Safety and outcome of revascularization treatment in patients with acute ischemic stroke and COVID-19: the Global COVID-19 Stroke Registry

Marto, J.P.; Strambo, D.N.; Ntaios, G.; Nguyen, T.; Herzig, R.; Czlonkowska, A.; ... ; Global Covid-19 Stroke Registry

RESEARCH ARTICLE

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

The Global COVID-19 Stroke Registry

João Pedro Marto, MD,* Davide Strambo, MD,* George Ntaios, MD, Thanh N. Nguyen, MD, FRCPC, Roman Herzig, MD, PhD, Anna Czlonkowska, MD, PhD, Jelle Demeestere, MD, Ossama Yassin Mansour, MD, PhD, Alexander Salerno, MD, Susanne Wegener, MD, Philipp Baumgartner, MD, Carlo W. Cereda, MD, Giovanni Bianco, MD, Morin Beyeler, MD, Marcel Arnold, MD, Emmanuel Carrera, MD, Paolo Machi, MD, Valerian Altersberger, MD, Leo Bonati, MD, Henrik Gensicke, MD, Manuel Bolognese, MD, Nils Peters, MD, Stephan Wetzel, MD, Marta Magriço, MD, João Nuno Ramos, MD, João Sargento-Freitas, MD, Rita Machado, MD, Carolina Maia, MD, Egídio Machado, MD, Ana Paiva Nunes, MD, Patricia Ferreira, MD, Teresa Pinho e Melo, MD, Mariana Carvalho Dias, MD, André Paula, MD, Manuel Alberto Correia, MD, et al.

Correspondence
Dr. Marto
joao.pedro.seabra.marto@gmail.com

Neurology® 2023;100:e739-e750. doi:10.1212/WNL.0000000000201537

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.

MORE ONLINE

COVID-19 Resources
For the latest articles, invited commentaries, and blogs from physicians around the world
NPub.org/COVID19

CME Course
NPub.org/cmelist

*These authors contributed equally to this work.

The Author Byline is continued at the end of the article.

Author affiliations appear at the end of the article.

Authors, their locations, and their contributions are listed at links.lww.com/WNL/C618

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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).

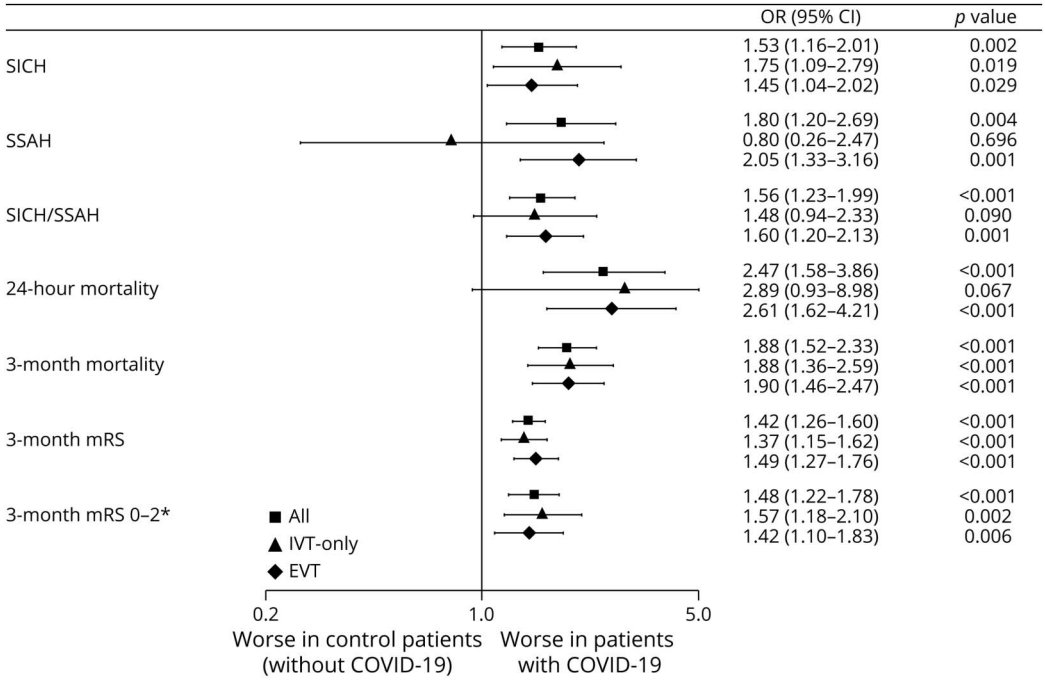
We performed a further analysis in the EVT group to evaluate the potential heterogeneity of a COVID-19 effect on outcomes in bridging vs direct mechanical thrombectomy (DMT) patients. We assessed this by adding an interaction term between COVID-19 status and IVT to the multivariable logistic regression 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				0.155
None	2,462 (19.2%)	133 (17.9%)	2,329 (19.3%)		2,462 (60.5%)	133 (56.8%)	2,329 (60.7%)					
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

