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# Incidence, Characteristics and Outcomes of Large Vessel Stroke in COVID-19 Cohort: An International Multicenter Study

**BACKGROUND:** While there are reports of acute ischemic stroke (AIS) in coronavirus disease 2019 (COVID-19) patients, the overall incidence of AIS and clinical characteristics of large vessel occlusion (LVO) remain unclear.

**OBJECTIVE:** To attempt to establish incidence of AIS in COVID-19 patients in an international cohort.

**METHODS:** A cross-sectional retrospective, multicenter study of consecutive patients admitted with AIS and COVID-19 was undertaken from March 1 to May 1, 2020 at 12 stroke centers from 4 countries. Out of those 12 centers, 9 centers admitted all types of strokes and data from those were used to calculate the incidence rate of AIS. Three centers exclusively transferred LVO stroke (LVOs) patients and were excluded only for the purposes of calculating the incidence of AIS. Detailed data were collected on consecutive LVOs in hospitalized patients who underwent mechanical thrombectomy (MT) across all 12 centers.

**RESULTS:** Out of 6698 COVID-19 patients admitted to 9 stroke centers, the incidence of stroke was found to be 1.3% (interquartile range [IQR] 0.75%-1.7%). The median age of LVOs patients was 51 yr (IQR 50-75 yr), and in the US centers, African Americans comprised 28% of patients. Out of 66 LVOs, 10 patients (16%) were less than 50 yr of age. Among the LVOs eligible for MT, the average time from symptom onset to presentation was 558 min (IQR 82-695 min). A total of 21 (50%) patients were either discharged to home or discharged to acute rehabilitation facilities.

**CONCLUSION:** LVO was predominant in patients with AIS and COVID-19 across 2 continents, occurring at a significantly younger age and affecting African Americans disproportionately in the USA.

**KEY WORDS:** COVID-19, Acute ischemic stroke, Large vessel occlusion, Epidemiology

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**A** novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected more than 8 million people across the globe. The incidence of acute ischemic stroke (AIS) in coronavirus disease 2019 (COVID-19) patients is just beginning to be elucidated, but whether the clinical profile of

AIS in such patients is different from the pre-COVID-19 era is yet to be established.<sup>1-5</sup> Recent studies have shown that patients with COVID-19 appear to have a heightened risk of AIS compared with patients with influenza.<sup>6</sup> Given that SARS-CoV-2 affects multiple systems, which potentially increases the risk of embolic

**ABBREVIATIONS:** ACE, angiotensin converting enzyme; AIS, acute ischemic stroke; CMV, cytomegalovirus; CRP, C-reactive protein; CTA, CT angiogram; DIC, disseminated intravascular coagulopathy; ER, emergency room; HERMES, Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials; IQR, interquartile range; MRA, MR angiogram; MT, mechanical thrombectomy; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; sICH, symptomatic intracerebral hemorrhage; tPA, tissue plasminogen activator; VZV, varicella zoster virus

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stroke, including coagulation, endothelium, cardiac rhythm, and hypoxia,<sup>7,8</sup> it is important to understand if acute LVO stroke (LVOs), the most disabling stroke subtype, may be occurring at an increased rate in COVID-19 patients. In addition, it is important to determine whether the clinical characteristics of LVOs in COVID-19 patients and outcomes of treatment with mechanical thrombectomy (MT), with or without IV tissue plasminogen activator (tPA), differ from those in non-COVID-19 patients. While stroke is not typically the primary presentation of COVID-19, recent evidence has been emerging regarding acute stroke in COVID-19 patients. Most alarmingly, stroke is being increasingly reported in young adults with COVID-19.<sup>9,10</sup>

## METHODS

### Patient Selection

We conducted a cross-sectional, international multicenter retrospective study of laboratory-confirmed COVID-19 patients with acute LVOs consecutively admitted between March 1 and May 1 in 12 thrombectomy capable stroke centers located in the USA, United Kingdom, Spain, and Italy. The ethical review boards of participating institutions approved the study. Given the retrospective nature of the study, patient consent was waived. Patients with AIS were identified as patients presenting with focal neurological symptoms. Diagnosis of AIS required confirmation by brain computed tomography (CT) or magnetic resonance imaging (MRI). LVO was defined as an occlusion of internal carotid artery, M1 segment of middle cerebral artery, or basilar artery confirmed by CT angiogram (CTA) or MR angiogram (MRA) as per the individual institutional protocol.

