Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Using Clinical and Echocardiographic Characteristics to Characterize the Risk of Ischemic Stroke in Patients with COVID-19

Connor P. Oates, a Solomon W. Bienstock, b Michael Miller, a Gennaro Giustino, b Tatyana Danilov, c Nina Kukar, d Nikola Kocovic, a Dylan Sperling, a Ranbir Singh, a Daniel Benhuri, c Frans Beerkens, a Anton Camaj, b Stamatios Lerakis, b Lori Croft, b Laura K. Stein, e and Martin E. Goldman, b

Background: COVID-19 has been associated with an increased incidence of ischemic stroke. The use echocardiography to characterize the risk of ischemic stroke in patients hospitalized with COVID-19 has not been explored. Methods: We conducted a retrospective study of 368 patients hospitalized between 3/1/2020 and 5/31/2020 who had laboratory-confirmed infection with SARS-CoV-2 and underwent transthoracic echocardiography during hospitalization. Patients were categorized according to the presence of ischemic stroke on cerebrovascular imaging following echocardiography. Ischemic stroke was identified in 49 patients (13.3%). We characterized the risk of ischemic stroke using a novel composite risk score of clinical and echocardiographic variables: age <55, systolic blood pressure >140 mmHg, anticoagulation prior to admission, left atrial dilation and left ventricular thrombus. Results: Patients with ischemic stroke had no difference in biomarkers of inflammation and hypercoagulability compared to those without ischemic stroke. Patients with ischemic stroke had significantly more left atrial dilation and left ventricular thrombus (48.3% vs 27.9%, p = 0.04; 4.2% vs 0.7%, p = 0.03). The unadjusted odds ratio of the composite novel COVID-19 Ischemic Stroke Risk Score for the likelihood of ischemic stroke was 4.1 (95% confidence interval 1.4-16.1). The AUC for the risk score was 0.70. Conclusions: The COVID-19 Ischemic Stroke Risk Score utilizes clinical and echocardiographic parameters to robustly estimate the risk of ischemic stroke in patients hospitalized with COVID-19 and supports the use of echocardiography to characterize the risk of ischemic stroke in patients hospitalized with COVID-19.

Key Words: COVID-19—Ischemic stroke—Echocardiography—Risk score—Stroke prevention

Introduction

Coronavirus disease 2019 (Covid-19) caused by infection with SARS-CoV-2 has been associated with a variety of systemic complications resulting in substantial morbidity and mortality. Early case series identified an elevated incidence of ischemic stroke in patients with COVID-19. In retrospective studies, ischemic stroke has been identified in 0.5-5.8% of patients hospitalized with COVID-19. Infection with COVID-19 has been independently associated with acute ischemic stroke compared with control subjects and the severity of COVID-19 syndrome correlates with
risk acute stroke. The likelihood of ischemic stroke is markedly higher in patients hospitalized with COVID-19 infection compared with controls hospitalized with influenza infection. The pathophysiology underlying the association between ischemic stroke and COVID-19 is an area of active investigation. Infection alone has previously been identified as a risk factor for acute stroke. COVID-19 has also been associated with endothelial damage, microvascular thrombi formation, immune-modulated cytokine-release syndrome, arrhythmia and myocardial dysfunction that may all contribute to the burden of ischemic stroke. The limited pathophysiological understanding of the relationship between COVID-19 and ischemic stroke has not yet translated into serologic, radiographic or clinical markers that robustly characterize the risk of ischemic stroke in patients with COVID-19. Etiology of ischemic stroke in several small cohorts of patients with COVID-19 has been estimated utilizing the gold standard TOAST classification system. Most of the COVID related ischemic strokes have been classified as either cardioembolic (14.3-40%) or strokes of undetermined source (35.0-42.8%) with a minority of strokes from small vessel occlusion (6-21.4%), stroke of other determined etiology (7.2-20%) and stroke from large-artery atherosclerosis (6-14.3%). The evaluation of risk factors for developing ischemic stroke has been limited in prior reports by the scarcity of echocardiographic studies in patients with COVID-19. In part, this has been due to a concerted effort to minimize exposure of healthcare workers, including echocardiographers, to patients with COVID-19. Thus, we characterized stroke in a cohort of patients with COVID-19 who underwent comprehensive cardiovascular imaging with transthoracic echocardiography (TTE) to identify risk factors for the development of ischemic stroke.

