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Letter to the Editor

Recanalization Outcomes and Procedural Complications in Patients With Acute Ischemic Stroke and COVID-19 Receiving Endovascular Treatment

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Dear Sir:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with an increased risk of cerebrovascular and other thrombotic events.[1] Previous studies have shown that patients with acute ischemic stroke (AIS) and coronavirus disease 2019 (COVID-19) have a worse functional outcome than those without concomitant SARS-CoV-2 infection.[2,3] In patients receiving acute revascularization treatments, our large retrospective analysis of the Global COVID-19 Stroke Registry revealed higher rates of intracranial bleeding and worse clinical outcomes in patients with AIS and COVID-19 compared to contemporary AIS controls without COVID-19.[4] Subsequent sub-analyses emphasized the impact of SARS-CoV-2 infection in this subgroup of patients showing differences in outcome between patients with asymptomatic COVID-19 and controls without COVID-19.[5]

Several factors can contribute to poorer outcomes in patients with AIS and COVID-19 undergoing acute revascularization treat-

ments,[2,3,6] including lower recanalization rates and higher rates of procedural complications after endovascular treatment (EVT).[7,8]

We aimed to assess recanalization outcomes and procedural complication rates in patients with AIS and COVID-19 undergoing EVT in an international cohort by comparing them with a contemporary control group of non–COVID-19 patients from the same centers.

We conducted a secondary analysis on the Global COVID-19 Stroke Registry.[4] Inclusion and exclusion criteria for the Global COVID-19 Stroke Registry were previously described.[4] For this study, only patients receiving EVT for intracranial occlusions were included (Supplementary Figure 1). All study procedures, study variables, and ethical standards were previously described.[4]

The primary outcome of this study was recanalization after EVT assessed by the modified Thrombolysis in Cerebral Infarction (mTICI) score. Secondary procedural outcomes were: (1) successful recanalization after EVT (mTICI ≥2b); (2) first pass effect; (3) number of passes during EVT; and (4) procedure duration. Secondary safety outcomes were: (1) arterial perforation observed during EVT; (2) reocclusion during EVT; and (3) embolization into new non-ischemic territory during EVT. To assess the association of COVID-19 with the primary outcome and secondary procedural outcomes, we used multivariable regression models entering as independent variables the COVID-19 status together with prespecified baseline clinical and radiological variables identified from previous literature as variables known to be associated with the outcomes of interest. Depending on whether the outcome was ordinal, binary, or continuous, we used ordered logit regression, logistic regression, and quantile regression models, respectively. Data regarding EVT complications were available for all COVID-19 patients but only in a subset of controls. As such, to evaluate the association between COVID-19 and EVT complications, we performed a 1:3 propensity-score matching procedure between COVID-19 patients and the subset of controls with EVT complication data available. The association between COVID-19 and EVT complications was assessed using univariable binary logistic regression on the matched population. A detailed description on the statistical analysis methodology is available in Supplementary Methods.

Of the 15,128 patients included in the Global COVID-19 Stroke Registry, 8,292 fulfilled the inclusion criteria for the present analysis (Supplementary Figure 1). Of these, 497 (6.0%) patients were diagnosed with COVID-19. Comparisons between groups are shown in Table 1.

In the adjusted analysis, COVID-19 was associated with worse final mTICI score, lower successful recanalization, and a trend toward a lower first pass effect (Table 2).

EVT procedural complications were assessed in 493 (99.0%) patients with COVID-19 and in 2,275 (29.0%) controls. Control patients with and without data on procedural complications had similar baseline characteristics (Supplementary Table 1). Among patients with information on procedural complications after EVT, 491 with COVID-19 and 2,246 in the control group had complete data on the covariates selected for matching and were included in the analysis. After propensity-score matching of these patients, COVID-19 patients and their matched controls had a well-balanced distribution of baseline characteristics (Supplementary Figure 2). Patients with COVID-19 had higher rates of arterial perforation and reocclusion during EVT, and a trend toward higher rates of embolization into a new non-ischemic territory (Table 3).

