Stroke

CLINICAL AND POPULATION SCIENCES

Impact of COVID-19 Infection on the Outcome of Patients With Ischemic Stroke

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BACKGROUND AND PURPOSE: We evaluated whether stroke severity, functional outcome, and mortality are different in patients with ischemic stroke with or without coronavirus disease 2019 (COVID-19) infection.

METHODS: A prospective, observational, multicentre cohort study in Catalonia, Spain. Recruitment was consecutive from mid-March to mid-May 2020. Patients had an acute ischemic stroke within 48 hours and a previous modified Rankin Scale (mRS) score of 0 to 3. We collected demographic data, vascular risk factors, prior mRS score, National Institutes of Health Stroke Scale score, rate of reperfusion therapies, logistics, and metrics. Primary end point was functional outcome at 3 months. Favourable outcome was defined depending on the previous mRS score. Secondary outcome was mortality at 3 months. We performed mRS shift and multivariable analyses.

RESULTS: We evaluated 701 patients (mean age 72.3±13.3 years, 60.5% men) and 91 (13%) had COVID-19 infection. Median baseline National Institutes of Health Stroke Scale score was higher in patients with COVID-19 compared with patients without COVID-19 (8 [3–18] versus 6 [2–14], P=0.049). Proportion of patients with a favourable functional outcome was 33.7% in the COVID-19 and 47% in the non-COVID-19 group. However, after a multivariable logistic regression analysis, COVID-19 infection did not increase the probability of unfavourable functional outcome. Mortality rate was 39.3% among patients with COVID-19 and 16.1% in the non-COVID-19 group. In the multivariable logistic regression analysis, COVID-19 infection was a risk factor for mortality (hazard ratio, 3.14 [95% CI, 2.10–4.71]; P<0.001).

CONCLUSIONS: Patients with ischemic stroke and COVID-19 infection have more severe strokes and a higher mortality than patients with stroke without COVID-19 infection. However, functional outcome is comparable in both groups.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: cerebrovascular disease ■ coronavirus ■ pandemics ■ prognosis ■ reperfusion ■ stroke ■ thrombectomy

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This article was sent to Marc Fisher, Senior Guest Editor, for review by expert referees, editorial decision, and final disposition.
The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.121.034883.
For Sources of Funding and Disclosures, see page 3917.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
HR	hazard ratio
ICU	intensive care unit
IQR	interquartile range
LVO	large vessel occlusion
mRS	modified Rankin Scale
MT	mechanical thrombectomy
NIHSS	National Institutes of Health Stroke Scale

The first patients with coronavirus disease 2019 (COVID-19) infection were identified in December 2019 in China[1] and the World Health Organization declared the pandemic on 11 March 2020. Starting in March 2020, the infection has affected about 1 500 000 individuals and caused >43 000 deaths in Spain as of November 2020. COVID-19 infection is associated with a global mortality of 2.3%,[1] but in critically ill patients the mortality rate may raise up to 21% to 49%,[1–3] mainly due to pulmonary complications and multiorgan failure.

Neurological complications, including stroke, occur frequently in patients with COVID-19, affecting up to 57% of them.[4,5] In 4 retrospective registries of hospitalized patients with COVID-19, the frequency of stroke ranged from 0.9% to 5%.[4–7] On the contrary, the pandemic has seriously compromised the application of well-established therapies and the ability of the health systems to continue caring for patients with stroke.[8,9]

Moreover, patients with vascular risk factors associated with stroke, such as aging, diabetes, hypertension, obesity, and previous cardiac or cerebrovascular disease are at increased risk of mortality and morbidity by the COVID-19.[3,10] It is unknown if patients with stroke and COVID-19 present worse functional and vital outcome than patients without the infection.

In the present study, we describe the clinical characteristics of ischemic stroke from a multicentre prospective cohort of consecutive patients in Catalonia (Spain) during the COVID-19 outbreak, and we focus on vital and functional outcome. Our hypothesis is that COVID-19 worsens the prognosis of patients with ischemic stroke compared with patients with stroke without the infection. We aim also to study whether this worse prognosis would be attributable to the harmful effects of the virus, to the logistical difficulties in extra and intrahospital care caused by the pandemic,[8,9,11] or to both factors. We hope that our contribution will help to improve the care of patients with ischemic stroke and concomitant COVID-19 infection.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

We conducted a prospective, observational, multicenter cohort study with 19 Hospitals in Catalonia, Spain. The recruitment of consecutive patients began between mid-March and early April 2020 depending on the Hospital, and ended on May 15th. The study was approved by the Ethics Committee of Hospital de la Santa Creu i Sant Pau as the study coordinator and thereafter, by the local Ethics Committee at each recruiting site. Patients or a legal representative gave written or verbal consent to participate. Consent for participation was waived in some centers, because the study did not include any diagnostic or therapeutic intervention and the outcomes planned are routinely registered in patients with stroke.

Study Population

Patients were eligible if they had had an acute ischemic stroke within 48 hours from the inclusion and presented a previous modified Rankin Scale (mRS) score of 0 to 3. We excluded patients presenting with (1) hemorrhagic stroke; (2) transient ischemic attack (defined as a new sudden onset of neurological deficit of ischemic origin with complete clinical recovery and absence of an acute ischemic lesion on neuroimaging); or (3) prior mRS score of >3.

