RESEARCH ARTICLE

Safety and Outcome of Revascularization Treatment in Patients With Acute Ischemic Stroke and COVID-19

The Global COVID-19 Stroke Registry

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Abstract

Background and Objectives

COVID-19–related inflammation, endothelial dysfunction, and coagulopathy may increase the bleeding risk and lower the efficacy of revascularization treatments in patients with acute ischemic stroke (AIS). We aimed to evaluate the safety and outcomes of revascularization treatments in patients with AIS and COVID-19.

Methods

This was a retrospective multicenter cohort study of consecutive patients with AIS receiving intravenous thrombolysis (IVT) and/or endovascular treatment (EVT) between March 2020 and June 2021 tested for severe acute respiratory syndrome coronavirus 2 infection. With a doubly robust model combining propensity score weighting and multivariate regression, we studied the association of COVID-19 with intracranial bleeding complications and clinical outcomes. Subgroup analyses were performed according to treatment groups (IVT-only and EVT).

Results

Of a total of 15,128 included patients from 105 centers, 853 (5.6%) were diagnosed with COVID-19; of those, 5,848 (38.7%) patients received IVT-only and 9,280 (61.3%) EVT (with or without IVT). Patients with COVID-19 had a higher rate of symptomatic intracerebral hemorrhage (SICH) (adjusted OR 1.53; 95% CI 1.16–2.01), symptomatic subarachnoid hemorrhage (SSAH) (OR 1.80; 95% CI 1.20–2.69), SICH and/or SSAH combined (OR 1.56; 95% CI 1.23–1.99), 24-hour mortality (OR 2.47; 95% CI 1.58–3.86), and 3-month mortality (OR 1.88; 95% CI 1.52–2.33). Patients with COVID-19 also had an unfavorable shift in the distribution of the modified Rankin score at 3 months (OR 1.42; 95% CI 1.26–1.60).

Discussion

Patients with AIS and COVID-19 showed higher rates of intracranial bleeding complications and worse clinical outcomes after revascularization treatments than contemporaneous non–COVID-19 patients receiving treatment. Current available data do not allow direct conclusions to be drawn on the effectiveness of revascularization treatments in patients with COVID-19 or to establish different treatment recommendations in this subgroup of patients with ischemic stroke. Our findings can be taken into consideration for treatment decisions, patient monitoring, and establishing prognosis.

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Glossary

ACE2 = angiotensin-converting enzyme 2; **AIS** = acute ischemic stroke; **DMT** = direct mechanical thrombectomy; **EVT** = endovascular treatment; **IQR** = interquartile range; **IVT** = intravenous thrombolysis; **mRS** = modified Rankin scale; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SICH** = symptomatic intracerebral hemorrhage; **SSAH** = symptomatic subarachnoid hemorrhage.

Trial Registration Information

The study was registered under ClinicalTrials.gov identifier NCT04895462.

Acute ischemic stroke (AIS) is a recognized complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] Inflammation, endothelial dysfunction, and coagulopathy are the pathophysiologic mechanisms involved in the development of arterial thrombotic events.[2-4]

The Global COVID-19 Stroke Registry showed that patients with AIS and COVID-19 have a worse functional outcome than those without SARS-CoV-2 infection,[5] which was later confirmed by other studies.[6-10] Several hypotheses may explain these findings: (1) broad multisystem complications of COVID-19, such as acute respiratory distress syndrome, shock, secondary infection, and pulmonary embolism[11]; (2) more severe ischemic strokes at admission[6-9]; and (3) longer time to revascularization treatments.[8,9]

In addition, because of the abovementioned mechanisms, the thrombo-inflammatory state, increased blood-brain barrier permeability, and derangement of the fibrinolytic system identified in patients with COVID-19[2] may affect the safety and efficacy of intravenous thrombolysis (IVT) and endovascular treatment (EVT), and contribute to poorer outcomes.

Case series and cohort studies have shown the feasibility of revascularization treatments in patients with AIS and COVID-19. Some of these studies documented lower recanalization rates[12,13] and higher rates of intracerebral hemorrhage[13] in patients with COVID-19 receiving EVT, but these studies were limited by the absence of a contemporary control group of non–COVID-19 patients, small sample size, or lack of 3-month outcome assessment. For these reasons, the question of the safety and efficacy of revascularization treatments in acute stroke patients with COVID-19 remains unanswered.[12-18]

In this context, our aim was to assess the safety and outcome of revascularization treatment in patients with AIS and COVID-19 in a large, multicenter, international cohort by comparison with a contemporary control group of non–COVID-19 patients with AIS from the same centers.

Methods

Study Design, Patient Selection, and Study Variables

This was a retrospective, international, cohort study of consecutive patients with AIS receiving IVT and/or EVT up to 24 hours from last time seen well, and according to each center's recommendations.

To participate in the study, each invited center needed to include at least 1 patient with COVID-19 and AIS treated with IVT and/or EVT. Patients were included from March 1, 2020 to June 30, 2021.

Patients with COVID-19 (exposed group) were defined as (1) patients with community-acquired SARS-CoV-2 infection confirmed by a positive 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 reperfusion treatment with positive PCR or antigen test within the first 7 days after treatment. Patients without COVID-19 (control group) were defined as patients without COVID-19–compatible symptoms and with a negative PCR or antigen test within the first 7 days after treatment.