### Data Collection and Analysis

We collected data on the total number of hospitalized COVID-19 and AIS patients, with detailed data on LVO/AIS patients in 9 of 12 stroke centers to define the incidence of AIS and proportion LVOs. The other 3 centers were exclusive MT referral centers and admitted all stroke subtypes, and hence were excluded for AIS incidence and LVOs proportion calculation, as they would not necessarily reflect the true burden of AIS in COVID-19 patients. The total number of AIS patients included those presenting to the emergency room (ER) and/or patients

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developing stroke during hospitalization. We did not include any outpatient AIS at these centers during this period. For characterizing detailed demographic and clinical features of LVOs patients eligible for MT as well as their response to MT, all 12 centers were included.

## RESULTS

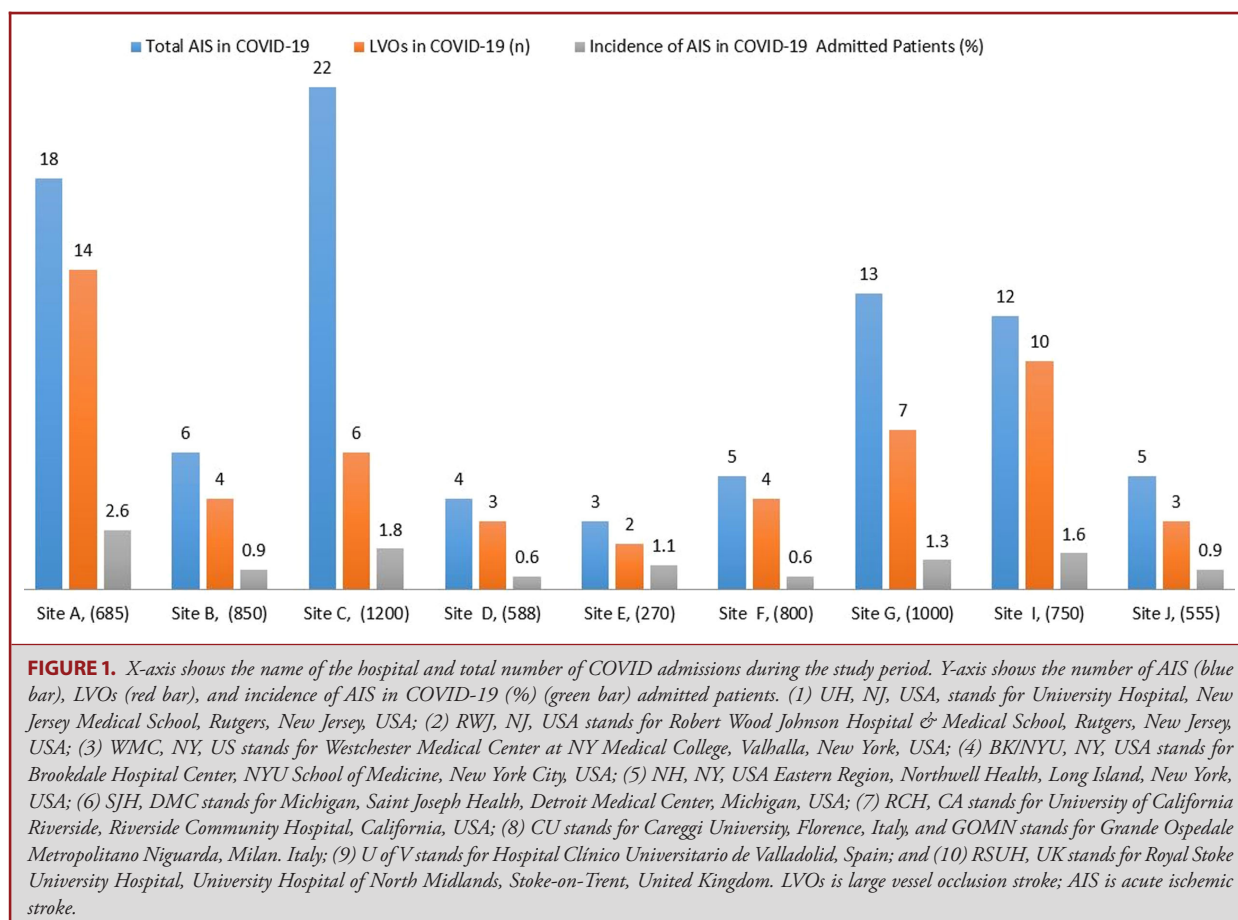
Out of a total of 6698 patients admitted with COVID-19 positive at 9 stroke centers during the study period, the incidence of stroke was 88/6698 (1.3%, IQR 0.75%-1.7%). Of these, 53/88 (60%) were LVOs (Figure 1). To define the clinical characteristics of COVID-19 positive LVOs, acute LVOs from all 12 centers were analyzed and a total of 66 patients were identified. In this cohort, the median age of LVOs patients was 51 yr (IQR 50-75 yr). Out of 66, a total of 42 (63%) of these patients underwent MT (Table 1). Out of 66 patients, 24 patients (36%) either arrived late or were too unstable for MT. The median age in this subgroup of patients undergoing MT was 54 yr (IQR 52-76 yr). Eight of these (8/42, 19%, IQR 32-46 yr) patients who underwent MT were under 50 yr of age (Table 2). One (1/8, 12%) patient in this young MT cohort died during hospitalization. Among the 8 US centers, African Americans (AAs) constituted 28% of all LVOs patients. The rate of internal carotid artery-middle cerebral artery (ie, ICA-MCA tandem) occlusion was 21%. The median time from symptom onset to presentation to an ER was 558 min (IQR, 83-695 min).