In this secondary analysis on the Global COVID-19 Stroke Registry, we found that patients with COVID-19 had worse recanalization outcomes and higher rates of procedural complications such as arterial perforation and reocclusion in comparison with contemporaneous patients with AIS without COVID-19. To our knowledge, this was the first study to show such associations in a large sample of consecutive patients with and without COVID-19 that used adjustment for potential confounders. The presented results add to our previous finding, showing higher rates of intracranial bleeding and worse clinical outcomes in patients with AIS and COVID-19 compared to contemporary AIS controls without COVID-19.[9]

Several pathophysiological mechanisms associated with COVID-19 may explain these findings. Endothelial inflammation and dysfunction, induced platelet aggregation, coagulation cascade activation, and formation of antiphospholipid antibody complexes associated with COVID-19 likely lead to higher clot burden and clot adherence.[9,10] This complex interplay probably results in lower recanalization and increased rates of reocclusion. These same mechanisms, combined with SARS-CoV-2-induced hyperfibrinolysis and direct viral-mediated damage to the neurovascular unit[9,10] may contribute to lower integrity of vessel walls and to subsequent elevated rates of arterial perforation. Alternatively, emboli in patients with COVID-19 may be more difficult to recanalize and retrieve due to the activation of the coagulation cascade activation, requiring more aggressive and longer EVT procedures with increased perforation risk.

Our analysis has several strengths, including the large sample size from 30 countries across five continents, increasing the validity and generalizability of our results.

Limitations of our study include the retrospective design, nonblinded assessment, and absence of centralized imaging review, which may have influenced our results. The use of different thrombectomy equipment and techniques by stroke interventionists may have affected our results but were tentatively addressed by adjustment with a center cluster level variable. A significant num-

Table 1. Baseline, stroke characteristics, imaging and treatment data

Variables	Total (n=8,292)	Controls (n=7,795)	COVID-19 (n=497)	*P*
Center volume*				<0.01
<100	671 (8.1)	585 (7.5)	86 (17.3)	
100–199	2,434 (29.4)	2,268 (29.1)	166 (33.4)	
200–299	3,343 (40.3)	3,194 (41.0)	149 (30.0)	
≥300	1,844 (22.2)	1,748 (22.4)	96 (19.3)	
Demographics				
Age (yr)	73 (63–81)	73 (63–81)	70 (60–79)	<0.01
Male sex	4,041 (48.8)	3,756 (48.2)	285 (57.3)	<0.01
Pre-stroke modified Rankin Scale				0.94
0	5,831 (73.0)	5,474 (73.0)	357 (72.9)	
1 to 2	1,648 (20.6)	1,545 (20.6)	103 (21.0)	
3 to 5	513 (6.4)	483 (6.4)	30 (6.1)	
Vascular risk factors				
Hypertension	5,763 (69.8)	5,434 (70.0)	329 (66.2)	0.08
Diabetes mellitus	2,060 (24.8)	1,893 (24.4)	167 (33.6)	<0.01
Dyslipidemia	3,743 (45.4)	3,541 (45.7)	202 (40.6)	0.03
Current smoking	1,734 (21.4)	1,646 (21.6)	88 (17.8)	0.05
Atrial fibrillation	3,078 (37.3)	2,907 (37.5)	171 (34.5)	0.20
Heart failure	1,183 (15.2)	1,109 (15.2)	74 (15.6)	0.85
Coronary artery disease	1,330 (16.4)	1,247 (16.3)	83 (17.3)	0.64
Active cancer	368 (5.0)	345 (5.0)	23 (5.1)	0.988
Treatment at stroke onset				
Oral anticoagulants	1,648 (19.9)	1,535 (19.8)	113 (22.7)	0.13
Antiplatelets	2,101 (25.5)	1,980 (25.6)	121 (24.4)	0.62
Statins	2,630 (33.7)	2,484 (33.9)	146 (30.9)	0.20
Stroke characteristics				
LTSW-to-door (min)	120 (66–263)	120 (66–264)	120 (61–260)	0.36
Admission NIHSS	16 (10–20)	16 (10–20)	17 (12–21)	<0.01
Vascular territories				0.40
Carotid	7,371 (90.0)	6,924 (88.9)	447 (90.1)	
Vertebrobasilar	729 (8.8)	693 (8.9)	36 (7.3)	
Multiple	186 (2.2)	173 (2.2)	13 (2.6)	
Admission systolic BP (mm Hg)	148 (130–165)	148 (130–165)	144 (130–160)	<0.01
Admission blood glucose (mmol/L)	6.9 (5.9–8.4)	6.9 (5.9–8.4)	7.2 (6.1–9.2)	<0.01
Acute imaging				
ASPECTS (or pc-ASPECTS)	9 (8–10)	9 (8–10)	9 (7–10)	<0.01
Most proximal arterial occlusion				0.11
Intracranial ICA	1,766 (21.3)	1,654 (21.2)	112 (22.5)	
MCA M1	4,156 (50.1)	3,906 (50.1)	250 (50.3)	
MCA M2-4	1,500 (18.1)	1,414 (18.1)	86 (17.3)	
ACA A1-2	48 (0.6)	46 (0.6)	2 (0.4)	
PCA P1-2	116 (1.4)	109 (1.4)	7 (1.4)	
BA	522 (6.3)	498 (6.4)	24 (4.8)	
V4	105 (1.3)	100 (1.3)	5 (1.0)	
Other	79 (0.9)	68 (0.9)	11 (2.2)	
Tandem lesion	1,255 (15.2)	1,166 (15.0)	89 (17.9)	0.09