The following exclusion criteria were used: (1) patients without a PCR or antigen test within the first 7 days after treatment; (2) patients with nosocomial SARS-CoV-2 infection after receiving revascularization treatments, defined as PCR or antigen tests becoming positive more than 7 days after treatment[19]; (3) patients with a suspected/probable case of SARS-CoV-2 infection according to the World Health Organization definition[20]; (4) patients with symptomatic SARS-CoV-2 infection with symptoms resolution more than 7 days before treatment; and (5) patients with asymptomatic SARS-CoV-2 infection with treatment performed more than 10 days after the first positive test for SARS-CoV-2.

All study variables are detailed in the Supplement (links.lww.com/WNL/C428). The reporting of this observational study is in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Standard Protocol Approvals, Registrations, and Patient Consents

Participating centers were requested to anonymize their data before sending it to the coordinating center (Stroke Centre, Department of Neurology, Lausanne University Hospital, Lausanne, Switzerland). 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 because of the retrospective nature of this study. This study was conducted according to the principles of the Declaration of Helsinki. In the coordinating center in Lausanne, Institutional Review Board approval and patient consent were not required according to the Swiss Federal Act on Research involving Human Beings from 2011 (HRA, Art. 3) because all data were anonymized and the project involved assessing the safety and quality of routine AIS management in the participating centers. The study was registered under ClinicalTrials.gov identifier NCT04895462.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Outcome Analysis

For the main outcome, we defined symptomatic intracerebral hemorrhage (SICH) according to the ECASS-2 definition (≥4-point worsening in NIHSS attributable to parenchymal hemorrhage).[21] As secondary outcomes, we defined (1) symptomatic subarachnoid hemorrhage (SSAH) (≥4-point worsening in NIHSS attributable to subarachnoid hemorrhage), (2) any symptomatic intracranial hemorrhage (SICH/SSAH) (combination of SICH and SSAH), (3) 24-hour mortality, (4) 3-month mortality, (5) 3-month modified Rankin scale (mRS), (6) favorable 3-month outcome (mRS ≤2 or equal to prestroke mRS), (7) presence of any radiologic hemorrhagic transformation, and (8) delta NIHSS at 24 hours (difference between admission NIHSS and NIHSS at 24 hours). If the patient was intubated, we considered the first NIHSS after extubation. For patients with extubation after 4 weeks or death before extubation, 24-hour NIHSS was quantified as 42; (9) recanalization after EVT measured by mTICI; (10) successful recanalization after EVT as final mTICI ≥ 2b; (11) number of passes during EVT; and (12) first pass effect.[22]

Statistical Analysis

We summarized continuous variables as median values with interquartile range (IQR) and categorical variables as absolute numbers and percentages. We compared baseline and outcome variables between the COVID-19 and control (without COVID-19) groups using the Pearson χ^2 test for categorical variables and Mann-Whitney *U* tests for continuous variables, as appropriate. We performed all analysis outcomes in the entire cohort and in the 2 treatment subgroups, IVT-only and EVT.

To assess the association between COVID-19 and poststroke outcomes, we used doubly robust estimation, which offers more robustness than a single-model approach of exposure or outcome modeling.[23] In detail, we calculated a doubly robust estimator of COVID-19 effect for each outcome of interest combining a logistic regression exposure model (with the COVID-19 status as a response variable) and an outcome regression model (with the outcome of interest as a response variable). For the binary outcomes, the outcome model was a logistic regression model, while 3-month mRS was an ordered logit regression model. We adjusted both exposure and outcome models for prespecified potential confounders identified from previous literature as variables known to be associated with the outcome of interest, namely, age, sex, NIHSS, ASPECTS, blood glucose, site of arterial occlusion, tandem lesion, time-to-treatment, and center volume. Additional confounders specific for different outcomes were entered in the respective models and are detailed in the Figure 1 legend.

We expressed the results of the doubly robust estimation as OR and confidence intervals. Given the potential clustering effect of patients from the same center, we included in each model the referring center as a cluster level variable and calculated cluster-robust standard errors.

To account for missing data of the independent covariates, we performed multiple imputation by the chained equation, generating 10 imputed data sets.[24] The rate of missing data for each variable is reported in eTable 1 (links.lww.com/WNL/C428). We performed analyses on each imputed data set; then, the estimates and the standard errors of the 10 imputed analyses were combined using the Rubin rules. We also conducted a sensitivity analysis including only patients with complete data (complete case analysis).

