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# Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza

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**IMPORTANCE** It is uncertain whether coronavirus disease 2019 (COVID-19) is associated with a higher risk of ischemic stroke than would be expected from a viral respiratory infection.

**OBJECTIVE** To compare the rate of ischemic stroke between patients with COVID-19 and patients with influenza, a respiratory viral illness previously associated with stroke.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective cohort study was conducted at 2 academic hospitals in New York City, New York, and included adult patients with emergency department visits or hospitalizations with COVID-19 from March 4, 2020, through May 2, 2020. The comparison cohort included adults with emergency department visits or hospitalizations with influenza A/B from January 1, 2016, through May 31, 2018 (spanning moderate and severe influenza seasons).

**EXPOSURES** COVID-19 infection confirmed by evidence of severe acute respiratory syndrome coronavirus 2 in the nasopharynx by polymerase chain reaction and laboratory-confirmed influenza A/B.

**MAIN OUTCOMES AND MEASURES** A panel of neurologists adjudicated the primary outcome of acute ischemic stroke and its clinical characteristics, mechanisms, and outcomes. We used logistic regression to compare the proportion of patients with COVID-19 with ischemic stroke vs the proportion among patients with influenza.

**RESULTS** Among 1916 patients with emergency department visits or hospitalizations with COVID-19, 31 (1.6%; 95% CI, 1.1%-2.3%) had an acute ischemic stroke. The median age of patients with stroke was 69 years (interquartile range, 66-78 years); 18 (58%) were men. Stroke was the reason for hospital presentation in 8 cases (26%). In comparison, 3 of 1486 patients with influenza (0.2%; 95% CI, 0.0%-0.6%) had an acute ischemic stroke. After adjustment for age, sex, and race, the likelihood of stroke was higher with COVID-19 infection than with influenza infection (odds ratio, 7.6; 95% CI, 2.3-25.2). The association persisted across sensitivity analyses adjusting for vascular risk factors, viral symptomatology, and intensive care unit admission.

**CONCLUSIONS AND RELEVANCE** In this retrospective cohort study from 2 New York City academic hospitals, approximately 1.6% of adults with COVID-19 who visited the emergency department or were hospitalized experienced ischemic stroke, a higher rate of stroke compared with a cohort of patients with influenza. Additional studies are needed to confirm these findings and to investigate possible thrombotic mechanisms associated with COVID-19.

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Coronavirus disease 2019 (COVID-19) has affected more than 8 million people and caused 440 000 deaths worldwide.[1] Although COVID-19 is primarily a respiratory illness, reports suggest that it may lead to a hypercoagulable state and thrombotic complications.[2-4] Recent publications from China, France, and New York raise the possibility that COVID-19 might increase the risk of ischemic stroke.[5-8] However, these studies lacked appropriate control groups. To evaluate whether COVID-19 is associated with a higher rate of ischemic stroke than would generally be expected from a viral respiratory infection, we compared the likelihood of acute ischemic stroke in patients with COVID-19 vs patients with influenza, a known stroke risk factor.[9]

### Key Points

**Question** How does the risk of acute ischemic stroke compare between patients with coronavirus disease 2019 (COVID-19) and patients with influenza, a respiratory virus previously associated with stroke?

**Findings** In this cohort study, 1916 patients with emergency department visits or hospitalizations with COVID-19 had an elevated risk of ischemic stroke compared with 1486 patients with emergency department visits or hospitalizations with influenza.

**Meaning** Patients with COVID-19 appear to have a heightened risk of acute ischemic stroke compared with patients with influenza.