Patients were classified according to the nucleic acid amplification tests (severe acute respiratory syndrome-coronavirus 2 [SARS-CoV-2] PCR from a throat swab) as COVID-19 or non-COVID-19. Patients without clinical, radiological, and epidemiological suspicion of COVID-19, who were not tested for COVID-19, were also classified as non-COVID-19. Clinical suspicion included dry cough, fever, myalgia, and hyposmia; radiological suspicion included the presence of bilateral patchy or confluent, bandlike ground-glass opacities, either on chest x-ray or chest CT scan; and epidemiological suspicion included any recent at-risk contact with a COVID-19 confirmed patient (defined by contact of 15 minutes or longer at a distance of <1.5 meters).

The following variables were recorded for all of the patients: demographic data: age and sex; vascular risk factors: previous ischemic stroke, previous intracerebral hemorrhage, arterial hypertension, diabetes, hypercholesterolemia, smoking habit, alcohol abuse, coronary artery disease, peripheral vascular disease, atrial fibrillation; drug treatment at admission (statins, antiplatelet, anticoagulants, angiotensin-converting enzyme inhibitors); prior mRS score; clinical data: National Institutes of Health Stroke Scale (NIHSS) score at admission and at 72 hours, neurological worsening defined as an increase of 4 or more points on the NIHSS score at 72 hours; imaging data: abnormal findings suggesting viral pneumonia in the chest CT and chest X-ray; Reperfusion therapies: intravenous thrombolysis, mechanical thrombectomy (MT), Thrombolysis In Cerebral Infarction scale score after MT; logistics and metrics: time from onset to admission at the Emergency Room, admission to the Stroke Unit, admission to the intensive care unit (ICU), Stroke Code activation, evaluation by a neurologist at admission, door-to-needle time (if intravenous thrombolysis), door-to-groin puncture time (if MT), days of hospitalization; Etiologic classification of stroke by the TOAST criteria (Trial of ORG 10172 in Acute Stroke Treatment).[12]

Clinical Outcomes

The primary end point was functional outcome at 3 months (±15 days), as measured by the mRS score and evaluated through a structured telephone-based interview performed by a central assessor who was unaware to whether the patient belonged or not to the COVID-19 infection group. A favourable outcome was defined depending on the previous mRS score: for patients with a previous mRS score of 0 to 2, the outcome was considered favourable when the score at discharge was 0, 1, or 2; for patients with a previous mRS score of 3, the outcome was favourable when the score at discharge was 3. The secondary outcome was mortality at 3 months. The local investigator recorded the most likely cause of death.

Statistical Analysis

First, we described the study population according to the COVID-19 status. Continuous variables were reported as means and standard deviations or medians and interquartile range (IQR) if they were not-normally distributed, as tested by the Shapiro-Wilk normality test. Categorical variables were expressed as counts and percentages. Bivariate analyses between both groups were performed using the Student *t* test or the Wilcoxon rank-sum test (when a nonparametric test was required) for continuous variables, and the χ^2 test for categorical variables.

Second, we performed a shift analysis using the unpaired Wilcoxon rank-sum test to demonstrate differences on the mRS score distribution at 3 months of follow-up between patients presenting or not a confirmed COVID-19 infection. We calculated also the common odds ratio of worsening of 1 point on the mRS on the presence of COVID-19 infection using ordinal logistic regression (unadjusted and adjusted for age and baseline NIHSS).

Third, we divided the study population between patients presenting favourable versus unfavourable functional outcome, as previously defined in clinical outcomes. Bivariate analyses were performed between these groups using the Student *t* test or the Wilcoxon rank-sum test (when a nonparametric test was required) for continuous variables, and the χ^2 test for categorical variables. Thereafter, we performed a multivariable logistic regression analysis to predict good functional outcome in our population. From an initial model including all the variables with $P<0.1$ in the bivariate analysis, we performed a stepwise backward regression modeling to select variables independently associated with the outcome. The final model was adjusted for potential confounders. A confounding effect was defined as an absolute change >10% in the regression coefficients when introducing the variable into the model.

Finally, we conducted a survival analysis for the secondary outcome (mortality) using Cox regression. Only variables showing a $P<0.1$ in the bivariate analysis were entered in the multivariable model and backward eliminated to a significance level of 0.05.

Statistical significance for all the analyses was set at 0.05 (2-sided). All the analyses were performed using Stata v.15 (TX).

RESULTS

Patients

We studied a total of 701 patients, whose mean age was 72.3±13.3 years and 424 (60.5%) of them were men. A total of 91 (13%) patients were diagnosed with COVID-19 infection and 610 without (including 206 patients who were not tested, but had no clinical, radiological or epidemiological suspicion of COVID-19).

