Stroke risk, phenotypes, and death in COVID-19
Systematic review and newly reported cases

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Abstract

Objectives
To investigate the hypothesis that strokes occurring in patients with coronavirus disease 2019 (COVID-19) have distinctive features, we investigated stroke risk, clinical phenotypes, and outcomes in this population.

Methods
We performed a systematic search resulting in 10 studies reporting stroke frequency among patients with COVID-19, which were pooled with 1 unpublished series from Canada. We applied random-effects meta-analyses to estimate the proportion of stroke among COVID-19. We performed an additional systematic search for cases series of stroke in patients with COVID-19 (n = 125), and we pooled these data with 35 unpublished cases from Canada, the United States, and Iran. We analyzed clinical characteristics and in-hospital mortality stratified into age groups (<50, 50–70, >70 years). We applied cluster analyses to identify specific clinical phenotypes and their relationship with death.

Results
The proportions of patients with COVID-19 with stroke (1.8%, 95% confidence interval [CI] 0.9%–3.7%) and in-hospital mortality (34.4%, 95% CI 27.2%–42.4%) were exceedingly high. Mortality was 67% lower in patients <50 years of age relative to those >70 years of age (odds ratio [OR] 0.33, 95% CI 0.12–0.94, $p = 0.039$). Large vessel occlusion was twice as frequent (46.9%) as previously reported and was high across all age groups, even in the absence of risk factors or comorbid conditions. A clinical phenotype characterized by older age, a higher burden of comorbid conditions, and severe COVID-19 respiratory symptoms was associated with the highest in-hospital mortality (58.6%) and a 3 times higher risk of death than the rest of the cohort (OR 3.52, 95% CI 1.53–8.09, $p = 0.003$).

Conclusions
Stroke is relatively frequent among patients with COVID-19 and has devastating consequences across all ages. The interplay of older age, comorbid conditions, and severity of COVID-19 respiratory symptoms is associated with an extremely elevated mortality.

Glossary

CI = confidence interval; **COVID-19** = coronavirus disease 2019; **CVT** = cerebral venous thrombosis; **ICH** = intracerebral hemorrhage; **LVO** = large vessel occlusion; **OR** = odds ratio; **SAH** = subarachnoid hemorrhage; **SARS-CoV** = severe acute respiratory syndrome coronavirus; **uOR** = unadjusted OR.

Coronavirus disease 2019 (COVID-19) is a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) 2 and is associated with elevated risk of venous and arterial thrombotic events.[1] Acute stroke has been reported among patients of all ages with COVID-19.[2] Specific concern has been raised about severe stroke occurring in young patients with COVID-19, some of them without preexisting risk factors.[3] However, to date, relatively little is known about the frequency, clinical characteristics, and outcomes of acute cerebrovascular events in patients with COVID-19. We hypothesized that stroke is a frequent complication among patients with COVID-19, that in-hospital mortality is higher in patients with stroke and COVID-19 compared to historical cohorts without COVID-19, and that young patients would show a higher mortality due to a higher incidence of large vessel occlusion (LVO). We therefore investigated the incidence, characteristics, and outcomes of patients with COVID-19 with acute stroke.

Methods

Standard protocol approvals, registrations, and patient consents

This study was approved by the Western University Research Ethics Board. All patients from Canada, Iran, and the United States included in these series provided their informed consent.

Objectives

This study aimed (1) to estimate the risk of stroke among hospitalized patients with COVID-19; (2) to quantify in-hospital mortality of patients with COVID-19 with stroke; (3) to analyze risk factor profiles, frequency of vascular comorbid conditions, subtypes, clinical characteristics, and outcomes of young patients with COVID-19 with stroke; (4) to derive clinical phenotypes of patients with stroke with COVID-19 based on unsupervised learning analyses; and (5) to compare in-hospital mortality between the derived clinical phenotypes.

Proportion of hospitalized patients with COVID-19 with acute stroke

To evaluate the proportion of patients with COVID-19 who sustained a stroke during either the presymptomatic or symptomatic period, we searched for publications reporting the number of cerebrovascular events (numerator) and the total number of patients admitted with COVID-19 (denominator). We identified potential studies by performing a systematic search of titles published in any language between November 1, 2019, and May 29, 2020. We used PubMed, medRxiv, bioRxiv, and Research Square search engines. We did not develop a specific review protocol for this study, but we systematically listed all search terms (tables e-1–e-3, data available from Dryad, doi.org/10.5061/dryad.n5tb2rbt5) and documented them in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (figures e-1 and e-2, data available from Dryad). Five neurologists were randomly paired to review each abstract. One neurologist reviewed the selected articles and confirmed the presence of inclusion and exclusion criteria. We applied a random-effects meta-analysis to estimate the proportion of patients with COVID-19 experiencing a new stroke. The primary outcome was the occurrence stroke of any type, defined as ischemic stroke, intracerebral hemorrhage (ICH), cerebral venous thrombosis (CVT), or subarachnoid hemorrhage (SAH). The secondary outcome was the occurrence of an ischemic stroke. We used the Agresti-Cuoll method to calculate confidence intervals (CIs) for individual studies. We calculated between-study variance τ^2 with the maximum-likelihood estimator. We reported the proportion and corresponding 95% CIs of patients with COVID-19 with acute stroke by pooling data using the Hartung-Knapp approach. We quantitatively assessed the presence of between-study heterogeneity with I^2 (<25% was considered low; 25%–50%, moderate; and >75%, high) and χ^2-based Q statistic (significant if $p < 0.1$). We used the risk of bias in non-randomized studies of interventions tool to assess the risk of bias and contour-enhanced funnel plots to assess publication bias.[4]

In-hospital mortality

To estimate the risk of death among hospitalized patients with COVID-19 with a new stroke occurrence, we performed an additional systematic search by applying the same search terms described for the above-mentioned meta-analysis. For these specific analyses, we looked for case reports and case series published in any language with full descriptions of clinical cases of patients with COVID-19 and stroke. COVID-19 diagnosis was defined as a confirmed positive PCR test or serology for SARS-CoV-2 with or without typical symptoms or radiographic findings. We included any case of stroke that occurred between 14 days before (COVID-19 incubation period estimated by the Centers for Disease Control[5]) and 60 days after the diagnosis of COVID-19. We pooled the data resulting from the literature search with case series from the London Ontario Stroke Registry (London, Ontario, Canada), the Miami Cardiac & Vascular Institute (Miami, FL), and the Mazandarn University of Medical Sciences (Sari, Mazandaran, Iran). We reported the

risk of in-hospital mortality among patients with all stroke types and ischemic stroke as proportions and 95% CIs.

