Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

COVID-19 Affects Short-Term, But Not 90-Day, Outcome in Patients With Stroke Treated With Mechanical Thrombectomy

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BACKGROUND: COVID-19 is associated with an increased stroke risk. Moreover, outcome at discharge was worse in patients with large-vessel occlusion stroke with concomitant COVID-19 receiving endovascular treatment (ET). We aimed to investigate the impact of concomitant COVID-19 on later functional outcome in patients with large-vessel occlusion stroke treated with ET.

METHODS: We analyzed patients from the GSR-ET (German Stroke Registry–Endovascular Treatment), an observational multicenter registry of patients with large-vessel occlusion stroke receiving ET. Baseline characteristics, procedural parameters, discharge parameters, and functional outcome at 90 days were compared between patients with concomitant COVID-19 and propensity score–matched controls (ratio, 1:4; matched for age, sex, prestroke modified Rankin Scale score, and stroke severity), and multivariable ordinal regression analysis was performed.

RESULTS: Among 4010 patients receiving ET between February 2020 and December 2021, 72 (1.8%) had concomitant COVID-19. Compared with 224 matched patients without COVID-19, they (n=56) were more severely affected, with a higher median National Institutes of Health Stroke Scale (NIHSS) score after 24 hours (NIHSS score, 14.5 [interquartile range {IQR}, 9–22] versus 12 [IQR, 6–18.75]; *P*=0.015), and NIHSS score and modified Rankin Scale score at discharge (NIHSS score, 12 [IQR, 6.75-16.75] versus 6 [IQR, 2–13]; *P*=0.001; and modified Rankin Scale score, 5 [IQR, 4–5] versus 4 [IQR, 2–5]; *P*=0.023), but functional outcome at 90-day follow-up was similar (modified Rankin Scale score, 4 [IQR, 4–6] versus 4 [IQR, 2–6]; *P*=0.34). After adjustment for prespecified confounders, COVID-19 was associated with worse functional outcome at discharge (common odds ratio [OR], 0.40 [95% CI, 0.19–0.80]; *P*=0.011), but not at 90-day follow-up (common OR, 0.72 [95% CI, 0.32–1.60]; *P*=0.43).

CONCLUSIONS: COVID-19 affected short-term, but not 90-day, functional outcome in patients with large-vessel occlusion stroke treated with ET. Hence, ET should not be withheld in patients with concomitant COVID-19.

Key Words: clinical outcome ■ COVID-19 ■ endovascular treatment ■ mechanical thrombectomy ■ stroke

Neurologic manifestations are frequent in COVID-19 caused by SARS-CoV-2, and they include acute cerebrovascular disease, such as ischemic stroke.[1–3] The latter may be related to activation of coagulation pathways in COVID-19, leading to thrombotic complications.[4–7] Several large

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observational studies have consistently shown that stroke in patients with concomitant COVID-19 is associated with younger age, higher stroke severity and mortality, and a higher frequency of large-vessel occlusion.[1,2,8,9]

Endovascular treatment (ET) is the standard procedure in patients with acute large-vessel occlusion stroke (LVOS).[10] The impact of concomitant COVID-19 on patients with LVOS treated with ET is the subject of ongoing research.[8,11,12] Although increased mortality and poorer outcome at discharge have consistently been found,[9,13–15] reliable data on outcome after the short-term phase remained scarce, mainly for 2 reasons. First, COVID-19–negative control groups are missing,[8,11,16] and comparison with historical controls[2,12,14] is problematic because of the impact of the COVID-19 pandemic on acute stroke care.[17] Second, most studies only reported outcome at discharge.[2,8,13,14]

Our study aims to overcome this paucity of information on functional outcome after the short-term phase. Leveraging a large national prospective multicenter registry of patients with LVOS treated with ET,[17] we compared patients with and without concomitant COVID-19 during the current pandemic. Adjusting for comorbidities and possible confounders, we investigated whether concomitant COVID-19 affects 90-day functional outcome after ET.

Nonstandard Abbreviations and Acronyms

ET	endovascular treatment
GSR-ET	German Stroke Registry–Endovascular Treatment
LVOS	large-vessel occlusion stroke
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale

CLINICAL PERSPECTIVE

What Is New?