Methods

Study design

We conducted a multicenter study with retrospective data collection of hospitalized patients with confirmed SARS-CoV-2 infection with polymerase chain reaction assay of nasal or pharyngeal swab specimens who underwent a formal TTE evaluation during their index hospitalization at Mount Sinai Hospital, Mount Sinai Beth Israel, Mount Sinai West, Mount Sinai Queens or Elmhurst Hospital in New York City (United States) between March 2020 and May 2020. Patients who only had point-of-care cardiac ultrasound were not included in this study. Approval for the study, without the need for patient consent, was obtained from each center’s respective institutional review board.

Data collection and endpoints

Data was collected from each center’s electronic health record and included patient demographic information, presenting vital signs and symptoms, comorbidities, home medications, chest x-ray findings, electrocardiogram findings, laboratory values echocardiographic findings, computed tomography imaging (CT), magnetic resonance imaging (MRI), inpatient treatments received and in-hospital outcomes. Definitions and reference values used in data collection are reported in the Supplement.

Patients were categorized according to the presence or absence of the diagnosis of acute or subacute ischemic stroke defined by CT or MRI during index hospitalization following echocardiographic exam. All patients were expressing neurologic deficits at the time of imaging. The etiology of all ischemic strokes was independently assessed by vascular neurologists based on the TOAST classification into large-artery atherosclerosis, cardioembolic, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology.

A variable of COVID-19 clinical severity was also included in univariate analysis. Patient clinical severity was characterized as mild-moderate if requiring hospitalization, severe if a patient required mechanical ventilation and most severe if a patient required mechanical ventilation and suffered shock.

Statistical analysis and risk score

Descriptive statistics were used to summarize the data. Categorical variables were summarized as counts and percentages, and compared using chi-squared tests. Continuous variables were reported as medians and interquartile ranges, and compared using Wilcoxon rank-sum tests.

A novel COVID-19 Ischemic Stroke Risk Score was developed using five variables associated with stroke that were identified with an unadjusted logistic regression model: (1) Age <55, (2) admission systolic blood pressure >140 mmHg, (3) anticoagulation prior to admission, (4) left atrial dilation defined as left atrial volume index (LAVI) >34 mL/m² and (5) presence of left ventricular (LV) thrombus. The presence of each variable was weighed equally and assigned a value of plus-one, except for anticoagulation prior to admission, which was assigned a value of minus-one. The risk score was calculated as the sum of the aforementioned variables and evaluated as a predictor of ischemic stroke. Area under the receiver operating characteristic curve was calculated for each variable and for the risk score. Each model was internally validated using bootstrap resampling for 100 iterations. The mean difference between the bootstrap model values and the values from the full dataset were subtracted from the final reported area under the curve.

Patients who were still hospitalized at the time of data freeze were regarded as having a censored length of stay.
No imputation was made for missing data. All analyses were performed with the use of Stata software version 16.1.

**Results**

A total of 368 patients were admitted with COVID-19 at five hospital centers in New York City between 3/1/2020 – 5/31/2020 and met inclusion criteria for this study by undergoing a comprehensive TTE during index hospitalization. 64/368 (17.4%) of all patients suffered stroke during hospitalization and 49/368 (13.3%) patients were diagnosed with ischemic stroke. 15/368 (4.1%) of patients were diagnosed with hemorrhagic stroke and excluded from the study. 95.9% of patients with ischemic stroke underwent CT of the brain without contrast, 67.4% underwent CT angiography of the head/neck and 71.5% underwent MRI imaging of the brain. 71.4% of patients with ischemic stroke underwent active telemetry monitoring for an average of 16.1 ± 15.0 days.

Ischemic stroke occurred in 49 of 368 (13.3%) patients with COVID-19 who underwent echocardiograms. Median age was 61 years and 65% of patients were male. Baseline clinical characteristics are summarized in Table 1. Patients suffering ischemic stroke had higher baseline systolic blood pressure and diastolic blood pressure at admission compared to patients without ischemic stroke (143 vs 125 mmHg, p = <0.01; 80 vs 73 mmHg, p = <0.01) (Table 2). Patients with and without ischemic stroke had similar COVID-19 clinical severity when grouped into those with mild-moderate disease requiring admission, pulmonary disease requiring mechanical ventilation, and severe disease requiring mechanical ventilation and shock (p = 0.74). There was no significant difference in CHA2DS2VASC score between patients with and without ischemic stroke (p = 0.48). Peak lactate value was the only significant differences in laboratory characteristics between patients with and without ischemic stroke (2.5 vs 3.2 mmol/L, p = 0.01) (Table 2).

