International controlled study of revascularization and outcomes following COVID-positive mechanical thrombectomy

Adam A. Dmytriw1,2 | Sherief Ghozy2 | Ahmad Sweid3 | Michel Piotin4 | Kimon Bekelis5 | Nader Sourour6 | Eytan Raz7 | Daniel Vela-Duarte8 | Italo Linfante8 | Guilherme Dabus8 | Max Kole9 | Mario Martínez-Galdámez10 | Shahid M. Nimjee11 | Demetrius K. Lopes12 | Amer E. Hassan13 | Peter Kan14 | Mohammad Ghorbani15 | Michael R. Levitt16 | Simon Escalard4 | Symeon Missios5 | Maksim Shapiro7 | Frédéric Clarençon6 | Mahmoud Elhorany6 | Rizwan A. Tahir9 | Patrick P. Youssef11 | Aditya S. Pandey17 | Robert M. Starke18 | Kareem El Naamani3 | Rawad Abbas3 | Ossama Y. Mansour19 | Jorge Galvan10 | Joshua T. Billingsley12 | Abolghasem Mortazavi13 | Melanie Walker16 | Mahmoud Dibas2 | Fabio Settecase20 | Manraj K. S. Heran20 | Anna L. Kuhn21 | Ajit S. Puri21 | Bijoy K. Menon22 | Sanjeev Sivakumar23 | Ashkan Mowla24 | Salvatore D’Amato1 | Alicia M. Zha25 | Daniel Cooke26 | Justin E. Vranic1 | Robert W. Regenhardt1 | James D. Rabinov1 | Christopher J. Stapleton1 | Mayank Goyal22 | Hannah Wu27,28,29 | Jake Cohen27,28,29 | David Turkel-Parella27,28,29 | Andrew Xavier30,31 | Muhammad Waqas32 | Vincent Tutino32 | Adnan Siddiqui32 | Gaurav Gupta33 | Anil Nanda33 | Priyank Khandelwal33 | Cristina Tiu34 | Pere C. Portela35 | Natalia Perez de la Ossa36 | Xabier Urra37 | Mercedes de Lera38 | Juan F. Arenillas38 | Marc Ribo39,40 | Manuel Requena39,40 | Mariangela Piano41 | Guglielmo Pero41 | Keith De Sousa42 | Fawaz Al-Mufti43 | Zafar Hashim44 | Sanjeev Nayak44 | Leonardo Renieri45 | Rose Du2 | Mohamed A. Aziz-Sultan2 | David Liebeskind46 | Raul G. Nogueira47 | Mohamad Abdalkader48 | Thanh N. Nguyen48 | Nicholas Vigilante49 | James E. Siegler49 | Jonathan A. Grossberg50 | Hassan Saad50 | Michael R. Gooch3 | Nabeel A. Herial3 | Robert H. Rosenwasser3 | Stavropoula Tjoumakaris3 | Aman B. Patel1 | Ambooj Tiwari27,28,29 | Pascal Jabbour3 | North American Neurovascular COVID-19 (NAN-C) Consortium & Society of Vascular and Interventional Neurology (SVIN) Investigators

1Neuroendovascular Program, Mass General Brigham Partners, Harvard Medical School, Boston, Massachusetts, USA
2Neuroradiology & Neurosurgery Services, Brigham & Women’s Hospital, Harvard Medical School, Boston, Massachusetts, USA
3Department of Neurological Surgery, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA
4Department of Interventional Neuroradiology, Rothschild Foundation Hospital, Paris, France
5Department of Neurosurgery, Good Samaritan Hospital Medical Center, New York, USA
6Department of Interventional Neuroradiology, Pitié-Salpêtrière Hospital, Paris, France
Abstract

Background and purpose: Previous studies suggest that mechanisms and outcomes in patients with COVID-19-associated stroke differ from those in patients with non-COVID-19-associated strokes, but there is limited comparative evidence focusing on these populations. The aim of this study, therefore, was to determine if a significant association exists between COVID-19 status with revascularization and functional outcomes.
INTRODUCTION

Since the first reported case in Wuhan, China, coronavirus disease 2019 (COVID-19) has been prevalent globally, with approximately 45 million cases and 730,000 deaths in the United States, up to October 8, 2021 [1]. According to the World Health Organization (WHO), there have been over 241 million cases and almost 5 million deaths worldwide [2]. Patients with COVID-19 are at higher risk of thrombotic events, with an estimated prevalence rate of 22%, which can further increase to up to 43% after admission to the intensive care unit [3]. Hypercoagulability in COVID-19 patients may be caused by disease-associated stasis, cytokine storm, dysfunctional endothelium, and platelet activation [3-5].

One form of thrombosis is acute ischemic stroke (AIS). The risk of AIS in COVID-19 patients may be elevated approximately three- to eightfold in the first 3 days of respiratory symptoms [6,7]. The reported prevalence of stroke among COVID-19 patients varies from 1.3% up to 4.9% and the rate of SARS CoV-2 infection among stroke admissions is estimated to be 3.3% [8-16]. While there have been a number of reports indicating an excess number of large vessel occlusion (LVO) strokes in patients with COVID-19 [8,17,18], there are limited data on the safety and outcomes of acute revascularization of LVO in COVID-19 patients [19,20]. To address current limitations, an international multicenter study was conducted to identify differences in the demographics and stroke characteristics of LVO patients with COVID-19 versus without COVID-19. Furthermore, we sought to evaluate whether COVID-19 has an independent association with revascularization and functional outcomes following the endovascular treatment.

MATERIALS AND METHODS

An international multicenter retrospective study of consecutively admitted COVID-19 patients with concomitant acute LVOs was performed between February 25 and December 30, 2020, across 50 international comprehensive stroke centers, from North America, Europe and the Middle East.

