Incidence, Characteristics and Clinical Relevance of Acute Stroke in Old Patients Hospitalized With COVID-19

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Abstract

Background: Stroke in the course of coronavirus disease (COVID-19) was associated with higher severity of respiratory symptoms and mortality, but little knowledge exists on older populations. We aimed to investigate the incidence, characteristics, and prognosis of acute stroke in old patients hospitalized with COVID-19.

Methods: Monocentric retrospective study of 265 older patients hospitalized with COVID-19 in geriatric wards, 11 of which having presented a stroke episode during hospitalization. Mortality rates and two-group comparisons (stroke vs non-stroke patients) were calculated and significant variables added in logistic regression models to investigate stroke risk factors.

Results: Combined ischemic and hemorrhagic stroke incidence was 4.15%. 72.7% of events occurred during acute care. Strokes presented with altered state of consciousness and/or delirium in 81.8%, followed by a focal neurological deficit in 45.5%. Ischemic stroke was more frequently unilateral (88.8%) and localized in the middle cerebral artery territory (55.5%). Smoking and a history of previous stroke increased by more than seven (OR 7.44; 95% CI 1.75-31.64; p=0.007) and five times (OR 5.19; 95% CI 1.50-17.92; p=0.009), respectively, the risk of stroke. Each additional point in body mass index (BMI) reduced the risk of stroke by 14% (OR 0.86; 95% CI 0.74-0.98; p=0.03). In-hospital mortality (32.1% vs. 27.3%; p>0.999) and institutionalization at discharge (36.4% vs. 21.1%; p=0.258) were similar between patients with and without stroke.

Conclusion: Incident stroke complicating COVID-19 in old patients was associated with active smoking, previous history of stroke, and low BMI. Acute stroke did not influence early mortality or institutionalization rate at discharge.

Introduction

Acute cerebrovascular complications have been reported through the course of bacterial and viral infections in both older and younger patients[1,2]. Multiple mechanisms may explain this phenomenon, such as a higher prothrombotic state induced by systemic inflammation, an increased incidence of arrhythmia such as atrial fibrillation, hypoxia leading to brain hypoperfusion, and possibly direct virus-induced vasculitis or endothelitis[3,4].

Several neurological complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have already been described, such as ischemic and hemorrhagic stroke, together with seizures, meningitis, encephalitis, and Guillain-Barre syndrome[5–8]. A recent systematic review polled 135 cases of ischemic stroke in patients with coronavirus disease 2019 (COVID-19), showing an incidence varying from 0.9 to 2.7%[9]. Acute stroke in the course of COVID-19 was associated with higher severity of respiratory symptoms and mortality in the acute phase.

However, the majority of studies available describe younger populations and little knowledge exists on acute stroke in old and very old patients with COVID-19. The overall incidence of stroke increases with age, as the general prevalence of cerebrovascular risk factors such as hypertension, diabetes, dyslipidemia, and atrial fibrillation. Likewise, older patients with COVID-19 present worse disease outcomes than younger patients, with increased mortality[10], having led to characterize them as a group at risk for more severe disease courses and complications.

This study aimed to describe the incidence, the clinical and imaging characteristics of stroke, as well as their relationship with early mortality and destination at the time of discharge, in a cohort of old and very old patients hospitalized with COVID-19**.** We hypothesize that the incidence of stroke in our COVID-19 population is higher than that described in the literature and that it is related with worse outcomes.

Methods

Design, Setting and Population

This monocentric cross-sectional retrospective study analyzed patients hospitalized in geriatric wards of the University Hospitals. In this cohort, patients were ineligible to intensive care based on a shared decision with patients and/or their representatives. Hospitalized patients with COVID-19 had one or more of these clinical features: a) pneumonia with a severity assessed by the CURB-65 score ≥2, b) new dependence on oxygen or increase of oxygen needs, c) a respiratory rate ≥20 breaths/minute, d) a decompensated chronic disease, e) severely altered general state of health, f) deteriorating clinical course.

We analyzed data from a total of 265 patients hospitalized with SARS-CoV-2 infection between March 13th 2020 and May 17th 2020 in the geriatric hospital, all of them included in the statistical analysis. The geriatric hospital is part of the University Hospitals, which were responsible during the first wave of the COVID-19 pandemic for hospitalizing all patients of its region, which has a population of approximately 500,000. This study was carried out in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement. This project was submitted and accepted by Geneva's committee for research ethics (project ID: 2020-00819)

Data Collection

Data regarding demographics, comorbidities, clinical symptoms, and laboratory analyses were retrospectively collected by one research nurse. In general, this information were obtained within the first 24 hours of hospitalization on an acute ward.