Patients with ischemic strokes had an average of 4.2 ± 4.1 days of COVID-19 related symptoms prior to presentation, and 40.8% of these patients presented with focal neurologic deficits. Patients were diagnosed with an ischemic stroke an average of 8.4 days ± 5.2 after expressing their first symptoms of COVID-19. Compared to patients without ischemic stroke, significantly more patients with ischemic stroke required an intensive care unit (71.4 vs 48.7%, p = <0.01) and the mean length of hospital stay for patients with ischemic stroke discharged from the hospital was 25.1 days ± 21.4. After subgrouping according to TOAST classification, 59.2% of ischemic strokes were identified as cryptogenic, 28.6% were cardioembolic, 4.1% were strokes of other determined etiologies, 4.1% were due to large-vessel atherosclerosis and 4.1% were due to small vessel occlusion.

On TTE (Table 3), patients with ischemic stroke were found to have a median ejection fraction of 60.5%. Patients with ischemic stroke had significantly more left atrial dilation compared to patients without ischemic stroke (48.3% vs 27.9%, p = 0.04). Of patients with ischemic stroke who underwent TTE, 12.5% had hypococontractile wall motion abnormalities and 12.5% had global dysfunction. 12.5% of patients with ischemic stroke had increased right ventricular size and 18.8% had decreased right ventricular function while the median pulmonary artery systolic pressure was 26 mmHg. 30.4% of patients with ischemic stroke who underwent peripheral saline contrast injection had evidence of right to left intracardiac or intrapulmonary shunting which was not significantly more frequent compared to patients without ischemic stroke (30.4 vs 20%, p = 0.23). 42.9% of patients with ischemic strokes who had a positive shunt study also had global cardiac dysfunction, right ventricular dysfunction and/or right ventricular dilation (42.9 vs 0.0%, p = 0.26). Significantly more left ventricular thrombus was seen in patients with ischemic stroke (4.2 vs 0.6%, p = 0.03) and all patients with left ventricular thrombi had regional wall motion abnormalities.

The COVID-19 Ischemic Stroke Risk Score was created based on five practical clinical variables that have been associated with ischemic stroke using a logistic regression model (Table 4). The unadjusted odds ratio of the composite risk score on the likelihood of ischemic stroke was 4.1 (95% confidence interval 1.4-16.1). The risk score was a significant predictor at the highest confidence level (p<0.01). The AUC for the risk score was 0.70 (Figure 1). With each integer increase in risk score (e.g., 2 to 3), the percentage of patients who experienced an ischemic stroke increased linearly by more than 20%. This trend was highly significant (p<0.01) (Figure 2).

**Discussion**

Though a hypercoagulable state, systemic endothelial inflammation with cytokine storm and underlying cardiomyopathy have been proposed as primary mechanisms of ischemic stroke in COVID-19, we found laboratory markers of inflammation (CRP, LDH, IL-6, ferritin, procalcitonin) and hypercoagulability (d-dimer) to be elevated in most patients affected by COVID-19 with no significant differences between patients with and without ischemic stroke.20 Neither inflammation of the cerebrovasculature nor hypercoagulability resulting in microthrombi can fully account for the incidence of ischemic strokes in our population. Similarly, the burden of traditional risk factors for stroke prior to hospitalization and measures of illness severity, reflected in the CHA2DS2VASC score and COVID-19 clinical severity score, respectively, were similar in COVID-19 patients with and without ischemic stroke. None of these variables added power to the COVID-19
Ischemic Stroke Risk Score and were not included in the model. Meanwhile, there is substantial evidence mounting that severe COVID-19 infection is associated with myocardial injury, cardiovascular dysfunction and new onset arrhythmias. To our knowledge, no prior studies have included echocardiograms to document cardiac