The institutional review boards of participating institutions reviewed and approved the study, and patient consent was waived based on the de-identified retrospective protocol with minimal risk. Diagnosis of COVID-19 was established using reverse-transcriptase PCR assays of nasopharyngeal samples for identification of SARS-CoV-2. Data will be made available by the corresponding author to qualified investigators upon reasonable request.

Data collection

Data collected included age, gender, comorbidities, clinical characteristics of the included COVID-19 patients, details of the involved vessels, procedural technique, and selected outcome measures (e.g.,
symptomatic intracerebral hemorrhage [sICH]). Onset to admission time was defined as the time from stroke onset to hospital arrival. Procedure duration was calculated as the time difference between arterial access and sheath removal. COVID-19 severity was determined based on the score and classification provided by the World Health Organization (WHO) [21]. In addition, classification of AIS subtype was performed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [22]. For the involved vessels, we used the same classification provided by our participating centers based on what was reported as first, second, third, and forth.

Study endpoints

Co-primary outcomes were: (i) optimal revascularization, defined as modified Thrombolysis in Cerebral Infarction (mTICI) grade 3; (ii) unfavorable functional outcome, at discharge and at 90 days, defined as modified Rankin Scale (mRS) score 3–6; and (iii) mortality at 90 days. Recanalization scoring was estimated without central imaging adjudication. Secondary outcomes were: (i) sICH, defined as reduction of four points on the National Institute of Health Stroke Scale (NIHSS) in association with any hemorrhage, at the judgment of the treating clinician; (ii) NIHSS score 24 h following mechanical thrombectomy.

Statistical analysis

All data were analyzed using R software version 4.1.1 using the packages “Rcmdr” and “glm2” [23]. Continuous variables are shown as means and standard deviation, with skewness and kurtosis tests used to evaluate the normal distribution, with comparisons made according to COVID-19 status (COVID-19 vs. non-COVID-19) using independent t-tests or Mann–Whitney U-tests, as appropriate. Categorical variables are reported as frequencies and percentages, with the chi-squared test or Fisher’s exact test used for comparisons, as appropriate. Finally, univariable logistic regression was used to test covariates predictive of revascularization (mTICI grade 2b or 3), and unfavorable outcome (mRS score 3–6). Interaction and confounding were assessed through stratification and relevant expansion covariates. Whenever possible, factors predictive on univariable analysis (p < 0.05) were entered into a backward multivariable logistic regression analysis, and the effect of COVID-19 was assessed to be clinically relevant in all models. Regression results are expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). A p value < 0.05 was taken to indicate significance for all statistical tests. The results presented here are reported in accordance with the Strengthening the Observational Reporting of Observational Studies guidelines. Missing data were not imputed.

Data availability

The relevant anonymized patient-level data are available on reasonable request from the authors.

RESULTS

The total cohort comprised 697 patients with LVO, 302 of whom had concomitant COVID-19 (43.3%). Patients with COVID-19 had a younger mean age than those without COVID-19 (61.1 ± 15.7 years vs. 71.0 ± 15.8 years; p < 0.001), with a lower proportion of female patients in the COVID-19 group (41.1% vs. 80.5%; p < 0.001). Functional status prior to stroke onset was significantly different, with a lower proportion of functional independence in the COVID-19 group (mRS score 0–2: 65.6% vs. 96.2%; p < 0.001 [Table 1]).

Comorbidities

Chronic heart disease (18.9% vs. 34.4%; p < 0.001) and atrial fibrillation (21.2% vs. 38.2%; p < 0.001) were less common in patients with COVID-19, while chronic liver disease (6.0% vs. 2.5%; p = 0.022) and type 2 diabetes mellitus (29.5% vs. 22.3%; p = 0.014) were more common. Hypertension, chronic lung disease and chronic kidney disease frequency did not differ between the groups (Table 1).

COVID-19 characteristics

The severity of COVID-19 at stroke onset was moderate in 73.3% of cases, severe in 14.8% and critical in 11.9%. Cough was the most frequent presenting symptom (48.7%), followed by fever (45.9%), pneumonia (14.4%), and acute respiratory distress syndrome (20.0%). COVID-19 diagnosis was established in 66.1% of the patients prior to stroke onset. The mean duration between COVID-19 symptoms and stroke onset was 8.8 ± 11.4 days, and in 33.9% of the COVID-19 group, stroke was the initial manifestation of the COVID-19 disease.

Stroke characteristics

Cardioembolic etiology represented a lower proportion in the COVID-19 group (12.9% vs. 49.6%), while large vessel atherosclerosis (37.6% vs. 16.5%) and cryptogenic stroke (16.8% vs. 0.0%) were observed at a higher proportion in the COVID-19 group (p < 0.001). The mean Albert Stroke Program Early Computed Tomography Score (ASPECTS) at admission was lower in COVID-19 group (21.2% vs. 38.2%; p < 0.001) and atrial fibrillation (21.2% vs. 38.2%; p < 0.001) were less common in patients with COVID-19, while chronic liver disease (6.0% vs. 2.5%; p = 0.022) and type 2 diabetes mellitus (29.5% vs. 22.3%; p = 0.014) were more common. Hypertension, chronic lung disease and chronic kidney disease frequency did not differ between the groups (Table 1).