## Methods

### Design

We conducted a retrospective cohort study at 2 hospitals in New York City, one of which is an academic quaternary care center and the other an academic community hospital. One part of the study population comprised patients 18 years or older who had confirmation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the nasopharynx by polymerase chain reaction and had an emergency department (ED) visit or hospitalization from March 4, 2020, through May 2, 2020. In parallel, we identified adult patients with an ED visit or hospitalization with laboratory-confirmed influenza A or B at our quaternary care hospital between January 1, 2016, and May 31, 2018, dates during which we had available data from the Cornell Acute Stroke Academic Registry (CAESAR), which we used to ascertain ischemic strokes in the influenza cohort. Influenza is a common viral respiratory illness that has been established as a risk factor for ischemic stroke,[9,10] so the comparison between COVID-19 and influenza allowed us to assess whether COVID-19 is associated with a heightened risk of ischemic stroke beyond that expected from a viral respiratory illness. Calendar years 2016 to 2018 encompassed severe (2017-2018) and moderate (2015-2016; 2016-2017) influenza seasons.[11] Patients with COVID-19 and influenza were identified using automated systems for electronic capture of clinical data established by the Weill Cornell Medicine Architecture for Research Computing in Health program.[12] The Weill Cornell Medicine institutional review board approved this study and waived the requirement for informed consent because the study was minimal risk and could not be practically conducted without a waiver.

### Measurements

We used manual abstraction and automated electronic data capture to collect information on demographics, vascular risk factors, presenting symptoms (ie, cough, fever, and dyspnea/hypoxia among other symptoms of a viral syndrome), severity of illness (ie, whether patients were admitted to an intensive care unit, received mechanical ventilation, or had prone positioning), laboratory values, imaging studies, medications administered, in-hospital mortality, and discharge disposition for patients with COVID-19 and influenza. The primary outcome was acute ischemic stroke. In the COVID-19 cohort, we screened for ischemic stroke by identifying all patients who underwent brain computed tomography (CT) or brain magnetic resonance imaging (MRI) or had an *International Classification of Diseases, 10th Revision, Clinical Modification* (*ICD-10-CM*) diagnosis for cerebrovascular disease (I60-I69) during their ED visit or hospitalization. Patients identified as having a possible ischemic stroke then had their medical records independently reviewed by 2 board-certified attending neurologists (vascular neurology or neurocritical care) to adjudicate a final diagnosis of acute ischemic stroke. Disagreements were resolved by the independent review of a third neurologist. Diagnoses of acute ischemic stroke required confirmation by CT or MRI.[13] Among the confirmed cases of ischemic stroke, the etiological mechanism was independently adjudicated by 2 study neurologists (with a third resolving disagreements) according to the Trial of Org 10172 Acute Stroke Treatment criteria and the Embolic Stroke of Undetermined Source classification.[14,15] In the influenza cohort, ischemic stroke was ascertained by merging in data from CAESAR. The methods for stroke adjudication and etiological subtype classification in CAESAR have been previously published[16] and are the same as the methods described previously for the COVID-19 cohort; ascertainment of ischemic stroke was on the basis of clinical and imaging data for both cohorts. Study neurologists also tabulated data on the National Institutes of Health stroke scale at the time of stroke diagnosis. This scale ranges from 0 to 42 and higher scores indicate more severe strokes.

### Analysis

We used descriptive statistics with exact confidence intervals to characterize the study population and to calculate proportions of patients with acute ischemic stroke. Comparisons were made using the $\chi^2$ test or Wilcoxon rank sum test for unadjusted comparisons. For the primary analysis comparing the risk of ischemic stroke between the COVID-19 and influenza cohorts, logistic regression models were adjusted for age, sex, and race. Race was abstracted from the hospital's electronic medical records.

We performed several sensitivity analyses. First, we restricted the COVID-19 and influenza cohorts to patients who were admitted to the hospital. Second, because we lacked data

regarding patients with influenza at our academic community hospital, we evaluated the risk of ischemic stroke in patients with COVID-19 and influenza at only our academic quaternary care center. Third, we further adjusted our primary multivariable logistic regression model for the total number of vascular risk factors present, which included hypertension, hyperlipidemia, diabetes, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, and morbid obesity (defined as a body mass index [calculated as weight in kilograms divided by height in meters squared] of ≥35). Fourth, in addition to demographics and the number of vascular risk factors present, we further adjusted the logistic regression model for intensive care unit (ICU) admission.