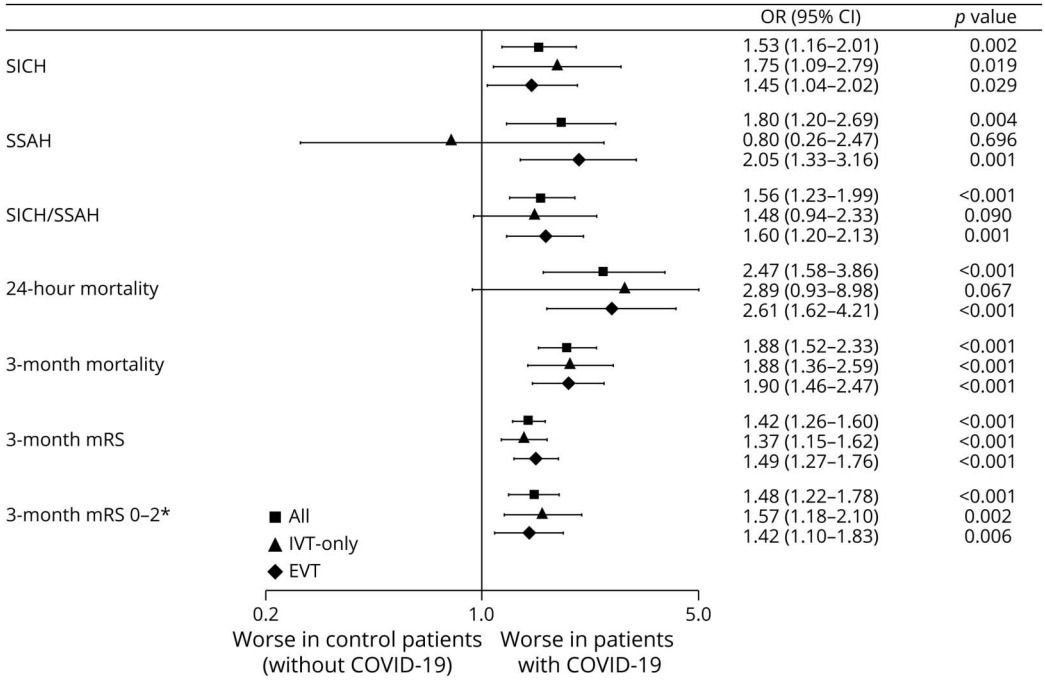
We performed a further analysis in the EVT group to evaluate the potential heterogeneity of a COVID-19 effect on outcomes in bridging vs direct mechanical thrombectomy (DMT) patients. We assessed this by adding an interaction term between COVID-19 status and IVT to the multivariable logistic regression outcome models adjusted for the same confounders as the main analysis. For this analysis, we reported the *p*-value of the interaction term and the effect of COVID-19 in the 2 groups (bridging and DMT).

All tests were two-sided, and *p*-values <0.05 were considered significant. Given that this was a retrospective study with an exploratory analysis, no correction for multiple outcome testing was applied. In addition, a power calculation was not performed because previous data to estimate the expected effect of COVID-19 on the outcome of interest in revascularized stroke patients were lacking. We performed statistical analysis with R statistical software, version 4.0.3.

Results

We included 15,128 patients from 105 participating centers. The median age was 71.6 (IQR 13.8) years, 7,767 (51.4%)

Figure 1 Forest Plot of Intracranial Bleeding Complications, Mortality, and Disability Comparing Patients With COVID-19 and Controls of the Whole Cohort and IVT-Only and EVT Subgroups



*Or mRS equal to prestroke mRS, if > 2. All models were adjusted for age, sex, NIHSS, ASPECTS, blood glucose, site of arterial occlusion, tandem lesion, time-to-treatment, and center volume. SICH, SAH, and SICH/SAH models were also adjusted for systolic blood pressure and previous antithrombotic therapy. Mortality and mRS models were also adjusted for prestroke mRS, cancer, and coronary heart disease. Models on the entire cohort were also adjusted for type of revascularization treatment (IVT-only vs EVT). Models on the EVT cohort were also adjusted for IVT, number of device passes, and successful revascularization. IVT, intravenous thrombolysis; EVT, endovascular treatment; SICH, symptomatic intracerebral hemorrhage; SSAH, symptomatic subarachnoid hemorrhage; mRS, modified Rankin Scale.

were male, and 5,848 patients (38.7%) were treated with IVT-only and 9,280 patients (61.3%) with EVT (of whom 4,841 had direct EVT and 4,439 bridging). For participating patients, 1,666 (11%) came from low-volume centers, 4,743 (31.4%) from medium-volume centers, 5,663 (37.4%) from high-volume centers, and 3,056 (20.2%) from very high-volume centers.

Overall, 853 (5.6%) patients were diagnosed with COVID-19, and 14,275 patients (94.4%) were COVID-19–negative controls. SARS-CoV-2 infection was most frequently diagnosed at stroke onset (n = 387, 45.5%), followed by diagnosis before stroke (n = 324, 38.1%) and then diagnosis during hospital admission (n = 139, 16.4%). Regarding COVID-19–related symptoms, 306 patients (36.0%) were asymptomatic and at home at stroke onset, 241 (28.4%) were symptomatic and at home, 266 (31.3%) were admitted to a hospital ward, and 37 (4.3%) were in an intensive care unit.

Patients with COVID-19 were younger, more frequently male; had a higher prevalence of diabetes mellitus and dyslipidemia; and had a lower prevalence of current smoking. Stroke severity according to the NIHSS and admission blood glucose was higher in patients with COVID-19, while admission systolic blood pressure and ASPECTS were lower. Patients with COVID-19 more frequently had stroke of other determined cause and a lower proportion of stroke of undetermined etiology (Table 1).