The majority of patients had elevated serological markers of inflammation with a mean C-reactive protein (CRP) and D-dimer of 48 and 997, respectively. With regard to outcomes of reperfusion therapy in this LVO cohort, the thrombolysis in cerebral infarction (TICI) > 2b reperfusion rate was 81% (34/42) and parenchymal hematoma type 1 (PH1) rate was 14% (5/42) with no symptomatic intracerebral hemorrhage (sICH). Out of 42 patients, 21 (50%) patients who underwent MT were discharged home or to an acute rehabilitation center, while the remainder were discharged to a skilled nursing facility or remain hospitalized over the study period (Figure 2). The majority of patients in the COVID-19 LVO cohort (53/66, 81%) presented to the ER. A total of 13 (13/66, 19%) patients had LVOs during hospitalization. The incidence of LVOs in AA and young patients in non-COVID-19 cohort was 6% and 14%, respectively (data collected from 9 out of 12 centers).

## DISCUSSION

Over the past several months, the SARS-CoV-2 pandemic has rapidly encompassed the globe, inflicting millions with COVID-19. Stroke can be one of the presenting features or complications of SARS-CoV-2. We report a demographic and clinical profile of AIS in COVID-19 patients, which is distinct from AIS pre-COVID-19.

Our findings of an incidence of AIS of 1.3% (IQR .75-1.7) is similar to AIS incidence in a recent study of 2 centers in New York. This is lower than the initial report from Mao et al



and closer to the report by Yaghi et al.<sup>1,2,6</sup> Furthermore, our study shows a substantially higher rate of LVOs in COVID-19, including tandem occlusions, as compared to other stroke subtypes. The reported incidence of LVO in AIS is estimated to be 20% to 38% of total strokes outside the context of COVID-19.<sup>11</sup> In our cohort, LVO incidence was much higher at 60% (53 of 88 patients) at 9 centers. These LVOs occur in a much younger age group than would otherwise be expected, and in the USA, they also seem to affect African Americans disproportionately as compared to historical controls.<sup>4,12-14</sup> We believe that the pathophysiology of COVID-19 likely leads to this higher incidence of LVO in AIS. Another possibility is that those with non-LVO strokes are not presenting to hospitals for evaluation.<sup>15</sup> A few recent series have noted a decline in both stroke volume and patient reluctance to attend the ER. We noted a similar worrisome trend in our overall cohort with 17 out of 66 LVO patients arriving with near-complete infarcts, which were too late for possible MT.<sup>13,15,16</sup>

### Proposed Mechanism of LVO in COVID-19 Patients

Our results are consistent with an increased risk of AIS in those without traditional risk factors as an emerging

hallmark of COVID-19.<sup>6</sup> Early speculation surrounding vascular occlusion in COVID-19 also focused on disseminated intravascular coagulopathy (DIC), given that this phenomenon befalls the critically ill.<sup>17</sup> Markers of inflammation, including CRP, demonstrated consistent elevation in our cohort. However, the laboratory findings in these patients do not always support a formal diagnosis of DIC, and one would have expected a similar incidence in prior historical coronavirus epidemics.