- Patients positive for COVID-19 and undergoing mechanical thrombectomy had worse functional outcomes at discharge.
- Outcomes converged during follow-up; and after 3 months, COVID-19 was no longer associated with a significantly worse functional outcome.

What Are the Clinical Implications?

- The achievement of comparable outcomes in patients with and without COVID-19 justifies dedicated and extensive efforts in endovascular therapy of patients positive for COVID-19 with large-vessel occlusion stroke.

METHODS

The data supporting the findings of this study are available from the corresponding author on reasonable request. This study was designed and conducted following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.

We used data from the GSR-ET (German Stroke Registry–Endovascular Treatment; ClinicalTrials.gov Identifier: NCT03356392). The GSR-ET is an ongoing, academic, open-label, multicenter registry enrolling consecutive patients with LVOS undergoing ET. The study was conducted in accordance with the Declaration of Helsinki and was centrally approved by the institutional review board of the Ludwig-Maximilians University Munich (689-15) and institutional review boards according to local regulations. Detailed methods of the GSR-ET have been published previously.[18,19] For the current analysis, patients treated between February 2020 and December 2021 for anterior circulation LVOS were included if information on concomitant SARS-CoV-2 infection was available (Figure S1). COVID-19 was defined as a positive result for SARS-CoV-2 determined by lateral flow antigen tests or polymerase chain reaction testing, according to published recommendations.[20]

Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS), and outcome and premorbid disability were rated by the modified Rankin Scale (mRS). The mRS score at 90-day follow-up was obtained during outpatient visits to a vascular neurologist or, if not available, using a structured telephone interview. Baseline infarct size was assessed with the Alberta Stroke Program Early CT [Computed Tomography] Score. Reperfusion success was defined as a modified Thrombolysis in Cerebral Infarction grade of 2b to 3.[21] Symptomatic intracranial hemorrhage was defined as intracranial hemorrhage on 24-hour follow-up CT and at least a 4-point NIHSS score increase.[22]

The neurologic end points were functional outcome measured by mRS at discharge and at 90-day follow-up.[10] Secondary end points were the rate of good functional outcome, defined as mRS score of 0 to 2 at