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Table 1. Continued

Variables	Total (n=8,292)	Controls (n=7,795)	COVID-19 (n=497)	*P*
Stroke etiology				<0.01
Large artery atherosclerosis	1,599 (19.3)	1,498 (19.2)	101 (20.3)	
Cardioembolism	3,921 (47.3)	3,715 (47.7)	206 (41.5)	
Small vessels disease	26 (0.3)	25 (0.3)	1 (0.2)	
Dissection	188 (2.3)	178 (2.3)	10 (2.0)	
Other determined cause	386 (4.7)	320 (4.1)	66 (13.3)	
Undetermined	2,172 (26.2)	2,059 (26.4)	113 (22.7)	
Acute revascularization treatment				
IV thrombolysis	3,866 (46.6)	3,655 (46.9)	211 (42.5)	0.06
LTSW-to-puncture (min)	273 (187–412)	272 (187–412)	285 (190.2–410.8)	0.63
General anesthesia	2,941 (35.7)	2,718 (35.1)	223 (45.0)	<0.01

Values are presented as median (interquartile range) or as n (%).
LTSW, last-time-seen-well; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; ASPECTS, Alberta Stroke Program Early CT Score; pc-ASPECTS, posterior circulation ASPECTS; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; V4, vertebral artery, segment 4.
*Refers to the number of patients included by each center in the study.

Table 2. Recanalization outcomes after endovascular treatment

Variables	Total (n=8,292)	Controls (n=7,795)	COVID-19 (n=497)	Crude OR (95% CI)	Adjusted OR (95% CI)
Final mTICI				0.70 (0.58 to 0.86)*	0.72 (0.59 to 0.89)*
0–1	658 (8.0)	597 (7.7)	61 (12.3)		
2a	442 (5.3)	404 (5.2)	38 (7.6)		
2b	2,111 (25.5)	1,988 (25.5)	123 (24.7)		
2c	877 (10.6)	815 (10.5)	62 (12.5)		
3	4,182 (50.6)	3,969 (51.1)	213 (42.9)		
Successful recanalization (mTICI ≥2b)	7,170 (86.7)	6,772 (87.1)	398 (80.1)	0.59 (0.47 to 0.75)	0.59 (0.44 to 0.79)
First pass effect	2,498 (30.2)	2,376 (30.5)	122 (24.6)	0.74 (0.60 to 0.91)	0.79 (0.63 to 1.00)
Total number of device passes				1.21 (0.96 to 1.53)†	1.13 (0.88 to 1.44)†
1	3,855 (46.5)	3,642 (46.7)	213 (42.9)		
2	1,972 (23.8)	1,860 (23.9)	112 (22.5)		
3	1,236 (14.9)	1,152 (14.8)	84 (16.9)		
>3	1,229 (14.8)	1,141 (14.6)	88 (17.7)		
Procedure duration	40 (25–65)	40 (25–65)	40 (25–65)	0.00 (-3.74 to 3.74)‡	-2.25 (-6.24 to 1.74)‡