Only in 5 (5.5%) patients, the infection was diagnosed before the stroke and in the remainder, COVID-19 was detected after hospitalization. Among patients with confirmed COVID-19 infection, 42 (46.2%) presented respiratory insufficiency during hospitalization (pO2 <60 mm Hg) requiring oxygen therapy, 26 (28.6%) were admitted to the ICU and 20 (22.0%) required mechanical ventilation. Table 1 shows details of demographics, vascular risk factors, clinical data, blood test, and treatment aspects. Bivariate comparison between patients with confirmed COVID-19 infection and patients without are shown also in Table 1. Both groups were similar for most variables, except that the median baseline NIHSS score was 2 points higher in the COVID-19 group compared with the non-COVID-19 group at admission (median NIHSS [IQR], 8 [3–18] versus 6 [2–14]; $P=0.049$) and at the 72 hours follow-up (median NIHSS [IQR], 4 [1–14] versus 3 [1–8]; $P=0.042$). Also, patients with COVID-19 were less frequently admitted to the Stroke Unit (31.9% versus 55.7%; $P<0.001$) and by cons, they were more frequently admitted to the ICU (28.6% versus 3.3%; $P<0.001$). As expected, some analytical abnormalities known to be associated with the SARS-CoV-2 infection such as lymphopenia, elevation of D-dimer levels or a prolonged prothrombin time were more frequent in patients with COVID-19.

There were 239 patients diagnosed with a large-vessel occlusion (LVO) and 136 (56.9%) of them underwent MT. There were 39 (42.9%) patients with a LVO in the COVID-19 group and 200 (32.8%) in the non-COVID-19 group ($P=0.059$). Clinical characteristics of the patients diagnosed with LVO are detailed in Table I in the Data Supplement. Remarkably, baseline NIHSS score, proportion of patients who received fibrinolysis, proportion of patients treated with MT and rates of successful recanalization were similar between patients with and without COVID-19.

During the first week of recruitment, patients with COVID-19 represented the 41.7% of the totals of strokes while none COVID-19 patients were detected during the last week of the study. Figure I in the Data Supplement shows the weekly proportion of patients with COVID-19 during the recruitment.

Primary Outcome

We obtained the mRS score at 3 months from 679 patients and 22 patients were lost during the follow-up. The shift analysis showed a median mRS score at 3 months of 4 (IQR, 2–6) in the patients with COVID-19 and 3 (IQR, 1–4) in the non-COVID-19 patients ($P<0.001$; Figure 1). Ordinal logistic regression analysis of the primary end point showed a common odds ratio (indicating the odds

 Stroke. 2021;52:3908–3917. DOI: 10.1161/STROKEAHA.121.034883

Table 1. Demographics, Vascular Risk Factors, and Clinical Data of the Patients

	All patients (n=701)	COVID-19 (n=91)	Non-COVID-19 (n=610)	*P* value
Demographics				
Age, mean (SD)	72.3 (13.3)	71.6 (12.3)	72.4 (13.5)	0.603
Sex (men), n (%)	424 (60.5)	58 (63.7)	366 (60.0)	0.496
Vascular risk factors				
Prior ischemic stroke, n (%)	142 (20.3)	14 (15.4)	128 (21.0)	0.215
Prior intracerebral hemorrhage, n (%)	11 (1.6)	0 (0.0%)	11 (1.8)	0.196
Arterial hypertension, n (%)	509 (72.6)	62 (68.1)	447 (73.3)	0.304
Diabetes, n (%)	235 (33.5)	37 (40.7)	198 (32.5)	0.122
Obesity, n (%)	105 (15.0)	11 (12.1)	94 (15.4)	0.407
Hypercholesterolemia, n (%)	359 (51.2)	43 (47.3)	316 (51.8)	0.418
Current smoking, n (%)	155 (22.1)	19 (20.9)	136 (22.3)	0.761
Alcohol abuse, n (%)	41 (5.9)	5 (5.5)	36 (5.9)	0.877
Coronary artery disease, n (%)	98 (14.0)	12 (13.2)	86 (14.1)	0.815
Peripheral artery disease, n (%)	49 (7.0)	6 (6.6)	43 (7.1)	0.874
Atrial fibrillation, n (%)	135 (19.3)	19 (20.9)	116 (19.0)	0.674
Prior treatments				
Statins, n (%)	288 (41.1)	37 (40.7)	251 (41.1)	0.930
Antiplatelet therapy, n (%)	240 (34.2)	33 (36.3)	207 (33.9)	0.662
Anticoagulation, n (%)	118 (16.8)	17 (18.7)	101 (16.6)	0.613
ACE inhibitor, n (%)	288 (41.1)	33 (36.3)	255 (41.8)	0.316
Prior mRS score, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0.764
NIHSS score				
Baseline, median (IQR)	6 (2–15)	8 (3–18)	6 (2–14)	0.049
At 72 h, median (IQR)	3 (1–8)	4 (1–14)	3 (1–8)	0.042
Neurological worsening, n (%)*	193 (36.2)	15 (20.6)	142 (30.9)	0.072
Lung infiltrates on the chest x-ray, n (%)	118 (16.8)	63 (69.2)	55 (9.0)	<0.001
Vital signs at admission				
Systolic blood pressure, mmHg, mean (SD)	152 (28)	138 (26)	154 (27)	<0.001
Heart rate, bpm, median (IQR)	77 (68–90)	80 (70–92)	77 (67–90)	0.139
Respiratory rate, rpm, median (IQR)	18 (16–20)	20 (18–22)	18 (16–20)	<0.001
Body temperature, °C, median (IQR)	36 (35.8–36.4)	36.3 (36–36.7)	36 (35.8–36.2)	<0.001
Oxygen saturation (%), median (IQR)	97 (96–99)	96 (94–98)	97 (96–99)	0.009
Blood test at admission				
Creatinine, mg/dL, median (IQR)	0.89 (0.71–1.10)	0.89 (0.67–1.03)	0.89 (0.71–1.10)	0.591
Urea, mg/dL, median (IQR)	40 (31–53)	40 (33–57)	40 (31–52)	0.155
Hemoglobin, g/L, median (IQR)	13.7 (12.4–14.9)	12.8 (11.5–14.0)	13.9 (12.6–15.0)	<0.001
Platelets, $\times 10^9$/L, median (IQR)	215 (174–268)	224 (171–341)	213 (176–264)	0.026
Leukocytes ($\times 10^9$/L), median (IQR)	8.7 (6.8–11.0)	8,3 (6,5–11,3)	8.7 (6.9–10.9)	0.536
Lymphocytes (x10^9/L), median (IQR)	1.6 (1.1–2.2)	1.2 (0.7–1.8)	1.7 (1.2–2.2)	<0.001
Coagulation status at admission				
Prothrombin time (INR), median (IQR)	1.08 (1.00–1.20)	1.17 (1.03–1.30)	1.06 (1.00–1.16)	<0.001
Partial activated thromboplastin time (ratio), median (IQR)	1.00 (0.90–1.15)	1.04 (0.94–1.37)	1.00 (0.90–1.12)	0.009
D-dimer, ng/mL, median (IQR)†	940 (366–2173)	1760 (681–4798)	796 (339–1687)	<0.001
Reperfusion therapies				
Intravenous rtPA, n (%)	154 (22.0)	14 (15.4)	140 (23.0)	0.104
Mechanical thrombectomy, n (%)	134 (19.1)	18 (19.8)	118 (19.3)	0.731
TICI ≥2b, n (%)	107 (79.9)	12 (66.7)	95 (81.9)	0.134