It is increasingly understood that SARS-CoV-2 trespass of the blood-brain barrier occurs at the level of the lung alveolar capillary network or alternatively via the ganglia responsible for taste and smell. In both instances, this is at least partly facilitated by affinity for endothelial angiotensin converting enzyme (ACE) II receptors. Hematogenous spread subsequently invites thrombosis by complex interplay of endothelial damage, antiphospholipid antibody formation, reactive oxygen species generation, and downstream phenomena.<sup>18</sup> As an ACE2-seeking virus, we suggest that capillary endothelial damage likely predisposes to recurrent stroke.<sup>19</sup> Cerebral involvement of influenza virus, varicella zoster virus (VZV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV) has been

**TABLE 1. Large Vessel Occlusion in COVID-19 Confirmed Patients: Demographics, Comorbidities, Hospitalization Events, and Outcomes**

Characteristics	Young stroke <sup>a</sup> (18-49 yr)	Nonyoung stroke (> 50 yr)	Overall group
Large vessel occlusion (LVO) in COVID-19 (n)	10	56	66
Median age (yr) (range)	36 (27-49)	73 (51-87)	51 (27-87)
MT performed (%)	8 (80)	34(60)	42 (63)
<b>Characteristics of LVO undergoing MT<sup>b</sup></b>			
Median NIHSS (IQR)	11 (15-22)	18 (14-24)	18 (12-24)
<b>Sex</b>			
Male, n (%)	5 (62)	16(47)	21 (50)
Female, n (%)	3 (37)	18(53)	21(50)
<b>Race/ethnicity, n (%)</b>			
White	2 (25)	22 (64)	24 (57)
African American	2 (25)	9(26)	11(26)
Hispanic/Latino	1 (12.5)	4 (11)	5 (11)
Asian/Pacific Islander/others	1 (12)	1 (3)	2 (5)
<b>Stroke sign and symptoms</b>			
Median NIHSS (IQR)	11(15-22)	18 (14-24)	13 (12-24)
<b>LVO, n (%)</b>			
Right MCA	1 (12)	9 (26)	11 (26)
Left MCA	6 (75)	13 (38)	19 (45)
Distal ICA + right or left MCA occlusion (tandem)	1 (12)	8 (23)	9 (21)
BA	0	4 (11)	4 (9)
Median time from last known well to ER (min)	408.5	345	558.5
IQR	80-747	82-555	82-695
<b>Laboratory studies (median, IQR)</b>			
D-dimer, ng/mL	1683 (202-4332)	912 (223-3260)	997 (223-3286)
White-cell count x 10 <sup>3</sup> /mm <sup>3</sup>	8.71 (8-11.725)	7.4 (3.5-9.77)	8 (5.2- 10)
Ferritin, ng/mL	1064 (10-1100)	368 (0-654)	511 (12-720)
C-reactive protein, mg/L	59 (22-107)	39 (5.95-41.5)	48 (6.15-56.25)
Absolute neutrophil count, %	7.85 (5.05-11.1)	4.3 (4-8.6)	9.5 (5.15- 10)
Absolute lymphocyte count, %.	5.75 (2.1-17)	1.5(1-8.5)	5.4 (1.3-10)
<b>COVID-19 symptoms, n(%)</b>			
Fever	2 (25)	11 (32)	12 (28)
Cough	5/8 (62)	18/(52)	24 (57)
SOB	2/8 (25)	15/34(44)	16(38)
<b>Chest X-ray infiltrate</b>			
Unilateral	3/8 (37.5)	9/34 (26)	12/42 (28)
Bilateral	4/8(50)	28/34(82)	32/42 (76)
Intubation on presentation <sup>c</sup>	2/8 (25)	5(14)	7/42 (16)
<b>Angiographic results</b>			
TICI 0-2A	1/8(12)	7/34 (20)	8/42 (19)
TICI 2B/3	7/8 (87)	27/34 (80)	34/42 (81)
> PH1	2/8 (25)	4/32 (11)	6/40 (14)
sICH	0	0	0
<b>Preexisting conditions/comorbidities, n (%)</b>			
Hypertension	1 (12)	28 (82)	29 (69)
Hyperlipidemia	1 (12)	18 (52)	19 (45)
Diabetes mellitus	4 (50)	9 (26)	13 (30)
Afib	0 (0)	10 (34)	10 (23)
Smoking (active)	0	8 (23)	8 (19)
Known, hypercoagulable	0	0	0
<b>Treatment</b>			
IV-rtPA	3/8 (37)	16/34 (47)	19/42 (45)
Anticoagulation	3/8 (37)	3/34 (8)	6/42 (14)
Antithrombotic agent	5/8 (75)	25/34 (73)	31/40 (73)
Statins	7/8 (87.5)	24/32 (70)	31/40 (73)
Azithromycin	3/8 (37.5)	10/34 (29)	13/42 (30)