### Table 1. Baseline characteristics of patients admitted with COVID-19.

| Background Characteristics | Ischemic Stroke (n=49) | No Ischemic Stroke (n=304) | P-value |
|----------------------------|------------------------|---------------------------|---------|
| Age                        | 58 (49-68)             | 61 (51-72)                | 0.28    |
| Male sex                   | 32 (65.3)              | 207 (65.1)                | 0.96    |
| Race                       |                        |                           | 0.27    |
| White                      | 18/42 (42.9)           | 100/251 (39.8)            |         |
| Black                      | 12/42 (28.6)           | 51/251 (20.3)             |         |
| Asian                      | 3/42 (7.1)             | 46/251 (18.3)             |         |
| Other                      | 9/42 (21.4)            | 54/251 (21.5)             |         |
| Hispanic ethnicity         | 15/45 (33.3)           | 111/281 (39.5)            | 0.64    |
| BMI                        | 27 (24-33)             | 28 (25-33)                | 0.66    |
| Past Medical History       |                        |                           |         |
| Hypertension               | 28/49 (22.5)           | 185/304 (60.9)            | 0.64    |
| Diabetes                   | 20/49 (40.8)           | 127/304 (41.7)            | 0.90    |
| Coronary artery disease    | 10/49 (20.4)           | 53/304 (17.4)             | 0.69    |
| Prior myocardial infarction| 1/49 (2.0)             | 15/302 (5.0)              | 0.71    |
| Prior stroke               | 4/49 (8.2)             | 19/304 (6.3)              | 0.54    |
| Chronic kidney disease     | 5/49 (10.2)            | 51/304 (16.8)             | 0.30    |
| End stage renal disease    | 4/49 (8.2)             | 26/304 (8.6)              | 0.93    |
| Anemia                     | 5/49 (10.2)            | 48/304 (15.8)             | 0.39    |
| COPD                       | 2/49 (4.1)             | 19/304 (6.3)              | 0.79    |
| Asthma                     | 6/49 (12.2)            | 31/304 (10.2)             | 0.67    |
| Heart failure              | 4/49 (8.2)             | 31/304 (10.2)             | 0.80    |
| Atrial fibrillation        | 3/49 (6.1)             | 35/304 (11.5)             | 0.33    |
| Prior Medication Use       |                        |                           |         |
| ACE/ARB                    | 11/49 (22.5)           | 75/302 (24.8)             | 0.63    |
| ARNI                       | 1/49 (2.0)             | 1/302 (0.3)               | 0.26    |
| Beta Blocker               | 11/49 (22.5)           | 85/302 (28.2)             | 0.49    |
| Calcium Channel Blocker    | 12/49 (24.5)           | 72/302 (23.8)             | 0.92    |
| Diuretics                  | 6/49 (12.2)            | 41/302 (13.6)             | 0.80    |
| Insulin                    | 7/49 (14.3)            | 42/300 (13.9)             | 0.95    |
| Statin                     | 13/49 (26.5)           | 115/302 (38.1)            | 0.15    |
| Aspirin                    | 15/49 (30.6)           | 85/302 (28.2)             | 0.73    |
| Anticoagulation            | 2/49 (4.1)             | 36/302 (11.9)             | 0.14    |
| DOAC                       | 1/49 (2.0)             | 32/303 (10.6)             | 0.06    |
| Anti-arrhythmic            | 0/49 (0.0)             | 10/303 (3.3)              | 0.37    |
| Immunosuppression          | 2/49 (4.1)             | 32/303 (10.6)             | 0.20    |
| CHA2DS2VASC^               |                        |                            |         |
| 0                          | 7/49 (14.3)            | 6/304 (1.9)               | 0.58    |
| 1                          | 13/49 (26.5)           | 53/304 (17.6)             |         |
| 2                          | 9/49 (18.4)            | 92/304 (30.1)             |         |
| 3                          | 7/49 (14.3)            | 90/304 (29.5)             |         |
| 4                          | 8/49 (16.3)            | 42/304 (13.8)             |         |
| >=5                        | 5/49 (10.2)            | 21/304 (7.2)              |         |
| Mean CHA2DS2VASC           | 2.3                    | 2.5                       | 0.48    |

Values are presented as median and interquartile range, as n and percentage or as a mean.

^Composite score including age 65-74, age >=75, female sex, diabetes mellitus, hypertension, congestive heart failure, prior stroke and evidence of vascular disease

BMI = Body mass index, COPD = chronic obstructive pulmonary disease, ACE/ARB = ACE-Inhibitor/angiotensin receptor blocker, ARNI = angiotensin receptor–neprilysin inhibitors, DOAC = direct oral anticoagulant

Ischemic Stroke Risk Score and were not included in the model. Meanwhile, there is substantial evidence mounting that severe COVID-19 infection is associated with myocardial injury, cardiovascular dysfunction and new onset arrhythmias.
involvement and establish the role of echocardiography in ischemic stroke in patients hospitalized with COVID-19.

To prospectively identify patients with COVID-19 at risk for ischemic stroke, we created a novel composite COVID-19 Ischemic Stroke Risk Score to risk stratify patients within our cohort based on several clinical observations and echocardiographic findings that have been previously associated with ischemic stroke. Left atrial dilation and the presence of LV thrombus are recognized risk factors for ischemic stroke that were observed to occur with greater frequency in patients who had ischemic stroke in our population.\(^{23-25}\) The burden of ischemic stroke in patients less than 55 years of age in our population is congruent with the observation that incidence of ischemic stroke, particularly large vessel occlusive stroke, has occurred with higher incidence in younger patients with COVID-19 compared to controls.\(^{26}\) An elevated admission systolic blood pressure, defined in this study as >140 mmHg, was significantly higher in patients with ischemic stroke despite diagnosis of ischemic stroke occurring a median 7 days (1-17) from admission and was also included. Lastly, we chose to treat anticoagulation prior to admission as a protective factor in our risk score given the burden of

