by the World Health Organization (Table S1).¹⁵

The reporting is in accordance with the Strengthening of the Reporting of Observational Studies in Epidemiology guidelines.¹⁶

Standard Protocol Approvals and Registration

Data from each participating center were anonymized and sent to the coordinating center (Lausanne University Hospital). According to the local ethics committee regulations and national laws, each center was responsible for obtaining ethical approval for data collection and international data sharing. Informed consent was waived due to the retrospective nature of this study with anonymized data. This study was conducted according to the principles of the Declaration of Helsinki. In the coordinating center in Lausanne, approval of the institutional review board and patient consent was not required according to the Swiss Federal Act on Research Involving Human Beings (2011, Human Research Act, Article 3) as all data were anonymized and the project involved assessing safety and quality of routine AIS management in participating centers.

The study was registered under <https://www.clinicaltrials.gov/NCT04895462>.

Outcomes

For the main outcome, we defined symptomatic intracerebral hemorrhage (SICH) according to ECASS-2 ([European Cooperative Acute Stroke Study]; ≥ 4 -point worsening in the NIHSS score attributable to parenchymal hemorrhage).¹⁷ As secondary outcomes, we defined symptomatic subarachnoid hemorrhage (SSAH; ≥ 4 -point worsening in the NIHSS score attributable to subarachnoid hemorrhage), any symptomatic intracranial hemorrhage (SICH/SSAH; combination of SICH and SSAH), 24-hour mortality, 3-month mortality, 3-month modified Rankin Scale (mRS), favorable 3-month outcome (mRS score ≤ 2 or equal to prestroke mRS score), the presence of any radiological hemorrhagic transformation, recanalization after EVT measured by modified Treatment in Cerebral Infarction at the last angiography series, successful recanalization after EVT as final modified Treatment in Cerebral Infarction score $\geq 2b$, the number of passes during EVT, and recanalization at first pass.¹⁸ All outcomes were assessed locally at each center by the investigators, unblinded to the patient's COVID status during the acute phase of the stroke.

Statistical Analysis

We summarized continuous variables as median values with interquartile range and categorical variables as absolute numbers and percentages. We compared baseline and outcome variables between AS-COVID, S-COVID, and COVID-19 negative groups using the Pearson χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables, as appropriate. Multiple pairwise comparison between groups was corrected using the Dunnett method. We performed all analyses of outcomes on the overall cohort and the 2 treatment subgroups: IVT only and EVT.

To assess the association of AS-COVID and S-COVID with the primary outcome (SICH) and with 5 of the secondary outcomes (SSAH, SICH/SSAH, 24-hour and 3-month mortality, 3-month mRS score, and favorable 3-month outcome), we performed multivariable regression analysis for each outcome. For the remaining secondary outcomes, we performed a univariable analysis.

Regarding the multivariable analyses, for the binary outcomes, the model was a logistic regression model, while it was an ordered logit regression model for a 3-month mRS score. The models were adjusted for prespecified potential confounders identified from the previous literature as variables known to be associated with the outcome of interest, namely, age, sex, NIHSS score, Alberta Stroke Program Early Computed Tomography Score, blood glucose, site of arterial occlusion, tandem lesion, time to treatment (last-time-seen-well-to-needle for IVT and last-time-seen-well-to-groin delay for EVT when applicable), and center volume. Additional confounders specific to different outcomes were entered into the respective models and are detailed in the legend of Figure 1. Given the high prevalence of in-hospital stroke in the COVID-19 group, we also performed a sensitivity analysis by repeating the main multivariable analyses and including adjustments for the in-hospital stroke variable.

We expressed the results of the multivariable regression models as odds ratio and CIs. Given the potential clustering

effect of patients from the same center, we included the referring center in each model as a cluster-level variable and calculated cluster-robust SEs.

To account for missing data of the covariates, we performed multiple imputations by chained equation, generating 10 imputed data sets.¹⁹ The rate of missing data for each variable in the registry has already been reported in the previous article.¹³ We performed analyses on each imputed data set, and then, the estimates and the SEs of the 10 imputed analyses were combined using Rubin rules.