Stroke treatment

The mean duration of time from last known normal to access was shorter in the COVID-19 group (357.4 ± 513.3 min vs. 474.4 ± 365.1 min; p = 0.009), while the mean door-to-arterial access duration
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TABLE 1 Baseline characteristics of the patients with large vessel occlusion with and without COVID-19

| Variables                                      | Non-COVID-19 (N = 395) | COVID-19 (N = 302) | Total (N = 697) | p  |
|------------------------------------------------|-------------------------|--------------------|----------------|----|
| Mean (SD) age, years                           | 71.0 (15.8)             | 61.1 (15.7)        | 67.1 (16.5)    | <0.001* |
| Gender: female, n (%)                          | 318 (80.5)              | 124 (41.1)         | 442 (63.4)     | <0.001* |
| Pre-admission mRS score 0–2, n (%)             | 380 (96.2)              | 198 (65.6)         | 578 (82.9)     | <0.001* |
| Mean (SD) NIHSS score at admission             | 14.3 (7.5)              | 17.2 (8.5)         | 15.4 (8.0)     | <0.001* |
| Hypertension, n (%)                            | 271 (68.8)              | 174 (57.6)         | 445 (63.8)     | 0.104 |
| Chronic heart disease, n (%)                   | 136 (34.4)              | 57 (18.9)          | 193 (27.7)     | <0.001* |
| Chronic lung disease, n (%)                    | 76 (19.2)               | 60 (19.9)          | 136 (19.5)     | 0.575 |
| Chronic kidney disease, n (%)                  | 43 (10.9)               | 28 (9.3)           | 71 (10.2)      | 0.791 |
| Chronic liver disease, n (%)                   | 10 (2.5)                | 18 (6.0)           | 28 (4.0)       | 0.022* |
| Diabetes mellitus (type 2), n (%)              | 88 (22.3)               | 89 (29.5)          | 177 (25.4)     | 0.014* |
| Atrial fibrillation, n (%)                     | 151 (38.2)              | 64 (21.2)          | 215 (30.8)     | <0.001* |
| New onset atrial fibrillation, n (%)           | 0 (0.0)                 | 21 (7.0)           | 21 (3.0)       | 0.238 |

Note: Missing data count per variable: age, n = 53; gender n = 17; pre-admission mRS score, n = 70; NIHSS at admission, n = 72; hypertension, n = 40; chronic heart disease, n = 24; chronic lung disease, n = 22; chronic kidney disease, n = 24; chronic liver disease, n = 22; diabetes mellitus (type 2), n = 31; atrial fibrillation, n = 417.

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

*Statistically significant.

was longer in the COVID-19 group (87.5 ± 63.5 min vs. 71.6 ± 80.0 min; p = 0.043). Intravenous tissue plasminogen activator (tPA) administration was less common in the COVID-19 group (23.5% vs. 33.4%; p < 0.001). A higher proportion of mechanical thrombectomy procedures was performed under general anesthesia in the COVID-19 group (31.5% vs. 19.1%; p < 0.001), while mean thrombectomy pass number (1.8 ± 1.5 vs. 1.9 ± 1.2; p = 0.520), first pass effect (53.3% vs. 49.1%; p = 0.395), and stenting rates (7.3% vs. 8.6%; p = 0.584) were comparable among the two groups (Table 3). The mean duration of the procedure to achieve revascularization was prolonged in the COVID-19 group (62.2 ± 47.3 vs. 51.9 ± 31.9; p = 0.002). Moreover, there was a higher proportion of mTICI grade 3 outcomes in the control group (66.6% vs. 25.5%; p < 0.001 [Table 3]).

Complications, functional outcomes, and mortality

The procedure-related complication rate was higher among COVID-19 patients (26.6% vs. 10.0%; p < 0.001), with 19.7% of the complications in the COVID-19 group being symptomatic. There was no significant difference in sICH (6.6% vs. 5.6%; p = 0.683) nor in NIHSS score at 24 h after thrombectomy (11.9 ± 10.8 vs. 12.2 ± 8.2; p = 0.807) between the COVID-19 and non-COVID-19 groups.

The length of hospital stay was longer in the COVID-19 group (15.5 ± 17.6 days vs. 8.4 ± 8.5 days; p < 0.001). Poor functional outcome (mRS score 3–6) at discharge was observed in a significantly higher proportion of patients in the COVID-19 group (37.1% vs. 9.6%; p < 0.001), and favorable functional outcome (mRS 0–2) at 90-day follow-up was observed in a lower proportion of COVID-19 patients versus non-COVID-19 patients (10.6% vs 59.0%; p < 0.001). Similarly, the mortality rate was more than twofold higher in the COVID-19 group (42.0% vs. 19.1; p < 0.001 [Table 3]).

Predictors of revascularization mTICI grade 3

In the univariable model, absence of COVID-19 infection (OR 0.33, 95% CI 0.23–0.48; p < 0.001), female gender (OR 2.56, 95% CI 1.78–3.69; p < 0.001), and higher ASPECTS (OR 1.15, 95% CI 1.04–1.27; p = 0.007) were predictors of better revascularization (mTICI grade 3). Accounting for other possible confounders, only COVID-19 status (OR 0.30, 95% CI 0.12–0.77; p = 0.012) and female sex (OR 2.83, 95% CI 1.31–6.15; p = 0.008) were independent predictors (Table 4).