| Presenting Vitals | Ischemic Stroke (n=49) | No Ischemic Stroke (n=304) | P-value |
|-------------------|-----------------------|---------------------------|---------|
| Temperature, Celsius | 36.9 (37-38) | 37.0 (37-38) | 0.22 |
| Systolic blood pressure | 143 (127-163) | 125 (112-142) | <0.01 |
| Diastolic blood pressure | 80 (70-90) | 73 (62-84) | <0.01 |
| Heart rate | 91 (83-100) | 101 (86-115) | 0.02 |
| Labs | Ischemic Stroke (n=49) | No Ischemic Stroke (n=304) | P-value |
| Creatinine, peak | 1.3 (0.9-3.7) | 1.7 (1.0-4.7) | 0.18 |
| White blood cells | 9.9 (7.4-13.3) | 8.7 (5.9-12.6) | 0.12 |
| Platelets | 251 (197-330) | 225 (166-307) | 0.06 |
| C-reactive protein, peak | 224 (92-319) | 223 (98-300) | 0.50 |
| Interleukin 6, peak | 144 (69-517) | 118 (46-349) | 0.68 |
| Lactate dehydrogenase, peak | 706 (395-1034) | 674 (437-987) | 0.88 |
| Ferritin, peak | 1425 (589-3478) | 1612 (584-3426) | 0.84 |
| D-dimer, baseline | 3.7 (1.5-15.1) | 3.4 (1.3-20.0) | 0.46 |
| D-dimer, peak | 13.0 (3.1-20.0) | 12.1 (3.2-20.0) | 0.23 |
| Lactate, peak | 2.5 (1.7-3.5) | 3.2 (2.2-5.1) | 0.01 |
| Procalcitonin, peak | 0.9 (0.2-11.5) | 1.1 (0.2-5.4) | 0.92 |
| Alanine aminotransferase, peak | 92 (42-186) | 69 (34-155) | 0.40 |
| Troponin baseline, times above or below upper limit of normal | 0.75 (0.25-5.0) | 0.75 (0.25-3.25) | 0.48 |
| Troponin peak, times above or below upper limit of normal | 3.75 (0.43-21.75) | 2.25 (0.50-17.70) | 0.89 |
| Cardiac injury, baseline | 21/49 (42.9) | 128/319 (40.1) | 0.72 |
| Cardiac injury, peak | 28/49 (57.1) | 201/319 (63.0) | 0.61 |
| Hospital Course | Ischemic Stroke (n=49) | No Ischemic Stroke (n=304) | P-value |
| Intensive Care Unit Admission | 35/49 (71.4) | 148/304 (48.7) | <0.01 |
| Pulmonary Embolism | 3/49 (6.1) | 22/303 (7.3) | 0.77 |
| Atrial Arrhythmia | 9/49 (18.4) | 70/304 (22.9) | 0.47 |
| Acute Kidney Injury | 24/49 (49.0) | 173/304 (56.9) | 0.35 |
| Renal Replacement Therapy | 10/49 (20.4) | 80/303 (26.4) | 0.67 |
| Shock | 19/49 (38.8) | 138/304 (45.4) | 0.75 |
| Acute Respiratory Distress Syndrome | 19/49 (38.8) | 131/304 (43.1) | 0.35 |
| Intubation | 25/49 (51.0) | 129/304 (43.0) | 0.32 |
| Days on Mechanical Ventilation | 10 (4-30) | 7 (1-23) | 0.40 |
| Length of Stay | 17 (7-44) | 13 (6-28) | 0.13 |
| Death | 12/49 (24.5) | 87/302 (28.8) | 0.61 |
| Days to Death | 19 (11-36) | 15 (9-26) | 0.32 |

Values are presented as a median and interquartile range or as n and percentage.
cardioembolic stroke in our population, evolving evidence of COVID-19 induced hypercoagulability and a numerically greater percentage of patients without ischemic stroke who were prescribed anticoagulation prior to admission.