Characteristics	Young stroke <sup>a</sup> (18-49 yr)	Nonyoung stroke (>50 yr)	Overall group
Hydroxychloroquine	1/8 (12.5)	14/34 (41)	15/40 (35)
Disposition, n (%)			
Home	3/8 (37)	5/34 (23)	8/42 (19)
Acute rehabilitation	3/8 (37)	10/34 (35)	13/42 (30)
Skilled nursing facility	1/8 (12)	4/34 (11)	5/42 (11)
Currently still inpatient	0	6/34 (17)	6/42 (14)
Death in hospital, n, (%)	1/8 (12)	9/32 (28)	10/42 (23)

IQR, interquartile range; VTE, venous thromboembolism; IV-rtPA, intravenous recombinant tissue plasminogen activator; ICA, internal carotid artery; BA, basilar artery; MCA, middle cerebral artery. Reference range: C-reactive protein (CRP), 0-5 mg/L; D-dimer, 90-500 ng/mL; ferritin, 20-400, ng/mL; absolute neutrophil % x 10<sup>3</sup> /ul, absolute lymphocyte % 10<sup>3</sup> /ul; NIHSS, National Institutes of Health Stroke Scale ranging from 0 to 42, with a higher number indicating more severe stroke; TICI, thrombolysis in cerebral infarction score, ranging from TICI 0 (no vessel recanalization), TICI 2A (<50% vessel recanalization), TICI 2B (>50% vessel recanalization), TICI 2C (>90% vessel recanalization) to TICI 3 (complete vessel recanalization); PH, parenchymal hemorrhage with mass effect: PH1 < 30% of the infarcted area with mild space-occupying effect and PH2 > 30% of the infarcted area with significant space-occupying effect; sICH, symptomatic intracerebral hemorrhage; DM, diabetes mellitus; HTN, hypertension.

<sup>a</sup>Young was defined as age less than 50 yr.

<sup>b</sup>The clinical, laboratory, angiographic, and neurological outcomes were calculated in COVID-19 patients who underwent mechanical thrombectomy.

<sup>c</sup>Not including intubations required for general anesthesia in the operating room.