Clinical characteristics and in-hospital mortality of young patients with COVID-19 with stroke

We used the pooled dataset of case series and unpublished cases of COVID-19 and stroke to estimate the risk of in-hospital mortality. We documented demographic data, risk factors, comorbid conditions, brain and vascular imaging findings, results of coagulation tests, and outcomes. We did not include data on duration of follow-up, stroke severity, mechanisms of ischemic strokes, medications, and length of hospital stay in this report because they were inconsistently and incompletely reported in the majority of the reviewed publications. If the severity of COVID-19 respiratory symptoms was not reported, we used any of the following criteria to define the disease as severe/critical: hypoxia, admission to the intensive care unit, or mechanical ventilation requirement. To investigate differences between young and older patients with COVID-19, we stratified patients into 3 age categories. Given discrepancies in the classification of patients with stroke as young, we chose the definition of <50 years of age used in a recent review article.[6] Because some case series included in this analysis reported age decades instead of exact ages,[7] we used a similar approach for classifying older age strata into 50 to 70 and >70 years. Accordingly, we defined age groups as young (<50 years old), middle-aged (50–70 years old), and older (>70 years old).[6] For the purpose of this analysis, the young category was the main age group of interest. The main outcome was in-hospital mortality. We quantified continuous variables as medians and interquartile ranges. We used χ^2 and Mann-Whitney U tests for comparing proportions and medians across the 3 age strata. We used 2-sided z tests to compare proportions between 2 age groups. We estimated unadjusted odds ratios (uORs) and 95% CIs for in-hospital mortality for young patients relative to the rest of the cohort.

Clinical phenotyping of patients with COVID-19 with stroke

We applied an unsupervised learning approach to develop clinical phenotypes of patients with COVID-19 with stroke by conducting agglomerative hierarchical cluster analyses, which allows for mitigating biases related to previously acquired non–COVID-19 stroke knowledge.[8] The benefit of this approach is that patients are grouped into phenotypes or clusters based on common characteristics instead of classic categorization approaches (e.g., stratification in age groups), which could sometimes be arbitrary (e.g., defining the age cutoff for classifying a patient as young). We applied Gower distances with the maximum linkage clustering method.[9] For the sake of dataset completeness, we included the covariables most consistently reported in case reports and case series (table 1). We used silhouette and C-index analyses to inform the total number of clusters.[10] We decided the final number of clusters by applying clinical consensus between 2 coauthors (S.F. and L.A.S.). We created cluster heat maps to help understand the characteristics of each stroke phenotype in patients with COVID-19.

Differences in in-hospital mortality across stroke phenotypes

We compared proportions of in-hospital mortality among clinical phenotypes identified through unsupervised learning. For analyses resulting in 2 clusters, we estimated ORs and 95% CIs. For analyses resulting in >2 clusters, we identified the one with the highest in-hospital mortality and compared it against each of the remaining cohorts separately and as a single group by estimating ORs and 95% CIs. We did not perform logistic regression analyses because all variables needed for the multivariable analysis were used to develop the clusters through unsupervised learning. We estimated the unadjusted risk of in-hospital mortality for all variables that were statistically more frequent in the clusters showing the highest in-hospital mortality.

We conducted all analyses with R version 3.6.2 (R Core Team, Vienna, Austria, 2014). We used the Meta and Metaphor packages for the meta-analyses and Cluster and ClusterCrit for the cluster analyses.

Data availability

Data will be shared after ethics approval if requested by other investigators for purposes of replicating the results.

Results

Proportion of patients with COVID-19 with stroke

The systematic search for the meta-analysis of proportion of patients with COVID-19 experiencing a new stroke resulted in 2,628 titles, of which we reviewed 150 in full-text format (figure e-1, data available from Dryad, doi.org/10.5061/dryad.n5tb2rbt5). The final cohort included a total of 3,306 patients with COVID-19 with stroke of any type and 5,322 with ischemic stroke from 10 studies and 1 newly reported cohort from Canada. Overall, 1.8% (95% CI 0.9%–3.7%) of patients with COVID-19 experienced a new stroke, and 1.5% (95% CI 0.8%–2.8%) had an ischemic stroke (figure 1). Heterogeneity between studies was high for the estimates of both any stroke (I^2 = 84%, $p < 0.01$) and ischemic stroke (I^2 = 82%, $p < 0.01$). The funnel plots were asymmetric, suggesting publication bias. The overall risk of bias was moderate (figure e-2, data available from Dryad).

In-hospital mortality

Among 2,628 unique titles identified in the search strategy of case reports and case series describing patients with COVID-19 with stroke, we reviewed 252 in full-text format, resulting in the final inclusion of 42 studies (figure e-3, data available from Dryad, doi.org/10.5061/dryad.n5tb2rbt5) and 1 additional study that is currently under review.[11] The total study cohort comprised 160 cases: 125 identified through the

Table 1 Characteristics of 160 patients with COVID-19 with all types of stroke, stratified by age