In addition, our institution's policy regarding testing for COVID-19 changed during the study period. Initially, our institution only tested for COVID-19 in patients with symptoms of a viral respiratory syndrome, such as fever, cough, and dyspnea. Based on the availability of testing materials, guidance from governmental health organizations, and the recognition of a broader spectrum of clinical presentations, our institution began testing all patients who presented to the ED or hospital regardless of symptoms on April 4, 2020. We explored the effect of these testing practices in 3 complementary sensitivity analyses. First, we limited the COVID-19 and influenza cohorts to patients who had presenting symptoms of a viral respiratory illness; this analysis thus focused on patients with symptomatic infection with COVID-19 and influenza. Second, we limited the COVID-19 and influenza cohorts to patients who had presenting symptoms of a viral respiratory illness and were hospitalized. Third, we limited the cohort of patients with COVID-19 to those who had an ED visit or hospitalization after April 4, 2020, at which time all patients with an ED visit or hospitalization were tested for COVID-19 infection regardless of their presenting complaints. This analysis reflects the risk of ischemic stroke among all patients testing positive for COVID-19 in the hospital or ED setting, irrespective of symptoms.

We defined statistical significance by an α error of .05. Statistical analyses were performed using Stata (version 15.1; StataCorp).

## Results

### COVID-19 Cohort

From March 4, 2020, through May 2, 2020, there were 1916 patients with ED visits or hospitalizations with COVID-19 at our 2 hospitals. This includes 1497 patients with COVID-19 identified at our academic quaternary care center and 419 patients with COVID-19 identified at our academic community hospital. The median age was 64 years (interquartile range [IQR], 51-76 years), 1111 (57%) were men, and vascular comorbidities were common (**Table 1**). The top presenting complaints were dyspnea/hypoxia (1358 [71%]), cough the IMD 7.3 OLF issue (July 20) (1297 [68%]), and fever (1275 [67%]). There were 330 patients with severe COVID-19 infection (17%) who required mechanical ventilation.

**Table 1. Characteristics of Patients With COVID-19 Infection, Stratified by the Diagnosis of Acute Ischemic Stroke**

| Characteristic[a] | No. (%) | |
|---|---|---|
| | Acute ischemic stroke (n = 31) | No acute ischemic stroke (n = 1885) |
| Demographic | | |
| Age, median (IQR), y | 69 (66-78) | 64 (50-76) |
| Men | 18 (58) | 1083 (57) |
| Race[b] | | |
| White | 9 (29) | 537 (28) |
| Black | 3 (10) | 243 (13) |
| Asian | 8 (26) | 248 (13) |
| Other/unknown | 11 (36) | 857 (46) |
| Hispanic ethnicity | 1 (3) | 368 (20) |
| Vascular risk factors | | |
| Body mass index[c] | 28 (23-34) | 28 (24-32) |
| Hypertension | 30 (97) | 1158 (61) |
| Diabetes | 23 (74) | 806 (43) |
| Hyperlipidemia | 17 (55) | 576 (31) |
| Atrial fibrillation | 17 (55) | 293 (16) |
| Chronic kidney disease | 8 (26) | 300 (16) |
| Coronary artery disease | 16 (52) | 479 (25) |
| COPD | 4 (13) | 181 (10) |
| Clinical characteristics | | |
| ICU admission | 19 (61) | 455 (24) |
| Mechanical ventilation | 11 (35) | 319 (17) |
| Prone positioning | 9 (29) | 237 (13) |
| Laboratory data, median (IQR) | | |
| Initial D-dimer, μg/mL | 1.930 (0.559-5.285) | 0.682 (0.340-1.986) |
| Initial ESR, mm/h | 89 (60-106) | 71 (45-99) |
| Initial WBC count, /μL | 10 300 (6900-12 900) | 6900 (5000-9700) |
| Initial platelet count, $\times 10^3/\mu L$ | 210 (178-269) | 208 (160-275) |
| Initial troponin I, ng/mL | 0.03 (0.03-0.09) | 0.03 (0.03-0.06) |

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IQR, interquartile range; WBC, white blood cell.