Values are presented as median (interquartile range) or as n (%).
OR, odds ratio; CI, confidence interval; mTICI, modified Thrombolysis in Cerebral Infarction.
*Common adjusted odds ratio for higher mTICI; †Common adjusted odds ratio for higher number of passes; ‡Beta coefficient from quantile regression. Multivariable models displayed no multicollinearity (maximal variance inflation factor of 1.1).

Table 3. Procedural complications during endovascular treatment

Variables	Total (n=1,964)	Controls (n=1,473)	COVID-19 (n=491)	Adjusted OR (95% CI)	*P*
Arterial perforation observed during EVT	29 (1.5)	17 (1.2)	12 (2.4)	2.14 (1.12–4.10)	0.02
Embolization into a non-ischemic territory during EVT	76 (3.9)	48 (3.3)	28 (5.7)	1.79 (0.97–3.32)	0.06
Reocclusion of recanalized artery during EVT	89 (4.5)	46 (3.1)	43 (8.8)	2.98 (1.75–5.09)	<0.01

Values are presented as numbers (proportions).
OR, odds ratio; CI, confidence interval; EVT, endovascular treatment.

ber of centers did not report safety outcomes in control patients, which could have biased our results.

In conclusion, in this cohort study, patients with AIS and COVID-19 receiving EVT had lower rates of recanalization and a higher risk of arterial perforation and reocclusion, in comparison with contemporary AIS controls without COVID-19. These findings may contribute to the poorer outcome found in patients with AIS and COVID-19.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.04077.

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Conflicts of interest

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Author contribution

Conceptualization: JPM, DS, GN, PM. Study design: JPM, DS, GN, PM. Data collection: all authors. Statistical analysis: DS. Writing—original draft: JPM, DS; GN, PM. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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Supplementary Methods