		Age groups, y			
	All patients (n = 160)	<50 (n = 29)	50–70 (n = 74)	>70 (n = 57)	*p* Value
Demographics					
Median (IQR) age, y	65.0 (54.0, 76.3)	37.5 (33.0, 44.0)	62.0 (55.0, 65.0)	78.0 (75.0, 84.0)	<0.001
Female sex, n (%)[a]	55 (43.0)	9 (40.9)	23 (40.4)	23 (46.9)	0.77
Risk factors, n (%)					
No risk factors	26 (16.4)	13 (44.8)	8 (11.0)	5 (8.8)	<0.001
Hypertension	100 (62.9)	6 (20.7)	47 (64.4)	47 (82.5)	<0.001
Diabetes mellitus	65 (40.9)	10 (34.5)	31 (42.5)	24 (42.1)	0.74
Dyslipidemia	44 (27.7)	6 (20.7)	21 (28.8)	17 (29.8)	0.64
Smoking	12 (7.5)	1 (3.4)	7 (9.6)	4 (7.0)	0.56
Comorbid conditions, n (%)					
Previous stroke/TIA	18 (11.3)	1 (3.4)	7 (9.6)	10 (17.5)	0.12
Atrial fibrillation	24 (15.1)	0 (0.0)	12 (16.4)	12 (21.1)	0.033
Coronary artery disease	28 (17.6)	1 (3.4)	11 (15.1)	16 (28.1)	0.013
Chronic kidney disease	6 (3.8)	1 (3.4)	4 (5.5)	1 (1.8)	0.54
Obesity	11 (6.9)	1 (3.4)	6 (8.1)	4 (7.0)	0.70
Cancer	8 (5.0)	0 (0.0)	5 (6.8)	3 (5.3)	0.36
Clinical features of COVID-19					
Severe/critical COVID-19, n (%)	92 (57.5)	13 (44.8)	43 (58.1)	36 (63.2)	0.26
No COVID-19 symptoms before stroke, n (%)	49 (30.8)	14 (48.3)	17 (23.3)	18 (31.6)	0.047
Time from COVID-19 symptoms to stroke, d[b]	8.0 (5.0, 15.0)	8.0 (7.0, 14.0)	12.0 (5.3, 17.8)	5.0 (3.0, 10.0)	0.08
Event type, n (%)					
Ischemic stroke	126 (78.8)	22 (75.9)	57 (77.0)	47 (82.5)	0.69
Intracerebral hemorrhage	24 (15.0)	4 (13.8)	10 (13.5)	10 (17.5)	0.80
Subarachnoid hemorrhage	3 (1.9)	1 (3.4)	2 (2.7)	0 (0.0)	0.42
Cerebral venous thrombosis	7 (4.4)	2 (6.9)	5 (6.8)	0 (0.0)	0.13
Laboratory findings, n (%)[c]					
Elevated D-dimer	96 (82.1)	20 (90.9)	46 (80.7)	30 (78.9)	0.47
Positive APLA	12 (54.5)	1 (20.0)	8 (80.0)	3 (42.9)	0.07
Prolonged PTT	18 (20.2)	3 (27.3)	10 (25.0)	5 (13.2)	0.35
Thrombocytopenia	12 (11.2)	1 (6.7)	8 (16.7)	3 (6.8)	0.27
Elevated fibrinogen	35 (85.4)	8 (66.7)	19 (95.0)	8 (88.9)	0.09
Elevated cardiac troponin	30 (40.5)	5 (71.4)	15 (48.4)	10 (27.8)	0.050
Outcomes, n (%)					
Venous thromboembolism[d]	11 (11.8)	2 (10.0)	6 (13.6)	3 (10.3)	0.88
Deceased	55 (34.4)	6 (20.7)	24 (32.4)	25 (43.9)	0.15
Home/rehabilitation	68 (42.5)	14 (48.3)	30 (40.5)	24 (42.1)	

Continued

Table 1 Characteristics of 160 patients with COVID-19 with all types of stroke, stratified by age *(continued)*

Still hospitalized	37 (23.1)	9 (31.0)	20 (27.0)	8 (14.0)

Abbreviations: APLA = antiphospholipid antibodies; COVID-19 = coronavirus disease 2019; IQR = interquartile range; PTT = partial thromboplastin time.
[a] Data on sex were available for 128 patients.
[b] Data are median (IQR) days.
[c] Data were not available for all cases.
[d] Venous thromboembolism includes deep venous thrombosis and pulmonary embolism.

systematic literature search, 5 from London (Canada), 29 from Sari (Iran), and 1 from Miami (FL) (table e-4, data available from Dryad). All 160 patients in this cohort were admitted to the hospital. Two of the cases from Sari were included in a case series accepted for publication after being incorporated into this dataset and when the systematic search was already closed.[12] Among 6 patients with COVID-19 with stroke identified in London, 1 patients did not provide consent to have data included in the descriptive case series. None of these 160 cases except for 5 patients from London were included in the meta-analyses performed for estimating the occurrence of stroke in patients with COVID-19.

The median age was 65.0 (interquartile range 54.0, 76.3) years (table 1). Among 128 cases for whom information about sex was available, 55 (43.0%) were female. The numbers of patients with ischemic stroke, ICH, CVT, and SAH were 126

(78.8%), 24 (15.0%), 7 (4.4%), and 3 (1.9%). There were 55 in-hospital deaths among patients with strokes of all types considered together (34.4%, 95% CI 27.2%–42.4%) and 45 among 126 with ischemic strokes (35.7%, 95% CI 27.5%–44.8%). After the exclusion of patients who were still hospitalized and thus with uncertain outcome, there were 55 deaths among 123 patients with stroke (44.7%, 95% CI 35.9%–53.5%) and 45 deaths among 100 patients with ischemic stroke (45.0%, 95% CI 35.3%–54.8%).

Young patients with COVID-19 with stroke of any type

In the age-stratified descriptive analysis for 160 patients with all types of stroke (table 1), there were 29 who were <50 years of age. On unadjusted analyses, those <50 years of age were the ones most likely to have no previous risk factors or comorbid conditions (42.9%, $p < 0.001$), and

Figure 1 Proportion of patients with COVID-19 with any stroke and ischemic stroke
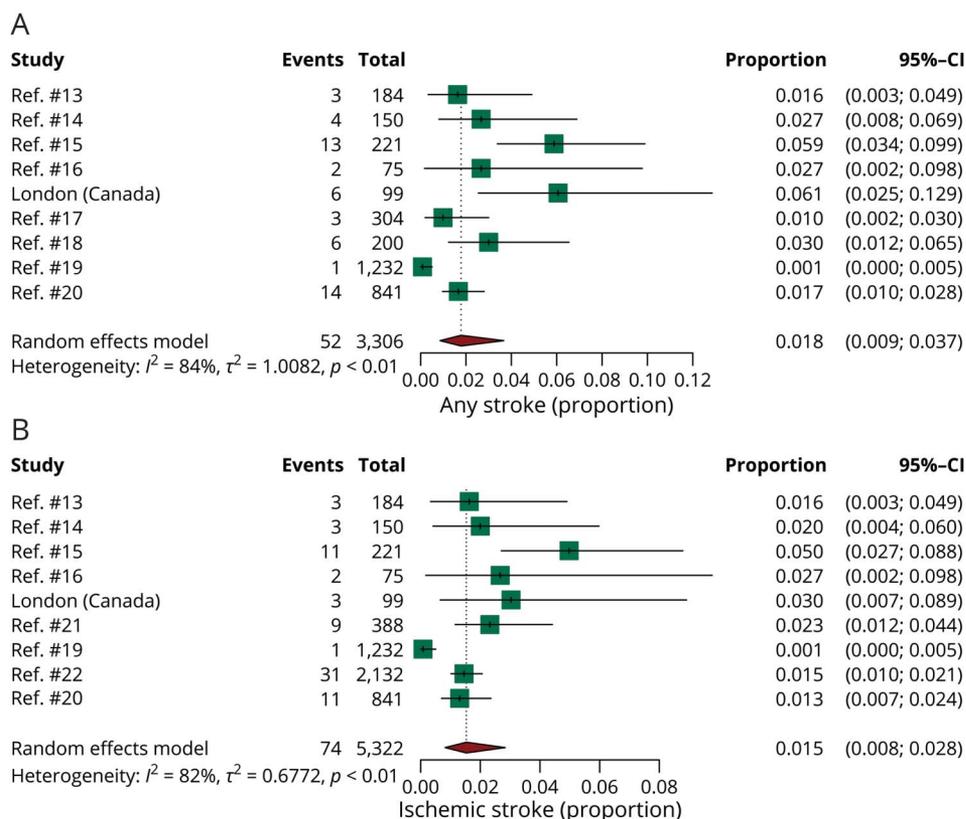
(A) Random-effect meta-analysis for any stroke: ischemic stroke, intracerebral hemorrhage, cerebral venous thrombosis, and subarachnoid hemorrhage. (B) Random-effects meta-analysis for ischemic stroke. London (Canada) refers to unpublished cohort of patients admitted to London Health Sciences Centre, London, Ontario, Canada. CI = confidence interval; COVID-19 = coronavirus disease 2019.