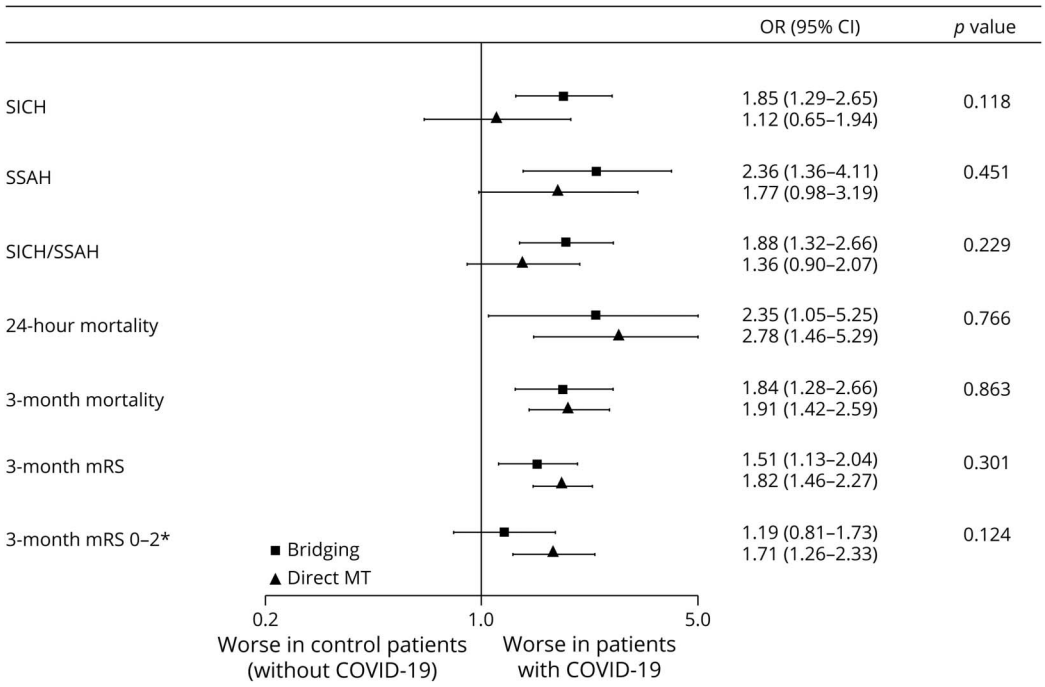
Values are presented as median (interquartile range) or as numbers (proportions). IVT, intravenous thrombolysis; EVT, endovascular treatment; LTSW, last time seen well; mTICI, modified treatment in cerebral infarction.

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.