All tests were 2 sided, and $P < 0.05$ was considered significant. As this was a retrospective study, no correction for multiple-outcome testing was applied. We did not perform a power calculation because prior data estimating the expected effect of COVID-19 on the outcome of interest in revascularized stroke patients was lacking. We performed statistical analysis with R statistical software, version 4.0.3.

RESULTS

Of 15 128 patients in the Global COVID-19 Stroke Registry, 4 were excluded because of missing data on COVID-19 symptoms, leaving 15 124 patients for the present analysis. The median age was 71.6 (interquartile range, 13.8) years, 7766 (51%) were men, 5845 patients (38.6%) were treated with IVT only, and 9279 patients (61.4%) were treated with EVT (of whom 4840 [52%] had direct EVT and 4439 [48%] had bridging).

Overall, 849 (5.6%) patients were diagnosed with COVID-19: 395 (46%) with asymptomatic (AS-COVID group) and 454 (54%) with symptomatic disease (S-COVID group). In patients with symptomatic infection, COVID-19 diagnosis was more frequent before stroke onset, while in asymptomatic patients, COVID-19 was more frequently detected within 24 hours of stroke onset ($P < 0.001$; Table 1). Patients with symptomatic disease more often had in-hospital strokes compared with asymptomatic patients (46.9% versus 22.8%; $P < 0.001$). Among the 213 patients with symptomatic infection and in-hospital stroke, 17% ($n = 37$) were admitted to the intensive care unit at the time of stroke onset, while the remaining were admitted to a hospital ward.

Compared with controls, both groups of patients with AS-COVID and S-COVID had a higher prevalence of diabetes, lower prevalence of active smoking, higher baseline NIHSS score, and admission blood glucose. Patients with S-COVID were younger than controls and more frequently men and had a lower prevalence of arterial hypertension and dyslipidemia, a lower systolic blood pressure, and a lower baseline Alberta Stroke Program Early CT Score (Table 1; Tables S2 and S3 for baseline description of IVT only and EVT cohorts).

The frequencies of each outcome in the AS-COVID, S-COVID, and control groups are shown in Table S4. The mRS score distribution of the 3 groups is displayed in the overall cohort (Figure 2) and IVT and EVT cohorts (Figure S1A and S1B).