In the IVT-only subgroup, patients with COVID-19 and controls had the same differences in their baseline characteristics as in the whole cohort except for a nonsignificant difference in age, sex, and dyslipidemia, while in the EVT subgroup, patients with COVID-19 additionally had a higher frequency of preadmission treatment with oral anticoagulants (Table 1). Among patients treated with IVT (IVT-only or bridging), the last time seen well-to-needle time was not different between patients with COVID-19 and controls [179 minutes (IQR 125) vs 176 minutes (IQR 125), respectively; p-value = 0.667].

In the EVT subgroup, patients with COVID-19 had a higher rate of general anesthesia, a greater number of device passes, a worse final mTICI, and lower rates of successful recanalization and first pass effect. We found no differences in symptoms-to-treatment times, treatment duration, and symptoms-to-recanalization times (Table 2). The univariable outcome analysis is presented in eTable 2 in the Supplement (links.lww.com/WNL/C428).

On the doubly robust adjusted outcome analysis on multiple imputed data sets, patients with COVID-19 showed a higher

Table 1 Baseline, Stroke Characteristics, and Imaging Data for the Whole Cohort, IVT-Only, and EVT Subgroups

Variables	Whole cohort				IVT-only				EVT			
	Total (n = 15,128)	COVID-19 (n = 853)	Controls (n = 14,275)	*p* Value	Total (n = 5,848)	COVID-19 (n = 329)	Controls (n = 5,519)	*p* Value	Total (n = 9,280)	COVID-19 (n = 524)	Controls (n = 8,756)	*p* Value
Demographics												
Age, years	71.6 (13.8)	69.7 (13.9)	71.7 (13.8)	<0.001	72.1 (14.0)	70.7 (13.8)	72.2 (14.0)	0.064	71.2 (13.7)	69 (13.9)	71.3 (13.7)	<0.001
Male sex	7,767 (51.3%)	494 (57.9%)	7,273 (51.0%)	<0.001	3,222 (55.1%)	190 (57.8%)	3,032 (55.0%)	0.349	4,545 (49.0%)	304 (58.0%)	4,241 (48.5%)	<0.001
Prestroke mRS				1.000				0.521				0.626
0–2	13,341 (91.5%)	770 (91.5%)	12,571 (91.3%)		4,987 (88.2%)	285 (87.4%)	4,702 (88.3%)		8,354 (93.4%)	485 (94.0%)	7,869 (93.3%)	
>2	1,261 (8.4%)	72 (8.4%)	1,189 (8.6%)		665 (11.8%)	41 (12.6%)	624 (11.7%)		596 (6.7%)	31 (6.0%)	565 (6.7%)	
Vascular risk factors												
Atrial fibrillation	4,554 (30.2%)	244 (28.7%)	4,310 (30.3%)	0.329	1,140 (19.6%)	60 (18.3%)	1,080 (19.6%)	0.603	3,414 (37%)	184 (35.2%)	3,230 (37.1%)	0.412
Heart failure	1781 (12.7%)	110 (13.4%)	1,671 (12.6%)	0.572	475 (8.8%)	29 (8.9%)	446 (8.8%)	1.000	1,306 (15.1%)	81 (16.2%)	1,225 (15%)	0.496
Arterial hypertension	10,666 (70.8%)	579 (67.9%)	10,087 (71%)	0.057	4,233 (72.6%)	231 (70.2%)	4,002 (72.8%)	0.340	6,433 (69.7%)	348 (66.4%)	6,085 (69.8%)	0.106
Diabetes mellitus	3,815 (25.4%)	284 (33.3%)	3,531 (24.9%)	<0.001	1,537 (26.4%)	108 (32.8%)	1,429 (26%)	0.008	2,278 (24.7%)	176 (33.6%)	2,102 (24.1%)	<0.001
Dyslipidaemia	6,955 (46.2%)	361 (42.3%)	6,594 (46.5%)	0.020	2,730 (46.9%)	145 (44.1%)	2,585 (47.1%)	0.314	4,225 (45.8%)	216 (41.2%)	4,009 (46.1%)	0.033
Coronary artery disease	2,435 (16.6%)	137 (17%)	2,298 (16.6%)	0.823	941 (16.8%)	50 (16.5%)	891 (16.8%)	0.948	1,494 (16.6%)	87 (17.3%)	1,407 (16.5%)	0.691
Current smoking	3,123 (21.1%)	130 (15.3%)	2,993 (21.5%)	<0.001	1,169 (20.4%)	36 (11%)	1,133 (20.9%)	<0.001	1954 (21.6%)	94 (18%)	1860 (21.8%)	0.049
Active cancer	634 (4.9%)	34 (4.5%)	600 (4.9%)	0.672	215 (4.4%)	11 (3.8%)	204 (4.4%)	0.711	419 (5.2%)	23 (4.9%)	396 (5.2%)	0.890
Prestroke treatment												
Oral anticoagulants	2,138 (14.2%)	137 (16.1%)	2001 (14.1%)	0.123	353 (6.1%)	17 (5.2%)	336 (6.1%)	0.560	1785 (19.4%)	120 (22.9%)	1,665 (19.1%)	0.039
Antiplatelets	4,437 (29.5%)	227 (26.7%)	4,210 (29.6%)	0.070	2091 (35.9%)	102 (31%)	1989 (36.2%)	0.065	2,346 (25.4%)	125 (24%)	2,221 (25.5%)	0.453
Statins	4,920 (33.9%)	256 (31.0%)	4,664 (34.0%)	0.079	2016 (34.6%)	105 (32%)	1911 (34.8%)	0.335	2,904 (33.3%)	151 (30.3%)	2,753 (33.5%)	0.154
Stroke characteristics												
LTSW-to-door	180.6 (206.0)	178.5 (210.2)	180.7 (205.8)	0.770	131.7 (129.9)	133.8 (138.5)	131.5 (129.4)	0.775	213.6 (238.8)	208.3 (242.4)	213.9 (238.6)	0.622
Admission NIHSS	12 (6–18)	15 (8–20)	12 (6–18)	<0.001	7 (4–12)	9 (5–15)	6 (4–11)	<0.001	16 (10–20)	17 (12–21)	15 (10–20)	<0.001
Vascular territory				0.152				0.419				0.265
Anterior circulation	12,566 (85.0%)	737 (86.7%)	11,829 (84.9%)		4,385 (78.8%)	267 (81.4%)	4,118 (78.7%)		8,181 (88.8%)	470 (90%)	7,711 (88.7%)	