Author Byline *(Continued)*

Pedro Castro, MD, PhD, Elsa Azevedo, MD PhD, Luís Albuquerque, MD, José Nuno Alves, MD, Joana Ferreira-Pinto, MD, Torcato Meira, MD, Liliana Pereira, MD, Miguel Rodrigues, MD, Andre Pinho Araujo, MD, Marta Rodrigues, MD, Mariana Rocha, MD, Ângelo Pereira-Fonseca, MD, Luís Ribeiro, MD, Ricardo Varela, MD, Sofia Malheiro, MD, Manuel Cappellari, MD, Cecilia Zivelonghi, MD, Giulia Sajeva, MD, Andrea Zini, Mauro Gentile, MD, Stefano Forlivesi, Ludovica Migliaccio, MD, Maria Sessa, MD, Sara La Gioia, MD, Alessandro Pezzini, MD, Davide Sangalli, MD, Marialuisa Zedde, MD, Rosario Pascarella, MD, Carlo Ferrarese, MD, PHD, Simone Beretta, MD, Susanna Diamanti, MD, Ghil Schwarz, MD, Giovanni Frisullo, MD, Simona Marcheselli, MD, Pierre Seners, MD, Candice Sabben, MD, Simon Escalard, MD, Michel Piotin, MD, PhD, Benjamin Maïer, MD, MSc, Guillaume Charbonnier, MD, Fabrice Vuillier, MD, Loïc Legris, Pauline Cuisenier, MD, Francesca R. Vodret, MD, Gaultier Marnat, MD, Jean-Sebastien Liegey, MD, Igor Sibon, MD, PhD, Fabian Flottmann, MD, Gabriel Broocks, MD, Nils-Ole Gloyer, MD, Ferdinand O. Bohmann, MD, Jan Hendrik Schaefer, MD, Christian Nolte, MD, Heinrich J. Audebert, MD, Eberhard Siebert, MD, Marek Sykora, MD, Wilfried Lang, MD, Julia Ferrari, MD, Lukas Mayer-Suess, MD, Michael Knoflach, MD, Elke Ruth Gizewski, MD, Jeffrey Stolp, MD, Lotte J. Stolze, MD, Jonathan M. Coutinho, MD, PhD, Paul Nederkoorn, MD PhD, Ido van den Wijngaard, MD, PhD, Joke De Meris, MD, Robin Lemmens, MD, Sylvie De Raedt, MD, PhD, Fenne Vandervorst, MD, Matthieu Pierre Rutgers, MD, Antoine Guilmot, MD, Anne Dusart, MD, Flavio Bellante, MD, Patricia Calleja-Castaño, MD, Fernando Ostos, MD, Guillermo González-Ortega, MD, Paloma Martín-Jiménez, MD, Sebastian García-Madrona, MD, Antonio Cruz-Culebras, MD, Rocio Vera, MD, Maria Consuelo Matute, MD, Blanca Fuentes, MD, María Alonso-de-Leciñana, MD, Ricardo Rigual, MD, Exuperio Díez-Tejedor, MD, Soledad Perez-Sanchez, MD, Joan Montaner, MD, PhD, Fernando Díaz-Otero, MD, Natalia Pérez-de-la-Ossa, MD, Belén Flores-Pina, MD, Lucia Muñoz-Narbona, MD, Angel Chamorro, MD, PhD, Alejandro Rodríguez-Vázquez, MD, Arturo Renú, MD, PhD, Oscar Ayo-Martin, MD, PhD, Francisco Hernández-Fernández, MD, PhD, Tomas Segura, MD, Herbert Tejada-Meza, MD, Daniel Sagarra-Mur, MD, Marta Serrano-Ponz, MD, Thant Hlaing, MD, Isaiah See, MD, Robert Simister, MD, David Werring, FRCP, PhD, Espen Saxhaug Kristoffersen, MD, PhD, Annika Nordanstig, MD, PhD, Katarina Jood, MD, Alexandros Rentzos, MD, Libor Šimůnek, MD, Dagmar Krajíčková, MD, Antonín