Complete statistical analysis description

Continuous variables were summarized as median values with interquartile range and categorical variables as absolute numbers and percentages. We compared baseline and outcome variables between coronavirus disease 2019 (COVID-19) patients and COVID-19 negative control group using Pearson's chi-squared test for categorical variables and Mann–Whitney U test for continuous variables. To assess the association of COVID-19 with the primary outcome and secondary procedural outcomes, we used multivariable regression models entering as independent variables the COVID-19 status together with prespecified baseline clinical and radiological variables identified from previous literature as variables known to be associated with the outcomes of interest. These potential confounders were age, sex, National Institutes of Health Stroke Scale (NIHSS); Alberta Stroke Program Early CT Score (ASPECTS), site of arterial occlusion, tandem lesions, last-time-seen-well-to-puncture delay, intravenous thrombolysis (IVT), and general anesthesia. Depending on whether the outcome was ordinal, binary, or continuous, we used ordered logit regression, logistic regression, and quantile regression models, respectively. The results of ordered logit regression and logistic regression model were expressed as odds ratios (OR) and 95% confidence intervals (CI), and the results of quantile regression were expressed as beta coefficients and 95% CIs. Given the risk of clustering effect of patients from the same center, we included the referring center in each model as a cluster level variable and calculated cluster-robust standard errors. To account for missing data of the covariates, we performed multiple imputations by chained equation, generating ten imputed data sets. The rate of missing data for each variable in the registry has been reported in a previous paper. We performed analyses on each imputed dataset, and then the estimates and the standard errors of the ten imputed analyses were combined using Rubins' Rules. To assess collinearity among the covariates in the multivariable models, we calculated the adjusted generalized variance inflation factor for each covariate. Data regarding endovascular treatment (EVT) complications were available for all COVID-19 patients but only in a subset of controls. As such, to evaluate the association between COVID-19 and EVT complications, we performed a 1:3 propensity-score matching procedure between COVID-19 patients and the subset of controls with EVT complication data available. A propensity score model was fitted by logistic regression to assign a probability to each patient belonging to COVID-19 or control groups. Covariates entered in the model were age, sex, baseline NIHSS, large artery atherosclerosis etiology, baseline ASPECTS, site of arterial occlusion, tandem lesions, stroke vascular territory, last-time-seen-well (LTSW)-to-puncture delay, IVT and general anesthesia. Patients in the control group with characteristics most akin to COVID-19 patients were then selected through nearest neighbor matching and for each COVID-19 patient, three control patients with the closest propensity scores were selected. Subsequently, the association between COVID-19 and EVT complications was assessed using univariable binary logistic regression on the matched population and results were expressed as OR and their 95% CIs. All tests were two-sided and *P*-values <0.05 were considered significant. As this was a retrospective study, no correction for multiple outcome testing was applied. We did not perform a power calculation since prior data estimating the expected effect of COVID-19 on the outcome of interest in revascularized stroke patients was lacking. We performed statistical analysis with R statistical software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Supplementary Table 1. Comparison between control patients included and excluded in procedural complications analysis

Variables	Excluded (n=5,520)	Included (n=2,275)
Center volume*		
<100	393 (7.1)	192 (8.4)
100–199	1,608 (29.1)	660 (29.0)
200–299	1,933 (35.1)	1,261 (55.4)
≥300	1,586 (28.7)	162 (7.1)
Demographics		
Age (yr)	74 (63–82)	73 (63–81)
Male sex	2,644 (47.9)	1,112 (48.9)
Pre-stroke modified Rankin Scale		
0	3,951 (75.3)	1,523 (67.6)
1 to 2	971 (18.5)	574 (25.5)
3 to 5	326 (6.2)	157 (7.0)
Vascular risk factors		
Arterial hypertension	3,782 (69.0)	1,652 (72.7)
Diabetes mellitus	1,222 (22.3)	671 (29.6)
Dyslipidemia	2,420 (44.2)	1,121 (49.4)
Current smoking (or stopped <2 years)	1,080 (20.2)	566 (25.1)
Atrial fibrillation	2,042 (37.2)	865 (38.1)
Heart failure	700 (13.3)	409 (20.0)
Coronary artery disease	825 (15.1)	422 (19.4)
Active cancer	213 (4.2)	132 (7.3)
Treatment at stroke onset		
Oral anticoagulants	1,152 (21.0)	383 (17.0)
Antiplatelets	1,382 (25.2)	598 (26.4)
Statins	1,795 (33.9)	689 (33.8)
Stroke characteristics		
LTSW-to-door (min)	122 (67–271.8)	115 (65–240)
NIHSS admission	16 (10–20)	15 (10–20)
Vascular territories		
Carotid	4,938 (89.5)	1,986 (87.3)
Vertebrobasilar	492 (8.9)	201 (8.8)
Multiple territories	85 (1.5)	88 (3.9)
Admission systolic BP (mm Hg)	148 (130–165)	150 (130–168)
Admission blood glucose (mmol/L)	6.8 (5.8–8.4)	7.0 (6.0–8.4)
Acute imaging		
ASPECTS (or pc-ASPECTS)	9 (7–10)	9 (8–10)
Most proximal arterial occlusion		
Intracranial ICA	1,161 (21.0)	493 (21.7)
MCA M1	2,818 (51.0)	1,088 (47.8)
MCA M2-4	950 (17.2)	464 (20.4)
ACA A1-2	37 (0.7)	9 (0.4)
PCA P1-2	74 (1.3)	35 (1.5)
BA	355 (6.4)	143 (6.3)
V4	77 (1.4)	23 (1.0)
Other	48 (0.9)	20 (0.9)
Tandem lesion	799 (14.5)	367 (16.1)
Stroke etiology		
Large artery atherosclerosis	1,093 (19.8)	405 (17.8)
Cardioembolism	2,649 (48.0)	1,066 (46.9)
Small vessels disease	20 (0.4)	5 (0.2)
Dissection	147 (2.7)	31 (1.4)
Other determined cause	240 (4.3)	80 (3.5)
Undetermined	1,371 (24.8)	688 (30.2)
Acute revascularization treatment		
IV thrombolysis	2,573 (46.6)	1,082 (47.6)
LTSW-to-puncture (min)	280 (193–420)	255 (175–400)
General anesthesia	1,898 (34.6)	820 (36.2)