The Functional Independence Measure (FIM) was performed by a nurse, based on observation during the first 24 hours after hospital admission. It reflects functional status and physical function, with a point score ranging from 18 to 126, higher scores corresponding to better functionality[11]. The Clinical Frailty Score (CFS) was calculated by the physician in charge, reflecting the state of older patients before hospitalization[12]. Higher CFS scores (from 5 to 8) correspond to more severe degrees of frailty, with a terminally ill patient assigned the highest score. The Cumulative Illness Rating Scale-Geriatric (CIRS-G) was performed at admission, measuring a patient's comorbidity burden by taking into account chronic diseases as well as the severity of acute illnesses, with higher scores representing a higher overall burden[13]. The severity of respiratory symptoms was assessed using the Pneumonia Severity Index (PSI)[14] and the abovementioned CURB-65[15]. The Modified Ranking Score (MRS) finally assesses functional recovery after a stroke. It varies from 0 (no symptoms) to 6 (dead).[16]

Cerebrovascular complications were defined as a diagnosis of stroke with neuroimaging confirmation by CT or MRI, including both ischemic stroke and intracranial hemorrhage. We included all cases occurring during the hospitalization from the time of COVID-19 diagnosis to hospital discharge or death. Hence, stroke diagnoses documented during the acute and rehabilitation hospital stays were included in the analysis. For all stroke cases identified within the cohort, an extensive review of the electronic medical record and imaging results was performed by a geriatrician and a neuroradiologist. Stroke cases were classified with respect to their localization, extent of ischemia, and vascular territory.[17] Patients that were suspected to present a stroke underwent standardized neuroimaging by CT or MRI, which were routinely performed according to our in-house protocols.

Statistical Analysis

Categorical variables are expressed in numbers and proportions, while continuous variables in means and standard deviations. A two-group comparison (patients with and without stroke) was performed using Fisher's exact test and independent t-test for categorical and continuous variables, respectively. For the CHA_2DS_2-VASc and HAS-BLED scores from the stroke group, results are expressed as medians with minimum and maximum values. Because of the low number of stroke occurrences within the cohort, only univariate logistic regression models were calculated to identify stroke predictors. The variable selection was based on statistically significant differences observed in the two-group comparison (patients with and without stroke). Furthermore, for the significant variables, we performed a trend analysis to study the relationship with stroke occurrence[18].

Statistical analysis was performed using Stata software version 16.1 (Stata Corp., College Station, TX, USA).

Results

Characteristics of the study population and stroke risk factors

The cohort consisted of 265 patients with a mean age of 85.9 ±6.5 years, 43% were male, and the in-hospital mortality rate was 32.1%. Acute stroke was confirmed in 11 patients, which corresponds to an incidence of 4.15% (Figure 1). Mortality was similar between patients with (32.1%) and without stroke (27.3%, p>0.999), and there were no differences regarding age, sex, or length of stay on an acute ward.

Stroke patients had a higher prevalence of active smoking (27.3% vs. 4.8%; p=0.019), as well as history of previous stroke (45.5% vs. 13.8%; p=0.014). On the other hand, tiredness was less frequently reported in the group of stroke patients (9.1% vs. 50.2%; p=0.010) with a trend towards higher "asymptomatic" status at hospital admission (27.3% vs. 7.7%; p=0.056). Interestingly, stroke patients had a lower BMI than those without stroke (20.7 ±3.5 vs. 24.9 ±6.4; p=0.002). While their mean BMI value was within the "normal" range, 45.5% of calculated BMIs were in the underweight range (<20 kg × m^{-2}), while no patient with acute stroke was categorized with obesity (BMI ≥30 kg × m^{-2}) (Figure 2). The trend towards a lower BMI in the stroke group was statistically significant (p=0.038).

There were no differences regarding other cerebrovascular risk factors, except for dyslipidemia, which was more frequent in stroke patients, but with a borderline statistically significant p-value (63.6% vs. 33.2%; p=0.051). Similarly, we did not observe differences in comorbidity burden, functional status, or the prevalence of frailty and the severity of COVID-19 disease course between the two groups (Table 1).

In the univariate logistic regression model of stroke prediction, active smoking and previous stroke remained significant predictors, increasing by more than seven times and by more than five times, respectively, the risk of stroke. Similarly, a higher BMI was protective, as each additional point in BMI reduced the risk of stroke by approximately 14% (Table 2).