Independent of traditional laboratory markers of hypercoagulability or a severely inflammatory state, the composite COVID-19 Ischemic Stroke Risk Score allows for robust risk stratification of patients hospitalized with COVID-19. This is not a simple reflection of the burden of cardioembolic stroke in our population and reinforces the complex pathophysiology of ischemic stroke. It has been hypothesized that COVID-19 can cause catastrophic endothelial dysfunction that manifests clinically as ischemic stroke, pulmonary embolus, deep vein thrombosis and myocardial dysfunction.27-28 It is possible that abnormalities visualized on an echocardiogram can indicate severity of gross endothelial dysfunction from COVID-19 that has proven challenging to quantify using non-specific serologic markers such as interleukin 6 (IL-6) or qualify

Table 3. Transthoracic echocardiogram characteristics.

|                  | Ischemic Stroke (n=49) | No Ischemic Stroke (n=304) | P-value |
|------------------|------------------------|---------------------------|---------|
| Ejection fraction, % | 60 (54-65)             | 60 (50-65)                | 0.60    |
| Left atrial volume index (mL/m²) | 30 (22-42)             | 28 (21-38)                | 0.33    |
| Left atrial dilation | 14/29 (48.3)           | 46/165 (27.9)             | 0.04    |
| Left ventricular end diastolic volume (mL) | 106 (86-129)           | 104 (80-133)              | 0.74    |
| Left ventricular end systolic volume (mL) | 40 (29-57)             | 43 (30-62)                | 0.71    |
| Diastolic dysfunction | 25/49 (51.0)           | 155/304 (51.1)            | 0.99    |
| Aortic regurgitation | 6/48 (12.5)            | 35/292 (11.9)             | 0.92    |
| Aortic stenosis | 1/48 (2.1)             | 15/292 (5.1)              | 0.71    |
| Mitral regurgitation | 11/48 (22.9)           | 89/295 (30.2)             | 0.39    |
| Tricuspid regurgitation | 14/48 (29.2)           | 132/296 (44.6)            | 0.06    |
| Wall motion abnormalities | 6/48 (12.5)           | 41/298 (13.8)             | 0.81    |
| Global dysfunction | 6/48 (12.5)             | 36/299 (12.0)             | 0.84    |
| Left ventricular thrombus | 2/48 (4.2)             | 2/299 (0.7)               | 0.03    |
| Pericardial effusion | 2/48 (4.2)             | 26/299 (8.7)              | 0.27    |
| Right ventricular size, increased | 6/48 (12.5)           | 76/296 (25.7)             | 0.05    |
| Right ventricular function, abnormal | 9/48 (18.8)           | 76/296 (25.7)             | 0.37    |
| Positive shunt study | 7/23 (30.4)             | 1/5 (20.0)                | 0.23    |
| Positive shunt study + presence of global dysfunction, RV dilation or RV dysfunction | 3/7 (42.9) | 0/2 (0.0) | 0.26 |

Values are presented as a median and interquartile range or as n and percentage. All units of measure are listed in the supplement.

Table 4. COVID-19 ischemic stroke risk score.

|                  | Ischemic Stroke (n=49) | No Ischemic Stroke (n=304) | Odds Ratio (95% CI) | P-Value |
|------------------|------------------------|---------------------------|---------------------|---------|
| Age <55          | 20/49 (40.8)           | 93/304 (30.6)             | 1.6 (0.8-3.0)       | 0.16    |
| SBP >140         | 41/49 (83.7)           | 179/304 (58.9)            | 2.8 (1.2-6.5)       | <0.01   |
| Prior Anticoagulation | 2/49 (4.1)             | 36/302 (11.9)             | 0.2 (0.0-1.7)       | 0.14    |
| Left Atrial Dilation | 14/29 (48.3)           | 46/165 (27.9)             | 2.4 (1.0-5.9)       | 0.04    |
| Left Ventricular Thrombus | 2/49 (4.2)             | 2/299 (0.7)               | 6.8 (0.5-95.7)      | 0.02    |
|                  | 1.41                    | 0.88                       | 4.1 (1.4-16.1)      | <0.01   |

COVID-19 Stroke Risk Score: composite value formed by the sum of five dichotomous variables assigned values of +1 (age <55, SBP >140 mmHg, left atrial dilation, left ventricular thrombus) and -1 (prior anticoagulation). Values are presented as an odds ratio and 95% confidence interval.

Fig. 1. Receiver Operator Characteristic Curve for COVID-19 Ischemic Stroke Risk Score. A receiver operator characteristic curve analysis demonstrating the diagnostic accuracy of the COVID-19 Ischemic Stroke Risk Score with the area under the curve calculated to be 0.6981.
with characteristics of illness severity such as need for mechanical ventilation.