Krajina, MD, Robert Mikulik, MD, PhD, Martina Cviková, MD, Jan Vinklárek, MD, David Školoudík, MD, Martin Roubec, MD, Eva Hurtikova, MD, Rostislav Hrubý, MD, Svatopluk Ostry, MD, Ondrej Skoda, MD, Marek Pernicka, MD, Lubomir Jurak, MD, PhD, Zuzana Eichlová, MD, Martin Jíra, MD, Martin Kovar, MD, Michal Panský, MD, Pavel Mencl, MD, Hana Palouskova, MD, Aleš Tomek, MD, Petr Janský, MD, Anna Olšerová, MD, Martin Sramek, MD, Roman Havlicek, MD, Petr Malý, MD, Lukáš Trakal, MD, Jan Fiksa, MD, Matěj Slovák, MD, Michal Adam Karlinski, MD, PhD, Maciej Nowak, MD, Halina Sienkiewicz-Jarosz, MD, Anna Bochynska, MD, Pawel Wrona, MD, Tomasz Homa, MD, Katarzyna Sawczynska, MD, Agnieszka Slowik, MD, PhD, Ewa Wlodarczyk, MD, Marcin Wiacek, MD, Izabella Tomaszewska-Lampart, MD, Bartosz Sieczkowski, MD, Halina Bartosik-Psujek, MD, Marta Bilik, MD, Anna Bandzarewicz, MD, Malgorzata Dorobek, MD, PhD, Justyna Zielinska-Turek, MD, Marta Nowakowska-Kotas, MD, Krystian Obara, MD, Paweł Urbanowski, MD, Slawomir Budrewicz, MD, Maciej Guziński, MD, Milena Świtońska, MD, Iwona Rutkowska, MD, Paulina Sobieszak-Skura, MD, Beata M. Labuz-Roszak, MD, PhD, Aleksander Debiec, MD, Jacek Staszewski, MD, Adam Stępień, MD, Jacek Zwiernik, MD, Grzegorz Wasilewski, MD, Cristina Tiu, MD, Elena Oana Terecoasă, MD, Razvan Alexandru Radu, MD, Anca Negrila, MD, Bogdan Dorobat, MD, Cristina Panea, MD, Vlad Tiu, MD, Simona Petrescu, MD, Atilla Ozdemir, MD, Mostafa Mahmoud, MD, Hussam El-Samahy, MD, Hazem Abdelkhalek, MD, Jasem Al-Hashel, MD, Ismail Ibrahim Ismail, MD, Athari Salmeen, MD, Abdoreza Ghoreishi, MD, Sergiu Ionut Sabetay, MD, Hana Gross, MD, Piers Klein, Mohamad Abdalkader, MD, Pascal Jabbour, MD, Kareem El Naamani, MD, Stavropoula Tjoumakaris, MD, Rawad Abbas, MD, Ghada A. Mohamed, MD, Alex Chebl, MD, Jiangyong Min, MD, Majesta Hovingh, MD, Jenney P. Tsai, MD, Muhib Khan, MD, Krishna Nalleballe, MD, Sanjeeva Onteddu, MD, Hesham Masoud, MD, Mina Michael, MD, Navreet Kaur, MD, Laith Maali, MD, Michael G. Abraham, MD, Priyank Khandelwal, MD, Ivo Bach, MD, Melody Ong, MD, Denis Babici, MD, Ayaz M. Khawaja, MD, Maryam Hakemi, BSN, MS, AGNP, Kumar Rajamani, MD, Vanessa Cano-Nigenda, MD, Antonio Arauz, MD, PhD, Pablo Amaya, MD, Natalia Llanos, MD, Akemi Arango, MD, Miguel Ángel Vences, MD, Jose Dominguo Barrientos Guerra, MD, Rayllene Caetano, MD, Rodrigo Targa Martins, MD, Sergio Daniel Scollo, MD, Patrick Matic Yalung, MD, Shashank Nagendra, MD, Abhijit Gaikwad, MD, Kwon-Duk Seo, MD, Georgios Georgiopoulos, MD, Raul G. Nogueira, MD, Patrik Michel, MD, PhD, and the Global COVID-19 Stroke Registry