Values are presented as median (interquartile range) or n (%).
LTSW, last-time-seen-well; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; ASPECTS, Alberta Stroke Program Early CT Score; pc-ASPECTS, posterior circulation ASPECTS; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; V4, vertebral artery, segment 4.
*Refers to the number of patients included by each center in the study.

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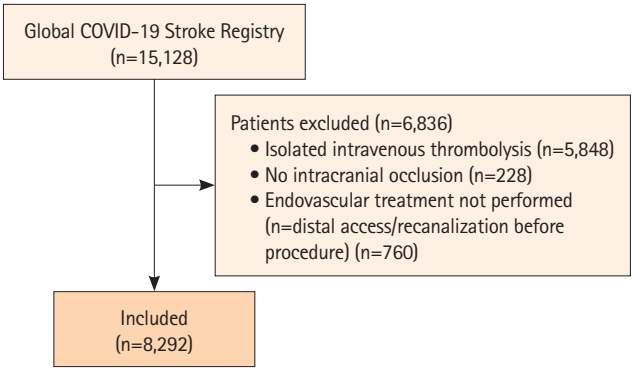
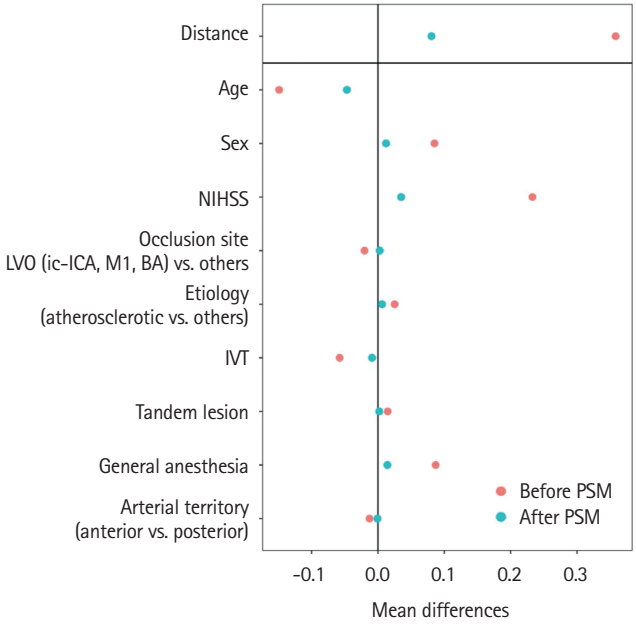


Supplementary Figure 1. Inclusion flowchart.



Supplementary Figure 2. Standardized mean differences before (red points) and after (blue points) propensity-score matching (PSM) between the patients with COVID-19 and controls, for the variables used for matching. NIHSS, National Institutes of Health Stroke Scale; LVO, large vessel occlusion; ic-ICA, intracranial internal carotid artery; M1, middle cerebral artery (M1 segment); BA, basilar artery; IVT, intravenous thrombolysis.

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