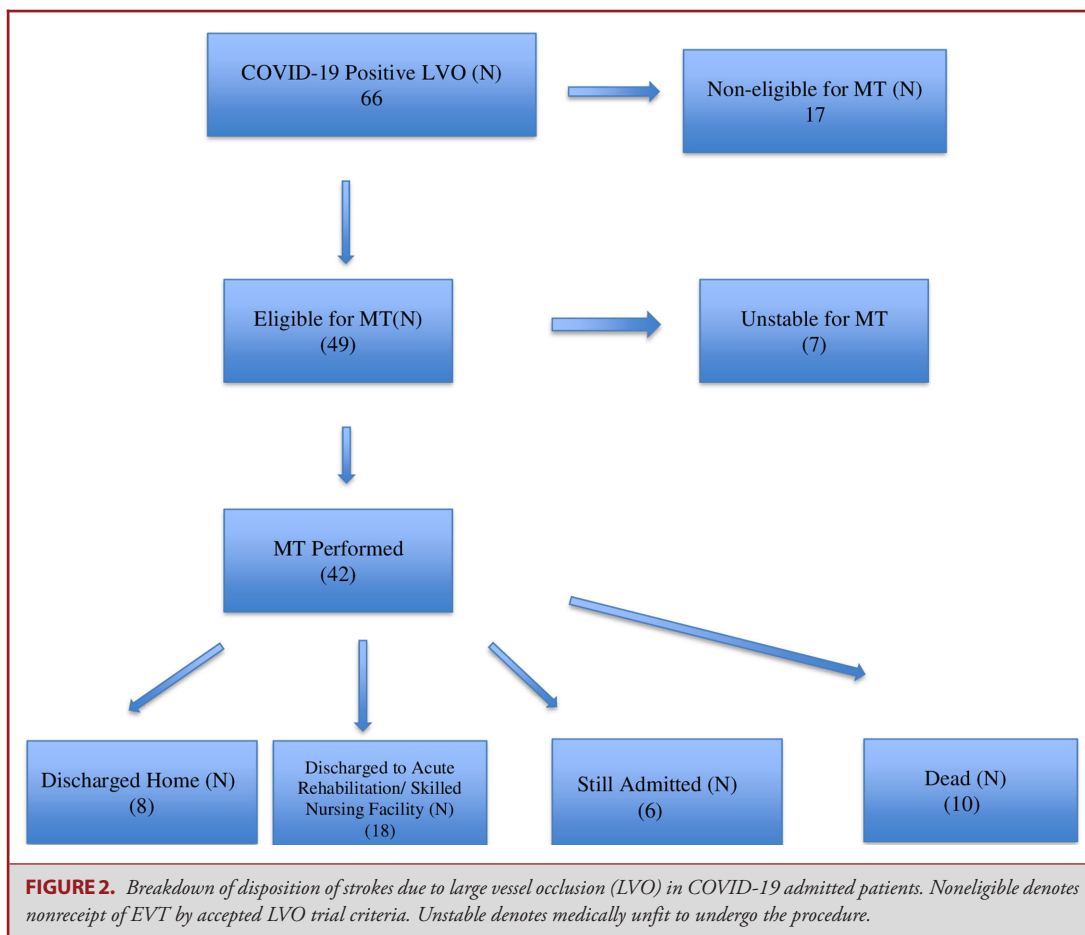
Variable <sup>a</sup>	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age	27	33	37	38	39	40	49	49
Sex	Male	Female	Male	Male	Female	Male	Male	Female
Race	AS	AA	H	C	H	AA	H	C
NIHSS <sup>b</sup>	18	17	22	6	12	26	19	25
Region, country	NYC, USA	NJ, USA	NJ, USA	NYC, USA	NYC, USA	NYC, USA	NYC, USA	Spain
Stroke risk factors	None	None	DM	None	None	HTN, DM	DM.	None
Location of LVO	Left distal ICA to MCA	Left MCA	Left MCA	Right MCA	Left MCA	Left MCA	Left MCA	Left MCA
Time to presentation (h)	12	2.2	4	1	12	15	1	2.5
TICI score	2A	2B	2C	2B	3	2C	2B	3
COVID-19 symptoms	Cough	Cough, fever, chills	Cough	Cough, fever, SOB	None	Cough	SOB	None
Chest X-ray	Infiltrate B/L lungs	Unremarkable	Infiltrate in both lungs	Infiltrate in both lungs	Unremarkable	Right lung infiltration	Unremarkable	Right lung infiltration
Fibrinogen, mg/dL	970	339	368	623	Not sent	542	170	403
D-dimer, ng/mL	5446	4964	2312	2439	Not Sent	769	601	1054
Ferritin, ng/mL	592	970	703	1533	Not sent	207	130	100
CRP, mg/L	22	22	107	83	Not sent	56	19	9.3
White cell count, per mm <sup>3</sup>	17.4	8	8	5.7	9.42	26	8	12.3
Treatment	IVrtPA, DAPT, converted to lovenox on day13	Aspirin 81 mg	Aspirin 81 mg	IV-rtPA, aspirin 81 mg	Xarelto	Full dose lovenox	Aspirin 81 mg	Aspirin 100 mg
Outcome	Acute rehab	Death	Acute rehab	Home	Home	Acute rehab	Home	Home

<sup>a</sup>Reference ranges are as follows: C-reactive protein (CRP) 0-5 mg/L, D-dimer 90-500 ng/mL, ferritin 20-400 ng/mL.