Stroke characteristics and prognosis

Of the 11 patients with acute stroke, 81.8% were ischemic (9/11) and 18.2% hemorrhagic (2/11). The stroke events occurred after an average of 15.2 days from COVID-19 diagnosis, and the majority of patients presented stroke during the acute care stay (8/11; 72.7%). Three patients had a simultaneous diagnosis of COVID-19 and acute stroke, whereas another three patients presented a stroke of late occurrence, occurring during the stay on a geriatric rehabilitation ward 25, 45 and 70 days after COVID-19 diagnosis (Supplementary Table S2). An altered state of consciousness and/or delirium were the most frequent clinical manifestation of stroke, reported in 81.8% of cases (9/11). In five patients (45.5%), a focal neurological deficit was present at the time of brain imaging. Thromboembolic risk assessed by the CHA2DS2-VASc score showed a median score of 5 (range, 3-7) in stroke patients, and a HAS-BLED score bleeding risk with a median of 3 (range, 1-5). Among patients with ischemic stroke, 22.2% (2/9) took oral anticoagulant treatment (acenocoumarol or rivaroxaban) for atrial fibrillation by the time of stroke diagnosis, while three patients were under aspirin (acetylsalicylic acid) or clopidogrel medication. The majority of patients with ischemic stroke (55.5%) had no ongoing antithrombotic treatment, while a statin that had been prescribed previously had been maintained in 45.45% of cases.

A large vessel occlusion was reported in 22.2% of ischemic stroke cases (2/9). Furthermore, strokes were mainly limited to one side (5/9 right, 3/9 left) and the middle cerebral artery territory was affected in more than half of all cases (5/9; 55.5%), followed by the posterior cerebral artery (3/9), and vertebrobasilar territories (2/9). One patient had a stroke in the posterior and middle artery junction territory, whereas ischemic lesions in multiple territories were diagnosed in two cases (Supplementary Table S1).

Regarding the etiology of ischemic stroke, a cardioembolic cause was identified in 3 cases (44.5%), followed by artery-to-artery embolization in 2 cases and microangiopathic disease in 1 case. Furthermore, one patient presented a junctional ischemic stroke as a consequence of reduced blood flow and hypoperfusion. Ischemic stroke was classified as cryptogenic in two cases, with no etiology determined in the acute workup.

By the end of the hospital stay, three patients (27.3%) died between 3 and 6 days after the stroke occurrence, whereas four (36.4%) were institutionalized in a nursing home. In-hospital mortality rates were similar between patients with and without acute stroke, as well as institutionalization rates at hospital discharge (21.1% vs 36.4%; p=0.258). All survivors presented moderate to severe disability at discharge according to the MRS (Supplementary Figure S1). Only one patient was eligible for intravenous tissue plasminogen activator treatment, with no complications reported.

Additional features in neuroimaging

There was a high burden of cerebral small vessel disease in patients with stroke, with more than half of patients presenting concomitant lacunes (54.5%). Early confluent to confluent white matter lesions were described in 81.8% of cases and 45.5% of patients had at least one cerebral microbleed, in a classical deep or lobar topography. Additionally, all images were carefully reviewed with no evidence of features of other concomitant neurological complications such as meningitis, encephalitis, or vasculitis.

Discussion

In this study, we report a higher incidence of stroke in a cohort of old and very old patients with COVID-19, compared to previous descriptions in younger cohorts. However, strokes did not add a supplementary risk of dying, and old and very old patients that survived COVID-19 and an acute stroke had a similar risk of institutionalization at hospital discharge as compared to patients without a stroke. Importantly, active smoking, previous stroke history, together with a low BMI, were significant predictors of cerebrovascular complications in this age group. Stroke was frequently manifested by delirium and/or altered state of consciousness, and the middle cerebral artery territory was the most frequently affected brain region. Although more prevalent in the acute setting, stroke was also reported as a complication in the post-COVID-19 rehabilitation phase.

The higher incidence of stroke in this study compared to previous reports is probably the result of the higher age and the consequent higher prevalence of cerebrovascular risk factors. To the best of our knowledge, we reported for the first time the incidence of stroke in a cohort of old and very old patient. Historical population-based studies demonstrated an early case fatality related to all types of stroke varying from 20 to 30% worldwide[19]. Although the mortality observed in this study is within this range, it did not differ from COVID-19 patients without a stroke. It is possible that stroke is a significant predictor of early mortality in younger patients with COVID-19, but not in older patients with more severe disease courses and a worse global health state[20]. The high rates of overall in-hospital mortality in older patients due to COVID-19 possibly overpasses the effect of stroke morbidity alone. This and the lower lethality of SARS-CoV-2 infection in younger patients strengthen the hypothesis that complications such as stroke would be more relevantly indicative of a worse prognosis in younger COVID-19 patients. Long-term follow-up of our patients will clarify whether mortality, institutionalization and rehospitalization rates after hospital discharge will remain similar between groups.