Predictors of unfavorable outcomes (mRS score 3–6)

Unfavorable outcomes were higher with increasing age (OR 1.04, 95% CI 1.02–1.06; p < 0.001) and NIHSS score at admission (OR 1.10, 95% CI 1.06–1.15; p < 0.001). Accounting for possible confounders (including pre-admission mRS score), age (OR 1.04, 95% CI 1.02–1.06; p < 0.001) and NIHSS score (OR 1.10, 95% CI 1.06–1.15; p < 0.001) persisted as independent risk factors for unfavorable outcomes (Table 5). A sensitivity analysis including only patients with a pre-admission mRS score of 0–2, found higher rates of unfavorable outcome among COVID-19 patients at 3 months (OR 2.10, 95% CI 1.08–3.99; p = 0.025); however, this association was not significant after controlling for other variables (OR 0.81, 95% CI 0.22–2.59; p = 0.731 [Table S1]). A summary of predictors of mTICI grade 3 and mRS score 3–6 is presented in Figure S1.
DISCUSSION

Our global collaborative effort to pool data on patients with LVO during the COVID-19 pandemic provided us with the opportunity to explore the impact of COVID-19 on interventional outcomes in this population. From analyses of compiled cases from 50 institutions worldwide, our data suggest that COVID-19 patients with concomitant LVO have poorer functional outcome and rates of

### TABLE 2 Summary of the included large vessel occlusions

| Variables                                           | Non-COVID-19 (N = 395) | COVID-19 (N = 302) | Total (N = 697) | p       |
|-----------------------------------------------------|-------------------------|-------------------|-----------------|---------|
| **Stroke classification, n (%)**                    |                         |                   |                 |         |
| Large vessel atherosclerosis (50% or more narrowing in an artery) | 64 (16.5)               | 76 (37.6)         | 140 (23.8)      | <0.001* |
| Cardioembolic                                       | 192 (49.6)              | 26 (12.9)         | 218 (37.0)      |         |
| Other (dissection, hypercoagulable)                 | 131 (33.8)              | 66 (32.7)         | 197 (33.5)      |         |
| Cryptogenic                                         | 0 (0.0)                 | 34 (16.8)         | 34 (5.8)        |         |
| Mean (SD) number of vessels involved                | 1.3 (0.5)               | 1.4 (0.9)         | 1.4 (0.8)       | 0.236   |
| **Vessel involved, n (%)**                          |                         |                   |                 |         |
| ICA                                                 | 35 (9.0)                | 9 (25.7)          | 44 (10.4)       | <0.001* |
| MCA (M1 segment)                                    | 156 (40.2)              | 3 (8.6)           | 159 (37.6)      |         |
| MCA (M2 segment)                                    | 89 (22.9)               | 3 (8.6)           | 92 (21.7)       |         |
| ACA (A1 segment)                                    | 4 (1.0)                 | 3 (8.6)           | 7 (1.7)         |         |
| ACA (A2 segment)                                    | 4 (1.0)                 | 15 (42.9)         | 19 (4.5)        |         |
| Extracranial carotid                                | 62 (16.0)               | 0 (0.0)           | 62 (14.7)       |         |
| Basilar                                             | 24 (6.2)                | 2 (5.7)           | 26 (6.1)        |         |
| MCA (M3/4 segments)                                 | 10 (2.6)                | 0 (0.0)           | 10 (2.4)        |         |
| Vertebral                                           | 4 (1.0)                 | 0 (0.0)           | 4 (0.9)         |         |
| **Second vessel involved (if more than one), n (%)**|                         |                   |                 |         |
| ICA                                                 | 7 (8.5)                 | 4 (7.4)           | 11 (8.1)        | 0.002*  |
| MCA (M1 segment)                                    | 39 (47.6)               | 10 (18.5)         | 49 (36.0)       |         |
| MCA (M2 segment)                                    | 18 (22.0)               | 8 (14.8)          | 26 (19.1)       |         |
| ACA (A1 segment)                                    | 5 (6.1)                 | 13 (24.1)         | 18 (13.2)       |         |
| ACA (A2 segment)                                    | 3 (3.7)                 | 4 (7.4)           | 7 (5.1)         |         |
| Extracranial carotid                                | 0 (0.0)                 | 3 (5.6)           | 3 (2.2)         |         |
| Basilar                                             | 1 (1.2)                 | 1 (1.9)           | 2 (1.5)         |         |
| PCA                                                 | 2 (2.4)                 | 6 (11.1)          | 8 (5.9)         |         |
| MCA (M3/4 segments)                                 | 6 (7.3)                 | 4 (7.4)           | 10 (7.4)        |         |
| Vertebral                                           | 1 (1.2)                 | 1 (1.9)           | 2 (1.4)         |         |
| **Third vessel involved (if more than two), n (%)** |                         |                   |                 |         |
| MCA (M1 segment)                                    | 6 (31.6)                | 2 (50.0)          | 8 (34.8)        | 0.149   |
| MCA (M2 segment)                                    | 5 (26.3)                | 1 (25.0)          | 6 (26.1)        |         |
| ACA (A1 segment)                                    | 7 (36.8)                | 0 (0.0)           | 7 (30.4)        |         |
| ACA (A2 segment)                                    | 1 (5.3)                 | 0 (0.0)           | 1 (4.3)         |         |
| PCA                                                 | 0 (0.0)                 | 1 (25.0)          | 1 (4.3)         |         |
| **Fourth vessel involved (if more than three), n (%)**|                         |                   |                 |         |
| MCA (M1 segment)                                    | 0 (0.0)                 | 8 (42.1)          | 8 (36.4)        | 0.244   |
| MCA (M2 segment)                                    | 3 (100.0)               | 7 (36.8)          | 10 (45.5)       |         |
| ACA (A1 segment)                                    | 0 (0.0)                 | 3 (15.8)          | 3 (13.6)        |         |
| PCA                                                 | 0 (0.0)                 | 1 (5.3)           | 1 (4.5)         |         |

Note: Missing data count per variable: stroke classification, n = 108; ASPECTS, n = 152; vessel involved, n = 273.

Abbreviations: ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; COVID-19, coronavirus disease 2019; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; SD, standard deviation.

*Statistically significant.
revascularization compared to non-COVID-19 patients, with a mortality rate reaching up to 42%. The likelihood of achieving complete revascularization was reduced by 70%, compared to patients without COVID-19, in our collaboration. Our data are supported by contemporary reports of poorer outcomes in patients with AIS in the setting of COVID-19, albeit without controls, which is a key advantage of our current report [24-30]. Similarly to the present study, other analyses also suggest that COVID-19 is an independent predictor of LVO, less favorable functional outcome at follow-up, and increased mortality [19,30,31,32,33].