Continued

Table 1 Baseline, Stroke Characteristics, and Imaging Data for the Whole Cohort, IVT-Only, and EVT Subgroups *(continued)*

	Whole cohort				IVT-only				EVT			
Variables	**Total (n = 15,128)**	**COVID-19 (n = 853)**	**Controls (n = 14,275)**	***p* Value**	**Total (n = 5,848)**	**COVID-19 (n = 329)**	**Controls (n = 5,519)**	***p* Value**	**Total (n = 9,280)**	**COVID-19 (n = 524)**	**Controls (n = 8,756)**	***p* Value**
Posterior circulation	1724 (11.7%)	82 (9.7%)	1,642 (11.8%)		908 (16.3%)	45 (13.7%)	863 (16.5%)		816 (8.9%)	37 (7.1%)	779 (9%)	
Multiple territories	488 (3.3%)	31 (3.6%)	457 (3.3%)		270 (4.8%)	16 (4.9%)	254 (4.8%)		218 (2.4%)	15 (2.9%)	203 (2.3%)	
Admission SBP	152.7 (27.2)	147 (25.4)	153 (27.3)	<0.001	157.7 (28)	151.2 (26.9)	158.1 (28)	<0.001	149.3 (26.1)	144.2 (24.1)	149.6 (26.2)	<0.001
Admission blood glucose	7.6 (3)	8.4 (3.8)	7.5 (3)	<0.001	7.5 (3.2)	8.5 (4.1)	7.5 (3.1)	<0.001	7.6 (2.9)	8.3 (3.5)	7.6 (2.9)	<0.001
Acute imaging												
ASPECTS[a]	10 (8–10)	9 (8–10)	10 (8–10)	<0.001	10 (9–10)	10 (8–10)	10 (9–10)	<0.001	9 (8–10)	9 (7–10)	9 (8–10)	0.008
Most proximal arterial occlusion				0.602				0.122				
None	2,462 (19.2%)	133 (17.9%)	2,329 (19.3%)		2,462 (60.5%)	133 (56.8%)	2,329 (60.7%)					0.155
Intracranial ICA	2039 (15.5%)	134 (17.8%)	1905 (15.3%)		159 (3.9%)	17 (7.3%)	142 (3.7%)		1880 (20.6%)	117 (22.5%)	1763 (20.5%)	
MCA M1	4,808 (36.4%)	280 (37.2%)	4,528 (36.4%)		329 (8.1%)	24 (10.3%)	305 (8%)		4,479 (49.1%)	256 (49.3%)	4,223 (49.1%)	
MCA M2-4	2,323 (17.6%)	129 (17.1%)	2,194 (17.6%)		622 (15.3%)	36 (15.4%)	586 (15.3%)		1701 (18.6%)	93 (17.9%)	1,608 (18.7%)	
ACA A1-2	94 (0.7%)	5 (0.7%)	89 (0.7%)		43 (1.1%)	3 (1.3%)	40 (1%)		51 (0.6%)	2 (0.4%)	49 (0.6%)	
PCA P1-2	282 (2.1%)	16 (2.1%)	266 (2.1%)		148 (3.6%)	9 (3.9%)	139 (3.6%)		134 (1.5%)	7 (1.4%)	127 (1.5%)	
BA	656 (5%)	29 (3.9%)	627 (5%)		78 (1.9%)	5 (2.1%)	73 (1.9%)		578 (6.3%)	24 (4.6%)	554 (6.4%)	
V4	180 (1.4%)	8 (1.1%)	172 (1.4%)		68 (1.7%)	3 (1.3%)	65 (1.7%)		112 (1.2%)	5 (1%)	107 (1.2%)	
Other	277 (2.1%)	17 (2.3%)	260 (2.1%)		160 (3.9%)	4 (1.7%)	156 (4.1%)		117 (1.3%)	13 (2.5%)	104 (1.2%)	
Tandem lesion	2,534 (19.2%)	104 (14.3%)	1,459 (12.1%)	0.088	169 (4.6%)	13 (6.2%)	156 (4.5%)	0.305	1,394 (15.3%)	91 (17.5%)	1,303 (15.2%)	0.174
Stroke aetiology				<0.001				<0.001				<0.001
Large artery atherosclerosis	2,783 (18.4%)	157 (18.4%)	2,626 (18.4%)		953 (16.3%)	51 (15.5%)	902 (16.3%)		1830 (19.7%)	106 (20.2%)	1724 (19.7%)	
Cardioembolism	5,996 (39.6%)	309 (36.2%)	5,685 (39.8%)		1,659 (28.4%)	88 (26.8%)	1,571 (28.5%)		4,337 (46.7%)	222 (42.4%)	4,115 (49.0%)	
Small vessel disease	671 (4.4%)	33 (3.9%)	638 (4.5%)		671 (11.5%)	33 (10.0%)	638 (11.6%)		0 (0.0%)	0 (0.0%)	0 (0.0%)	
Dissection	288 (1.9%)	15 (1.8%)	273 (1.9%)		77 (1.3%)	5 (1.5%)	72 (1.3%)		211 (2.3%)	10 (1.9%)	201 (2.3%)	