they had the lowest frequency of hypertension (20.7%, *p* < 0.001), atrial fibrillation (0.0%, *p* = 0.033), and coronary artery disease (3.4%, *p* = 0.013). Strokes in younger patients were most likely to occur before the onset of COVID-19 symptoms (48.3%, *p* = 0.047). There were no differences between age groups in the proportion of patients with severe or critical COVID-19 or in types of stroke. The most frequent laboratory finding was elevated D-dimer (82.1%), although there were no significant differences compared to middle-aged or older groups. Young patients showed the highest frequency of cardiac troponin elevation (71.4%, *p* = 0.050). The unadjusted risk of in-hospital death in patients <50 years of age was lower than among those >70 years of age (uOR 0.33, 95% CI 0.12–0.94, *p* = 0.039), but there were no differences in the risk of in-hospital death between young patients and the rest of the cohort (uOR 0.44, 95% CI 0.16–1.15, *p* = 0.09). The latter lack of significance is probably underpowered (power for 2-sided α of 0.5 = 51.9%).

Young patients with COVID-19 with ischemic stroke

In the age-stratified descriptive analysis of 126 ischemic stroke cases, there were 22 (17.4%) patients <50 years of age (table 2). Young patients with ischemic strokes were the age group with the highest proportion with no risk factors or comorbid conditions (40.9%, *p* < 0.001) and with the lowest prevalence of hypertension (27.3%, *p* < 0.001) and atrial fibrillation (0.0%, *p* = 0.048). Young patients were the most likely to experience an ischemic stroke in the absence of any prior COVID-19 respiratory symptoms (50.0%, *p* = 0.014) and to present with an LVO (68.8%, *p* = 0.049). Despite this, the risk young patients presenting with LVO was not higher than that of the rest of the cohort (uOR 2.46, 95% CI 0.83–7.30, *p* = 0.10). We found no differences between age groups in the proportion of patients receiving IV thrombolysis (tissue plasminogen activator) or mechanical thrombectomy. Patients with ischemic stroke who were <50 years of age showed the highest frequency of elevated cardiac troponin (80.0%, *p* = 0.046). There were no differences in the unadjusted risk of death between young (<50 years of age) and older (>70 years of age) patients (uOR 0.48, 95% CI 0.16–1.45, *p* = 0.19) or between young patients and the rest of cohort (uOR 0.63, 95% CI 0.23–1.73, *p* = 0.37).

Cluster analysis for all strokes

The hierarchical cluster analysis for all strokes included 158 of 160 patients and resulted in 3 phenotypes (figure e-4, data available from Dryad, doi.org/10.5061/dryad.n5tb2rbt5). Two patients were excluded because of being outliers or having missing data. Cluster 1 had the lowest burden of hypertension, diabetes mellitus, and dyslipidemia, with 40.0% of cases in the cluster having no known risk factors or comorbid conditions (figure 2 and table e-5, data available from Dryad doi.org/10.5061/dryad.n5tb2rbt5). Cluster 1 was also the most heterogeneous in terms of types of strokes, including ischemic events, ICH, CVT, and SAH cases. Cluster 2 was the

largest (n = 82) and comprised exclusively ischemic stroke cases. It had an intermediate burden of risk factors and comorbid conditions and the lowest proportion of patients with severe or critical COVID-19 respiratory symptoms (42.7%, *p* < 0.001). Cluster 3 comprised the largest proportion of individuals > 70 years old (58.6%, *p* = 0.006), the lowest percentage of young patients (10.3%, *p* < 0.001), and the highest burden of risk factors (e.g., hypertension, diabetes mellitus, and dyslipidemia) and cardiovascular comorbid conditions, including prior stroke or TIA (27.6%, *p* = 0001), atrial fibrillation (41.4%, *p* < 0.001), and coronary artery disease (37.9%, *p* = 0.001). Almost all patients in cluster 3 had severe or critical COVID-19 respiratory symptoms (96.9%, *p* < 0.001).

Cluster analysis for ischemic stroke

The cluster analysis for ischemic stroke included 124 patients and resulted in 2 phenotypes (figure 3 and table e-6, data available from Dryad, doi.org/10.5061/dryad.n5tb2rbt5). Two patients were excluded because of being outliers or having missing data. Cluster 1 had a higher proportion of patients <50 years of age than cluster 2 (28.9% vs 11.4%, *p* < 0.038) and a lower prevalence of atrial fibrillation (6.7% vs 24.1%, *p* = 0.028) and coronary artery disease (6.7% vs 24.1%, *p* = 0.028). The proportion of patients presenting with severe or critical COVD-19 respiratory symptoms was also lower in cluster 1 relative to cluster#2 (6.7% vs 94.2%, *p* < 0.001). There were no additional significant differences between clusters except for a higher prevalence of chronic kidney disease in cluster 1 (11.1% vs 0.0%, *p* = 0.011).

Differences in in-hospital mortality across stroke phenotypes

In the analysis including all strokes, the proportion not surviving hospitalization was highest for cluster 3 (58.6%, 95% CI 40.7%–76.5%, *p* < 0.001) (table e-7, data available from Dryad, doi.org/10.5061/dryad.n5tb2rbt5). In-hospital mortality of cluster 3 was higher than that of cluster 1 (odds ratio [OR] 4.63, 95% CI 1.70–12.6, *p* = 0.003) and cluster 2 (OR 3.05, 95% CI 1.27–7.31, *p* = 0.012). Compared to clusters 1 and 2 considered together, patients in cluster 3 had a higher risk of in-hospital death (OR 3.52, 95% CI 1.53 to 8.09, *p* = 0.003). Among the variables showing significant differences between cluster 3 and other clusters, the only one associated with in-hospital mortality was the severity of COVID-19 respiratory symptoms (OR 6.56, 95% CI 2.91–14.76, *p* < 0.001) (table e-8, data available from Dryad).