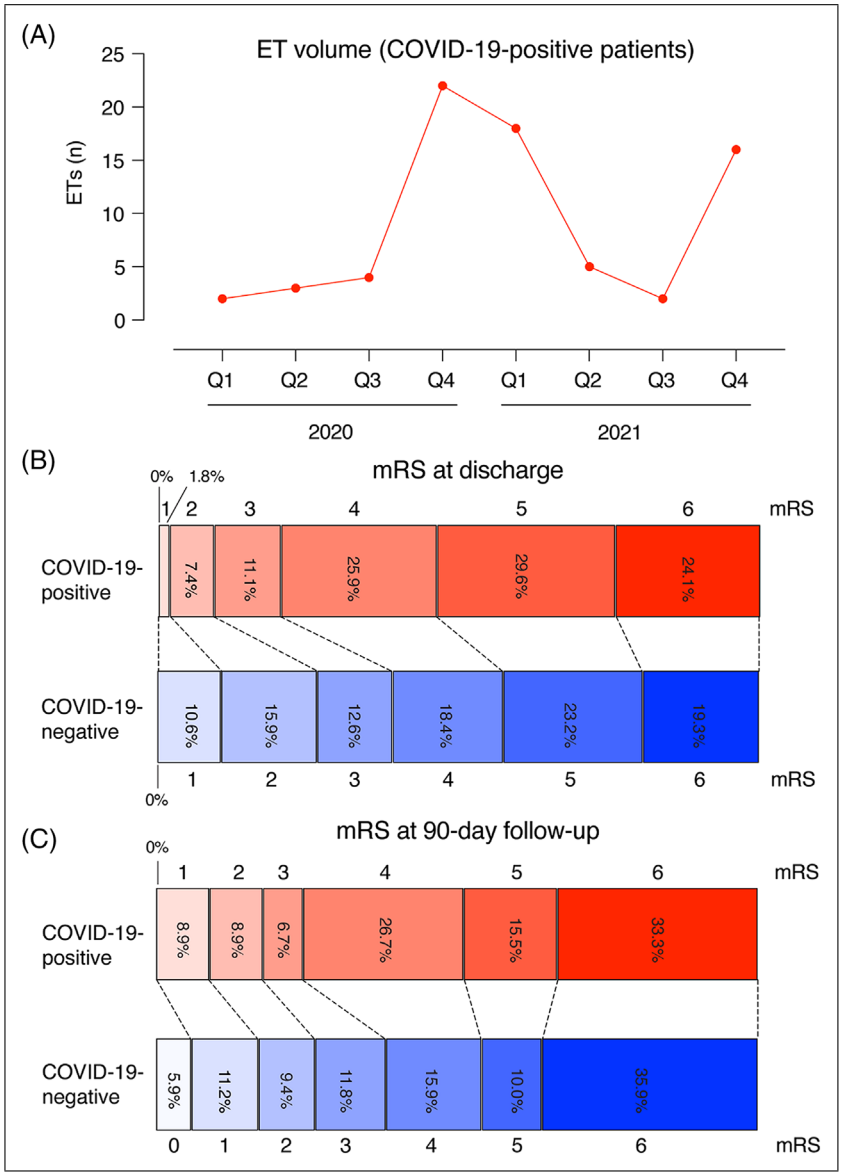

Figure. Temporal distribution and clinical outcome of patients with COVID-19 with large-vessel occlusion stroke receiving endovascular treatment (ET). **A**, Temporal distribution of ET of patients positive for COVID-19. **B** and **C**, Percentage of modified Rankin Scale (mRS) scores at discharge and at 90-day follow-up for matched patients with and without concomitant COVID-19.

90-day follow-up, with regard to prestroke clinical condition, NIHSS score at 24 hours and discharge, symptomatic intracranial hemorrhage, in-hospital mortality, and mortality at 90-day follow-up. Delayed functional independence was defined as mRS score of 3 to 5 at discharge but good functional outcome (mRS score, 0–2) at 90-day follow-up,[23] and delayed functional dependence was defined as mRS score of 0 to 2 at discharge but mRS score of 3 to 6 at 90-day follow-up.

The impact of concomitant COVID-19 on functional outcome at discharge and 90-day follow-up was analyzed with ordinal regression analysis, including the prespecified confounders age, sex, premorbid mRS score, Alberta Stroke Program Early CT Score, NIHSS score at admission, time from symptom onset to groin puncture, intravenous thrombolysis, number of thrombectomy maneuvers, and successful recanalization.[10,24]

Propensity score matching without replacement was further performed to select a cohort of patients without SARS-CoV-2 infection matched for age, sex, premorbid mRS score, NIHSS score, and Alberta Stroke Program Early CT Score, with the nearest-neighbor approach without caliper restriction using a matching ratio of 1:4. Missing data were not imputed for this analysis. Standard descriptive statistics were provided, and group differences were evaluated with unpaired Student *t*-test, Mann-Whitney *U* test, Fisher exact test, and χ^2 test, where appropriate. The level of significance was set at

Table 1. Multivariable Ordinal Regression Models for Prediction of Better Functional Outcome in Patients With LVOS Receiving ET

	mRS at discharge			mRS at 90 d		
	cOR	95% CI	*P* value	cOR	95% CI	*P* value
COVID-19	0.40	0.19–0.8	0.011	0.72	0.32–1.6	0.425
Age	0.97	0.96–0.98	<0.001	0.95	0.95–0.96	<0.001
Female sex	1.03	0.85–1.23	0.787	0.91	0.74–1.11	0.344
NIHSS score at admission	0.89	0.88–0.90	<0.001	0.90	0.89–0.92	<0.001
ASPECTS	1.14	1.08–1.20	<0.001	1.15	1.08–1.22	<0.001
Premorbid mRS score	0.80	0.75–0.87	0.001	0.67	0.61–0.73	<0.001
Symptom onset to groin puncture	0.97	0.95–0.99	0.008	0.98	0.96–1.01	0.131
IVT	1.08	1.08–1.58	0.005	1.45	1.18–1.78	<0.001
No. of maneuvers	0.87	0.82–0.92	<0.001	0.88	0.82–0.93	<0.001
mTICI grade ≥2b	3.36	2.52–4.48	<0.001	3.08	2.24–4.26	<0.001

ASPECTS indicates Alberta Stroke Program Early CT [Computed Tomography] Score; cOR, common odds ratio; ET, endovascular treatment; IVT, intravenous thrombolysis; LVOS, large-vessel occlusion stroke; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; and NIHSS, National Institutes of Health Stroke Scale.