Continued

Table 1 Baseline, Stroke Characteristics, and Imaging Data for the Whole Cohort, IVT-Only, and EVT Subgroups *(continued)*

Variables	Whole cohort				IVT-only				EVT			
	Total (n = 15,128)	COVID-19 (n = 853)	Controls (n = 14,275)	*p* Value	Total (n = 5,848)	COVID-19 (n = 329)	Controls (n = 5,519)	*p* Value	Total (n = 9,280)	COVID-19 (n = 524)	Controls (n = 8,756)	*p* Value
Other determined aetiology	762 (5%)	118 (13.8%)	644 (4.5%)		347 (5.9%)	51 (15.5%)	296 (5.4%)		415 (4.5%)	67 (12.8%)	348 (4%)	
Undetermined	4,628 (30.6%)	220 (25.8%)	4,408 (30.9%)		2,141 (36.6%)	101 (30.7%)	2040 (37%)		2,487 (26.8%)	119 (22.7%)	2,368 (27%)	

Abbreviations: ACA1/2 = first and second segments of anterior cerebral artery; ASPECTS = Alberta Stroke Program Early CT Score; BA = basilar artery; EVT = endovascular treatment; ICA = internal carotid artery; IVT = intravenous thrombolysis; LTSW = last time seen well; M1/2/3/3 = first, second, and third segments of middle cerebral artery; mRS = modified Rankin scale; NIHSS = NIH Stroke Scale; PCA = first and second segments of posterior cerebral artery; SBP = systolic blood pressure; V4 = fourth segment of vertebral artery. Values are presented as median (interquartile range) or as numbers (proportions).
[a] In posterior circulation stroke, it corresponds to posterior circulation ASPECTS.

rate of SICH (OR 1.53; 95% CI 1.16–2.01), SSAH (OR 1.80; 95% CI 1.20–2.69), and SICH/SSAH (OR 1.56; 95% CI 1.23–1.99). They also had higher 24-hour mortality rates (OR 2.47; 95% CI 1.58–3.86) and 3-month mortality rates (OR 1.88; 95% CI 1.52–2.33), worse 3-month mRS shift (OR 1.42; 95% CI 1.26–1.60), and 3-month favorable outcomes (OR 1.48; 95% CI 1.22–1.78) (Figure 1 and eFigure 1, links.lww.com/WNL/C428). The analysis performed only on patients with a complete data set gave similar results (eTable 3, links.lww.com/WNL/C428).

In patients with 24-hour mortality, patients with COVID-19 did not have a statistically significant higher rate of SICH/SSAH (OR 2.07; 95% CI 0.93–4.61) (eTable 4, links.lww.com/WNL/C428).

The same outcome differences were found in the analysis stratified by treatment subgroup, except for the nonsignificant association with SSAH, SICH/SSAH, and 24-hour mortality in the IVT-only group ([OR 0.80; 95% CI 0.26–2.47], [OR 1.48; 95% CI 0.94–2.33], and [OR 2.89; 95% CI 0.93–8.98], respectively; Figure 1).

In the EVT subgroup, bridging–COVID-19 patients showed an increased risk of SICH, SSAH, and SICH/SSAH, in contrast to DMT–COVID-19 patients who did not (Figure 2). However, the interaction analysis with IVT did not show statistically significant differences. The baseline features of bridging and DMT patients are presented in eTable 5 (links.lww.com/WNL/C428). No statistically significant differences were found when we analyzed the presence of hemorrhagic transformation according to ECASS II subgroups (eTable 6).

Discussion

In our large cohort study designed to assess the safety and outcome of acute revascularization treatment in patients with AIS and COVID-19, we found that these patients had higher rates of SICH, SSAH, 24-hour and 3-month mortality, and worse 3-month functional outcomes than contemporaneous patients without COVID-19 receiving treatment.