Affiliation

Department of Neurology (J.P.M., M.M.), Hospital de Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal; Stroke Centre (D.S., A.S., P.M.), Neurology Service, Department of Neurological Sciences, Lausanne University Hospital, Switzerland; Department of Internal Medicine (G.N.), Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece; Department of Neurology, Radiology (T.N.N.), Boston Medical Center, Boston University School of Medicine, MA; Department of Neurology (R.H., L.S., D.K.), Comprehensive Stroke Centre, Charles University Faculty of Medicine and University Hospital, Hradec Králové, Czech Republic; 2nd Department of Neurology (A.C., M.A.K., M.N.), Institute of Psychiatry and Neurology, Warsaw, Poland; Neurology Department (J.D., R.L.), Leuven University Hospital, Belgium; Alexandria University Hospitals and Affiliated Stroke Network (O.Y.M.), Egypt; Department of Neurology (S.W., P.B.), University Hospital of Zurich, Switzerland; Stroke Center (C.W.C., G.B.), Neurocenter of Southern Switzerland, EOC, Lugano; Stroke Center (M.B, M.A.), Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland; Stroke Centre (E.C.), Geneva University Hospital, Switzerland; Department of Neuroradiology (P.M.), Geneva University Hospital, Switzerland; Stroke Centre (V.A, L.B., H.G.), University Hospital Basel and University of Basel, Switzerland; Stroke Centre (M.B.), Kantonsspital Lucerne, Switzerland; Stroke Centre (N.P., S.W.), Hirslanden Hospital, Zurich, Switzerland; Department of Neuroradiology (J.N.R.), Hospital de Egas