<sup>b</sup>Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher numbers indicating more severe stroke.

MCA, middle cerebral artery; ICA, internal cerebral artery; LVO, large vessel occlusion; TICI score, thrombolysis in cerebral infarction score, ranging from TICI 0 (no vessel recanalization), TICI 2A (<50% vessel recanalization), TICI 2B (>50% vessel recanalization), TICI 2C (>90% vessel recanalization) to TICI-3 (complete vessel recanalization); IV-rtPA, intravenous tissue recombinant plasminogen activator; DM, diabetes mellitus; HTN, hypertension; SOB, shortness of breath; AA, African American; C, Caucasian; H, Hispanic; A, Asian; M, male; F, female; NYC, New York City; NJ is New Jersey.





demonstrated to be a risk factor for stroke.<sup>6,20</sup> It remains unclear if SARS-CoV-2 leads to increased risk of stroke by weakening the intima of arteries (thereby increasing the risk for dissection), by causing a generalized hypercoagulable state, or by a combination of both factors. Nonetheless, AIS in those without traditional risk factors is an emerging hallmark of COVID-19, unprecedented in the modern era of previous viral pandemics, and a distinguishing characteristic compared with other coronavirus infections.<sup>6</sup>

### Stroke in the Young

Despite many different definitions, AIS in those younger than 50 yr of age is considered “young” per the majority of large series.<sup>12</sup> Approximately 10% to 15% of all ischemic strokes occur in young adults under 50 yr old. Of those, LVOs constitute approximately one-third of overall ischemic strokes. Oxley et al recently reported cases of LVOs in COVID-19 patients less than 50 yr of age.<sup>9</sup> We noted a similar trend with 10 (16%) cases being under 50 yr of age. Out of these 10 younger LVOs cases, 8 underwent MT. Interestingly, in our international cohort, the majority of cases in the young age group (8/10) were from the NYC metropolitan area. The mean age of this young cohort of

LVO was 35 yr (range 32–46). All of the cases had elevated markers of inflammation.

There is also an over-representation of AA in the USA in our MT cohort (28%), suggesting a disproportionately higher race-ethnic-related incidence consistent with the overall higher rates of COVID-19 seen among African Americans.<sup>14,21</sup> Our findings are reassuring with regard to treatment outcomes with reperfusion rates, and intracranial hemorrhage rates similar to historical MT data.<sup>13</sup> Similar revascularization rates have been reported in HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials), a large meta-analysis of pre-COVID MT trials for LVO. Compared with this era, MT appears to be similarly efficacious, but the propensity for LVO in COVID-19 to affect younger patients and patients with concurrent acute disease (eg, respiratory disease) complicates comparison.<sup>13</sup> As the majority of COVID-19 LVOs patients who underwent MT were not primarily sick with COVID-19 syndrome but rather came to the ER for their stroke symptoms, their mortality rate was lower than the rates reported in patients primarily hospitalized for COVID-19.<sup>22,23</sup> It remains to be seen that the long-term outcomes on these patients will contribute to our understanding of this process.

## Limitations

This study has several limitations. There are no long-term outcome data for AIS patients beyond the study period. We did not collect the total number of stroke admissions and compared them to previous years or to the non-COVID-19 cohort as our focus was to define the incidence of AIS and characteristic of LVO strokes in admitted COVID-19 patients. We included patients who had LVOs but were not candidates for MT; however, there is certainly a possibility that some patients who developed LVOs in hospital were not screened for AIS if they were too unwell and had limited neurological examinations while on ventilators. As mentioned previously, there is a possibility that patients with minor strokes and less-disabling strokes are less likely to seek medical attention during this pandemic, which may have skewed the data in favor of LVO strokes. We do not have long-term follow-up data; hence, disposition was used in lieu of 90-d modified Rankin Scale (mRS). In order to bring these data in an expedited fashion to the medical community, comparison was made to historical data rather than the pre-COVID-19 data at each center.

## CONCLUSION

This international multicenter study reports a multicentric observational experience of a substantially higher proportion of the LVOs subtype occurring at a younger-than-usual median age among all strokes in COVID-19 patients. These data have implications for urgent research into thromboprophylaxis to prevent large arterial emboli in patients with COVID-19, including those who may not have traditional vascular risk factors.

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