An interesting result of this study was the high prevalence of underweight patients in the stroke group. Previous studies suggested the existence of the “obesity paradox” in stroke, with obesity being a significant cardiovascular risk factor but having at the same time a “protective” effect on prognosis after an event, with a lower mortality when compared to “normal weight” patients[21]. Although malnutrition is associated with increased lengths of hospital stay, rehospitalization and mortality after stroke[22], its role as a predictor of stroke occurrence is less well understood, with conflicting evidence[23]. Only a few population-based studies demonstrated too low weight to be an independent predictor of cardiovascular disease, with a stronger association with stroke compared to heart attack and angina, especially in women[24,25]. Underweight is usually a proxy of malnutrition and sarcopenia, which are possible mechanisms related to a higher cardiovascular disease risk[26,27]. Another hypothesis relies on the fact that underweight is mainly the result of cardiovascular disease burden, associated with the presence of multiple chronic diseases and consequent poor nutritional status and cachexia, especially in older patients[28].

Focal neurological signs were less frequent than delirium and a decreased level of consciousness as stroke manifestations in this study. The latter may be present in up to 48% of patients with acute stroke[29] and is usually associated with older age, previous stroke, multiple comorbidities, stroke localization, and the extent of ischemia[30–32]. Our cohort presents several risk factors for unspecific clinical manifestations of stroke, such as older age and a high comorbidity burden including delirium and cognitive impairment, explaining our findings.

A recent grouped analysis of the first 160 stroke cases reported in the course of COVID-19 showed that 76.6% of patients presented stroke in the middle cerebral artery territory. In the subgroup of patients older than 70 years (the oldest patient having had 74.3 years of age), it remained the most frequent territory affected, but dropped to 69% with an increased proportion of vertebrobasilar territory ischemia. We found a similar pattern in our study of still older patients, in whom the middle artery territory remained the most frequently affected, although with at a lower prevalence than among the younger cases reported, followed by the posterior cerebral artery and vertebrobasilar territories. Importantly, in very old patients, stroke was mostly related to a thromboembolic event and associated with risk factors. We found no evidence for a direct effect of the SARS-CoV-2 virus, as advocated by other reports[33].

This study has several limitations. Firstly, the cross-sectional analysis of cerebrovascular risk factors allowed us to describe phenotypes of patients at risk, but not to assess causality. Secondly, our cohort represents a very specific population of older patients ineligible for intensive care, thus caution is warranted when extrapolating the results to other settings. Finally, the small number of stroke cases in this study prevented us from calculating multiple variable models of prediction, and some negative findings may be a mere consequence of a lack of statistical power in the analysis.

Conclusion

In conclusion, clinicians should be aware that incident stroke in patients with COVID-19 is more frequent in old and very old patients, typically manifesting by delirium and decreased level of consciousness, with the middle cerebral artery territory being the most commonly affected. Previous stroke, active smoking, and low BMI were associated with a higher occurrence of stroke in the old and very old age group. In this study, stroke influenced neither the early mortality rate, nor the prevalence of institutionalization by the time of hospital discharge.

Declarations

Ethics approval and consent to participate

Because of the urgent need to develop knowledge regarding COVID-19, patients and members of the public were not directly involved in the study conception. An institutional review board was created to coordinate and validate all COVID-19 related research protocols. In addition, the project was submitted and accepted by Geneva's committee for research ethics (project ID: 2020-00819). Because this is an observational retrospective study, the need for consent to participate was waived by the same committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflict of interest to declare.

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This study did not receive any funding.

Author Contributions

A.M., M.S. and F.H. conceived of the presented idea. A.M. and F.H. performed the statistical analysis. M.S., C.G., C.S., G.G., D.Z., E.C., M.V. and L.G. verified the analytical methods. C.G., C.S., G.G., D.Z., E.C., M.V. and

L.G supervised the findings of this work and the analysis of the results. All authors discussed the results and contributed to the final manuscript.

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Authors' information

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Tables

Table 1. Characteristics of patients with ischemic and hemorrhagic types of acute stroke compared to those without stroke