A previous large observational study showed that patients with COVID-19 probably have an increased risk of intracranial hemorrhage,[25] which is in line with the increased risk of ICH and SSAH after revascularization treatment for AIS. Endothelial dysfunction is likely a main mechanism of this observation.[2,3] SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor, causing ACE2 depletion, which in turn is associated with increased bradykinin levels promoting endothelial tight junction disruption, and therefore increased blood-brain barrier permeability. SARS-CoV2 infection was also shown to induce hyperfibrinolysis due to excessive plasmin-mediated fibrin cleavage.[2] Hyperfibrinolysis additionally promotes blood-brain barrier

Table 2 Treatment Characteristics of EVT Patients

Variables	Total (n = 9,280)	COVID-19 (n = 524)	Controls (n = 8,756)	*p* Value
Revascularization treatment				0.024
Direct EVT	4,841 (52.2%)	299 (57.1%)	4,542 (51.9%)	
Bridging	4,439 (47.8%)	225 (42.9%)	4,214 (48.1%)	
LTSW-to-puncture	352.5 (251.4)	352.6 (254.6)	352.5 (251.2)	0.998
General anesthesia	3,342 (36.4%)	236 (45.2%)	3,106 (35.9%)	<0.001
Final mTICI score				<0.001
0	688 (7.5%)	46 (8.8%)	642 (7.4%)	
1	185 (2.0%)	21 (4.0%)	164 (1.9%)	
2a	482 (5.2%)	40 (7.6%)	442 (5.1%)	
2b	2,322 (25.3%)	131 (25.0%)	2,191 (25.3%)	
2c	993 (10.8%)	65 (12.4%)	928 (10.7%)	
3	4,510 (49.1%)	221 (42.2%)	4,289 (49.5%)	
Successful recanalization (mTICI ≥2b)	7,825 (85.2%)	417 (79.6%)	7,408 (85.6%)	<0.001
First pass effect	2,549 (28%)	124 (23.7%)	2,425 (28.3%)	0.026
Number of device passes				0.032
0	456 (5.1%)	17 (3.3%)	439 (5.2%)	
1	3,939 (44.1%)	215 (41.3%)	3,724 (44.3%)	
2	2023 (22.7%)	115 (22.1%)	1908 (22.7%)	
3	1,256 (14.1%)	84 (16.1%)	1,172 (13.9%)	
>3	1,253 (14%)	90 (17.3%)	1,163 (13.8%)	
LTSW-to-reperfusion	401.3 (251.5)	400 (256.2)	401.4 (251.3)	0.905
Procedure duration	51.4 (41.2)	49.8 (36.4)	51.5 (41.5)	0.313

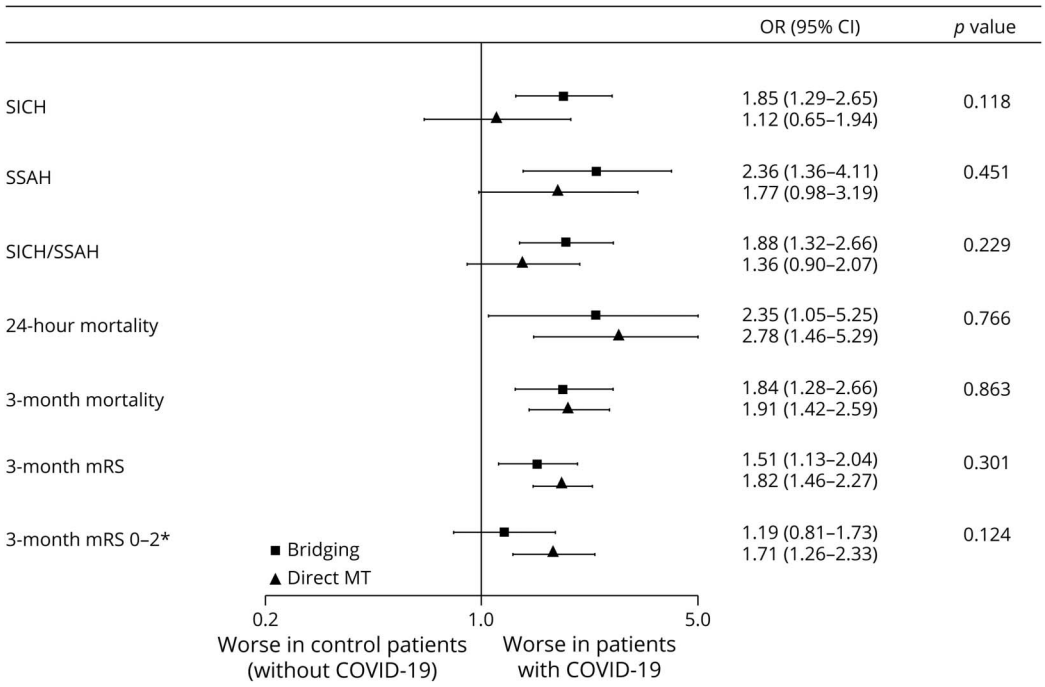
Values are presented as median (interquartile range) or as numbers (proportions). IVT, intravenous thrombolysis; EVT, endovascular treatment; LTSW, last time seen well; mTICI, modified treatment in cerebral infarction.

permeability in a bradykinin-dependent manner.[26] In addition, vasculitis and leukoencephalopathy similar to posterior reversible encephalopathy were described in anatomopathological studies of patients with COVID-19 and associated with an excess of hemorrhagic lesion.[27] Other pathophysiologic mechanisms, such as increased systemic inflammation independent of SARS-CoV2 infection,[28] may also explain the higher rate of cerebral bleeding complications in our cohort. Of note, a higher risk of hemorrhagic transformation may also be present in patients with recent infections by other pathogens.[29]