SI conversion factors: To convert D-dimer to nmol/L, multiply by 5.476; platelet count to $\times 10^9$/L, multiply by 1; troponin I to μg/L, multiply by 1; WBC to $\times 10^9$/L, multiply by 0.001.

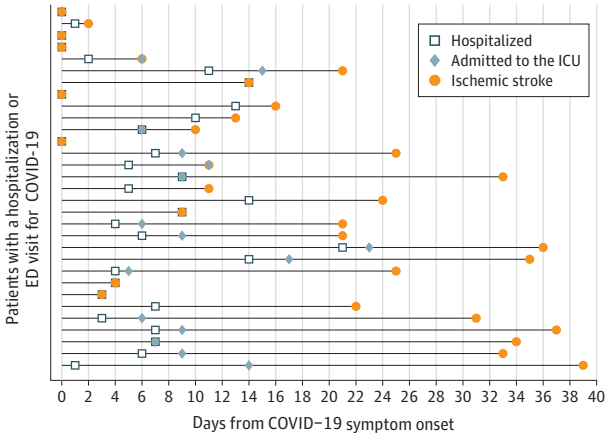
[a] Data are reported as number (%) for categorical variables and median (IQR) for continuous variables.

[b] Percentages were rounded up and therefore many not add to 100%.

[c] Calculated as weight in kilograms divided by height in meters squared.

Of the 1916 patients with COVID-19, 31 patients (1.6%; 95% CI, 1.1%-2.3%) had an acute ischemic stroke. Among the 1683 hospitalized patients with COVID-19, 31 (1.8%; 95% CI, 1.3%-2.6%) had an acute ischemic stroke; no patients with ED treat-and-release visits had an acute ischemic stroke. Among 1752 patients with COVID-19 who presented to the ED or hospital with symptoms of a viral respiratory illness, 27 (1.5%; 95% CI, 1.0%-2.2%) had an acute ischemic stroke, whereas among 998 patients testing positive during a period of universal screening irrespective of symptoms, 19 (1.9%; 95% CI, 1.2%-3.0%) had an acute ischemic stroke. The median duration from COVID-19

Figure. Timeline in Days From Coronavirus Disease 2019 (COVID-19) Symptom Onset to Acute Ischemic Stroke Diagnosis




Horizontal lines represent individual patients with a hospitalization or emergency department (ED) visit for COVID-19 infection who had acute ischemic stroke. A white square indicates the day of hospitalization, a gray diamond indicates the day of intensive care unit (ICU) admission, if applicable, and an orange circle indicates the day of acute ischemic stroke diagnosis. For patients who did not have preceding typical COVID-19 symptoms, the day of their stroke was considered the day of COVID-19 symptom onset. For patients with typical symptoms of COVID-19 but without a clear onset date, the date of hospital presentation was considered the day of onset.

Table 2. Characteristics of Acute Ischemic Stroke Among Patients With COVID-19 Infection

| Characteristic[a] | Acute ischemic stroke (n = 31) |
|---|---|
| Stroke symptoms were presenting complaint | 8 (26) |
| NIH Stroke Scale score, median (IQR) | 16 (6-23) |
| Stroke mechanism[b,c] | |
| Cardioembolic | 13 (42) |
| Large-artery atherosclerosis | 2 (7) |
| Small vessel disease | 0 (0) |
| Other determined | 0 (0) |
| Cryptogenic | 16 (52) |
| ESUS | 5(16) |
| Multiple causes | 3 (10) |
| Incomplete evaluation | 8 (26) |
| Multiple cerebrovascular territories involved | 17 (55) |
| Antiplatelet use prior to stroke | 7 (23) |
| Anticoagulant use prior to stroke | 4 (13) |
| Intravenous thrombolysis administered | 3 (10) |
| Mechanical thrombectomy performed | 2 (7) |
| Symptomatic hemorrhagic transformation | 2 (7) |

Abbreviations: COVID-19, coronavirus disease 2019; ESUS, embolic stroke of undetermined source; IQR, interquartile range; NIH, National Institutes of Health.