In the analysis limited to patients with ischemic stroke, cluster 2 was the one with the highest in-hospital mortality (48.1%, 95% CI 37.1%–59.1%, *p* < 0.001) (table e-9, data available from Dryad, doi.org/10.5061/dryad.n5tb2rbt5). This risk was higher than that of cluster 1 (OR 6.02, 95% CI 2.29–15.83, *p* < 0.001). Among the variables showing significant differences between clusters 2 and 1, the only one associated with in-hospital mortality was the severity of COVID-19 respiratory symptoms (OR 9.51, 95% CI 3.41–26.58, *p* < 0.001) (table e-10, data available from Dryad).

Table 2 Characteristics of 126 patients with COVID-19 with ischemic stroke, stratified by age

		Age groups, y			
	All patients (n = 126)	<50 (n = 22)	50–70 (n = 56)	>70 (n = 48)	p Value
Demographics					
Median (IQR) age, y	65.0 (54.0, 76.3)	37.5 (33.0, 44.0)	62.0 (55.0, 65.0)	78.0 (75.0, 84.0)	<0.001
Female sex, n (%)[a]	44 (46.8)	7 (46.7)	16 (40.0)	21 (53.8)	0.47
Risk factors, n (%)					
No risk factors	16 (12.8)	9 (40.9)	5 (8.9)	2 (4.3)	<0.001
Hypertension	85 (68.0)	6 (27.3)	38 (67.9)	41 (87.2)	<0.001
Diabetes mellitus	56 (44.8)	9 (40.9)	25 (44.6)	22 (46.8)	0.90
Dyslipidemia	41 (32.8)	6 (27.3)	20 (35.7)	15 (31.9)	0.76
Smoking	9 (7.2)	1 (4.5)	5 (8.9)	3 (6.4)	0.77
Comorbid conditions, n (%)					
Previous stroke/TIA	15 (12.0)	1 (4.5)	7 (12.5)	7 (14.9)	0.46
Atrial fibrillation	23 (18.4)	0 (0.0)	12 (21.4)	11 (23.4)	0.048
Coronary artery disease	23 (18.4)	1 (4.5)	9 (16.1)	13 (27.7)	0.06
Chronic kidney disease	6 (4.8)	1 (4.5)	4 (7.1)	1 (2.1)	0.49
Obesity	9 (7.1)	1 (4.5)	5 (8.8)	3 (6.4)	0.78
Cancer	5 (4.0)	0 (0.0)	3 (5.4)	2 (4.3)	0.55
Clinical features of COVID-19					
Severe/critical COVID-19, n (%)	77 (61.1)	10 (45.5)	36 (63.2)	31 (66.0)	0.24
No COVID-19 symptoms before stroke, n (%)	37 (29.6)	11 (50.0)	10 (17.9)	16 (34.0)	0.014
Time from COVID-19 symptoms to stroke, d[b]	8.0 (5.0, 15.0)	8.0 (7.0, 14.0)	12.0 (5.3, 17.8)	5.0 (3.0, 10.0)	0.18
Vascular and brain imaging, n (%)					
Large vessel occlusion[c]	46 (46.9)	11 (68.8)	14 (34.1)	21 (51.2)	0.049
Infarct limited to the left side	30 (32.3)	6 (40.0)	15 (38.5)	9 (23.1)	0.27
Infarct limited to the right side	42 (45.2)	9 (60.0)	13 (33.3)	20 (51.3)	0.13
Bilateral infarcts	20 (21.5)	0 (0.0)	11 (28.2)	9 (23.1)	0.07
Middle cerebral artery territory	72 (76.6)	12 (80.0)	33 (82.5)	27 (69.2)	0.36
Anterior cerebral artery territory	8 (8.5)	1 (6.7)	4 (10.0)	3 (7.7)	0.90
Posterior cerebral artery territory	12 (12.8)	1 (6.7)	6 (15.0)	5 (12.8)	0.71
Vertebrobasilar territory	17 (18.1)	1 (6.7)	7 (17.5)	9 (23.1)	0.37
Multiple territories	29 (30.9)	1 (6.7)	15 (37.5)	13 (33.3)	0.08
Laboratory findings, n (%)[d]					
Elevated D-dimer	86 (82.7)	18 (90.0)	40 (81.6)	28 (80.0)	0.62
Positive APLA	11 (64.7)	1 (33.3)	7 (87.5)	3 (50.0)	0.16
Prolonged PTT	14 (22.2)	3 (37.5)	7 (26.9)	4 (13.8)	0.27
Thrombocytopenia	8 (10.1)	0 (0.0)	5 (14.7)	3 (8.8)	0.35
Elevated fibrinogen	32 (88.9)	8 (72.7)	16 (94.1)	8 (100.0)	0.11
Elevated cardiac troponin	28 (45.2)	4 (80.0)	14 (56.0)	10 (31.2)	0.046

Continued

Table 2 Characteristics of 126 patients with COVID-19 with ischemic stroke, stratified by age *(continued)*

| | All patients (n = 126) | Age groups, y | | | p Value |
		<50 (n = 22)	50–70 (n = 56)	>70 (n = 48)	
Treatment, n (%)					
IV tissue plasminogen activator	16 (12.9)	6 (28.6)	5 (8.9)	5 (10.6)	0.06
Mechanical thrombectomy	15 (12.1)	3 (14.3)	7 (12.5)	5 (10.6)	0.91
Outcomes, n (%)					
Venous thromboembolism[e]	9 (13.0)	1 (7.1)	5 (15.6)	3 (13.0)	0.73
Deceased	45 (35.7)	6 (27.3)	18 (31.6)	21 (44.7)	0.36
Home/Rehabilitation	55 (43.7)	11 (50.0)	24 (42.1)	20 (42.6)	
Still hospitalized	26 (20.6)	5 (22.7)	15 (26.3)	6 (12.8)	

Abbreviations: APLA = antiphospholipid antibodies; COVID-19 = coronavirus disease 2019; IQR = interquartile range; PTT = partial thromboplastin time.
[a] Data on sex and vascular territory were available for 94 patients.
[b] Data are median (IQR) days.
[c] Data on large vessel occlusion were available for 98 patients.
[d] Data were not available for all cases.
[e] Venous thromboembolism includes deep venous thrombosis and pulmonary embolism.

Discussion

Several findings from this study investigating stroke risk, characteristics, and outcomes among patients with COVID-19 deserve discussion (figure 4). Consistent with the main study hypothesis, the proportion of patients with COVID-19 experiencing a stroke was high relative to patients with other viral respiratory diseases. In-hospital mortality was exceedingly high for patients with COVID-19 with strokes of any type and ischemic stroke. In-hospital mortality was higher for young patients with COVID-19 with stroke of any type than for those >70 years of age. However, this was not found among patients with ischemic stroke. The presence of LVO was high across all ages but was not statistically significantly higher for the youngest age group. By applying unsupervised learning, we identified specific phenotypes of patients with COVID-19 with stroke, characterized by the interplay of older age, cardiovascular comorbid conditions, and severe COVID-19 respiratory symptoms, which were associated with increased risk of death. The severity of COVID-19 respiratory symptoms was the factor most strongly associated with stroke mortality.