Characteristics	Total	No stroke	Stroke	p value
	N=265	N=254	N=11	
Age, years	85.9 ± 6.5	85.8 ± 6.6	87.1 ± 4.5	0.398
Length of stay in acute care, days	12.6 ± 7.7	12.7 ± 7.7	11.9 ± 7.8	0.645
Male sex	114 (43.0%)	109 (42.9%)	5 (45.5%)	>0.999
Help in ADL/IADL	127 (47.9%)	121 (47.6%)	6 (54.5%)	0.762
Mortality	85 (32.1%)	82 (32.3%)	3 (27.3%)	>0.999
Number of medications	7.4 ± 4.1	7.4 ± 4.1	6.4 ± 3.0	0.286
Heart failure	93 (36.5%)	90 (36.9%)	3 (27.3%)	0.750
COPD	30 (11.4%)	27 (10.7%)	3 (27.3%)	0.117
Active smoking	15 (5.7%)	12 (4.8%)	3 (27.3%)	0.019
Kidney disease	74 (28.2%)	70 (27.9%)	4 (36.4%)	0.510
Diabetes under treatment	63 (24.0%)	60 (23.9%)	3 (27.3%)	0.728
Cognitive impairment	134 (51.0%)	127 (50.4%)	7 (63.6%)	0.540
Active neoplasia	23 (8.8%)	22 (8.8%)	1 (9.1%)	>0.999
History of coronary disease	36 (13.6%)	35 (13.8%)	1 (9.1%)	>0.999
History of stroke	40 (15.2%)	35 (13.8%)	5 (45.5%)	0.014
Atrial fibrillation	61 (23.1%)	58 (22.9%)	3 (27.3%)	0.719
Hypertension	187 (70.8%)	179 (70.8%)	8 (72.7%)	>0.999
Dyslipidemia	91 (34.5%)	84 (33.2%)	7 (63.6%)	0.051
BMI, kg × m^{-2}	24.8 ± 6.4	24.9 ± 6.4	20.7 ± 3.5	0.002
Asymptomatic	22 (8.5%)	19 (7.7%)	3 (27.3%)	0.056
Cough	160 (61.5%)	155 (62.2%)	5 (45.5%)	0.344
Dyspnea	99 (38.1%)	95 (38.2%)	4 (36.4%)	>0.999
Tiredness	126 (48.5%)	125 (50.2%)	1 (9.1%)	0.010
Falls	30 (11.5%)	28 (11.2%)	2 (18.2%)	0.369
Delirium	53 (20.4%)	49 (19.7%)	4 (36.4%)	0.242
FIM (18-126)	71.8 ± 29.4	72.2 ± 29.7	62.1 ± 20.7	0.222

CIRS-G (0-56)	19.1 ± 6.2	19.0 ± 6.3	20.3 ± 2.3	0.170
CFS ≥5	190 (80.9%)	182 (80.5%)	8 (88.9%)	>0.999
PSI (0-395)	126.1 ± 53.9	125.9 ± 54.7	130.7 ± 32.3	0.650
CURB-65				0.960
1-2	168 (63.6%)	161 (63.6%)	7 (63.6%)	
3	86 (32.6%)	82 (32.4%)	4 (36.4%)	
4-5	10 (3.8%)	10 (4.0%)	0 (0.0%)	
FiO_2, %	26.4 ± 9.6	26.5 ± 9.6	24.2 ± 7.5	0.394
Lymphocytes, G/l	1.2 ± 1.3	1.2 ± 1.3	1.0 ± 0.5	0.361
Pro-brain natriuretic peptide, pg/ml	5904.0 ± 10525.5	5129.4 ± 8216.0	25657.8 ± 32622.7	0.297
C-reactive protein, mg/l	67.8 ± 72.0	66.4 ± 71.1	98.1 ± 89.1	0.270

Abbreviations: ADL = activities of daily living; IADL = instrumental activities of daily living; COPD = chronic obstructive pulmonary disease; BMI = body mass index; FIM = Functional Independence Measure; CIRS-G = Cumulative Illness Rating Scale-Geriatric; CFS = Clinical Frailty Score; PSI = pneumonia severity index; FiO_2 = Fraction of inspired oxygen.

Table 2. Univariate logistic regression models for stroke predictors

	OR	95% CI	p value
Active smoking	7.44	1.75-31.64	0.007
Previous stroke	5.19	1.50-17.92	0.009
Body mass index	0.86	0.74-0.98	0.03