Moniz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal; Department of Neurology (J.S.-F., R.M., C.M.), Centro Hospitalar Universitário de Coimbra, Portugal; Department of Neuroradiology (E.M.), Centro Hospitalar Universitário de Coimbra, Portugal; Stroke Unit (A.P.N., P.F.), Hospital de São José, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal; Stroke Unit (T.P.e.M., M.C.D., A.P.), Department of Neurology, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal; Department of Neuroradiology (M.A.C.), Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal; Department of Neurology (P.C., E.A.), Centro Hospitalar Universitário São João, Porto, Portugal; Department of Neuroradiology (L.A.), Centro Hospitalar Universitário São João, Porto, Portugal; Departments of Neurology (J.N.A., J.F.-P.), and Neuroradiology (T.M.), Hospital de Braga, Portugal; Department of Neurology (L.P., M.R.), Hospital Garcia de Orta, Almada, Portugal; Department of Neuroradiology (A.P.A., M.R.), Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal; Department of Neurology (M.R.), Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal; Department of Neurology (A.P.-F, L.R.), Unidade Local de Saúde de Matosinhos, Portugal; Department of Neurology (R.V., S.M.), Centro Hospitalar Universitário do Porto, Portugal; Stroke Unit (M.C., C.Z.), Azienda Ospedaliera Universitaria Integrata, Verona, Italy; IRCCS Istituto delle Scienze Neurologiche di Bologna (A.Z., M.G., S.F., L.M.), Department of Neurology and Stroke Centre, Maggiore Hospital, Bologna, Italy; Department of Neurology (M.S., S.L.G.), ASST Papa Giovanni XXIII, Bergamo, Italy; Department of Clinical and Experimental Sciences (A.P.), Neurology Clinic, University of Brescia, Italy; Department of Neurology and Stroke Unit (D.S.), Azienda Socio Sanitaria Territoriale, Lecco, Italy; Neurology Unit (M.Z.), Stroke Unit, Azienda Unità Sanitaria-IRCCS di Reggio Emilia, Italy; Neuroradiology Unit (R.P.), Azienda Unità Sanitaria-IRCCS di Reggio Emilia, Italy; Department of Neurology (C.F., S.B., S.D.), San Gerardo Hospital, Department of Medicine and Surgery and Milan Centre for Neuroscience, University of Milano Bicocca, Monza, Italy; Stroke Unit (G.S.), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; Department of Neurology (G.F.), Policlinico Universitario Agostino Gemelli, Rome, Italy; Emergency Neurology and Stroke Unit (S.M.), IRCCS Humanitas Clinical and Research Center, Rozzano, Italy; Department of Neurology (C.S., S.E.), Hôpital Fondation Ade Rothschild, Paris, France; Department of Interventional Neuroradiology (M.P., B.M.), Hôpital Fondation Ade Rothschild, Paris, France; Department of Interventional Neuroradiology (G.C., F.V.), Centre Hospitalier Régional Universitaire, Hôpital Jean Minjoz, Besançon, France; Neurology (F.L., P.C, F.R.V.), Stroke Unit, Centre Hospitalier Universitaire, Grenoble Alpes, France; Department of Interventional and Diagnostic Neuroradiology (J.-S.L., I.S.), Bordeaux University Hospital, France; Department of Diagnostic and Interventional Neuroradiology (F.F, G.B., N.-O.G.), University Medical Center-Hamburg-Eppendorf, Germany; Department of Neurology (F.O.B., J.H.S.), University Hospital Frankfurt, Goethe University, Germany; Department of Neurology and Centre for Stroke Research (H.J.A.), Berlin Institute of Health, Charité-Universitätsmedizin Berlin, Germany; Department of Neuroradiology (E.S.), Charité-Universitätsmedizin Berlin, Germany; Department of Neurology (M.S, W.L., J.F.), St. John's Hospital, Vienna, Austria; Departments of Neurology (L.M.-S., M.K.), and Neuroradiology (E.R.G.), Medical University of Innsbruck, Austria; Department of Neurology (J.S., L.J.S., J.M.C.), Amsterdam University Medical Centers, Netherlands; Department of Neurology (I.v.d.W., J.d.M.), Haaglanden Medical Centre, Hague and Department of Radiology, Leiden University Medical Centre, Netherlands; Department of Neurology (S.D.R., F.V.), Universitair Ziekenhuis Brussel, Centre for Neurosciences, Vrije Universiteit Brussel, Belgium; Department of Neurology (M.P.R, A.G.), Stroke Unit, Europe Hospitals, Brussels, Belgium; Department of Neurology (A.D., F.B.), Centre Hospitalier Universitaire de Charleroi, Belgium; Department of Neurology and Stroke Centre (P.C.-C., F.O., P.M.-J.), Hospital Universitario de OctubreInstituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain; Department of Neurology and Stroke Centre (A.C.-C., R.V., M.C.M.), Hospital Universitario Ramón y Cajal, Ramon y Cajal Institute for Health Research (IRYCIS), Madrid, Spain; Department of Neurology and Stroke (B.F, M.A.d.L., R.R., E.D.D.), Centre Hospital La Paz Institute for Health Research-IdiPAZ (La Paz University Hospital-Universidad Autónoma de Madrid), Spain; Department of Neurology (S.P.-S., J.M.), Hospital Universitario Virgen Macarena, Seville, Spain; Stroke Centre (F.D-.O.), Hospital General Universitario Gregorio Marañón, Madrid, Spain; Stroke Unit (B.F.-P., J.M.-N.), Germans Trias Hospital, Barcelona, Spain; Department of Neurology (A.C, A.R.-V., A.R), Comprehensive Stroke Centre, Hospital Clinic from Barcelona, Spain; Department of Neurology (O.A.-M, F.H.-F.), Complejo Hospitalario Universitario de Albacete; Stroke Unit (H.T.-M.), Department of Neurology, and Interventional Neuroradiology Unit, Hospital Universitario Miguel Servet, Spain; Stroke Unit (D.S.