We found that the occurrence of stroke among hospitalized patients with COVID-19 was relatively high (1.8%, 95% CI 0.9%–3.7%) compared to patients with other viral respiratory infections or even sepsis. We found similar results in the meta-analysis for ischemic stroke (1.6%, 95% CI 0.8%–2.8%). The observed risk of stroke was double that reported in patients with SARS-CoV-1 (0.75%)[23] or severe sepsis (0.78%).[24] The risk of ischemic stroke was 8 times higher than that reported among hospitalized patients with influenza (0.2%).[25] Although high, these numbers likely constitute an underestimate of the actual frequency of stroke among patients with COVID-19 because of missed stroke diagnoses in those who were not extubated after prolonged periods or did not survive mechanical ventilation.[26] The lack of autopsies[27] and restrictions on investigations related to safety recommendations[28] or hospital policies may have contributed to further underestimation of the risk of stroke among hospitalized patients with COVID-19. Furthermore, the well-recognized drop in the number of patients with acute cerebrovascular symptoms seeking medical attention in the COVID-19 era also may have contributed to the underestimation of the frequency of stroke occurrence in this population.[29]

In-hospital mortality was remarkably high for the whole cohort (≈35%) and even higher (≈45%) after the exclusion of patients whose outcome was undetermined at the time their cases were reported (e.g., those who were still admitted). In-hospital mortality in this cohort of patients with COVID-19, which comprised mainly cases with ischemic stroke, was higher than recently reported in a cohort of patients with COVID-19 with acute ischemic stroke (27.6%).[30] It was also higher than reported 30-day case fatality rates for ischemic stroke, ranging from 9% to 19%,[31] or in-hospital mortality of patients with stroke admitted to intensive care units, ranging between 14.7% and 21.9%.[32,33] It must be noted that the limited testing in several countries may have led to inflation of death rates. The elevated incidence of potentially fatal thrombotic complications in patients with COVID-19 and stroke could have contributed to their increased risk of death. Indeed, we found that the combination of deep vein thrombosis and pulmonary embolism was frequent among patients with COVID-19 with stroke, affecting ≈11% and ≈13% of all strokes and ischemic strokes. This number is >10 times higher than the reported incidence of pulmonary embolism within 30 days of ischemic stroke occurrence in a Canadian population-based study

(0.78%).[24] Pulmonary embolism also may explain paradoxical embolism in patients with COVID-19 with ischemic stroke, as recently documented in 2 COVID-19 cases showing a thrombus in transit through a patent foramen ovale.[35,36]

Patients <50 years of age with any stroke or ischemic stroke had the lowest prevalence of hypertension and atrial fibrillation compared to other age groups. Young patients with stroke of any type also had the lowest prevalence of coronary artery disease. Approximately 50% of patients <50 years of age experienced their strokes before the onset of COVID-19 respiratory symptoms, and this was significantly more frequent than in other age groups. This finding may imply that, in the COVID-19 era, younger patients presenting to the emergency department with acute stroke would need to be tested for SARS-CoV-2 even in the absence of specific symptoms or regardless of having passed a COVID-19 screen.

The frequency of LVO was highest among young patients (68.8%). However, this difference was marginally significant ($p = 0.049$), and the unadjusted odds of young patients for presenting more frequently with an LVO than the rest of the cohort was nonsignificant (uOR 2.46, 95% CI 0.83–7.30, $p = 0.10$). This may be due to the lack of adjustment, the study sample size, or publication bias. In addition, the nonsignificant differences in the proportion of patients presenting with LVO could be due to a consistently high prevalence of LVO across all age groups. Indeed, the observed overall 46.9% prevalence of LVO in the whole cohort of patients with ischemic stroke was almost twice as high as the 29.2% recently reported in a population-based study.[37] Similarly, 68.8% of patients with ischemic stroke who were <50 years of age in our study had an LVO compared to 29.7% in the same population-based study.[37] The high prevalence of LVO in the context of a low burden of comorbid conditions in young patients with COVID-19 with stroke strongly supports the role of hypercoagulability as a cause of arterial thrombosis in this age group. This concept is further reinforced by the >4 times higher proportion of cases with elevated D-dimer in our cohort of patients with ischemic stroke (82.7%), particularly

Figure 2 Main characteristics of clinical phenotypes of all strokes derived from unsupervised learning
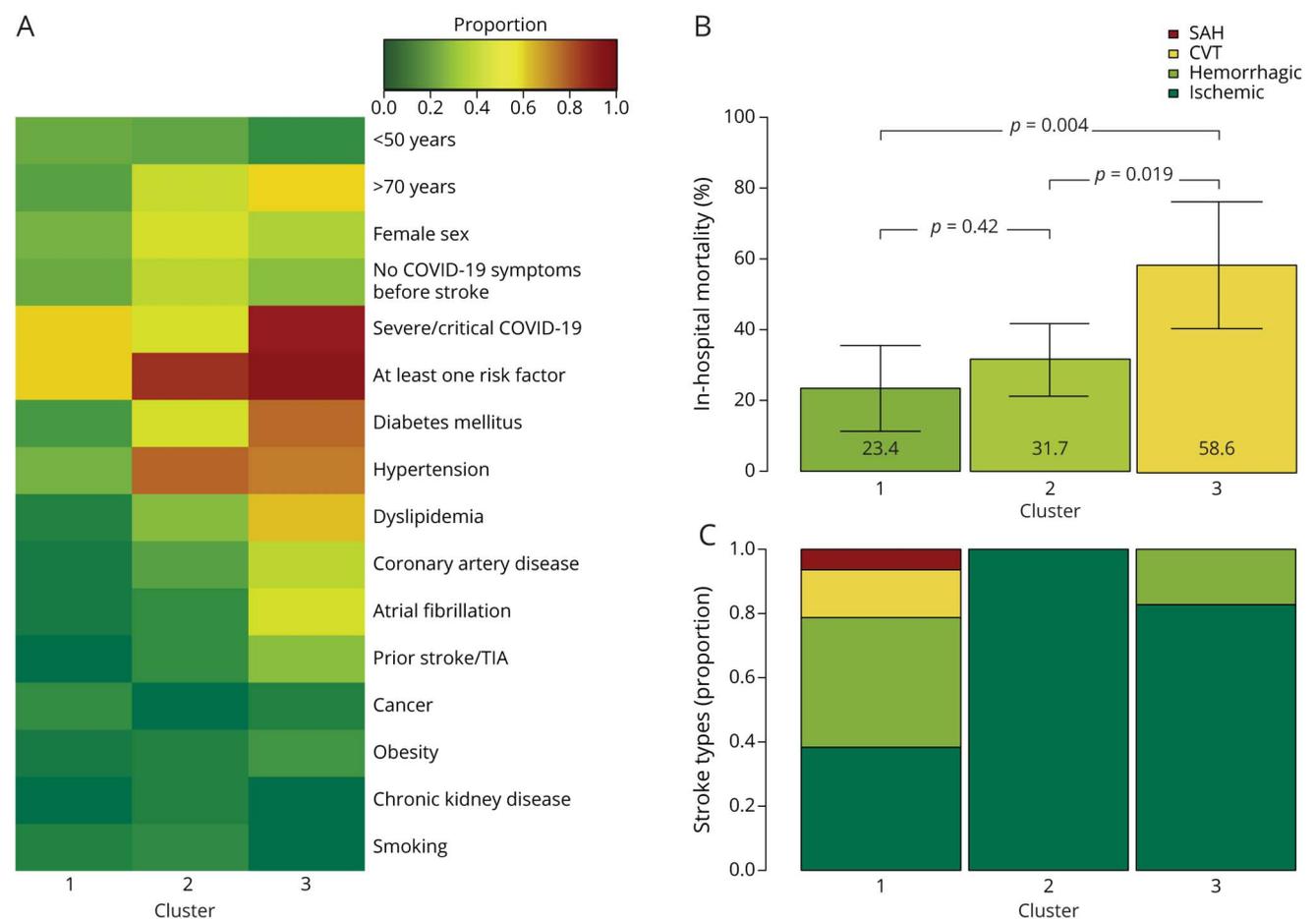
(A) Heat map showing relative frequencies of main characteristics of each stroke phenotype. Heat map shows the salient characteristics of cluster 3, with the highest proportion of severe coronavirus disease 2019 (COVID-19) respiratory symptoms, diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, coronary artery disease, and previous stroke, all showing significant differences compared to other clusters. (B) Main subtype of stroke by clinical phenotype. (C) In-hospital mortality by clinical phenotypes. Data on outcomes were not used to develop the clusters. CVT = cerebral venous thrombosis; SAH = subarachnoid hemorrhage.