0.05, and all tests were 2 sided. Statistical calculations were performed with R (version 4.2.1; R Core Team; 2022).

RESULTS

Within the GSR-ET, 4665 patients received ET after the first confirmed COVID-19 case in Germany. Among those, 4010 patients had a documented COVID-19 test result, which was positive in 72 cases (1.8%; Figure S1). The temporal distribution of COVID-19–positive admissions reflected the national COVID-19 incidence in Germany, with the highest number of infected patients in the last quarter of 2020, the first quarter of 2021, and the end of 2021 (Figure A).

The median age of patients with LVOS with COVID-19 was 76 years, and 47.2% were women, which was similar to 77 years and 53.6%, respectively, for patients without COVID-19; and 2.8% of patients were aged <45 years in both cohorts. We observed a trend ($P<0.1$) toward higher stroke severity, longer time from symptom onset to admission, longer time from groin puncture to flow restoration, and longer hospital stay, as well as higher mortality at discharge in patients with COVID-19 (Table S1). Intravenous thrombolysis was administered in 41.7% and 44.0% of patients with and without COVID-19, respectively ($P=0.72$), and successful recanalization was achieved in 82.9% and 87.0% of cases, respectively ($P=0.29$). Cardioembolism was the most common cause in patients with COVID-19. Although symptomatic intracranial hemorrhage rates were similar (2.9% versus 3.7%; $P=1.0$), the NIHSS score of patients with COVID-19 was higher at both 24 hours and discharge (both $P<0.001$). Furthermore, patients with COVID-19 had a worse functional outcome at both 24 hours ($P<0.001$) and discharge ($P=0.001$), which was no longer statistically significant at 90-day follow-up ($P=0.09$; Table S1 and Figure S2A–S2B). Mortality at 90-day follow-up was similar among patients with and without COVID-19 (37.9% versus 35.8%; $P=0.78$).

In multivariable ordinal regression analyses, concomitant COVID-19 was associated with worse functional outcome at discharge, with a common odds ratio (OR) of 0.40 (95% CI, 0.19–0.80; $P=0.011$) for an mRS shift toward a better outcome, but not at 90-day follow-up (common OR, 0.72 [95% CI, 0.32–1.60]; $P=0.43$; Table 1). These analyses confirmed known prognostic factors, such as younger age, lower NIHSS score at admission, higher Alberta Stroke Program Early CT Score, lower premorbid mRS score, intravenous thrombolysis, lower number of thrombectomy maneuvers, and successful recanalization, as predictors for a better functional outcome (all $P<0.01$; Table 1).

To further analyze the impact of concomitant COVID-19 on ET outcomes, a cohort of patients without concomitant COVID-19 matched for premorbid status, baseline infarct severity, and main prognostic factors was selected (Table 2 and Figure S3). Within this population (56 with versus 224 patients without COVID-19), the durations from symptom onset or time last seen well to admission and from admission to groin puncture were also numerically longer in patients with COVID-19 compared with matched controls, whereas the recanalization time was similar (Table 2). Successful reperfusion was achieved in 81.8% and 85.9% of patients with and without COVID-19, respectively. Patients with COVID-19 had a higher NIHSS score at 24 hours (14.5 versus 12; $P=0.015$) and at discharge (12 versus 6; $P=0.001$). Although patients with COVID-19 had a worse functional outcome on discharge ($P=0.023$), there was no significant difference on 90-day follow-up ($P=0.34$; Figure B and C).