(*Continued*)

Table 1. Continued

	All patients (n=701)	COVID-19 (n=91)	Non-COVID-19 (n=610)	*P* value
Logistics and metrics				
Time between stroke onset and hospital arrival (min), median (IQR)	299 (115–720)	304 (105–710)	285 (115–720)	0.854
Stroke code activation, n (%)	402 (57.4)	45 (49.5)	357 (58.2)	0.103
Assessment by a neurologist in the Emergency Room, n (%)	557 (79.5)	77 (84.6)	480 (78.7)	0.192
Door-to-needle time (if IVT), median (IQR)	35 (26–50)	25 (20–40)	35 (27–50)	0.046
Door-to-groin puncture time (if MT), median (IQR)	72 (50–100)	77 (50–120)	71 (50–97)	0.302
Admission to the Stroke Unit, n (%)	369 (52.6)	29 (31.9)	340 (55.7)	<0.001
Admission to the ICU, n (%)	46 (6.6)	26 (28.6)	20 (3.3)	<0.001
Days in the Stroke Unit, median (IQR)	3 (1–4)	1.5 (0–3)	3 (1–4)	<0.001
Days of hospitalization, median (IQR)	5 (3–9)	8 (3–19)	5 (3–8)	<0.001
Stroke cause (TOAST), n (%)				0.055
Atherothrombotic	108 (15.4)	16 (17.6)	92 (15.1)	
Cardioembolic	210 (30.0)	30 (33.0)	180 (29.5)	
Lacunar	103 (14.7)	7 (7.7)	96 (15.7)	
Unusual	25 (3.6)	7 (7.7)	18 (3.0)	
Undetermined	255 (36.4)	31 (34.1)	224 (36.7)	

ACE indicates angiotensin-converting enzyme; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; IV, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue-type plasminogen activator; TICI, Thrombolysis in Cerebral Ischemia; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*Information available for 533 patients.

†Information available for 224 patients.

of worsening of 1 point on the mRS) of 2.26 (95% CI, 1.49–3.43; *P*<0.001) in the presence of COVID-19. After adjusting by age and baseline NIHSS score the common odds ratio was 2.03 (95% CI, 1.31–3.13; *P*=0.001).

The proportion of patients with a favourable functional outcome at 3 months of follow-up, was 30/89 (33.7%) in the COVID-19 group and 277/590 (47.0%) in the non-COVID-19 group, which represents a risk ratio for poor functional outcome of 1.25 (95% CI, 1.06–1.48; *P*=0.019). However, in the multivariable logistic regression analysis, COVID-19 infection was not independently associated with the probability of poor functional outcome after adjusting by age, baseline NIHSS score, admission to the ICU and prior history of diabetes. Details