[a] Data reported as number (%) unless otherwise specified.

[b] According to the Trial of Org 10172 Acute Stroke Treatment criteria and the ESUS classification.

[c] Percentages were rounded up and therefore many not add to 100%.

symptom onset to stroke diagnosis was 16 days (IQR, 5-28 days) (**Figure**). The median age of patients with acute ischemic stroke was 69 years (IQR, 66-78 years).

Stroke symptoms were the presenting complaint in 8 patients (26%), while 23 patients (74%) developed acute ischemic stroke while hospitalized. More than one-third of ischemic strokes (11 [35%]) occurred in patients who had severe COVID-19 infection and received mechanical ventilation. The median National Institutes of Health Stroke Scale score was 16 (IQR, 6-23) (**Table 2**). Patients who received a diagnosis of acute ischemic stroke were significantly older and on average had more stroke risk factors, higher laboratory markers of inflammation, and more critical illness than patients without ischemic stroke. The youngest patient with ischemic stroke in the cohort was age 51 years. The median initial plasma D-dimer value was 1.930 µg/mL (IQR, 0.559-5.285; to convert to nanomoles per liter, multiply by 5.476) in patients with ischemic stroke vs 0.682 µg/mL (IQR, 0.340-1.986) in patients without ischemic stroke ($P$ = .01). Among patients with acute ischemic stroke, intravenous thrombolysis was administered to 3 patients (10%) and mechanical thrombectomy was performed in 2 patients (7%). Inpatient mortality was 32% among patients with COVID-19 with ischemic stroke vs 14% among COVID-19 patients without ischemic stroke ($P$ = .003).

## Influenza Cohort

We identified 1486 patients with ED visits or hospitalizations with influenza from January 1, 2016, through May 31, 2018, at our academic quaternary care center. Their median age was 62 years (IQR, 42-78 years), 663 (45%) were men, and vascular comorbidities were common (**Table 3**). Symptoms of a viral respiratory illness were present in 1427 patients (96%), including cough (1188 [80%]), fever (833 [56%]), and dyspnea/hypoxia (553 [37%]). There were 48 patients (3%) with severe influenza infection who required mechanical ventilation. Of the 1486 patients with influenza, 3 patients (0.2%; 95% CI, 0.0%-0.6%) had an acute ischemic stroke (2 cardioembolic and 1 cryptogenic).

## Comparison of the COVID-19 and Influenza Cohorts

Compared with the 1916 patients with COVID-19, the 1486 patients with influenza were on average younger; more often women; less often had hypertension, diabetes, coronary artery disease, chronic kidney disease, or atrial fibrillation; and more often had hyperlipidemia. Patients with influenza were also less likely to be admitted to an ICU or receive mechanical ventilation and had lower D-dimer and erythrocyte sedimentation rate values.

In an unadjusted analysis, patients with COVID-19 were more likely to have an acute ischemic stroke than patients with influenza (odds ratio [OR], 8.1; 95% CI, 2.5-26.6). Our results were similar after adjustment for age, sex, and race (OR, 7.6; 95% CI, 2.3-25.2). The association between COVID-19 and acute ischemic stroke persisted across multiple sensitivity analyses, with the magnitude of relative associations ranging from 4.0 to 9.3 (**Table 4**). This included a sensitivity analysis that adjusted for the number of vascular risk factors and ICU admissions (OR, 4.6; 95% CI, 1.4-15.7).