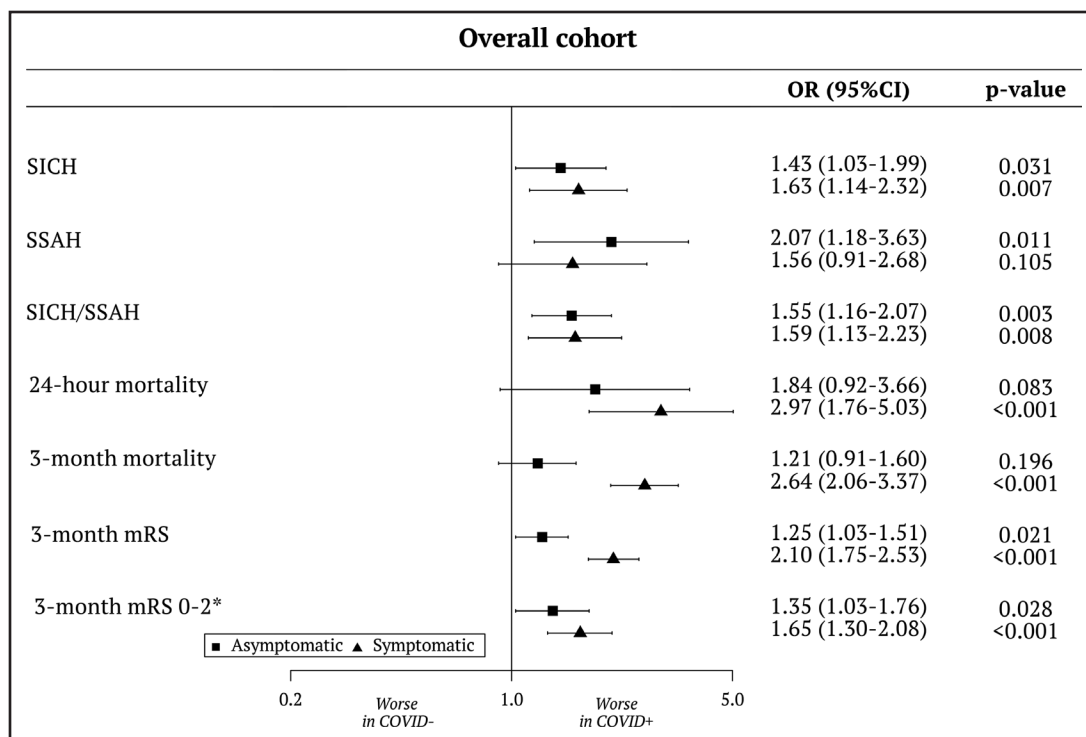


Figure 1. Forest plot of intracranial bleeding complications, mortality, and disability comparing patients with asymptomatic and symptomatic COVID-19 with COVID-negative controls.

All models were adjusted for age, sex, National Institutes of Health Stroke Scale score, Alberta Stroke Program Early Computed Tomography Score, blood glucose, site of arterial occlusion, tandem lesion, time to treatment (last-time-seen-well-to-needle for intravenous thrombolysis [IVT] and last-time-seen-well-to-groin delay for endovascular treatment [EVT] when applicable), and center volume. Symptomatic intracerebral hemorrhage (SICH), symptomatic subarachnoid hemorrhage (SSAH), and SICH/SSAH models were also adjusted for systolic blood pressure and previous antithrombotic therapy. Mortality and modified Rankin Scale (mRS) score models were adjusted for prestroke mRS score, cancer, and coronary heart disease. Models on the overall cohort were adjusted for revascularization treatment (IVT only vs EVT). Models on the EVT cohort were adjusted for IVT, the number of passes, and successful revascularization. OR indicates odds ratio. *Or return to prestroke mRS, in patients with prestroke mRS>2.

Patients with both AS-COVID and S-COVID had a higher crude proportion of SICH (COVID-controls, 5%; AS-COVID, 7.6%; and S-COVID, 9.4%) and SICH/SSAH (COVID-controls, 6.1%; AS-COVID, 9.6%; and S-COVID, 11.7%). These differences were significant in multivariable regression analyses (Figure 1): the adjusted odds ratios (aORs) for SICH were 1.43 (95% CI, 1.03–1.99) in AS-COVID and 1.63 (95% CI, 1.14–2.32) in S-COVID; for SICH/SSAH, the aORs were 1.55 (95% CI, 1.16–2.07) in S-COVID and 1.59 (95% CI, 1.13–2.23) in S-COVID. When assessing radiological hemorrhagic transformation, we observed an increased rate of parenchymal hematomas only in the S-COVID group (11.2% versus 7.7%; $P=0.014$; Table S4). Mortality at 24 hours and 3 months was increased in patients with S-COVID (24 hours: COVID-controls, 1.3%; S-COVID, 4.8%; aOR, 2.97 [95% CI, 1.76–5.03]; $P<0.001$; 3 months: COVID-controls, 19.5%; S-COVID, 40%; aOR, 2.64 [95% CI, 2.06–3.37]; $P<0.001$; Figure 1). Disability at 3 months was worse in the AS-COVID group compared with controls (aOR, 1.25 [95% CI, 1.03–1.51]) and worst in the S-COVID group (aOR, 2.10 [95% CI, 1.75–2.53]; Figure 1), with similar effects in the analysis with 3-month good disability outcome dichotomized as mRS score ≤ 2 (Figure 1).

Equivalent results were obtained in the multivariable analyses performed separately on the cohorts of patients treated with IVT only and EVT (Figure S2A and S2B). The results of the sensitivity analysis including adjustment for the in-hospital stroke variable demonstrated similar findings to the main analysis, albeit with a less prominent effect (Figure S2C).