In the treatment subgroup analysis, both IVT-only and EVT patients had an increased risk of ICH, while only EVT patients showed an increased risk of SSAH. Indeed, the higher bleeding risks in EVT patients could also derive from the above-discussed COVID-19 pathophysiologic mechanisms that can affect larger arteries, bringing more vulnerability for EVT procedure-related complications. A previous study has documented a vessel perforation rate of 5.5% in patients with COVID-19 and AIS,[18] not different from that described in unselected AIS patients without COVID-19, although the definition of vessel perforation and other procedural complications are not uniformly defined in the current literature.[30] A higher number of device passes in our patients with COVID-19 may result in higher degree of endothelial injury and bleeding risk. Finally, although the risk of SSAH in IVT-treated patients with COVID-19 did not seem to be increased, the proportion of this complication was very rare in both groups, meaning insufficient power to make definite conclusions. In line with our results, 2 previous small studies indicated an increased risk of bleeding complications after IVT and EVT in patients with COVID-19.[13,15]

Given the increased risk of SICH in the IVT group, we also investigated whether bridging was associated with a higher risk of intracranial hemorrhage than DMT. In this subgroup

Figure 2 Forest Plot of Intracranial Bleeding Complications, Mortality, and Disability Comparing Patients With COVID-19 and Controls in Bridging and Direct Mechanical Thrombectomy Treatments



*Or mRS equal to prestroke mRS, if > 2. mRS, modified Rankin Scale; MT, mechanical thrombectomy; SICH, symptomatic intracerebral hemorrhage; SSAH, symptomatic subarachnoid hemorrhage.

analysis, patients undergoing DMT had a nonsignificant lower risk of hemorrhagic complications in comparison with bridging, despite a numerically lower risk. This finding is similar to non–COVID-19 patients undergoing EVT.[31]

We found an increased 24-hour mortality risk in revascularized patients with COVID-19, with more than a third of the mortality being explained by the higher intracranial hemorrhage risk. Poorer posttreatment reperfusion due to microvascular thrombo-inflammation or endotheliitis[12] and early stroke recurrence[9] are potential additional contributors for the worse short-term and medium-term outcomes in patients with AIS and COVID-19.

Regarding larger arteries and their recanalization, previous studies have reported inconsistent data concerning EVT revascularization results in patients with COVID-19, with successful recanalization ranging from 56% to 100%[9,12-14,17,19] and first pass effect from 0% to 35.6%.[12,18] The procoagulant and proinflammatory states associated with COVID-19–related endothelial dysfunction[2] likely contribute to a higher clot burden and more difficult recanalization. In addition, small case series has described a high rate of clot fragmentation with distal embolization and repeated vessel occlusion in patients with COVID-19,[16,17] phenomena that can also add to the poorer EVT results. Together with a myriad of multisystem complications associated with COVID-19 and prolonged hospital stay,[6,11] the lower recanalization rate likely contributes to our findings of poorer short-term and medium-term outcomes in patients with COVID-19.

In our study, we did not find delays to revascularization treatment previously described in patients with AIS and COVID-19[8,9,13] and proposed as a factor contributing to the worse clinical outcomes. The centers in this study seem to have caught up with such delays during the long period of patient recruitment, which speaks to the resilience of many stroke systems because they learned to adapt to the COVID-19 surges, in contrast to the first months of the pandemic.

The strengths of our analysis are the large sample size with a low proportion of missing data, allowing for adjustments of multiple potential confounders. We enhanced representativeness by including patients from 30 countries across 5 continents. The use of the doubly robust statistical analyses may have helped to reduce multiple confounding biases.

Our study has limitations. Due to its retrospective design, registration bias cannot be excluded. It is likely that academic centers participated more in our study than primary stroke centers. Reporting bias, namely for outcomes, may have been influenced by the nonblinded assessment. As stated above, our clinical outcomes also depended on systemic COVID-19–related complications, not assessed in our study. Similarly, some patients with COVID-19 were possibly treated outside the usual stroke care systems, with potential effect on outcome, and this information is lacking. We were not able to collect data on the precise virus variants, pandemic waves, and vaccination status of our patients, which could have

influenced our results. The presence of renal failure and collaterals, known to be associated with patients' outcomes, were not assessed, and therefore not included in our models. Finally, our study design did not allow direct conclusions to be made on the effectiveness of revascularization treatments in patients with COVID-19 because we did not include an untreated comparison group.

In our international retrospective cohort study, patients with AIS and COVID-19 receiving revascularization treatment had higher rates of cerebral bleeding complications and worse short-term and medium-term clinical outcomes than contemporary AIS controls without COVID-19. The relatively large margin of benefit of revascularization treatments, in particular of EVT, and the rather small absolute numbers of symptomatic hemorrhage in patients with AIS and COVID-19 make it likely that revascularization treatments remain beneficial for these patients. Therefore, we suggest that these treatments continue to be given as rapidly as possible to patients with COVID-19 using the current treatment recommendations.

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