-M, M.F.P.), Department of Neurology, Hospital Universitario Miguel Servet, Spain; Stroke and Geriatric Medicine (T.H.), Aintree University Hospital, United Kingdom; Comprehensive Stroke Service (I.S., R.S.), University College London Hospitals NHS Foundation Trust and Stroke Research Centre, University College London, United Kingdom.; University College London (D.W.), Queen Square Institute of Neurology, London, United Kingdom; Department of Neurology (E.S.K.), Akershus University Hospital, Lørenskog and Department of General Practice, University of Oslo, Norway; Department of Clinical Neuroscience (A.N, K.J.), Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology (A.N, K.J.), Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden; Department of Radiology (A.R.), Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg and Department of Interventional and Diagnostic Neuroradiology, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden; Department of Radiology (A.K.), Comprehensive Stroke Centre, Charles University Faculty of Medicine and University Hospital, Hradec Králové, Czech Republic; International Clinical Research Centre (R.M., M.C., J.V.) and Department of Neurology, St. Anne´s University Hospital and Faculty of Medicine at Masaryk University, Brno, Czech Republic; Center for Health Research (D.S., M.R, E.H.), Faculty of Medicine, University of Ostrava, Czech Republic; Department of Neurology (R.H, S.V.), České Budějovice Hospital, Czech Republic; Department of Neurology (O.S., M.P.), Jihlava Hospital, Czech Republic; Neurocenter (L.J., Z.E., M.J.), Regional Hospital Liberec, Czech Republic; Cerebrovascular Centre (M.K., M.P., P.M.), Na Homolce Hospital, Prague, Czech Republic; Department of Neurology (H.P.), Karviná Miners Hospital Inc., Czech Republic; Cerebrovascular Centre (A.T, P.J, A.O.), University Hospital in Motol, Prague, Czech Republic; Cerebrovascular Centre (M.S., R.H, P.M., L.T.), Central Military Hospital, Prague, Czech Republic; Cerebrovascular Centre (J.F., M.S.), General University Hospital, Prague, Czech Republic; 1th Department of Neurology (H.S.-J, A.B.), Institute of Psychiatry and Neurology, Warsaw, Poland; Department of Neurology (P.W, T.H., K.S., A.S), University Hospital, Jagiellonian University, Cracow, Poland; Department of Neurology (M.W., L.T.-L., B.S.), Institute of Medical Sciences, Medical College of Rzeszow University, Poland; Department of Neurology and Stroke (M.B, A.B.), St. John Paul II Western Hospital, Grodzisk Mazowiecki, Poland; Department of Neurology (M.D, J.Z.), Central Clinical Hospital of the Ministry of the Interior and Administration, Warsaw, Poland; Departments of Neurology (M.N.-K., K.O., P.U.), and Radiology (M.G.), Wroclaw Medical University, Poland; Department of Neurosurgery and Neurology (M.S.), Nicolaus Copernicus University in Torun Ludwik Rydygier Collegium Medicum, Bydgoszcz, Poland; Stroke Intervention Centre (I.R., P.S.-S.), Department of Neurosurgery and Neurology, Jan Biziel University Hospital, Bydgoszcz, Poland; Department of Neurology (B.M.L.-R.), Institute of Medical Sciences, University of Opole, Poland; Clinic of Neurology (A.D., J.S., A.S.), Military Institute of Medicine, Warsaw, Poland; Department of Neurology (J.Z.), University of Warmia and Mazury, Olsztyn, Poland; Department of Radiology (C.W.), Provincial Specialist Hospital, Olsztyn, Poland; Department of Neurology (C.T., E.O.T., R.A.R., A.N.), University Emergency Hospital Bucharest, University of Medicine and Pharmacy "Carol Davila", Romania; Department of Radiology (B.D.), University Emergency Hospital Bucharest, Romania; Department of Neurology and Stroke Unit (C.P, V.T, S.P.), Elias University Emergency Hospital, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania; Department of Neurology (A.O.), Eskisehir Osmangazi University, Turkey; Ain Shams University Affiliated Saudi German Hospital (M.M., H.E.-S.), Egypt; Neuropsychiatry Department (H.A.), Tanta University, Egypt; Department of Neurology (J.A.-H.), Ibn Sina Hospital, Kuwait; Department of Neurology (I.I.I.), Jaber Al-Ahmad Hospital, Kuwait; Department of Neurology (A.G.), School of Medicine, Zanjan University of Medical Sciences, Iran; Stroke Unit (S.I.S.), Neurology Department, Hillel Yaffe Medical Center, Hadera, Israel; Department of Neurosurgery (P.J., K.E.N, S.T., R.A.), Thomas Jefferson University Hospital, PA; Departments of Radiology (G.A.M., P.G.N.), Neurology and Neurosurgery, Grady Memorial Hospital, Atlanta, GA; Department of Neurology (A.C.), Henry Ford Hospital, Detroit, MI; Comprehensive Stroke Centre and Department of Neurosciences (J.M., M.H., M.K.), Spectrum Health and Michigan State University; Department of Neurology (K.N., S.O.), University of Arkansas for Medical Sciences, Little Rock, AR; Department of Neurology (M.K.), Upstate University Hospital, NY; Department of Neurology (L.M., M.G.A.), University of Kansas Medical Centre; Endovascular Neurological Surgery and Neurology (P.K., I.B, M.O., M.B.), Rutgers, The State University of New Jersey, Newark; Department of Neurology (A.M.K.), Wayne State University, Detroit Medical Center, MI; Stroke Clinic (V.C.-N, A.A.), Instituto Nacional de Neurologia y Neurocirugia Manuel Velasco Suarez, Mexico City, Mexico; Department of Neurology (P.A.), Fundación Valle del Lili, Cali, Colombia; Centro de Investigaciones Clínicas (N.L., A.A.), Fundación Valle del Lili, Cali, Colombia; Department of Neurology (M.A.V.), Hospital Nacional Edgardo Rebagliati Martins, EsSalud, Lima, Péru; Hospital General San Juan de Dios (J.D.B.G.), Guatemala; Department of Neurology (R.C., R.T.M.), Hospital Nossa Senhora da Conceição Hospital, Porto Alegre, Brazil; Ramos Mejía Hospital (S.D.S.), Stroke Unit, Buenos Aires, Argentina; St. Luke's Medical Center (P.M.Y.), Global City, Philippines; Department of Neurology (S.N., A.G.), Grant Medical College and Sir JJ Hospital, Mumbai, India; Department of Neurology (K.-D.S.), National Health Insurance Service Ilsan Hospital, Goyang, Korea; School of Biomedical Engineering and Imaging Sciences (G.G.), St Thomas Hospital, King's College London, UK; Department of Clinical Therapeutics (G.G.), National and Kapodistrian University of Athens, Greece.