Table 2. Baseline, Periprocedural, and Outcome Characteristics of Patients With Concomitant COVID-19 and Controls (Matched for Age, Sex, Premorbid mRS Score, Stroke Severity, and Early Ischemic Changes on Imaging)

Characteristics	Patients positive for COVID-19 (n=56)*	Patients negative for COVID-19 (n=224)	*P* value
Age, median (IQR), y	76 (61.75–82)	76 (61.75–82)	NA†
Female sex, % (n)	48.2 (27)	46.9 (105)	NA†
Prestroke mRS score, median (IQR)	0 (0–3)	0 (0–3)	NA†
NIHSS score, median (IQR)	15 (12–20)	15 (11–19)	NA†
ASPECTS, median (IQR)	9 (8–10)	9 (7–10)	NA†
Cardiovascular risk factors, % (n)			
Dyslipidemia	47.2 (25)	45.1 (96)	0.88
Diabetes	30.2 (16)	19.6 (43)	0.10
Hypertension		76.1 (169)	1.0
Atrial fibrillation	28.8 (15)	37.5 (81)	0.26
Current smoking	17.3 (9)	19.5 (41)	0.85
Baseline medication, % (n)			
Antiplatelet therapy	31.4 (16)	30.0 (63)	0.87
Oral anticoagulation	2.0 (1)	2.9 (6)	1.0
Occluded vessel, % (n)			
ACA	3.6 (2)	3.1 (7)	1.0
ICA	33.9 (19)	29.9 (67)	0.63
MCA M1	44.6 (25)	59.4 (133)	0.051
MCA M2	30.4 (17)	29.9 (67)	1.0
Periprocedural results			
IVT, % (n)	44.4 (25)	50.2 (112)	0.66
mTICI grade ≥2b, % (n)	81.8 (45)	85.9 (189)	0.53
Passages, median (IQR)	2 (1–3)	2 (1–3)	0.28
Time SO to admission, median min (IQR)	125 (82–272)	100 (59.5–213.5)	0.19
Witnessed onset of stroke, % (n)	63.0 (29)	63.1 (118)	1.0
Time LSW to admission, median min (IQR)	649 (223–873)	453 (199.75–758.5)	0.69
Time admission to GRO, median min (IQR)	88 (46–148)	70.5 (53–108)	0.23
Time GRO to FLR, median min (IQR)	43 (29–65)	44.5 (26.75–76)	0.65
Hospital stay			
sICH after 24 h, % (n)	1.8 (1)	3.6 (8)	1.0
NIHSS score at 24 h, median (IQR)	14.5 (9–22)	12 (6–18.75)	0.015
Discharge NIHSS score, median (IQR)	12 (6.75–16.75)	6 (2–13)	0.001
Discharge mRS score, median (IQR)	5 (4–5)	4 (2–5)	0.023
Mortality at discharge, % (n)	24.1 (13)	19.3 (40)	0.45
Duration of stay, median (IQR), d	9 (3–19)	9 (5–12)	0.72
Cause, % (n)			0.65
Cardioembolism	39.6 (21)	55.2 (106)	
Dissection	0 (0)	1.8 (4)	
Large-artery atherosclerosis	35.8 (19)	29.2 (64)	
Other determined cause	5.7 (3)	4.1 (9)	
Undetermined cause	18.9 (10)	16.4 (36)	
Outcome			
mRS score at 90 d, median (IQR)	4 (4–6)	4 (2–6)	0.40
mRS score 0–2 at 90 d, % (n)	17.8 (8)	26.5 (45)	0.25
mRS score 0–1 at 90 d, % (n)	8.9 (4)	17.1 (29)	0.25
DFI, % (n)	9.8 (4)	10.1 (13)	1.0
DFD, % (n)	0 (0)	22.0 (9)	0.57
Mortality at 90 d, % (n)	33.3 (15)	35.9 (61)	0.86

ACA indicates anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT [Computed Tomography] Score; DFD, delayed functional dependence; DFI, delayed functional independence; FLR, flow restoration; GRO, groin puncture; ICA, internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; LSW, last seen well; MCA, middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage; and SO, symptom onset.

*Matching not performed for 16 cases because of missing data among matching variables.

†Parameter used for propensity score matching; please refer to Figure S3 for absolute standardized mean differences.

Mortality was similar both at discharge (P=0.45) and after 3 months (P=0.86). Further details are shown in Table 2.

DISCUSSION

Analyzing a prospectively collected cohort of patients with LVOS treated with ET, we provide novel data on functional outcome beyond discharge between patients positive for COVID-19 and contemporaneous controls. More important, we find that concomitant COVID-19 negatively affects short-term, but not 90-day, outcome after adjustments for possible confounders.