There are several limitations to this study. Not all stroke patients with COVID during the study time period received an echocardiogram. Dhamoon et al. identified a 1.9% incidence of stroke in all patients admitted across the same medical system. In this study period, 60.5% of all patients discharged with a diagnosis of ischemic stroke in the health system received an echocardiogram. While all patients that underwent a neurological work-up for ischemic stroke at participating hospitals included a comprehensive TTE, in-hospital mortality at these institutions was high during the study course and resources for more thorough cerebrovascular testing were limited. We have no data on any out-of-hospital cardiac monitoring that patients have undergone following ischemic stroke. Additionally, despite identifying patients from a large heterogeneous health system, the sample size of patients with ischemic stroke is modest and we have not validated the proposed risk score in a prospective population. Lastly, the study of COVID-19 is a rapidly advancing field and research design has been hampered by a scarcity of prospective and randomized data. We look forward to the results of the many active clinical trials that are aimed to guide management of antithrombotic therapy in patients with COVID-19, cardiovascular disease and ischemic stroke.31 We believe that our findings support the routine use of echocardiography in patients with COVID-19 to characterize the risk of ischemic stroke and suggest that the COVID-19 Ischemic Stroke Risk Score can be utilized to aid patient risk stratification and clinical decision-making.

Connor Oates and Solomon W. Bienstock participated in data collection, data analysis and drafting of the article. Michael Miller participated in data analysis and critical revision of the article. Tatyana Danilov, Nina Kukar, Nikola Kocovic, Dylan Sperling, Ranbir Singh, Daniel Benhuri, Frans Beerkens and Anton Camaj participated in data collection and critical revision of the article. Gennaro Giustino, Stamatios Lerakis, Lori Croft, Laura K. Stein and Martin E. Goldman participated in concept/design and critical revision of the article.

References

1. Abootalebi S, Aertker BM, Andalibi MS, Asdaghi N, Aykac O, Azarpazhooh MR, Bahit MC, Barlinn K, Basri H, Shahripour RB, et al. Call to Action: SARS-CoV-2 and CerebrovAscular DisordErs (CASCADE). J Stroke Cerebrovasc Dis 2020;29(9):104938.
2. Adams HP, Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35-41.
3. Belani P, Schefflein J, Kihira S, Rigney B, Delman BN, Mahmoudi K, Mocco J, Majidi S, Yeckley J, Aggarwal A, et al. COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke. AJNR Am J Neuroradiol 2020;41(8):1361-1364.
4. de Havenon A, Yaghi S, Mistry EA, Delic A, Hohmann S, Shippey E, Stulberg E, Tirschwell D, Frontera JA, Petersen NH, Anadani M. Endovascular thrombectomy

**Fig. 2. Incidence of Ischemic Stroke per COVID-19 Ischemic Stroke Risk Score.** A graph demonstrating the incidence of ischemic stroke with each integer increase in the COVID-19 Ischemic Stroke Risk Score within our cohort of patients hospitalized with COVID-19 who underwent transthoracic echocardiography.
in acute ischemic stroke patients with COVID-19: prevalence, demographics, and outcomes. J Neurointerv Surg 2020;12(11):1045-1048.

5. Dhamoon MS, Thaler A, Gururangan K, Kohli A, Sisiniea D, Wheelwright D, Mensching C, Fifi JT, Fara MG. Jette N and the Mount Sinai Stroke Investigators. Acute Cerebrovascular Events With COVID-19 Infection. Stroke. 2021;52(1):48-56.

6. Elkind MSV, Boehme AK, Smith CJ, Meisel A, Buckwalter MS. Infection as a Stroke Risk Factor and Determinant of Outcome After Stroke. Stroke. 2020;51(10):3156-3168.

7. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurolological associations of COVID-19. Lancet Neurol 2020;19(9):767-773.

8. Evans PC, Rainger GE, Mason JC, Gzik TJ, Ogu CE, Sta-mataki Z, Neil D, Hoefer IE, Fragiadaki M, Waltenberger J, et al. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. Cardiovasc Res 2020;116(14):2177-2184.

9. Ferkh A, Brown P, O’Keefe E, Zada M, Duggins A, Thia-galingam A, Altman M, Boyd A, Byth K, Kizana E, et al. Clinical and echocardiographic characteristics of cardio-embolic stroke. Eur J Neurol 2019;26(10):1310-1317.

10. Frontera JA, Sabadla S, Lalchan R, Fang T, Flusty B, Millar-Vernetti P, Snyder T, Berger S, Yang D, Granger A, et al. A Prospective Study of Neurologic Disorders in Hospitalized COVID-19 Patients in New York City. Neurology 2021;96(4):e575-e586.

11. Giustino G, Croft LB, Stefanini GG, Bragato R, Silbiger JJ, Ventimilla Z, Neil D, Hoefer IE, Fragiadaki M, Waltenberger J, et al. Characterization of Myocardial Injury in Patients With COVID-19. J Am Coll Cardiol 2020;76(18):2043-2055.

12. Goerlich E, Minhas A, Gilotra N, Barth AS, Mukherjee M, Parziale A, Wu KC, Hays AG. Left atrial function in patients with COVID-19 and its association with incident atrial fibrillation/flutter. J Am Soc Echocardiogr 2021.