The underlying pathophysiology that drives poorer outcomes for AIS in COVID-19 patients is subject to ongoing investigation. However, it is likely that COVID-19 influences patient conditioning for post-stroke recovery. Factors known to impede recovery after stroke include patient demographic factors, baseline functional status, and comorbidities [34]. In addition, stroke characteristics including severity

| Variables | Non-COVID-19 (N = 395) | COVID-19 (N = 302) | Total (N = 697) | p |
|-----------|------------------------|--------------------|----------------|---|
| Mean (SD) door to groin time, min | 71.6 (80.0) | 87.5 (63.5) | 76.7 (75.4) | 0.043* |
| Mean (SD) LKN to groin time, min | 474.4 (365.1) | 357.4 (513.3) | 442.8 (413.1) | 0.009* |
| tPA given, n (%) | 132 (33.4) | 71 (23.5) | 203 (29.1) | <0.001* |
| Mean (SD) number of passes during thrombectomy | 1.9 (1.2) | 1.8 (1.5) | 1.8 (1.3) | 0.520 |
| First pass effect, n (%) | 194 (49.1) | 161 (53.3) | 279 (40.0) | 0.395 |
| Stenting, n (%) | 34 (8.6) | 22 (7.3) | 56 (8.0) | 0.584 |
| Mean (SD) procedure duration, min | 51.9 (31.9) | 62.2 (47.3) | 56.4 (39.6) | 0.002* |
| Favorable revascularization (mTICI 2b-3) | 337 (85.3) | 154 (50.9) | 491 (86.3) | <0.001* |
| Favorable revascularization (mTICI 3) | 263 (66.6) | 77 (25.5) | 340 (48.8) | <0.001* |
| Complications during or after the procedure, n (%) | | | | |
| None | 352 (90.0) | 168 (73.4) | 521 (83.9) | <0.001* |
| Asymptomatic | 39 (10.0) | 16 (6.9) | 55 (8.9) | |
| Symptomatic | 0 (0.0) | 45 (19.7) | 45 (7.2) | |
| sICH, n (%) | 22 (5.6) | 20 (6.6) | 42 (6.0) | 0.683 |
| Mean (SD) NIHSS score 24 h post thrombectomy | 12.2 (8.2) | 11.9 (10.8) | 12.1 (9.1) | 0.807 |
| mRS score at discharge, n (%) | | | | |
| 0–2 | 131 (33.2) | 149 (49.3) | 280 (40.2) | <0.001* |
| 3–6 | 38 (9.6) | 112 (37.1) | 150 (21.5) | |
| NA | 226 (57.2) | 41 (13.6) | 267 (38.3) | |
| mRS score at 3 months follow-up, n (%) | | | | |
| 0–2 | 233 (59.0) | 32 (10.6) | 265 (38.0) | <0.001* |
| 3–6 | 73 (18.5) | 18 (6.0) | 91 (13.1) | |
| NA | 89 (22.5) | 252 (83.4) | 341 (48.9) | |
| Mean (SD) length of hospital stay, days | 8.4 (8.5) | 15.5 (17.6) | 15.5 (17.5) | <0.001* |
| Discharge, n (%) | | | | |
| Home | 81 (20.5) | 41 (13.6) | 122 (17.5) | <0.001* |
| Rehabilitation | 173 (43.8) | 56 (18.5) | 229 (32.9) | |
| Hospice | 23 (5.8) | 5 (1.7) | 28 (4.0) | |
| Nursing facility | 57 (14.4) | 17 (5.6) | 74 (10.6) | |
| Not reported/deceased | 61 (15.4) | 183 (60.6) | 244 (35.0) | |
| In-hospital mortality | 74 (19.1) | 111 (42.0) | 185 (28.4) | <0.001* |

Note: Missing data count per variable: door to groin, n = 271; LKN to groin, n = 264; tPA given, n = 80; number of passes, n = 112; first pass effect, n = 144; stenting, n = 65; procedure duration, n = 102; favorable revascularization, n = 127; complications, n = 75, sICH, n = 373; 24 h NIHSS, n = 161; mRS at discharge, n = 267; mRS at 3 months; n = 341; length of hospital stay, n = 92; discharge, n = 191.

Abbreviations: LKN, last known normal; mRS, modified Rankin Scale; mTICI, modified Treatment in Cerebral Infarction; NA, not available; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; sICH, symptomatic intracerebral hemorrhage; tPA, tissue plasminogen activator.

*Statistically significant.
and extent of stroke, location of ischemic tissue, time lag to treatment, concomitant pathologies, and other complications all affect post-stroke recovery [34]. The physiological state secondary to COVID-19 appears to further exacerbate damage caused by ischemia [35]. In particular, the heightened prothrombotic and proinflammatory state of COVID-19 may manifest in several ways, including AIS, vasculopathy, myocarditis, arrhythmias, thrombotic microangiopathy, coagulopathy and thrombocytopenia, tropism to endothelial cells via angiotensin-converting enzyme (ACE)-2 receptor, and inhibition of angiotensin (1–7) production [36-61]. It has been proposed that downregulation of ACE-2, leading to both arteriopathy and thrombosis, may play a central role in the development of stroke during COVID-19 [62-64].