Figures

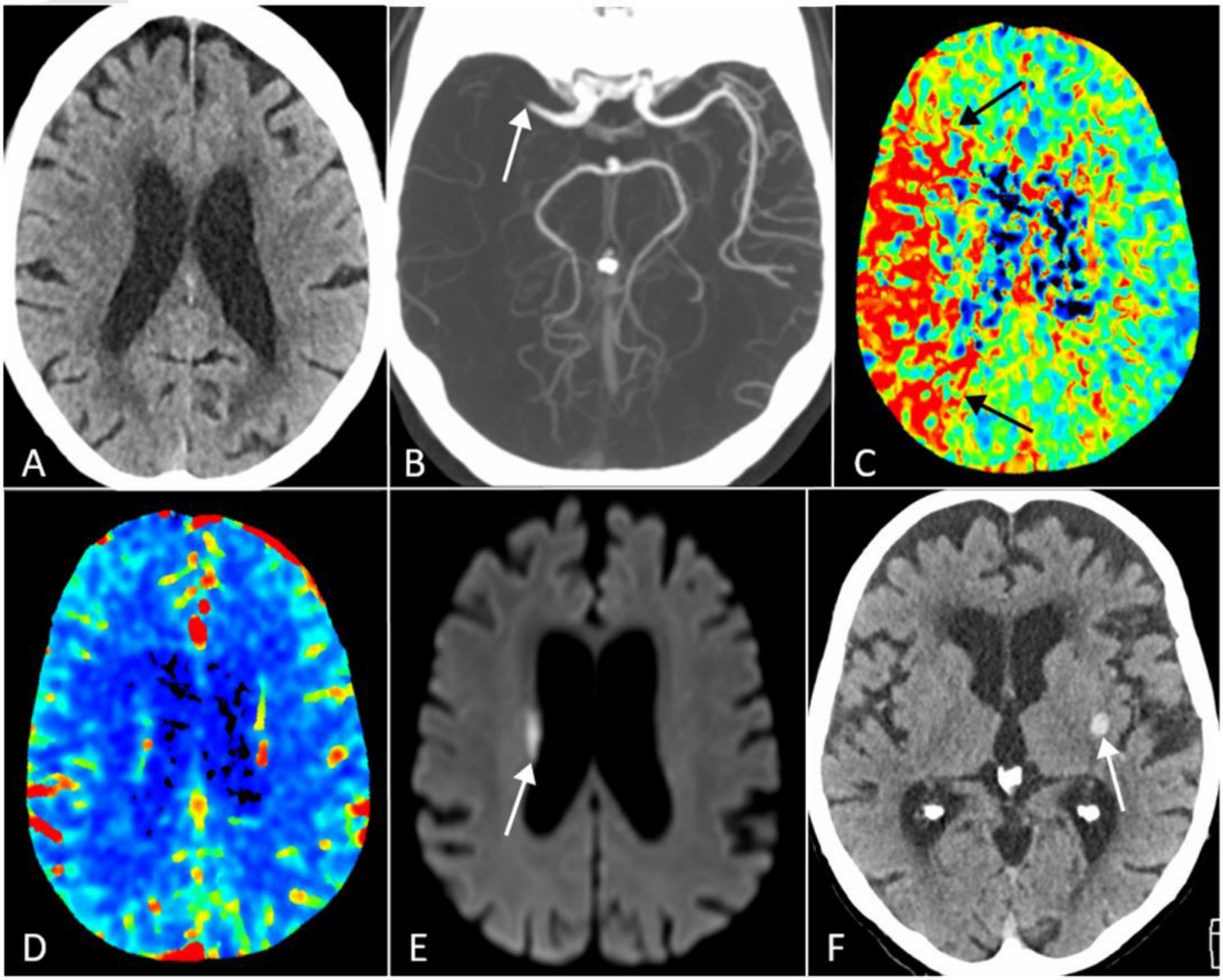
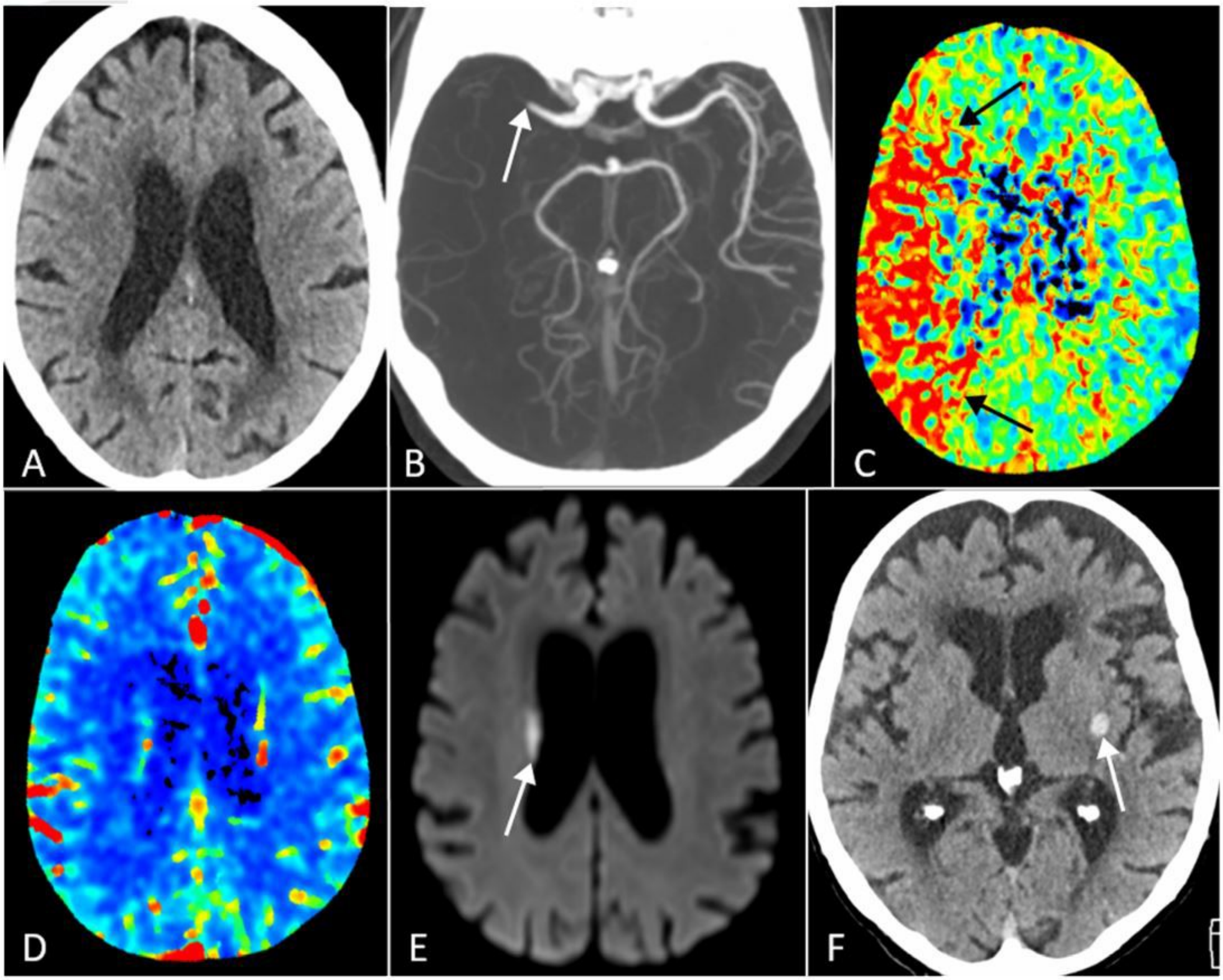