This finding contrasts with a multinational study including 302 patients with COVID-19 receiving ET, where 3-month follow-up was worse in patients with COVID-19.[13] Notably, the COVID-19–negative control group *a priori* showed favorable prognostic characteristics, such as a lower premorbid mRS score, a lower NIHSS score, and a significantly shorter time to groin puncture. Control group differences may thus provide an explanation for the divergent results. In multivariable analyses, COVID-19 remained an independent predictor of failed recanalization only, but not of poor functional outcome, although the link between failed recanalization and poor outcome is well established.[25] A recently published subgroup analysis on ET from the global COVID-19 stroke registry supports this link: patients with COVID-19 (n=524) had lower rates of successful recanalization and worse functional outcome at 3 months compared with controls.[26]

It is of concern that the functional outcome was inconsistently defined in previous reports. In most comparable trials, a good outcome is defined as an mRS score of $\leq$2 at 3 months after intervention.[10] In some previous studies, however, only functional outcome at discharge was investigated and found to be significantly worse for ET in patients positive for COVID-19.[12] One study, for example, reported a "devastating outcome" despite good reperfusion rates.[11] Furthermore, a COVID-19–negative control group was missing in this and other studies.[8,16] Our data show that patients positive for COVID-19 who are undergoing ET fare worse on both mRS and NIHSS scores at discharge. However, mortality was not increased in patients positive for COVID-19 compared with patients negative for COVID-19.

During the COVID-19 pandemic, there was a reduced number of patients with acute stroke, whereas the number of patients receiving ET remained stable or even increased.[27–29] Accordingly, although the overall incidence of ischemic stroke was reduced by 7% in a multinational study, comprehensive stroke centers continued to treat a high volume of patients with LVOS requiring ET.[29] Our study was conducted nationally and included mainly comprehensive stroke centers. Despite these differential effects on stroke incidence, the COVID-19 pandemic also led to a strain on health care resources, and consecutive adaptation processes may have had a relevant impact on practical stroke care.[30] We observed numerically longer periprocedural times in patients with COVID-19, which are a known negative predictor of functional outcome.[31] A French multicenter study confirmed treatment delays during the first wave of the pandemic, which was not replicated in a German cohort.[27,32]

In addition to the inherent limitations of a retrospectively analyzed prospective cohort, such as selection and indication bias, our study is limited by the sample size of patients with COVID-19. Although no statistically significant outcome differences were observed between groups at 90-day follow-up, the effect estimate suggests a potentially worse outcome in patients with COVID-19, and a larger study may be able to detect this association. However, the main finding of converging outcomes during follow-up appears robust to this limitation. Further limitations are the absence of information on COVID-19 symptoms and treatment, severity of infection, cause of death, and vaccination status, as well as posttreatment factors that might introduce unmeasured confounding. Strengths of our study include the use of a prospective real-world data collection of patients with anterior circulation LVOS from a nationwide registry, including follow-up data, the availability of contemporary controls, and the confirmation of the main findings by both multivariable regression and propensity score matching.

CONCLUSIONS

Because SARS-CoV-2 is likely to become endemic, concomitant COVID-19 in patients with acute LVOS will remain an important factor in acute stroke care. Our data suggest that COVID-19 per se is not a negative predictor of worse outcome in patients with LVOS. Rather, ET can achieve a comparable outcome in patients both positive and negative for COVID-19. In conclusion, the decision to initiate or withhold ET should not be based on the COVID-19 status.

Author Contributions

Felix J. Bode and Johannes M. Weller designed the study; Niklas M. Beckonert, Felix J. Bode, and Johannes M. Weller researched literature. Johannes

M. Weller analyzed the data. Niklas M. Beckonert and Johannes M. Weller wrote the first draft of the manuscript. Gabor C. Petzold revised the manuscript and figures. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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None.

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki and was centrally approved by the institutional review board of the Ludwig-Maximilians University Munich (689-15) and institutional review boards according to local regulations. Trial Registration: clinicaltrials.gov NCT03356392.

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Informed Consent

Participants or their legal representatives gave informed consent as described in the study protocol.[18]

Guarantor

Johannes M. Weller

Supplemental Materials

Supporting Information

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