Table 3. Characteristics of Patients With COVID-19 Infection vs Patients With Influenza Infection

| Characteristic[a] | No. (%) | |
|---|---|---|
| | COVID-19 (n = 1916) | Influenza (n = 1486) |
| Demographic | | |
| Age, median (IQR), y | 64 (51-76) | 62 (42-78) |
| Men | 1101 (57) | 663 (45) |
| Race[b] | | |
| White | 546 (29) | 631 (42) |
| Black | 246 (13) | 214 (14) |
| Asian | 256 (13) | 139 (9) |
| Other/unknown | 868 (46) | 502 (34) |
| Hispanic ethnicity | 369 (19) | 270 (23) |
| Vascular risk factors | | |
| Body mass index, median (IQR)[c] | 28 (24-32) | 26 (23-30) |
| Hypertension | 1188 (62) | 487 (33) |
| Diabetes | 829 (43) | 396 (27) |
| Hyperlipidemia | 593 (31) | 539 (36) |
| Atrial fibrillation | 310 (16) | 125 (8) |
| Chronic kidney disease | 308 (16) | 168 (11) |
| Coronary artery disease | 495 (26) | 125 (8) |
| COPD | 185 (10) | 168 (11) |
| Clinical characteristics | | |
| ICU admission | 474 (25) | 96 (6) |
| Mechanical ventilation | 330 (17) | 48 (3) |
| Prone positioning | 246 (13) | 2 (0) |
| Laboratory data, median (IQR) | | |
| Initial D-dimer, µg/mL | 0.687 (0.342-2.031) | 0.402 (0.270-0.778) |
| Initial ESR, mm/h | 71 (45-99) | 41 (21-65) |
| Initial WBC count, µL | 7000 (5000-9800) | 6700 (4900-9000) |
| Initial platelet count, $\times 10^3$/µL | 208 (161-274) | 179 (141-222) |
| Initial troponin I, ng/mL | 0.03 (0.03-0.06) | 0.03 (0.02-0.05) |

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

SI conversion factors: To convert D-dimer to nmol/L, multiply by 5.476; platelet count to $\times 10^9$/L, multiply by 1; troponin I to µg/L, multiply by 1; WBC to $\times 10^9$/L, multiply by 0.001.

[a] Data reported as number (%) for categorical variables and median (IQR) for continuous variables.

[b] Percentages were rounded up and therefore many not add to 100%.

[c] Calculated as weight in kilograms divided by height in meters squared.

Table 4. Logistic Regression Models Comparing the Odds of Acute Ischemic Stroke Among Patients With COVID-19 Infection vs Patients With Influenza Infection

| Analysis | Odds ratio (95% CI) |
|---|---|
| Primary analyses[a] | |
| Unadjusted | 8.1 (2.5-26.6) |
| Adjusted for age, sex, and race | 7.6 (2.3-25.2) |
| Sensitivity analyses | |
| Primary model also adjusting for vascular risk factors[b] | 6.2 (1.9-20.5) |
| Primary model also adjusting for vascular risk factors and ICU admission[c] | 4.6 (1.4-15.7) |
| Patients with viral syndrome symptoms[d] | 7.0 (2.1-23.4) |
| Patients with COVID-19 infection presenting from April 4, 2020, to May 2, 2020[e] | 8.3 (2.4-28.5) |
| Patients admitted to the hospital[f] | 5.6 (1.7-18.7) |
| Patients admitted to the hospital with viral syndrome symptoms[g] | 4.0 (1.2-13.7) |
| Patients treated at the quaternary care center[h] | 9.3 (2.8-30.8) |

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

[a] Data represent odds ratios (95% CI) with the reference group being patients with emergency department visits or hospitalizations with influenza.

[b] Analysis adjusted for age, sex, race, and the number of vascular risk factors present.

[c] Analysis adjusted for age, sex, race, the number of vascular risk factors present, and whether the patient was admitted to an ICU.

[d] Analysis limited to 1752 patients with COVID-19 and 1427 patients with influenza who had symptoms of a viral respiratory illness, such as fever, cough, dyspnea/hypoxia, or nasal congestion; adjusted for age, sex, and race.