Regarding EVT-related metrics and outcomes, the S-COVID group had a higher proportion of direct EVT versus bridging compared with the COVID-negative group (61% versus 51.9%; $P=0.004$). There was a higher proportion of general anesthesia use in the S-COVID compared with COVID-negative patients (47.8% versus 35.9%; $P<0.001$; Table 2). Patients with S-COVID, but not AS-COVID, had a worse final modified Treatment in Cerebral Infarction, a lower rate of successful recanalization, a lower rate of recanalization at first pass, and a higher number of device passes compared with controls (Table 2).

DISCUSSION

In this large international observational study on patients with AIS and COVID-19 undergoing acute revascularization treatment, we showed (1) the previously reported association

Table 1. Baseline Stroke Characteristics and Imaging Data for the Overall Cohort, the COVID-19 Negative, Symptomatic, and Asymptomatic SARS-CoV-2 Infection Groups

Variables	Total (N=15 124)	COVID-19 negative (n=14 275)	Asymptomatic COVID-19 (n=395)	Symptomatic COVID-19 (n=454)	P value (overall group comparison)	P value (asymptomatic vs COVID-19 negative)	P value (symptomatic vs COVID-19 negative)
Center volume							
<100	1665 (11%)	1475 (10.3%)	91 (23%)	99 (21.8%)	<0.001	<0.001	<0.001
100–199	4741 (31.3%)	4473 (31.3%)	128 (32.4%)	140 (30.8%)	0.877	0.878	0.968
200–299	5662 (37.4%)	5396 (37.8%)	129 (32.7%)	137 (30.2%)	0.001	0.073	0.002
≥300	3056 (20.2%)	2931 (20.5%)	47 (11.9%)	78 (17.2%)	<0.001	<0.001	0.153
Demographics							
Age, y	71.6 (13.8)	71.7 (13.8)	70.8 (14.3)	68.7 (13.4)	<0.001	0.362	<0.001
Sex, men	7766 (51.4%)	7273 (51%)	205 (51.9%)	288 (63.4%)	<0.001	0.918	<0.001
Prestroke independence (mRS score, ≤2)	13 338 (91.4%)	12 571 (91.4%)	356 (90.8%)	411 (92.2%)	0.779	0.914	0.804
Vascular risk factors							
Arterial hypertension	10 664 (70.8%)	10 087 (71%)	278 (70.4%)	299 (65.9%)	0.060	0.957	0.035
Diabetes	3814 (25.3%)	3531 (24.9%)	128 (32.4%)	155 (34.1%)	<0.001	0.001	<0.001
Dyslipidemia	6953 (46.2%)	6594 (46.5%)	175 (44.3%)	184 (40.5%)	0.032	0.629	0.024
Current smoking (or stopped <2 y)	3122 (21.1%)	2993 (21.5%)	58 (14.7%)	71 (15.8%)	<0.001	0.002	0.008
Heart failure	1780 (12.7%)	1671 (12.6%)	44 (11.4%)	65 (15%)	0.255	0.724	0.264
Coronary artery disease	2434 (16.6%)	2298 (16.6%)	68 (18.1%)	68 (15.9%)	0.684	0.687	0.910
Active cancer	634 (4.9%)	600 (4.9%)	14 (4%)	20 (5%)	0.722	0.667	0.997
Treatment at stroke onset							
Oral anticoagulants	2138 (14.2%)	2001 (14.1%)	61 (15.4%)	76 (16.7%)	0.221	0.699	0.213
Antiplatelets	4435 (29.5%)	4210 (29.6%)	115 (29.1%)	110 (24.3%)	0.050	0.967	0.029
Statins	4919 (33.9%)	4664 (34%)	125 (32.5%)	130 (29.8%)	0.149	0.772	0.121
Stroke characteristics							
Last-time-seen-well-to-door time, min	180.5 (206)	180.7 (205.8)	177.2 (203.7)	178.5 (215.5)	0.927	0.934	0.969
Admission NIHSS score	12 (6–18)	12 (6–18)	14 (7–18)	16 (9–20)	<0.001	0.020	<0.001
Vascular territories							
Carotid	12 562 (85%)	11 829 (84.9%)	342 (86.8%)	391 (86.5%)	0.396	0.516	0.585
Vertebrobasilar	1724 (11.7%)	1642 (11.8%)	42 (10.7%)	40 (8.8%)	0.131	0.741	0.108
Multiple territories	488 (3.3%)	457 (3.3%)	10 (2.5%)	21 (4.7%)	0.193	0.659	0.208
Admission systolic BP, mm Hg	152.7 (27.2)	153 (27.3)	151.2 (26.3)	143.3 (24.3)	<0.001	0.382	<0.001
Admission blood glucose, mmol/L	7.6 (3)	7.5 (3)	8.1 (3.6)	8.6 (3.9)	<0.001	<0.001	<0.001
Stroke cause							
Large artery atherosclerosis	2782 (18.4%)	2626 (18.4%)	68 (17.2%)	88 (19.4%)	0.718	0.798	0.834
Cardioembolism	5965 (39.4%)	5657 (39.6%)	149 (37.7%)	159 (35%)	0.110	0.691	0.094
Small vessel disease	701 (4.6%)	667 (4.7%)	19 (4.8%)	15 (3.3%)	0.388	0.990	0.315
Dissection	288 (1.9%)	273 (1.9%)	6 (1.5%)	9 (2%)	0.846	0.817	0.993
Other determined cause	761 (5%)	644 (4.5%)	51 (12.9%)	66 (14.5%)	<0.001	<0.001	<0.001
Undetermined	4627 (30.6%)	4408 (30.9%)	102 (25.8%)	117 (25.8%)	0.008	0.062	0.040
Acute imaging							
ASPECTS (or pc-ASPECTS)	10 (8–10)	10 (8–10)	9 (8–10)	9 (7–10)	<0.001	0.938	<0.001
Most proximal arterial occlusion							
None	2533 (19.2%)	2399 (19.3%)	77 (22.2%)	57 (14.1%)	0.012	0.305	0.019
Intracranial ICA	2039 (15.5%)	1905 (15.3%)	56 (16.2%)	78 (19.3%)	0.086	0.883	0.057
MCA: M1	4807 (36.4%)	4528 (36.4%)	127 (36.7%)	152 (37.6%)	0.876	0.991	0.851