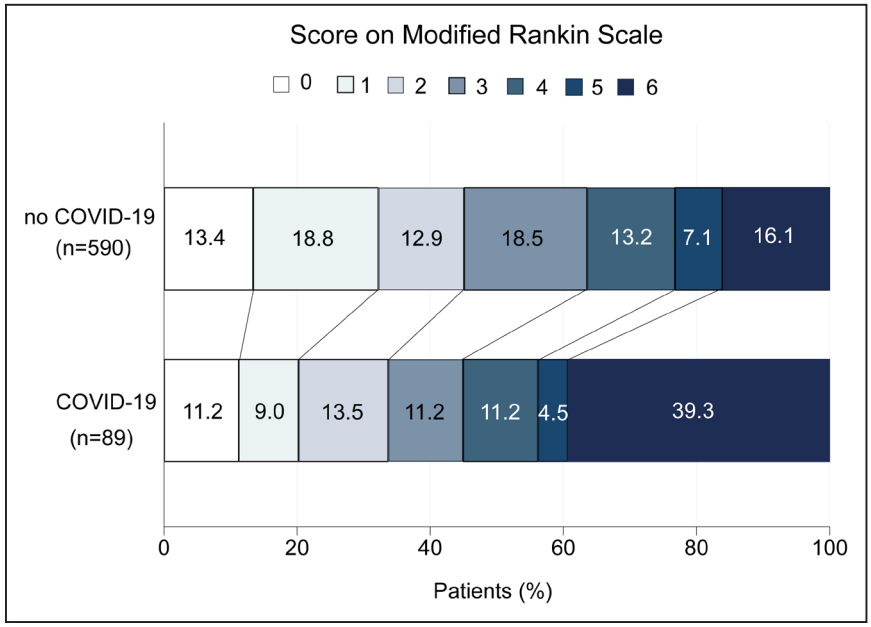

Figure 1. Scores on the modified Rankin Scale at 3 mo according to the coronavirus disease 2019 (COVID-19) infection status.

of the bivariate and the multivariable logistic regression analyses are shown in Tables 2 and 3. Obesity was not associated with functional outcome when comparing patients with and without COVID-19 infection (13.4% versus 16.1%, *P*=0.312). After excluding patients without a confirmed PCR test (n=206), the results of the multivariable logistic regression analysis did not change.

We observed that patients with LVO and COVID-19 were less likely to achieve a favourable functional outcome (33.3%) compared to patients without COVID-19 (50.5%), thought this difference was not statistically significant (*P*=0.079). In a multivariable logistic regression sensitivity analysis including only patients with LVO, COVID-19 was not independently associated with poor outcome after adjusting for age, baseline NIHSS, admission to ICU and reperfusion therapies (intravenous thrombolysis and MT; odds ratio, 1.68 [95% CI, 0.63–4.49]; *P*=0.297).

Table 2. Bivariate Analyses of Predictors of Functional Outcome at 90 Days of Follow-Up

	Good functional outcome (n=307)	Poor functional outcome (n=372)	*P* value
Age, mean (SD)	68.3 (13.5)	75.5 (13.3)	<0.001
Sex (men), n (%)	196 (63.8)	215 (57.8)	0.108
Obesity, n (%)	41 (13.4)	60 (16.1)	0.312
High blood pressure, n (%)	204 (66.5)	288 (77.4)	0.001
Diabetes, n (%)	87 (28.3)	143 (38.4)	0.006
Hypercholesterolemia, n (%)	145 (47.2)	214 (54.3)	0.057
Prior stroke, n (%)	60 (19.5)	84 (22.6)	0.335
Coronary artery disease, n (%)	38 (12.4)	59 (15.9)	0.197
Atrial fibrillation, n (%)	43 (14.0)	89 (23.9)	0.001
Prior statins, n (%)	116 (37.8)	164 (44.1)	0.097
Prior antiplatelet therapy, n (%)	95 (30.9)	139 (37.4)	0.080
Prior anticoagulation, n (%)	33 (10.8)	82 (22.0)	<0.001
Prior ACE inhibitor, n (%)	113 (36.8)	166 (44.6)	0.039
Baseline NIHSS score, median (IQR)	3 (1–7)	9 (4–19)	<0.001
Intravenous thrombolysis, n (%)	73 (23.8)	75 (20.2)	0.256
Mechanical thrombectomy, n (%)	38 (13.4)	93 (25.0)	<0.001
Any reperfusion therapy, n (%)	96 (31.3)	134 (36.0)	0.193
TICI ≥2b, n (%)*	33 (89.2)	70 (76.1)	0.093
Time interval between stroke onset and hospital arrival, min, median (IQR)	251 (106–716)	305 (115–728)	0.559
Stroke code activation, n (%)	169 (55.1)	220 (59.1)	0.283
Assessment by neurologists in the emergency room, n (%)	242 (78.8)	397 (79.8)	0.746
Admission to stroke unit, n (%)	165 (53.8)	191 (51.3)	0.533
Admission to ICU, n (%)	10 (3.3)	35 (9.4)	0.001
Confirmed COVID-19 infection	30 (9.8)	59 (15.9)	0.019

ACE indicates angiotensin-converting enzyme; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; and TICI, Thrombolysis in Cerebral Ischemia.

*Only in 129 patient who underwent MT.

Secondary Outcome

Mortality rate at 90 days was 39.3% among patients with COVID-19 and 16.1% in the non-COVID-19 patients, which represents a risk ratio of 2.44 (95% CI, 1.78–3.35; *P*<0.001). Figure 2 shows the Kaplan-Meier survival curve for both groups. In the multivariable Cox regression analysis, COVID-19 infection was independently associated with the probability of death within 3 months from the index stroke with a hazard ratio (HR) of 3.14 (95% CI, 2.10–4.71; *P*<0.001) after adjusting by age, baseline NIHSS score and admission to the Stroke Unit. Details of the bivariate and the multivariable logistic regression analyses are shown in Table II in the Data Supplement and Table 4. Neither obesity (HR, 0.65 [95% CI, 0.36–1.15]; *P*=0.135) nor diabetes (HR, 1.07 [95% CI, 0.75–1.54], *P*=0.710) was associated with higher mortality in patients with COVID-19 infection compared with patients without COVID-19 infection. After excluding patients without a confirmed PCR test (n=206), the SARS-CoV-2 infection persisted independently associated with mortality with a HR of 2.77 (95% CI, 1.80–4.25; *P*<0.001). Details of these bivariate and the multivariable Cox regression analyses are shown in Table III in the Data Supplement.