[e] Analysis limited to 998 patients with COVID-19 who had an emergency department visit or hospitalization after April 4, 2020, when all patients presenting to the emergency department or hospital were tested for COVID-19 infection regardless of symptoms; adjusted for age, sex, and race.

[f] Analysis limited to 1683 patients with COVID-19 and 815 patients with influenza who were hospitalized (excludes patients with emergency department treat-and-release visits); adjusted for age, sex, and race.

[g] Analysis limited to 1531 patients with COVID-19 and 759 patients with influenza who were hospitalized (excludes patients with emergency department treat-and-release visits) and had symptoms of a viral respiratory illness; adjusted for age, sex, and race.

[h] Analysis limited to patients with emergency department visits or hospitalizations for COVID-19 (n = 1497) or influenza (n = 1486) at our academic quaternary care center; adjusted for age, sex, and race.

## Discussion

Among 1916 patients with ED visits or hospitalizations with COVID-19 infection at 2 major hospitals in New York City, the rate of acute ischemic stroke was higher than the rate identified among patients who visited the ED or were hospitalized with influenza infection. Our results were consistent across multiple sensitivity analyses, including analyses that adjusted for the number of vascular risk factors and ICU admission status, a surrogate for severity of illness. Furthermore, we found that patients with COVID-19 infection who experienced an ischemic stroke were considerably more likely to die than patients with COVID-19 infection who did not experience an ischemic stroke.

Our understanding of the neurological complications of COVID-19 infection is limited. Among 214 patients hospitalized with COVID-19 infection in Wuhan, China, 3% had a stroke.[7] Among 13 patients with COVID-19 infection who underwent brain MRI in France, 23% had an ischemic stroke.[6] More recently, investigators found that among 3556 patients hospitalized with COVID-19 in New York City, 0.9% had an ischemic stroke.[8] Among the 1916 patients in this study with ED visits or hospitalizations with COVID-19 infection, 1.6% received a diagnosis of ischemic stroke. The rate of ischemic stroke among patients hospitalized with COVID-19 in this study was 1.8%, which is similar to that observed in the Wuhan cohort but higher than that observed in the study by Yaghi et al

in New York City.[7,8] Discrepancies in the rate of stroke may be explained by several factors. First, the method of stroke ascertainment varied across studies, and thus some patients with ischemic stroke may have been missed. Second, many hospitalized patients with COVID-19 infection are severely ill, which makes acquiring brain imaging challenging and at times impractical; as a consequence, the threshold to obtain brain imaging may have varied between institutions. Third, the demographic composition of patients included in these cohorts varied, and data suggest that races of color appear to be at heightened risk for severe disease.[17]

This systematic investigation expands our understanding of the characteristics, mechanisms, and short-term outcomes of acute ischemic stroke in patients with COVID-19 infection. We found that most ischemic strokes occurred in older age groups, those with traditional stroke risk factors, and people of color. We also noted that initial plasma D-dimer levels were nearly 3-fold higher in those who received a diagnosis of ischemic stroke than in those who did not. In-hospital strokes accounted for nearly three-quarters of all strokes, and more than one-third occurred in those treated with mechanical ventilation.

Our findings suggest that patients with COVID-19 infection may be at a greater risk of ischemic stroke than patients with influenza infection. There are several possible explanations for this finding. First, it has been established that acute viral infections, including influenza, act as triggers that increase the short-term risk of ischemic stroke and other arterial thrombotic events, such as myocardial infarction.[9,18,19] Implicated mechanisms include inflammation, prothrombotic coagulopathy, and endothelial injury.[19,20] COVID-19 infection in particular is associated with a vigorous inflammatory response accompanied by coagulopathy, with elevated D-dimer levels and the frequent presence of antiphospholipid antibodies, which may explain the high prevalence of thromboses seen in these patients.[2,3,21,22] Second, patients with COVID-19 infection are at heightened risk for medical complications, such as atrial arrhythmias, myocardial infarction, heart failure, myocarditis, and venous thromboses, all of which likely contribute to the risk of ischemic stroke.[23-26] Additionally, COVID-19 infection may on average result in a more severe respiratory syndrome than influenza infection, and this greater severity of illness may in part account for the greater rate of stroke seen in patients with COVID-19, especially regarding its associations with the cardiovascular and coagulation systems. Third, baseline stroke risk factors, such as hypertension, diabetes, and coronary artery disease, were more common in the cohort of patients with COVID-19 than in patients with influenza; however, even when adjusting for the number of vascular risk factors, we identified a higher risk of ischemic stroke with Covid-19 vs with influenza. How these and other unidentified factors unique to COVID-19 may play a role in the excess risk of stroke beyond the risk observed with other viral infections requires further investigation. Alternatively, the observed differences may reflect differences in testing for COVID-19 infection vs influenza infection, thresholds for hospital admission for these illnesses, and differences in clinical stroke diagnosis and imaging practices in patients with these 2 viruses.