13. Gupta A, Madhavan MV, Sehgal K, Nair M, Mahajan S, Sehrawat TS, Bikdeli B, Aaluvallila N, Ausiello JC, Wan EY, et al. Extrapolatory manifestations of COVID-19. Nat Med 2020;26(7):1017-1032.

14. Helms J, Kremer S, Merdji H, Clerc-Jebel R, Schenck M, Kummerlen C, Collange O, Boulay C, Fati-Kremer S, Ohana M, et al. Neurologic Features of Severe SARS-CoV-2 Infection. N Engl J Med 2020;382(23):2268-2270.

15. Huang C, Wang Y, Li X, Ren L, Jinanping Z, Hu Y, Zhang L, Fan G, Xu J, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

16. Jin Y, Ji W, Yang H, Chen S, Zhang W, Duan G. Endothe-lial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches. Sig Transduct Target Ther 2020;5(1):293.

17. Kirkpatrick JN, Mitchell C, Taub C, Kort S, Hung J, Sawa-minathna M. ASE Statement on Protection of Patients and Echocardiography Service Providers During the 2019 Novel Coronavirus Outbreak: Endorsed by the American College of Cardiology. J Am Coll Cardiol 2020;75(24):3078-3084.

18. Lang RM, Badano LP, Mor-Avi V, Afifalo J, Armstrong A, Emande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28(1):1-39. e14.

19. Larson AS, Savastano L, Kadirvel R, Kallmes DF, Hassan AE, Brinjikji W. Coronavirus Disease 2019 and the Cerebrovascular-Coronary Systems: What Do We Know So Far? J Am Heart Assoc 2020;9(13):e016793.

20. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, Wang D, Mao L, Jin H, Hu B. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020;5(3):279-284.

21. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):683-690.

22. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, Lantos J, Schenck EJ, Goyal P, Brunce SS, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. JAMA Neurol 2020;77(11):1-7.

23. Morassi M, Bagatto D, Cobelli M, D’Agostini S, Gigli GL, Bna C, Vogrigr A. Stroke in patients with SARS-CoV-2 infection: case series. J Neurol 2020;267(8):2185-2192.

24. Rothstein A, Oldridge O, Schwennesen H, Do D, Cuchiara BL. Acute Cerebrovascular Events in Hospitalized COVID-19 Patients. Stroke 2020;51(9):e219-e222.

25. Siepmann T, Sedghi A, Simon E, Winzer S, Barlinn J, De With K, Mirow L, Wolz M, Gruenewald T, Schroettner P, et al. Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis. Eur J Neurol 2021;28(1):238-247.

26. Spence JD, de Freitas GR, Pettigrew LC, Ay H, Liebeschid DS, Kase CS, Del Brutto OH, Hankey GJ, Venkata-subramanian N. Mechanisms of Stroke in COVID-19. Cerebrovasc Dis 2020;49(4):451-458.

27. Talasaz AH, Sadeghipour P, Kavakhand H, Aghakouchak-zadeh M, Kordzadeh-Kermani E, Van Tassel BW, Ghey-mati A, Ariannejad H, Hosseini SH, Jamalkhani S, et al. Recent Randomization Trials of Anti-Thrombotic Therapy for Patients With COVID-19: JACC State-of-the-Art Review. J Am Coll Cardiol 2021;11(21). S0735-1097(20)3057-7.

28. Tiwari A, Berekashvili V, Kulkovav V, Agarwal S, Khaneja A, Turkel-Parella D, Liff J, Farkas J, Nandakumar T, Zhou T, et al. Etiologic Subtypes of Ischemic Stroke in SARS-CoV-2 Patients in a Cohort of New York City Hospitals. Front Neurol 2020;11(7):1004.

29. Trifan G, Goldenberg FD, Caprio FC, Biller J, Schneck M, Khaja A, Terna T, Brorson J, Lazaridis C, Bulwa Z, et al. Characteristics of a Diverse Cohort of Stroke Patients with SARS-CoV-2 and Outcome by Sex. J Stroke Cerebrovasc Dis 2020;29(11):105314.

30. Turagam MK, Musikantow D, Goldman ME, Bassetly-Maruc A, Chu E, Shivismaruthy P, Lampert J, Kawamura I, Bokhari M, Whang W, et al. Malignant Arrhythmias in Patients with COVID-19: Incidence, Mechanisms and Outcomes. Circ Arrhythm Electrophysiol 2020;13(11):e008920.

31. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, Henninger N, Trivedi T, Lillemoe K, Alam S, et al. SARS-CoV-2 and Stroke in a New York Healthcare Sys-tem. Stroke 2020;51(7):2002-2011.