(Continued)

Table 1. Continued

Variables	Total (N=15 124)	COVID-19 negative (n=14 275)	Asymptomatic COVID-19 (n=395)	Symptomatic COVID-19 (n=454)	P value (overall group comparison)	P value (asymptomatic vs COVID-19 negative)	P value (symptomatic vs COVID-19 negative)
MCA: M2-M4	2322 (17.6%)	2194 (17.6%)	51 (14.7%)	77 (19.1%)	0.279	0.299	0.708
ACA: A1 and A2	94 (0.7%)	89 (0.7%)	3 (0.9%)	2 (0.5%)	0.824	0.933	0.843
PCA: P1 and P2	282 (2.1%)	266 (2.1%)	7 (2%)	9 (2.2%)	0.981	0.987	0.991
BA	656 (5%)	627 (5%)	15 (4.3%)	14 (3.5%)	0.307	0.799	0.281
V4	180 (1.4%)	172 (1.4%)	4 (1.2%)	4 (1%)	0.755	0.922	0.753
Other	277 (2.1%)	260 (2.1%)	6 (1.7%)	11 (2.7%)	0.609	0.877	0.619
Tandem lesion	1563 (12.2%)	1459 (12.1%)	44 (13.1%)	60 (15.3%)	0.130	0.803	0.100
In-hospital/ICU stroke	890 (6.3%)	587 (4.4%)	90 (22.8%)	213 (46.9%)	<0.001	<0.001	<0.001
Timing of COVID diagnosis*							
Known before stroke onset	323 (38%)	NA	78 (19.8%)	245 (54%)	<0.001	NA	NA
Diagnosed at stroke admission (first 24 h)	387 (45.6%)	NA	238 (60.2%)	149 (32.8%)	<0.001	NA	NA
Diagnosed >24 h after stroke admission	139 (16.4%)	NA	79 (20%)	60 (13.2%)	0.010	NA	NA
SARS-CoV-2 PCR test used							
PCR	802 (94.5%)	NA	367 (92.9%)	435 (95.8%)			
Antigen	47 (5.5%)	NA	28 (7.1%)	19 (4.2%)			