### Limitations

Our study has several limitations. First, we may have underestimated the true rate of ischemic stroke in patients hospitalized with COVID-19 infection because these patients are sometimes too unstable to undergo brain imaging. In addition, some patients with undiagnosed COVID-19 and stroke may have died before reaching the hospital. Conversely, the recent surge in COVID-19 in New York City could have affected the threshold for visiting the ED or hospitalization and therefore it is possible that patients who sought emergency care with COVID-19 in our cohort had more severe illness than patients who sought emergency care with influenza in past years. The increased risk of stroke in COVID-19 infection may thus reflect a greater severity of underlying illness. Second, although the findings from the sensitivity analysis restricted to hospitalized patients mirrored that of the primary analysis, we were unable to account for patients who had ED treat-and-release visits for COVID-19 or influenza and then were hospitalized for ischemic stroke at a different institution. Third, our study involved 2 hospitals and thus our results may not be generalizable to other settings. In particular, we were unable to estimate the population-level incidence of ischemic stroke among patients infected with SARS-CoV-2 and compare this incidence to the general population. Fourth, the testing criteria for COVID-19 and influenza likely differed and this could have affected the estimated rates of stroke within groups. Additionally, our institution's testing criteria for COVID-19 changed during the study period based on the availability of testing materials, guidance from governmental health organizations, and the recognition of a broader spectrum of clinical presentations.

## Conclusions

The proportion of patients with ED visits and hospitalizations with COVID-19 who had an acute ischemic stroke was higher than the proportion seen in patients who visited the ED or were hospitalized with influenza. These findings suggest that clinicians should be vigilant for symptoms and signs of acute ischemic stroke in patients with COVID-19 so that time-sensitive interventions, such as thrombolysis and thrombectomy, can be instituted if possible to reduce the burden of long-term disability. In the meantime, further elucidation of thrombotic mechanisms in patients with COVID-19 may yield better strategies to prevent disabling thrombotic complications like ischemic stroke.

ARTICLE INFORMATION

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**Author Contributions:** Dr Navi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Merkler and Parikh are co–first authors.
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**Conflict of Interest Disclosures:** Dr Merkler has received personal fees for medicolegal consulting on stroke. Dr Kamel serves as co–principal investigator for the National Institutes of Health (NIH)–funded ARCADIA trial, for which receives in-kind study drugs from the BMS-Pfizer Alliance and in-kind study assays from Roche Diagnostics, serves as a deputy editor for *JAMA Neurology*, serves as a steering committee member of Medtronic's Stroke AF trial (uncompensated), serves on an end point adjudication committee for a trial of empagliflozin for Boehringer-Ingelheim, and has served on an advisory board for Roivant Sciences associated with Factor XI inhibition. Dr Fink serves as the editor-in-chief of Neurology Alert, Relias LLC. Dr Segal has received personal fees for medicolegal consulting on stroke. Dr Navi serves as a data and safety monitoring board member for the Patient-Centered Outcomes Research Institute–funded TRAVERSE trial and has received personal fees for medicolegal consulting on stroke. No other disclosures were reported.

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