Of 131 patients who died during the follow-up, the cause of death was known for 93 (71.0%). Approximately, 1 out of 4 patients (22.1%) died from stroke complications and 20 (15.3%) died from COVID-19 complications. More details of the causes of death are summarized in Table IV in the Data Supplement.

Again, we focused in the subgroup of patients with LVO and we observed that patients with COVID-19 in this subgroup were more likely to die at 3 months (36.7%) compared to patients without COVID-19 (20.6%) with a HR of 2.96 (95% CI, 1.48–5.95; *P*=0.002) in the adjusted multivariable Cox regression analysis.

Markers of Infection Severity in Patients With COVID-19

In the multivariable Cox regression analysis, receiving anticoagulation therapy during hospitalization and baseline D-dimer levels were independently associated with mortality after adjusting by age, admission to the Stroke Unit and baseline NIHSS score. Details of the analysis on severity markers associated with the infection are detailed in Table V in the Data Supplement.

Stroke Outcomes and Admission Site in Patients With COVID-19

After excluding patients who required admission to the ICU, we observed a favourable outcome in 11 (40.7%)

Table 3. Results of the Multivariable Logistic Regression Analysis of Predictors of Functional Outcome at 90 Days of Follow-Up

	OR (for poor functional outcome)	95% CI	*P* value
Confirmed COVID-19 infection	1.17	0.67–2.05	0.574
Age	1.05	1.03–1.06	<0.001
Diabetes	1.70	1.18–2.46	0.004
Baseline NIHSS score	1.14	1.11–1.17	<0.001
Admission to ICU	3.30	1.37–7.90	0.008

COVID-19 indicates coronavirus disease 2019; ICU, intensive care unit; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

patients with COVID-19 who were admitted in a Stroke Unit versus 13 (35.1%) of patients who were admitted to a COVID unit (*P*=0.647). Similarly, we noted 10 (37.0%) patients with COVID-19 who died after being admitted to a Stroke Unit compared with 16 (43.2%) who were not (*P*=0.618).

DISCUSSION

In our multicenter and prospective study of consecutive patients with acute ischemic stroke conducted in Catalonia during the COVID-19 outbreak, about 1 out of 8 patients had a concomitant infection by SARS-CoV-2. Compared with patients without COVID-19 infection, those with ischemic stroke and concomitant COVID-19 infection had a more severe neurological deficit at admission and at 72 hours and higher mortality (3.1-fold). Although we found an increased probability of an unfavourable functional outcome by the shift analysis, this was not confirmed when this variable was dichotomized. We found also a higher risk of neurological deterioration during the acute stage in the COVID-19 group. Although we found some interference with routine acute stroke management in patients with COVID-19, these logistic difficulties were not associated with outcome except for a worse functional outcome in those patients who were admitted to the ICU and a greater probability of death in patients not admitted to the Stroke Unit, both observations probably confounded by the presence of COVID-19.

The strengths of our study include the prospective design, the high number of patients with stroke with COVID-19 infection, and the comparison with a group without COVID-19 infection who were attended during the same time period. We obtained the data at the peak of the outbreak in our country. Moreover, the multi-center design including comprehensive and primary stroke centers covering most of the territory of Catalonia, supports the generalizability of our findings.

Stroke is one of the possible neurological complications of COVID-19 and although intracerebral hemorrhage and cerebral venous thrombosis have also been reported, most patients suffer from ischemic stroke. Stroke may precede, be coincidental or be diagnosed after the COVID-19 infection. Reported cases of ischemic stroke are included in retrospective registries,[4–7] or in small series.[13–15] In a multicentre study[6] of 3 hospitals from New York, 32 (0.9%) of 3556 admitted patients had imaging proven ischemic stroke. A Spanish single-center study[5] reported that 11 out of 841 (1.3%) patients with COVID-19 infection had an ischemic stroke. We observed a remarkable decrease of the proportion of patients with ischemic stroke and COVID-19 infection that dropped from 41.7% at mid-March to 0% at mid-May as reflected