Figure 3 Main characteristics of clinical phenotypes of ischemic strokes derived from unsupervised learning
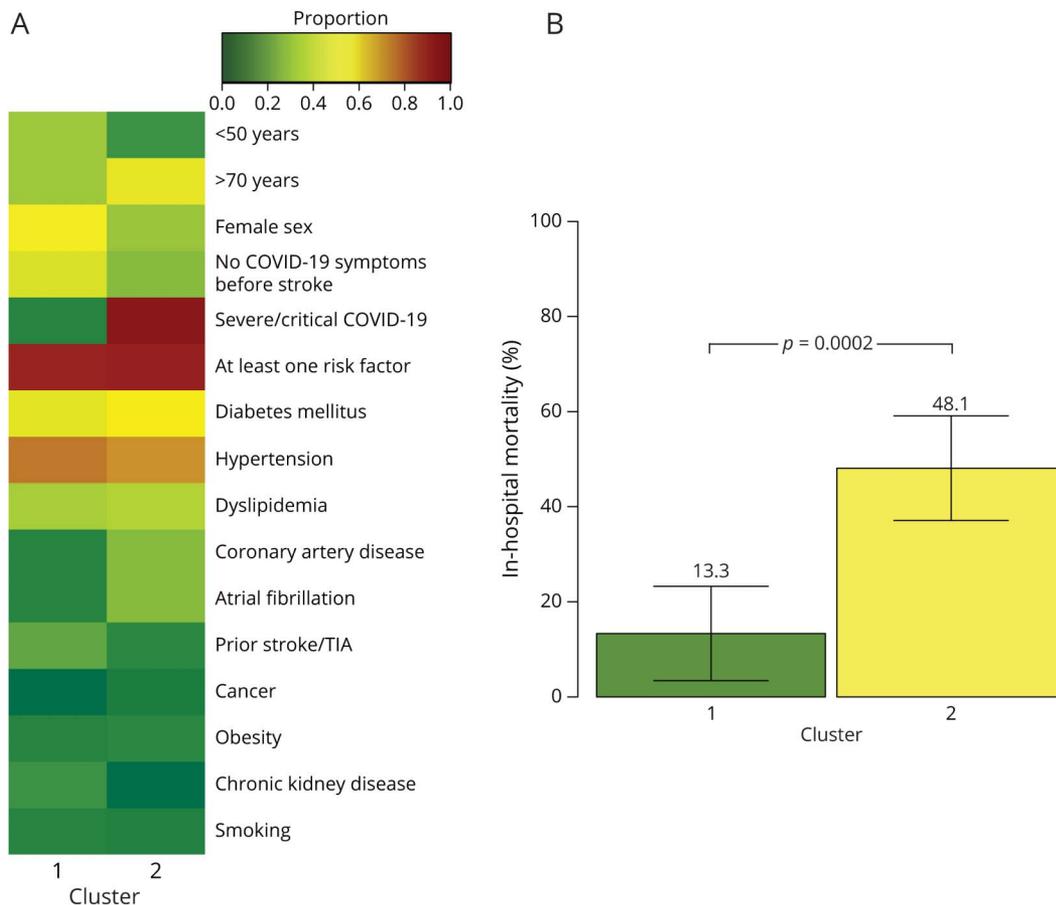

(A) Heat map showing relative frequencies of main characteristics of each ischemic stroke phenotype. (B) In-hospital mortality by clinical phenotypes. Data on outcomes were not used to develop the clusters. COVID-19 = coronavirus disease 2019.

among young patients (90.0%), compared to the overall reported prevalence among patients with COVID-19 (20.4%).[38] Furthermore, recent reports of free-floating thrombi in the carotid[39] or aortic[40,41] arteries of patients with COVID-19 without structural vessel wall abnormalities such as plaque ulceration, inflammation, or hemorrhage[29,30] suggest that COVID-19–related hypercoagulability could cause arterial thrombosis and embolism in the absence of underlying arterial wall disease. Only 3 of 11 (27%) young patients with an LVO received a mechanical thrombectomy. Considering that 50% of young patients with acute ischemic stroke had no COVID-19 respiratory symptoms before stroke onset, it is possible that some patients decided to stay home instead of seeking medical attention because of concerns of being exposed to SARS-CoV-2 in the emergency room.[29]