Understanding the characteristics of patients who develop LVO in the setting of COVID-19 is important for prognosis and immediate care. To achieve this, we performed one of the first comparative studies of COVID-19 and control patients with LVO. We found that the mean age of the COVID-19 cohort was younger than that of controls by approximately 10 years, which corroborates prior reported findings from other non-controlled studies [8,27,28,30,31,65,66,67,68]. This apparent incidence is almost fourfold higher than those in the general population. We also found a significantly higher representation of males in the COVID-19 group, which is consistent with previously reported non-controlled studies [28,30].

| Predictors                          | Univariable OR (95% CI) | Multivariable OR (95% CI) |
|-------------------------------------|-------------------------|---------------------------|
| **COVID status**                    |                         |                           |
| Non-COVID-19                        | Reference               |                           |
| COVID-19                            | 0.33 (0.23–0.48, p < 0.001) | 0.30 (0.12–0.77; p = 0.012) |
| Mean (SD) age                       | 1.01 (0.99–1.02; p = 0.306) | 0.99 (0.97–1.01; p = 0.223) |
| **Gender**                          |                         |                           |
| Male                                | Reference               |                           |
| Female                              | 2.56 (1.78–3.69, p < 0.001) | 2.83 (1.31–6.15; p = 0.008) |
| **Pre-admission mRS score**         |                         |                           |
| 0–2                                 | Reference               |                           |
| 3–6                                 | 1.48 (0.71–3.32; p = 0.313) | 1.69 (0.35–12.64; p = 0.547) |
| **NIHSS score at admission**        |                         |                           |
| Mean (SD)                           | 0.98 (0.96–1.00; p = 0.064) | 1.00 (0.96–1.05; p = 0.836) |
| **Chronic liver disease**           |                         |                           |
| No                                  | Reference               |                           |
| Yes                                 | 1.06 (0.41–2.93; p = 0.900) | 1.39 (0.30–10.09; p = 0.701) |
| **Diabetes**                        |                         |                           |
| No                                  | Reference               |                           |
| Yes                                 | 1.19 (0.81–1.77; p = 0.370) | 2.78 (1.33–6.31; p = 0.010) |
| **ASPECTS on admission**            |                         |                           |
| Mean (SD)                           | 1.15 (1.04–1.27; p = 0.007) | 1.14 (0.95–1.38; p = 0.153) |
| **Door to groin time (min)**        |                         |                           |
| Mean (SD)                           | 1.00 (0.99–1.00; p = 0.065) | 1.00 (0.99–1.00; p = 0.249) |
| **LKN to groin time (min)**         |                         |                           |
| Mean (SD)                           | 1.00 (1.00–1.00; p = 0.053) | 1.00 (1.00–1.00; p = 0.906) |
| **tPA given**                       |                         |                           |
| No                                  | Reference               |                           |
| Yes                                 | 0.92 (0.64–1.31; p = 0.634) | 0.77 (0.38–1.56; p = 0.472) |

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; LKN, last known normal; mRS, modified rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; tPA, tissue plasminogen activator; SD, standard deviation.

*Statistically significant.
Registry reported a similar latency of approximately 7 days between symptom onset and stroke [30]. The interval from symptom onset to hospital presentation was lower in the COVID-19 group, which may be consistent with previous studies that did not show a delay in endovascular thrombectomy time metrics during the COVID-19 era [73,74]. Factors that can increase the risk of stroke include infection, which can also concurrently worsen the severity of the stroke [75].

There was a significant difference between stroke classification according to TOAST criteria, with a higher proportion of patients with cryptogenic stroke in the COVID-19 group [22]. In our international experience, we found that stroke severity was generally worse in the COVID-19 cohort compared to controls, based on ASPECTS, NIHSS score at presentation, and the number of involved vessels. The etiology of strokes for patients with and without COVID-19 was also significantly different. Confirming the preliminary conclusions of smaller non-controlled studies, we found that COVID-19 LVO was associated with higher rates of strokes due to large vessel atherosclerosis or cryptogenic etiology, whereas non-COVID-19 LVO was more likely to be cardioembolic in etiology [18,76,77]. This further supports the suggestion that COVID-19 is a prothrombotic and proinflammatory systemic state which may induce LVO. Additionally, the cerebral distribution of strokes was also considerably different. Non-COVID-19 strokes were most frequently observed in the MCA-M1 distribution. However, COVID-19 LVO appeared more likely to occur in the anterior cerebral artery, for reasons that are yet to be elucidated. It should be noted that a non-negligible portion of the occlusion location data was not available in the current study.

When comparing our experience with those of other large analyses, we found that the Get With The Guidelines-Stroke (GWTG-Stroke) registry analysis reported comparable results in patients diagnosed with COVID-19. The authors reported a worse NIHSS score at presentation, and considerably greater proportions of patients with LVO stroke [31]. In our study, the rate of tPA administration was higher amongst non-COVID-19 patients. This may be related to several factors, but one contributor could have been barriers to stroke care for COVID-19 patients. Consistent with other clinical cerebrovascular studies, there was a relative global decline in intravenous thrombolysis, mechanical thrombectomy, ruptured aneurysm treatment, and aneurysmal subarachnoid hemorrhage admissions during the initial wave of the COVID-19 pandemic [15,78].