Values are presented as median (interquartile range) or as numbers (proportions). ACA: A1 and A2 indicates first and second segments of anterior cerebral artery; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; BA, basilar artery; BP, blood pressure; ICA, internal carotid artery; ICU, intensive care unit; MCA: M1-M4, first, second, third, and fourth segments of middle cerebral artery; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; PCA: P1 and P2, first and second segments of posterior cerebral artery; pc-ASPECTS, posterior circulation Alberta Stroke Program Early Computed Tomography Score; PCR, polymerase chain reaction; and V4, fourth segment of vertebral artery.

*Recorded in patients with COVID-19 only.

between COVID-19 and hemorrhagic complication after revascularization stroke treatments is present for both asymptomatic and symptomatic infections; (2) 24-hour and 3-month mortalities are increased in patients with S-COVID; (3) COVID-19 is associated with a worse 3-month disability regardless of the presence of its symptoms but to a greater extent in symptomatic patients; and (4) recanalization rates were lower, and

the number of EVT passes was higher only in patients with S-COVID, while no difference was observed between AS-COVID and COVID-negative controls.

The pathophysiological mechanisms associated with the risk of intracranial hemorrhage in patients with COVID-19 include systemic inflammation, endothelial dysfunction, increased blood-brain barrier permeability, hyperfibrinolysis,

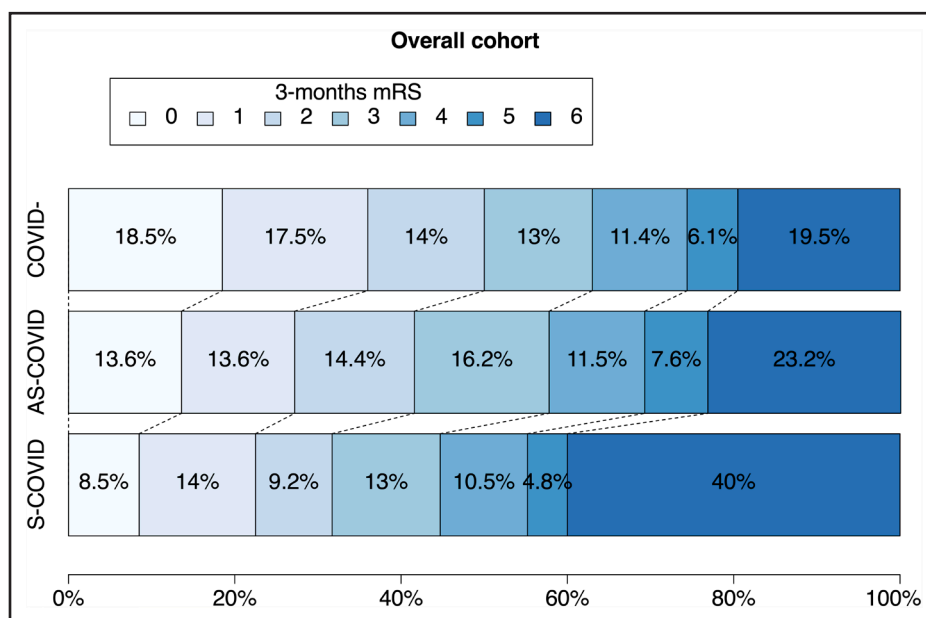


Figure 2. Three-month modified Rankin Scale (mRS) score distribution in asymptomatic COVID-19 (AS-COVID) and symptomatic COVID-19 (S-COVID) groups and controls.

