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ORIGINAL CONTRIBUTION

A case-control analysis of stroke in COVID-19 patients: Results of unusual manifestations of COVID-19–study 11

Eric Jorge García-Lamberechts MD, PhD[1] | Òscar Miró MD, PhD[2] | Marcos Fragiel MD[1] | Pere Llorens MD, PhD[3] | Sònia Jiménez MD, PhD[2] | Pascual Piñera MD, PhD[4] | Guillermo Burillo-Putze MD, PhD[5] | Alfonso Martín MD, PhD[6] | Francisco Javier Martín-Sánchez MD, PhD[1] | Javier Jacob MD, PhD[7] | Aitor Alquézar-Arbé MD, PhD[8] | Laura Ejarque Martínez MD[9] | Belén Rodríguez Miranda MD[10] | Martín Ruiz Grinspan MD[11] | María Jesús Domínguez MD[12] | Francisco Javier Teigell Muñoz MD[13] | Sara Gayoso Martín MD[14] | Ángel García García MD, PhD[15] | Marta Iglesias Vela MD[16] | Virginia Carbajosa MD, PhD[17] | Manuel Salido Mota MD[18] | María José Marchena González MD, PhD[19] | Carmen Agüera Urbano MD[20] | Jesus Porta-Etessam MD, PhD[21] | Elpidio Calvo MD, PhD[22] | Juan González del Castillo MD, PhD[1] | on behalf of the Spanish Investigators on Emergency Situations TeAm (SIESTA) network

[1]Emergency Department, Hospital Clínico San Carlos, IDISSC, Univesidad Complutense, Madrid, Spain

[2]Emergency Department, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Catalonia, Spain

[3]Emergency Department, Hospital General de Alicante, University Miguel Hernández, Elche, Alicante, Spain

[4]Emergency Department, Hospital Reina Sofía, Murcia, Spain

[5]Emergency Department, Hospital Universitario de Canarias, Tenerife, Spain

[6]Emergency Department, Hospital Universitario de Móstoles, Móstoles, Madrid, Spain

[7]Emergency Department, Hospital Universitari de Bellvitge, Barcelona, Catalonia, Spain

[8]Emergency Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Catalonia, Spain

[9]Emergency Department, Hospital General de Requena, Valencia, Spain

[10]Emergency Department, Hospital Universitario Rey Juan Carlos, Madrid, Spain

[11]Emergency Department, Hospital Universitario del Henares, Madrid, Spain

[12]Emergency Department, Hospital Universitario de Fuenlabrada, Madrid, Spain

[13]Emergency Department, Hospital Universitario Infanta Cristina de Parla, Madrid, Spain

[14]Emergency Department, Hospital Comarcal El Escorial, Madrid, Spain

[15]Emergency Department, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain

[16]Emergency Department, Complejo Asistencial Universitario de León, León, Spain

[17]Emergency Department, Hospital Universitario Rio Hortega, Valladolid, Spain

[18]Emergency Department, Hospital Universitario Regional de Málaga, Málaga, Spain

[19]Emergency Department, Hospital Universitario Juan Ramón Jiménez, Huelva, Spain

[20]Emergency Department, Hospital Costa del Sol de Marbella, Málaga, Spain

[21]Neurology Department, Hospital Clínico San Carlos, IDISSC, Universidad Complutense, Madrid, Spain

[22]Internal Medicine Department, Hospital Clínico San Carlos, IDISSC, Universidad Complutense, Madrid, Spain

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Correspondence
Eric Jorge García-Lamberechts, Emergency Department, Hospital Clínico San Carlos, Profesor Martín Lagos S/N, 28040, Madrid, Spain.
Email: ericjorge.lamber@gmail.com

Abstract

Objective: We investigated the incidence, predictor variables, clinical characteristics, and stroke outcomes in patients with COVID-19 seen in emergency departments (EDs) before hospitalization.

Methods: We retrospectively reviewed all COVID-19 patients diagnosed with stroke during the COVID-19 outbreak in 62 Spanish EDs. We formed two control groups: COVID-19 patients without stroke (control A) and non–COVID-19 patients with stroke (control B). We compared disease characteristics and four outcomes between cases and controls.

Results: We identified 147 strokes in 74,814 patients with COVID-19 seen in EDs (1.96‰, 95% confidence interval [CI] = 1.66‰ to 2.31‰), being lower than in non–COVID-19 patients (6,541/1,388,879, 4.71‰, 95% CI = 4.60‰ to 4.83‰; odds ratio [OR] = 0.42, 95% CI = 0.35 to 0.49). The estimated that standardized incidences of stroke per 100,000 individuals per year were 124 and 133 for COVID-19 and non–COVID-19 individuals, respectively (OR = 0.93 for COVID patients, 95% CI = 0.87 to 0.99). Baseline characteristics associated with a higher risk of stroke in COVID-19 patients were hypertension, diabetes mellitus, and previous cerebrovascular and coronary diseases. Clinically, these patients more frequently presented with confusion, decreased consciousness, and syncope and higher D-dimer concentrations and leukocyte count at ED arrival. After adjustment for age and sex, the case group had higher hospitalization and intensive care unit (ICU) admission rates (but not mortality) than COVID-19 controls without stroke (OR = 3.41, 95% CI = 1.27 to 9.16; and OR = 3.79, 95% CI = 1.69 to 8.50, respectively) and longer hospitalization and greater in-hospital mortality than stroke controls without COVID-19 (OR = 1.55, 95% CI = 1.24 to 1.94; and OR = 1.77, 95% CI = 1.37 to 2.30, respectively).