### Table 5

| Predictors                        | Univariable | Multivariable |
|-----------------------------------|-------------|---------------|
|                                   | OR (95% CI; p value) | OR (95% CI; p value) |
| COVID status                      |             |               |
| Non-COVID                         | Reference   |               |
| COVID                             | 1.80 (0.94-3.36; p = 0.071) | 0.82 (0.23-2.59; p = 0.743) |
| Age (years)                       |             |               |
| Mean (SD)                         | 1.04 (1.02-1.06; p < 0.001) | 1.04 (1.02-1.06; p < 0.001) |
| Gender                            |             |               |
| Male                              | Reference   |               |
| Female                            | 0.96 (0.56-1.69; p = 0.887) | 1.04 (0.50-2.23; p = 0.923) |
| Pre-admission mRS score           |             |               |
| 0–2                               | Reference   |               |
| 3–6                               | 2.58 (0.81-7.98; p = 0.096) | 3.28 (0.93-11.72; p = 0.061) |
| NIHSS score at admission          |             |               |
| Mean (SD)                         | 1.10 (1.06-1.13; p < 0.001) | 1.10 (1.06-1.15; p < 0.001) |
| Chronic liver disease             |             |               |
| No                                | Reference   |               |
| Yes                               | 1.69 (0.43-5.73; p = 0.413) | 1.80 (0.35-7.84; p = 0.443) |
| Diabetes                          |             |               |
| No                                | Reference   |               |
| Yes                               | 1.14 (0.64-1.98; p = 0.653) | 0.95 (0.48-1.85; p = 0.894) |
| ASPECTS on admission              |             |               |
| Mean (SD)                         | 0.92 (0.81-1.05; p = 0.206) | 0.96 (0.82-1.14; p = 0.640) |
| tPA given                         |             |               |
| No                                | Reference   |               |
| Yes                               | 0.87 (0.51-1.45; p = 0.588) | 0.82 (0.44-1.49; p = 0.515) |

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; COVID-19, coronavirus disease 2019; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; SD, standard deviation.

*Statistically significant.
The complexity of intervention and technical approach are other factors to be considered for mechanical thrombectomy for LVO. We assessed relative complexity between COVID-19 and non-COVID-19 groups by comparing indirect measures based on the duration of the procedure, number of vessels involved, number of passes, rate of complete and favorable revascularization, and technical complications. Our analysis suggests that having LVO with COVID-19 was associated with more involved vessels, longer procedure duration, and a lower rate of complete revascularization at the end of the procedure, albeit with a similar number of passes per occlusion. Furthermore, COVID-19 patients had a 70% lower likelihood of achieving mTICI grade 3. Our results are in line with those reported in prior non-controlled COVID-19 series and are consistent with historic mechanical thrombectomy data [8,67,68]. A possible explanation is the hypercoagulable state in COVID-19 patients, which may cause re-occlusion. In addition, among the COVID-19 patients undergoing thrombectomy, the intravascular clots were prone to fragment and migrate into both new vascular territories and into distal downstream vasculature, at higher rates than are otherwise typical. However, neither of these possible causes emerged as a pattern or were of a frequency great enough to be generalizable. A prospective, large-scale trial could help to answer such a question. Although we found the initial admission ASPECTS to be highly associated with successful revascularization, the association was not significant in the multivariate model. In the same context, time to groin puncture and whether or not tPA was given were also non-influential factors for revascularization in multivariable analysis. Of note, patients with diabetes had 2.78 higher odds of achieving mTICI grade 3 compared to controls, even after adjustment. The reason for the association with diabetes is unknown but possible hypotheses surround differences in etiology of stroke. Diabetic patients may have received treatment for more strict glycemic control, whereas, paradoxically, non-diabetic patients can encounter iatrogenic hyperglycemia with common COVID treatments such as dexamethasone. As a known inhibitor of fibrinolysis, hyperglycemia on admission was the only independent predictor of failed recanalization after tPA treatment [79,80].

Finally, we compared follow-up functional outcomes after Endovascular therapy (EVT) in patients with COVID-19 versus those without. We found, in our combined cohort, that good functional outcome at discharge and follow-up were significantly lower in the COVID-19 group. The mortality rate, when compared to prior published data, was significantly higher. Similarly, the GWTG-Stroke consortium and the Global COVID-19 Stroke Registry studies demonstrated that COVID-19 was an independent predictor of poor outcome and death [30,31]. Other factors such as diabetes and chronic liver disease history, admission ASPECTS, and tPA use were not associated with poor functional outcome on follow-up. In our cohort, we found that 24-h sICH and NIHSS scores were not significantly different with or without COVID-19. However, patients with COVID-19 had a prolonged hospital stay, which suggests that other factors prolong the perioperative and subsequent recovery process.

Strengths of this study include the fact that it is the first global multicenter controlled study for LVO in COVID-19. It highlights the value of institutional collaboration in addressing clinical questions in a timely and robust manner. The study also has several limitations. Its retrospective design means there is an element of selection bias, particularly when patients are chosen for mechanical thrombectomy. Due to the stress on resources created by the COVID-19 pandemic, some patients may not have received optimal advanced imaging and clinical follow-up, and, as such, there were missing data for several outcomes. Nevertheless, all missing data were within subsidiary variables. Occasionally, control for some cofounders was not possible due to insufficient data in patient records. Future prospective studies are needed to obtain a higher level of evidence.

In conclusion, COVID-19 was an independent predictor of incomplete revascularization in patients with stroke due to LVO in this controlled study. Patients are more often younger, more often male, and have higher morbidity/mortality rates.

**AUTHOR CONTRIBUTIONS**

Sherief Ghozy: Data curation (lead); formal analysis (lead); project administration (equal); software (equal); validation (equal); visualization (lead); writing – original draft (lead); writing – review and editing (equal). Ahmad Sweid: Conceptualization (equal); formal analysis (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). Michel Piotin: Formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). Nader-Antoine Sourour: Conceptualization (equal); methodology (equal); resources (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). Daniel Vela-Duarte: Investigation (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – review and editing (equal). Italo Linfante: Conceptualization (equal); data curation (equal); resources (equal); validation (equal); writing – review and editing (equal).