Table 2. Treatment Characteristics of EVT Patients

Variables	Total (N=9279)	COVID negative (n=8756)	Asymptomatic COVID (n=228)	Symptomatic COVID (n=295)	P value (overall group comparison)	P value (asymptomatic vs COVID negative)	P value (symptomatic vs COVID negative)
Revascularization treatment					0.008	0.999	0.004
Bridging	4439 (47.8%)	4214 (48.1%)	110 (48.2%)	115 (39%)			
Direct EVT	4840 (52.2%)	4542 (51.9%)	118 (51.8%)	180 (61%)			
Last-time-seen-well-to-puncture time, min	352.5 (251.4)	352.5 (251.2)	350.2 (266.4)	354.2 (246.1)	0.985	0.988	0.993
General anesthesia	3342 (36.4%)	3106 (35.9%)	96 (42.1%)	140 (47.8%)	<0.001	0.102	<0.001
Final mTICI score							
0	688 (7.5%)	642 (7.4%)	14 (6.1%)	32 (10.8%)	0.065	0.719	0.055
1	185 (2%)	164 (1.9%)	6 (2.6%)	15 (5.1%)	0.001	0.680	<0.001
2a	482 (5.3%)	442 (5.1%)	13 (5.7%)	27 (9.2%)	0.009	0.904	0.004
2b	2322 (25.3%)	2191 (25.3%)	55 (24.1%)	76 (25.8%)	0.904	0.900	0.981
2c	993 (10.8%)	928 (10.7%)	28 (12.3%)	37 (12.5%)	0.473	0.702	0.540
3	4509 (49.1%)	4289 (49.5%)	112 (49.1%)	108 (36.6%)	<0.001	0.990	<0.001
Successful recanalization	7824 (85.2%)	7408 (85.6%)	195 (85.5%)	221 (74.9%)	<0.001	1.000	<0.001
Recanalization at first pass	2548 (28%)	2425 (28.3%)	63 (27.8%)	60 (20.3%)	0.011	0.979	0.005
Total number of device passes							
0	456 (5.1%)	439 (5.2%)	8 (3.5%)	9 (3.1%)	0.142	0.440	0.190
1	3938 (44.1%)	3724 (44.3%)	100 (44%)	114 (38.9%)	0.188	0.996	0.131
2	2023 (22.7%)	1908 (22.7%)	59 (26%)	56 (19.1%)	0.170	0.426	0.277
3	1256 (14.1%)	1172 (13.9%)	29 (12.8%)	55 (18.8%)	0.055	0.854	0.039
>3	1253 (14%)	1163 (13.8%)	31 (13.7%)	59 (20.1%)	0.009	0.996	0.005
Last-time-seen-well-to-recanalization time, min	325 (234–467)	325 (234–467.3)	319.5 (230–461.2)	340 (238.7–459.3)	1.000	0.987	0.999
Procedure duration	40 (25–65)	40 (25–65)	38 (25.7–62)	40 (25–65)	1.000	0.274	0.994

Values are presented as median (interquartile range) or as numbers (proportions). EVT indicates endovascular treatment; and mTICI, modified Treatment in Cerebral Infarction.

and coagulopathy associated with the infection.^{4–6,20–24} These alterations have mainly been observed and are more pronounced in symptomatic patients with moderate or severe disease,²⁵ but they have also been described in asymptomatic infections.^{26–28} This would explain the excess of bleeding complications after revascularization treatment in patients with both S-COVID and AS-COVID.

The same biologic changes that increase the risk of bleeding in patients with COVID-19 also result in a higher clot burden, microvascular thromboinflammation, and endothelitis with subsequent impaired posttreatment reperfusion, thereby increasing the risk of stroke recurrence.^{11,29} These unfavorable effects may contribute to the greater disability outcomes observed in patients with S-COVID and, to a lesser extent, in those with asymptomatic infection.