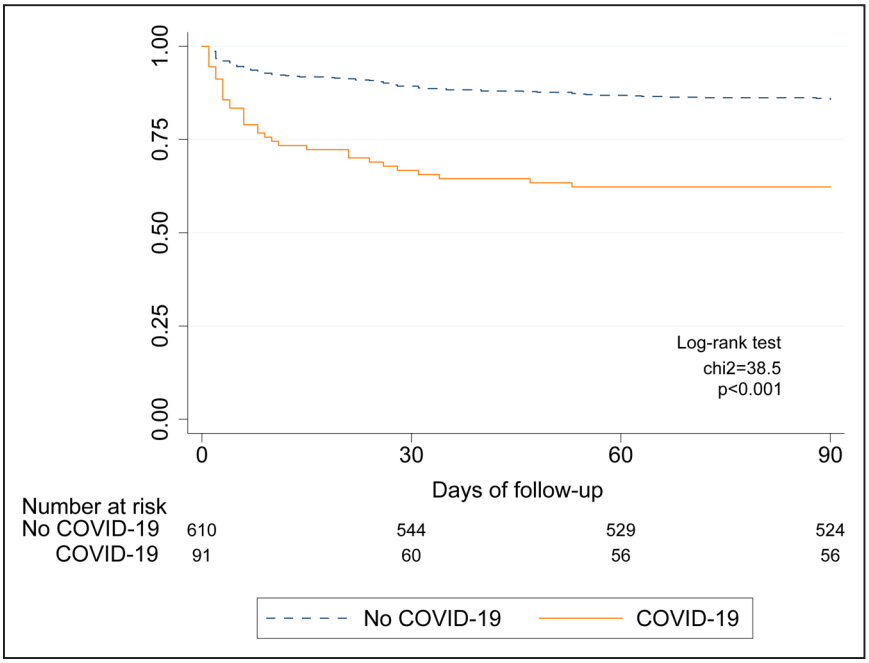

Figure 2. Kaplan-Meier survival curve for mortality at 3 mo according to the coronavirus disease 2019 (COVID-19) infection status.

 Stroke. 2021;52:3908–3917. DOI: 10.1161/STROKEAHA.121.034883

Table 4. Multivariable Cox Regression Analysis of Predictors of Mortality at 90 Days

	HR	95% CI	*P* value
Confirmed COVID-19 infection	3.14	2.10–4.71	<0.001
Age	1.06	1.05–1.08	<0.001
Baseline NIHSS score	1.13	1.05–1.08	<0.001
Admission to the stroke unit	0.57	0.40–0.82	0.003

COVID-19 indicates coronavirus disease 2019; HR, hazard ratio; and NIHSS, National Institutes of Health Stroke Scale.

in Figure I (Data Supplement) thus showing a clear decline as the first wave of the pandemic waned.

We hypothesized that patients with ischemic stroke and COVID-19 infection would have worse prognosis. Despite presenting similar demographic, risk factor profile and time from the onset of symptoms, stroke severity measured by the NIHSS score was higher in the patients with COVID-19. Moreover, NIHSS score remained higher at 72 hours, thus reflecting the persistence of a worse neurological deficit. A recent retrospective study[6] found also higher baseline NIHSS score in patients with COVID-19 infection compared with patients non-COVID-19 (median NIHSS score: 19 versus 8). In comparison, the severity of stroke in our cohort, was lower (median NIHSS score: 8 versus 6).

We observed a nonsignificant lower proportion of favorable functional outcome and a significant higher mortality rate in patients with COVID-19 than in patients without. Functional outcome has not been evaluated in previous studies. We report a difference in the proportion of favourable outcome between groups and a higher risk of increasing 1 point in the mRS score in the shift analysis in the COVID-19 group compared with the non-COVID 19 group. It is difficult to determine if these differences were due to worse stroke severity in the setting of a COVID-19 infection or due to difficulties in stroke care and stroke rehabilitation in patients diagnosed of COVID-19. Based on our data, we believe that both possibilities should be considered. However, it is important to highlight that the difference on functional outcome observed between groups was not significant in the logistic regression multivariable analysis after adjusting by other well-known predictors of poor outcome such as older age,[16,17] baseline NIHSS score, and also ICU admission. In addition to comorbidities such as cardiovascular diseases, older patients with COVID-19 infection present molecular differences[18] that explain this life-threatening evolution. Prior stroke also predicted a worse outcome. This agrees with other prognostic studies.[1,18–20] A recent study reported that a history of stroke in patients with COVID-19 infection was independently associated with an increase in severe events and poorer outcomes after a propensity-matched analysis.[19] The authors attributed these findings to more aggressive inflammatory responses, and more underlying coagulation disorders in patients with prior stroke. Finally, admission to the ICU also worsened the outcome. We may speculate that admission to the ICU is reserved for the most critically ill patients with life-threatening complications.

Regarding mortality, our results agree with recently published studies[6,21] that reported that in patients with stroke, infection with COVID-19 was associated with a higher case-fatality. Remarkably, the multivariable analysis in our cohort showed that the exposition to COVID-19 was independently associated with mortality after adjusting by age, stroke severity and admission to the stroke unit. Several aspects related to the COVID-19 infection may explain our observation including the respiratory distress and the multiorgan failure observed in some patients.[22] In addition, besides the cardiovascular risk, aging[18,22] may explain the life-threatening evolution. Obesity has been described as an independent variable associated with increased mortality in patients with COVID-19,[23] although in our study it was not associated with a worse functional or vital outcome. Its prognostic significance could be influenced by the presence of other coexisting prognostic variables. Furthermore, it should be noted that in most cases the body mass index was not available and we relied on the assessment of the local investigator. As detailed in Table IV in the Data Supplement, about 50% of the deaths in the COVID-19 group was due to COVID-19 complications, while deaths due to stroke complications or recurrent stroke were more common in the non-COVID-19 group. If we put together, the results of functional and vital outcome, our study suggests that, despite the high mortality in patients with COVID-19 infection, survivors will have a similar likelihood of a favorable functional outcome than patients with ischemic stroke who do not have concomitant COVID-19 infection. In the survival curves, the curves markedly separate in the first days but then remain parallel until 3 months.