Guilherme Dabus: Methodology (equal); resources (equal); software (equal); validation (equal); writing – review and editing (equal). Max Kole: Conceptualization (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). Mario Martinez-Galdmez: Investigation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). Shahid M. Nimjee: Investigation (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). Demetrius K. Lopes: Data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – review and editing (equal). Ameer E. Hassan: Conceptualization (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). Peter Kan: Formal analysis (equal); investigation (equal); methodology (equal);
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resources (equal); validation (equal); visualization (equal); writing – review and editing (equal).
Mohammad Ghorbani: Conceptualization (equal); data curation (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Michael R. Levitt: Conceptualization (equal); methodology (equal); resources (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).
Simon Escalard: Conceptualization (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Symeon Missios: Conceptualization (equal); formal analysis (equal); validation (equal); writing – review and editing (equal).
Maksim Shapiro: Conceptualization (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal).
Frederic Clarenion: Formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).
Mahmoud Elhorany: Data curation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Rizwan A. Tahir: Conceptualization (equal); data curation (equal); formal analysis (equal); resources (equal); validation (equal); writing – review and editing (equal).
Patrick P. Youssef: Data curation (equal); investigation (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).
Robert M. Starke: Conceptualization (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).
Kareem El Naamani: Formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal).
Rawad Abbas: Conceptualization (equal); methodology (equal); project administration (equal); resources (equal); validation (equal); writing – review and editing (equal).
Osama Yassin: Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); visualization (equal); writing – review and editing (equal).
Jorge Galvan: Conceptualization (equal); data curation (equal); project administration (equal); resources (equal); software (equal); writing – review and editing (equal).
Joshua T. Billingsley: Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); visualization (equal); writing – review and editing (equal).
Abolghasem Mortazavi: Data curation (equal); formal analysis (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal).
Melanie Walker: Formal analysis (equal); methodology (equal); resources (equal); supervision (equal); validation (equal); writing – review and editing (equal).
Fabio Settecase: Data curation (equal); investigation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Manraj K.S. Heran: Conceptualization (equal); data curation (equal); resources (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Anna L. Kuhn: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); validation (equal); writing – review and editing (equal).
Ajit S. Puri: Formal analysis (equal); methodology (equal); resources (equal); software (equal); validation (equal); writing – review and editing (equal).
B. K. Menon: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – review and editing (equal).
Sanjeev Sivakumar: Conceptualization (equal); formal analysis (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal).
Ashkan Mowla: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal).
Alicia M. Zha: Investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Daniel Cooke: Data curation (equal); methodology (equal); project administration (equal); resources (equal); validation (equal); writing – review and editing (equal).
Justin E. Vranic: Conceptualization (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Christopher J. Stapleton: Formal analysis (equal); methodology (equal); resources (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Mayank Goyal: Data curation (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal).
Hannah Wu: Investigation (equal); methodology (equal); project administration (equal); resources (equal); validation (equal); writing – review and editing (equal).
Jake Cohen: Methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).
David Turkel-Parella: Investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Andrew Xavier: Data curation (equal); formal analysis (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal).
Muhammad Wagas: Data curation (equal); methodology (equal); software (equal); validation (equal); writing – review and editing (equal).
Adnan H Siddiqui: Conceptualization (equal); methodology (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).
Gaurav Gupta: Conceptualization (equal); data curation (equal); formal analysis (equal); project
administration (equal); validation (equal); writing – review and editing (equal).

Anil Nanda: Conceptualization (equal); investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – review and editing (equal).

Priyank Khandelwal: Investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

Cristina Tiu: Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); writing – review and editing (equal).

Pere Cardona: Conceptualization (equal); methodology (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

Natilia Perez de la Ossa: Investigation (equal); methodology (equal); resources (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

Xabier Urra: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); validation (equal); writing – review and editing (equal).

JF Arenillas: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal).

Marc Ribó: Conceptualization (equal); formal analysis (equal); investigation (equal); resources (equal); validation (equal); writing – review and editing (equal).

Manuel Requena: Data curation (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal).

Guglielmo Pero: Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); visualization (equal); writing – review and editing (equal).

Keith De Sousa: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal).

Mariangela Piano: Formal analysis (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal).

Fawaz Al-Mufti: Conceptualization (equal); investigation (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

Zafar Hashim: Data curation (equal); investigation (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

Sanjeev Nayak: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – review and editing (equal).

Leonardo Renieri: Conceptualization (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

Rose Du: Conceptualization (equal); formal analysis (equal); methodology (equal); resources (equal); software (equal); validation (equal); writing – review and editing (equal).

Mohamed A. Aziz-Sultan: Data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

David Liebeskind: Conceptualization (equal); data curation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

R.G. Nogueira: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – review and editing (equal).

Mohamad Abdalkader: Conceptualization (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

Thanh N Nguyen: Conceptualization (equal); formal analysis (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

Nicholas Vigilante: Conceptualization (equal); data curation (equal); investigation (equal); resources (equal); validation (equal); writing – review and editing (equal).

Jonathan A Grossberg: Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – review and editing (equal).

Michael R. Gooch: Conceptualization (equal); data curation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal).

Nabeel Herial: Conceptualization (equal); investigation (equal); project administration (equal); resources (equal); validation (equal); writing – review and editing (equal).

Stavropoula Tjoumakaris: Conceptualization (lead); methodology (lead); supervision (lead); validation (lead); writing – review and editing (lead).

Aman B. Patel: Conceptualization (lead); formal analysis (equal); investigation (lead); methodology (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead).

Ambooj Tiwari: Conceptualization (lead); formal analysis (lead); supervision (lead); validation (lead); writing – original draft (lead); writing – review and editing (lead).

Pascal M. Jabbour: Conceptualization (lead); formal analysis (lead); supervision (lead); validation (lead); writing – original draft (lead); writing – review and editing (lead).

CONFLICT OF INTEREST

There are no relevant conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All procedures in the studies involving human participants were performed according to our institutional review board ethical standards and national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was reviewed and approved by our
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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.