Patients with ischemic stroke who were <50 years of age showed the highest frequency of elevated cardiac troponin (80.0%, p = 0.046). Increased cardiac troponin is a marker of either acute or chronic myocardial injury[42] and is strongly associated with the risk of stroke.[43] In the general population, factors most consistently associated with chronic myocardial injury are vascular risk factors and cardiovascular comorbid conditions such as atrial fibrillation and coronary artery disease.[42] In patients with stroke, elevated cardiac troponin is explained by either chronic (secondary to baseline underlying heart disease) or acute (neurogenically mediated or type 2 myocardial ischemia) myocardial injury. Considering that 44.8% of young patients with ischemic stroke in this cohort had no prior risk factors and that cardiac troponin was elevated in 80% of them, high troponin levels are likely the consequence of acute myocardial injury, which could play a role in the pathophysiology of acute ischemic stroke in young patients with COVID-19. This is further supported by the higher proportion of elevated cardiac troponin found in young patients with COVID-19 with ischemic stroke (80%) compared to historical cohorts of patients with ischemic stroke (40%)[44] and to other age groups in this cohort. Furthermore, a recent study showed that although only 5% of recovered patients had significantly elevated troponin levels at a median of 71 days after COVID-19 diagnosis, 78% had ongoing cardiac involvement and 60% had signs of myocardial inflammation on cardiac MRI.[45] This suggests that myocarditis is a potential stroke mechanism in COVID-19.[45]

Figure 4 Main study findings
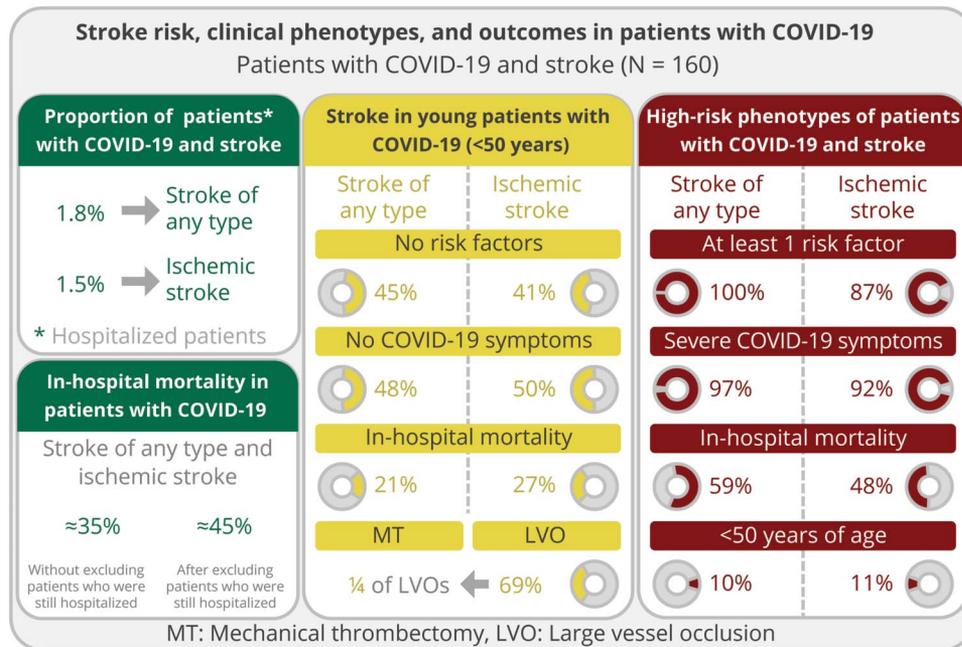
We identified specific stroke phenotypes consistently associated with increased mortality. Among patients with any stroke, cluster 3 was associated with >3 times higher in-hospital mortality than each of the remaining 2 clusters or both of them considered together. This stroke phenotype was characterized by the interplay of older age, a higher burden of risk factors and comorbid conditions, and a higher proportion of severe or critical COVID-19 cases. Among these variables, the only one significantly associated with in-hospital mortality on unadjusted univariable analyses was severe COVID-19 respiratory symptoms (OR 6.56, 95% CI 2.91–14.76, $p < 0.001$). Thus, COVID-19 severity likely plays a major role in the risk of death of patients with stroke. Similar results were found among patients with ischemic stroke.

This work represents a comprehensive review of available evidence addressing the relationship between COVID-19 and stroke based on a large number of cases identified through a systematic search and pooled with previously unpublished cases. Our results should be interpreted in the context of the study limitations. First, although the study sample is relatively large, its size still precludes multivariable regression analyses for ischemic strokes. Second, because most of the source data were pooled from case series and reports, completeness was not ideal. As a consequence, we were not able to inform about stroke severity (only a few studies reported NIH Stroke Scale scores), stroke mechanisms, regional differences, social determinants of health, or race. Third, we found moderate publication bias (funnel plots and risk of bias in nonrandomized studies of interventions tool). Due to the relatively low number of studies included in the meta-analyses, funnel plots could have underestimated the risk of bias. Fourth, data used in this study are likely subject to the consequences of publication bias (e.g., reporting more severe cases or cases of LVO in young patients). Fifth, these results may not be generalizable to other populations such as nonhospitalized patients. To mitigate these limitations and the previous knowledge bias about stroke in patients without COVID-19, we implemented an unsupervised learning approach by applying cluster analyses, which allowed us to establish clinical phenotypes associated with increased risk of death. This was possible by comprehensive documentation of other important variables. Rather than focusing on single variables and their individual association with outcomes, these analyses allowed the characterization of the interplay of clinical characteristics, risk factors, demographics, and comorbid conditions as a whole and their association with in-hospital mortality.

We found that the frequency of stroke occurrence is high among hospitalized patients with COVID-19. In-hospital mortality is also exceedingly higher than previously reported in patients without COVID-19 with stroke. LVO is twice as frequent as previously reported, and its prevalence is high across all age groups, even in the absence of risk factors or comorbid conditions, suggesting the role of COVID-19–related hypercoagulability. Specific clinical phenotypes characterized by the interplay of older age, a higher burden of cardiovascular comorbid conditions, and severe COVID-19 respiratory symptoms were associated with a substantial increase in the risk of death. COVID-19 severity seems to be the major determinant of death. Our findings should serve as information for guiding prognostication, resource allocation, and counseling of patients and their families.

Study funding

Disclosure

Publication history

Appendix Authors

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Maria Bres Bullrich, MD	Department of Clinical Neurologic Sciences, London Health Sciences Center, Western University, Ontario, Canada	Performed the systematic search, contributed to drafting the first version of the manuscript, and reviewed the manuscript for intellectual content
Amado Jimenez-Ruiz, MD	Heart & Brain Laboratory, Western University, Ontario, Canada	Performed the systematic search, contributed to drafting the first version of the manuscript, and reviewed the manuscript for intellectual content
Pablo Costantini, MD	Instituto de Neurología y Neurocirugía de Neuquén, Argentina	Performed the systematic search, contributed to drafting the first version of the manuscript, and reviewed the manuscript for intellectual content

Appendix *(continued)*

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