Mortalities at 24 hours and 3 months were only increased in patients with S-COVID, suggesting that the presence of symptoms is a significant factor in the risk of death after AIS revascularization treatments. In addition to the possible contribution of biologic alterations mentioned above, the increased mortality may be explained by respiratory and systemic complications related to COVID-19, which are more common in symptomatic patients.

Less favorable EVT procedural outcomes in patients with S-COVID are likely an additional factor contributing to the

worse disability and higher mortality. Worse outcomes may be explained by several potential mechanisms, including larger clots with different compositions, increased clot fragmentation leading to distal embolization, and repeated vessel reocclusion.^{30–32} We observed poorer EVT outcomes in patients with S-COVID only, while patients with asymptomatic infection did not show any differences compared with the control group. This finding is consistent with the notion that biologic alterations associated with COVID-19 correlate with disease severity and would only be severe enough in symptomatic patients to produce a measurable effect on EVT procedural outcomes. The hypothesis of a potential correlation between the symptom status of COVID-19 infection and the magnitude of its impact on AIS revascularization outcomes is also supported by the sensitivity analysis showing an attenuated effect of COVID-19 on revascularization outcomes after excluding in-hospital stroke. It is likely that patients already hospitalized for COVID-19 have more severe disease compared with those who are not.

Importantly, as previously reported in the Global COVID-19 Stroke Registry, we found no evidence of increased delay in revascularization treatment among patients with COVID-19 compared with controls. This lack of difference in treatment delays was consistent across both symptomatic and asymptomatic patients. These findings indicate

that care pathways for patients with AIS were maintained regardless of COVID-19 status and symptoms and suggest that treatment delays were unlikely to be a contributing factor to the observed worse outcomes.

Our analysis has several strengths, including the large sample size with a low proportion of missing data, enabling adjustments for confounders. The inclusion of patients from 30 countries across 5 continents enhances the generalizability of our study. To our knowledge, this is the largest study to assess the safety and outcome of acute revascularization treatment in AIS in relation to AS-COVID and S-COVID.

Our study has limitations. The retrospective design cannot exclude registration bias, as academic centers may have participated more than primary stroke centers. The nonblinded assessment may have influenced reporting bias, particularly for clinical and technical outcomes. The clinical outcomes evaluated may also depend on systemic COVID-19–related complications that were not assessed in our study. Some patients with COVID-19 may have been treated outside the usual stroke care pathways, which might have affected outcomes, but we lacked this information. We cannot exclude that patients with AIS with the most severe cases of COVID-19, who would have otherwise met the criteria for IVT or EVT, did not undergo reperfusion treatment. Even with these treatments, their outcomes might have remained highly unfavorable. Hence, our results may underestimate the effect of COVID-19 on stroke outcomes. We were unable to collect data on virus variants, pandemic wave, and vaccination status of our patients, which may have influenced our results.³³ The definition of AS-COVID was at stroke onset, and we cannot exclude that the disease became symptomatic after the stroke.

While we compared symptomatic and asymptomatic disease, our ability to assess the impact of COVID-19 severity on stroke outcomes was limited by the absence of detailed information on infection severity, aside from intensive care unit admission status. A separate analysis for this subgroup was unfeasible due to the limited number of patients admitted to the intensive care unit ($n=37$), precluding any meaningful statistical analysis.

Finally, our study design did not allow for conclusions about the effectiveness of revascularization treatments in patients with COVID-19 as we did not include an untreated comparison group.

CONCLUSIONS

In conclusion, in this international retrospective cohort study, patients with AIS, AS-COVID, and S-COVID receiving revascularization treatment had higher rates of intracranial bleeding and worse short- and medium-term disabilities compared with contemporary AIS controls without COVID-19. Higher 24-hour and 3-month mortalities were observed in patients with S-COVID but not asymptomatic patients. Nevertheless, it is likely

that revascularization treatments are still beneficial for both patients with AS-COVID and S-COVID, given the relatively large margin of benefit of these treatments, especially EVT, and the rather small absolute numbers of SICH in patients with AIS and COVID-19.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S2

APPENDIX

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