Figure 1

Illustrative images of neurologic complications in older patients hospitalized with COVID-19 pneumonia. A, B, C, D, and E, CT and MRI images of 89-year-old woman with left-sided hemiplegia. A, Non-contrast head CT did not show early CT signs of ischemia. B, CT angiogram showed occlusion of right middle cerebral artery (arrow). C, Perfusion CT mean transit time (MTT) images showed prolonged MTT in the entire right middle cerebral artery territory (arrows), whereas perfusion CT derived cerebral blood volume (D) remained symmetric between both hemispheres. E, Diffusion-weighted image of MRI study obtained one day later and after intravenous thrombolysis showed small area of infarction in right corona radiata (arrow). F, Non-contrast head CT image of 84-year-old woman with obnubilation showed isolated focus of intraparenchymal hemorrhage in left lentiform nucleus (arrow). No evidence of underlying vascular or tumoral pathology was found on subsequent MRI (not shown).



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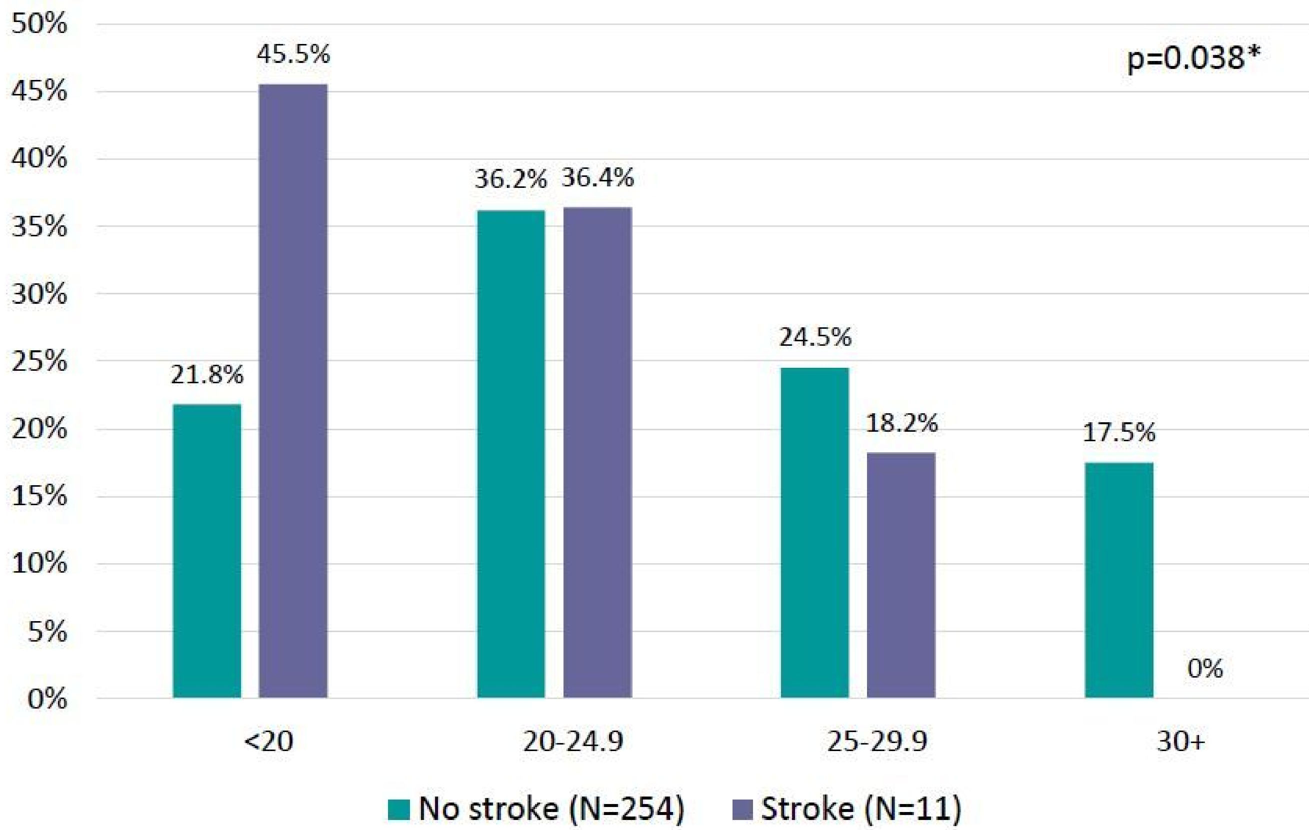
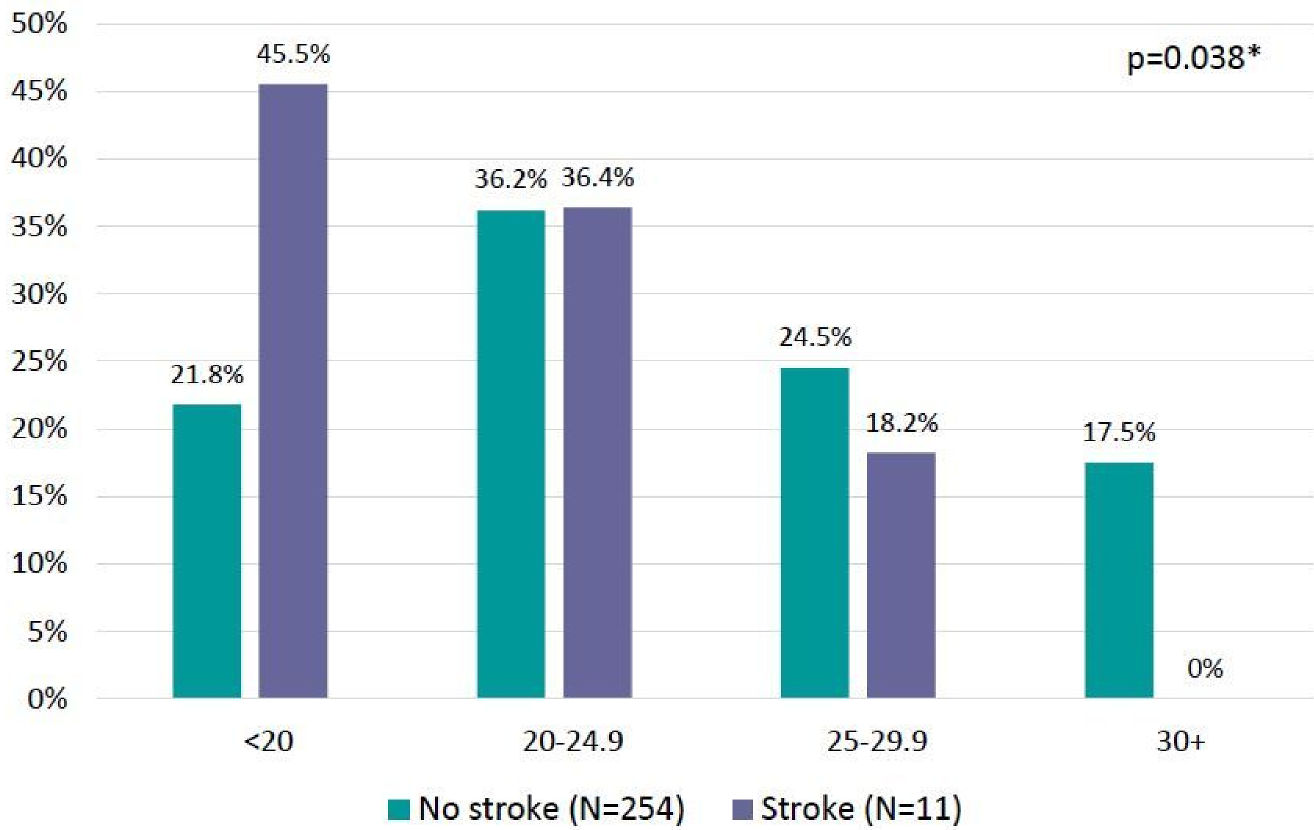


Figure 2

Distribution of body mass index (kg × m−2) categories in patients with and without stroke. *p-value corresponds to trend analysis of stroke incidence across body mass index categories.18



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Supplementary Files

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