Acknowledgment

The authors thank Melanie Price Hirt for English language correction and editing.

Study Funding

The Czech national stroke registry is supported by STROCZECH within CZECRIN Large Research Infrastructure (No. LM2018128) funded by the state budget of the Czech Republic.

Disclosure

R. Herzig: Research grants from the Ministry of Health of the Czech Republic (grant number DRO—UHHK 00179906) and Charles University, Czech Republic (grant number PROGRES Q40). C. Nolte: Research grants from German Ministry of Research and Education, German Center for Neurodegenerative Diseases, and German Center for cardiovascular Research; speaker and/or advisory fees from Abbott, Alexion, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer Pharma. S. Tjoumakaris: Advisory fees from Medtronic and MicroVention. J. Min: Advisory fees from Medtronic and Abbott. M. Khan: Research grants from National Institute of Health, Spectrum Health-Michigan State

University Research Alliance, and Genentech for research. P. Michel: Research grants from the Swiss National Science Foundation and Swiss Heart Foundation. All the other authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* April 27, 2022. Accepted in final form September 23, 2022. Submitted and externally peer reviewed. The handling editor was José Merino, MD, MPhil, FAAN.

Appendix Authors

Authors, their locations, and their contributions are listed at links.lww.com/WNL/C618.

References

1. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with Coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683-690.
2. Sashindranath M, Nandurkar HH. Endothelial dysfunction in the brain: setting the stage for stroke and other cerebrovascular complications of COVID-19. *Stroke.* 2021;52(5):1895-1904.
3. Sagris D, Papanikolaou A, Kvernland A, et al. COVID-19 and ischemic stroke. *Eur J Neurol.* 2021;28(11):3826-3836.
4. Mbonde AA, O'Carroll CB, Grill MF, Zhang N, Butterfield R, Demaerschalk BM. Stroke features, risk factors, and pathophysiology in SARS-CoV-2-infected patients. *Mayo Clinic Proc Innov Qual Outcomes.* 2022;6(2):156-165.
5. Ntaios G, Michel P, Georgiopoulos G, et al. Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: the global COVID-19 stroke registry. *Stroke.* 2020;51(9):e254–e258.
6. Dhamoon MS, Thaler A, Gururangan K, et al. Acute cerebrovascular events with COVID-19 infection. *Stroke.* 2021;52(1):48-56.
7. Perry RJ, Smith CJ, Roffe C, et al. Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case-control study. *J Neurol Neurosurg Psychiatry.* 2021;92(3):242-248.
8. Srivastava PK, Zhang S, Xian Y, et al. Acute ischemic stroke in patients with COVID-19: an analysis from get with the guidelines-stroke. *Stroke.* 2021;52(5):1826-1829.
9. Fuentes B, Alonso de Leciñana M, García-Madrona S, et al. Stroke acute management and outcomes during the COVID-19 outbreak: a cohort study from the madrid stroke network. *Stroke.* 2021;52(2):552-562. doi: 10.1161/strokeaha.120.031769
10. Strambo D, De Marchis GM, Bonati LH, et al Ischemic stroke in COVID-19 patients: mechanisms, treatment, and outcomes in a consecutive Swiss Stroke Registry analysis. *Eur J Neurol.* 2022;29(3):732-743.
11. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of Coronavirus disease 2019 (covid- 19): a Review. *JAMA.* 2020;324(8):782-793.
12. Escalard S, Maïer B, Redjem H, et al. Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19: experience from paris. *Stroke.* 2020;51(8):2540-2543.
13. Pezzini A, Grassi M, Silvestrelli G, et al. Impact of SARS-CoV-2 on reperfusion therapies for acute ischemic stroke in Lombardy, Italy: the STROKOVID network. *J Neurol.* 2021;268(10):3561-3568.
14. Cappellari M, Zini A, Sangalli D, et al. Thrombolysis and bridging therapy in patients with acute ischaemic stroke and COVID-19. *Eur J Neurol.* 2020;27(12):2641-2645.
15. Sasanejad P, Afshar Hezarkhani L, Arsang-Jang S, et al. Safety and outcomes of intravenous thrombolytic therapy in ischemic stroke patients with COVID-19: CASCADE initiative. *J Stroke Cerebrovasc Dis.* 2021;30(12):106121. doi: 10.1016/j.jstrokecerebrovasdis.2021.106121
16. Pop R, Hasiu A, Bolognini F, et al. Stroke thrombectomy in patients with COVID-19: initial experience in 13 cases. *AJNR Am J Neuroradiol.* 2020;41(11):2012-2016.
17. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J NeuroInterv Surg.* 2020;12(7):648-653.
18. Cagnazzo F, Piotin M, Escalard S, et al. European multicenter study of ET-COVID-19. *Stroke.* 2021;52(1):31-39.
19. European Centre for Disease Prevention and Control. 2021. *Surveillance Definitions for COVID-19*. ecdc.europa.eu/en/covid-19/surveillance/surveillance-definitions
20. WHO COVID-19 Case Definition. 2021. who.int/publications/i/item/WHO-2019-nCoV- Surveillance_Case_Definition-2020.2
21. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet.* 1998;352(9136):1245-1251.
22. Zaidat OO, Castonguay AC, Linfante I, et al. First pass effect: a new measure for stroke thrombectomy devices. *Stroke.* 2018;49(3):660-666.
23. Zetterqvist J, Sjölander A. Doubly robust estimation with the R package drgee. *Epidemiologic Methods.* 2015;4(1):69-86.
24. Buuren Sv, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw.* 2011;45(3):1-67.
25. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA covid-19 vaccine in a nationwide setting. *N Engl J Med.* 2021;385(12):1078-1090.
26. Marcos-Contreras OA, Martinez de Lizarrondo S, Bardou I, et al. Hyperfibrinolysis increases blood-brain barrier permeability by a plasmin- and bradykinin-dependent mechanism. *Blood.* 2016;128(20):2423-2434.
27. Hernández-Fernández F, Sandoval Valencia H, Barbella-Aponte RA, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. *Brain.* 2020;143(10):3089-3103.
28. Tiainen M, Meretoja A, Strbian D, et al Body temperature, blood infection parameters, and outcome of thrombolysis-treated ischemic stroke patients. *Int J Stroke.* 2013;8:632-638.
29. Consoli D, Vidale S, Arnaboldi M, et al. Infections and Chlamydia pneumoniae antibodies influence the functional outcome in thrombolysed strokes. *J Neurol Sci.* 2017;381:95-99.
30. Maslias E, Nannoni S, Ricciardi F, et al. Procedural complications during early versus late endovascular treatment in acute stroke: frequency and clinical impact. *Stroke.* 2021;52(3):1079-1082.
31. Fischer U. On behalf of the Improving Reperfusion strategies in Ischemic Stroke (IRIS) working group investigators, Direct mechanical thrombectomy versus bridging therapy—cumulative study-level meta-analysis of the DIRECT-MT, MR CLEAN-NOIV, DEVT, SKIP AND SWIFT-DIRECT Randomized Clinical Trials. *Eur Stroke J.* 2021;6(1S):514.