COVID-19 infection may possibly act as a trigger of conventional stroke causes.[24] It is possible that COVID-19 infection increases the risk of stroke, similarly to other viral infections.[16] In agreement with this assumption, patients from our cohort were typical of a stroke cohort, with a mean age of 72 years, predominance of men (60%) and a high proportion of patients with varied vascular risk factors. The higher proportion of strokes of unusual cause observed in the COVID-19 group may be explained by the multiple different COVID-19 related stroke pathogenesis described.[24] Among others, cytokine storm, prothrombotic state, antiphospholipid syndrome, other coagulopathies, myocardial injury, cardiac arrhythmias, and endothelial infection, they all have been proposed.[24–27] Finally, considering that the number of thrombectomies, a surrogate marker of LVO, was comparable in both groups, we did not find the previously reported[14] excess of young patients with large-vessel occlusion.

The pandemic has compromised seriously the ability of the health systems to care for patients with stroke and other acute medical emergencies, and these obstacles to the routine stroke care pathways may explain in part worse clinical outcomes. This has been reported by several authors in Spain[8,9] and other countries.[11,16,28,29] In our cohort, we found that compared to patients without COVID-19 infection, the COVID-19 group were less often admitted to the stroke unit, and had a longer hospital stay. However, assessment by a neurologist was performed at admission in about 80% of patients in both groups, and the proportion of patients treated with IVT or with MT as well as in-hospital times were also comparable. Remarkably, when analyzing the primary and secondary outcomes in patients with COVID-19 according to the site of admission (Stroke Unit versus COVID unit) we did not find significant differences. Although there is no doubt that the pandemic notably stressed the health care system, this affected non-COVID-19 patients as well as patients with COVID-19, with some differences between groups that had no influence on vital or functional outcome as assessed by the multivariable analysis.

Our study has some limitations. Patients were recruited within the first 48 hours of evolution, and therefore, the onset of the stroke had to be known. This prevented the inclusion of patients whose stroke was discovered after days or weeks in the ICU, and who often were intubated or under the effect of sedative medication. The stroke of these patients could be more severe and have different pathogenesis. Additionally, this is a hospital-based study and, therefore, the frequency and severity of the stroke associated with the COVID-19 infection may be biased towards more severe cases, assuming that the milder ones may not have sought medical attention or may not have gone to the hospital. Our classification of patients as COVID-19 or non-COVID-19 could be incorrect in some patients and lead to under diagnosis. In most patients a PCR test was performed, which can give false negatives results.[30,9]. Our study design does not allow us to reliably distinguish between asymptomatic carriers and uninfected patients. This is important as recent studies suggest that 17% to 20% of SARS-CoV-2 infected patients are completely free of symptoms.[31] These patients are able to transmit the infection although less than symptomatic patients. However, we would like to emphasize that the results of the sensitivity analysis of patients excluding those in whom a PCR was not available were consistent with those reached in the analysis of the whole sample.The frequency of neurological worsening was measured in within the first 72 hours of hospital admission. The frequency and reasons for neurological and general worsening beyond 72 hours are not detailed in our study. Evidently, the higher proportion of ICU admissions and the higher frequency of intubation in patients in the COVID-19 group indicate that severe complications associated with the COVID infection were determinants of the worse prognosis at 3 months in this group. Finally, despite adjusting our results according to the admission of the patients to the Stroke Unit, we did not have information of the specific treatments that received patients not admitted to the Stroke Unit. This was probably different across participating centers and could have influenced poor outcomes in some sites due to suboptimal stroke care. However, when analyzing stroke outcomes of patients with COVID-19 in our study according to the admission site (Stroke Unit versus COVID unit) there were no significant differences. Further studies will help to elucidate whether changes in the standard stroke care of these patients influence functional outcome and mortality beyond COVID-19 infection.

CONCLUSIONS

Our study illustrates the characteristics of ischemic stroke with concomitant COVID-19 infection, focusing in its prognosis, establishes the relative frequency of this infection at a single historical moment, and reports the logistical difficulties that occurred during the peak of the pandemic. Future studies will allow us to establish whether the physiopathology of this subtype of stroke is different from that of stroke without infection, whether patients should receive specific treatment and how the health system should adapt in the face of a threat such as the one we have suffered. It is important to emphasize that, despite a higher mortality, it seems that in patients with ischemic stroke there are no persistent effects of the viral infection that prevent a favourable recovery, or at least this probability is the same as that of patients who have suffered the stroke but without the COVID-19 infection.

ARTICLE INFORMATION

Received December 19, 2020; final revision received June 16, 2021; accepted July 20, 2021.

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Sources of Funding

The study was funded by Instituto de Salud Carlos III, Redes Temáticas de Investigación Cooperativa en Salud (INVICTUS PLUS), RD 06/0019/0010 and FEDER (Fondo Europeo de Desarrollo Regional).

Disclosures

Dr Guisado-Alonso reports grants from a Río Hortega Research Contract (CM18/00065) from the Instituto de Salud Carlos III, Ministry of Science and Innovation (Government of Spain) outside the submitted work. Dr Krupinski reports personal fees from Ferrer, from Gedeon, and from Takeda outside the submitted work. The other authors report no conflicts.

Supplemental Materials

Online Tables I–V
Online Figure I

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