Conclusions: The incidence of stroke in COVID-19 patients presenting to EDs was lower than that in the non–COVID-19 reference sample. COVID-19 patients with stroke had greater need for hospitalization and ICU admission than those without stroke and longer hospitalization and greater in-hospital mortality than non–COVID-19 patients with stroke.

KEYWORDS
cerebrovascular disease, clinical characteristics, COVID-19, incidence, outcome, risk factors, SARS-Cov-2, stroke

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is predominantly characterized by involvement of the lower respiratory tract and the cardiovascular system. In addition, neurologic manifestations and complications have been described during the natural history of COVID-19, including dysgeusia, anosmia, headache encephalopathy, impaired consciousness, skeletal muscle injury, Guillain-Barre syndrome, meningoencephalitis, and acute cerebrovascular diseases.[1] Regarding the latter, it is well known that acute respiratory infections can trigger cardiovascular events,[2,3] including viral infections such as influenza, which have shown to increase the risk of stroke.[4] However, it is unclear whether there really is a link between infection by SARS-CoV-2 and stroke. Factors associated with a higher risk of stroke, such as diabetes, hypertension, and previous history of cerebrovascular disease are also quite prevalent in COVID-19 patients and increase the severity and mortality of COVID-19 itself.[5] Moreover, previous cerebrovascular disease has been identified as a prevalent comorbidity among COVID-19 patients.[6] A recent meta-analysis showed that previous cerebrovascular disease was associated with increased risk of poor outcomes in

COVID-19 patients,[7] and according to this higher incidence of severe COVID-19, close monitoring of this subset of patients in the intensive care unit (ICU) care has been suggested.[8]

In addition to predisposing baseline risk factors, other potential mechanisms leading to an increased risk of stroke in COVID-19 patients have been reported and include the hypercoagulability state present in some COVID-19 patients.[1] Some of them are the increase of systemic inflammation with a cytokine storm,[9] prolonged immobilization of COVID-19 patients favoring blood stasis and thrombosis, the development of cardioembolism from virus-related cardiac injury,[10] and direct viral invasion of the nervous system that has been associated with hemorrhagic necrotizing encephalopathy.[11] Nevertheless, the real incidence of stroke in patients with COVID-19 is currently unknown, and the risk factors associated with stroke development are unclear. Bearing in mind all these uncertainties, we planned the current study, with the following specific objectives: (1) to determine the frequency of stroke in patients with COVID-19, (2) to uncover the predictor variables associated with the development of stroke in patients with COVID-19, (3) to describe whether there is any distinctive clinical characteristics in these patients in comparison with stroke observed in non-COVID-19 patients, and (4) to investigate the outcomes of COVID-19 patients presenting stroke.

METHODS

Study design and setting

This was a retrospective, case-control, multicenter study that reviewed the medical reports of COVID-19 patients presenting to a Spanish emergency department (ED) diagnosed with stroke during ED assessment and management before hospitalization. In Spain, the first case of SARS-CoV-2 infection was detected on January 31, 2020, and, accordingly, the definition of the COVID-19 period for patient inclusion in this study was set from March 1 to April 30, 2020. During this 61-day period, 213,435 cases of COVID-19 were confirmed in Spain by the Ministry of Health.[12]

This study forms part of the Unusual Manifestations of Covid-19 (UMC-19) project, which was designed to investigate the potential relationship between COVID-19 and 10 different entities that could be influenced by SARS-CoV-2 infection: spontaneous pneumothorax, acute pancreatitis, meningoencephalitis, Guillain-Barre syndrome, myopericarditis, acute coronary syndrome, deep venous thrombosis, pulmonary embolism, stroke, and gastrointestinal bleeding.[13–21] The main objectives of the UMC-19 project were common for all entities and consisted of the description of incidence, predictor variables, clinical characteristics and outcomes for each particular entity, using as comparators COVID-19 patients who did not develop the entity as well as non–COVID-19 patients who did present the entity.

The investigators of the UMC-19 project initially contacted 152 Spanish EDs, which roughly constitute half of the 312 hospital EDs of the Spanish public health network. Eighty-one of these EDs reported interest in participating and analyzed the protocol, and finally 62 agreed to participate and contributed the required data (Figure 1). These 62 hospitals serve a population of 15.5 million (33% of the overall Spanish population of 46.9 million) and are a quite balanced representation of the Spanish territory (12 of the 17 Spanish autonomous communities were represented), type of hospital (community, reference, and high-technology university hospitals were included), and involvement in the pandemic.[6]

The investigation of stroke in COVID-19 patients, one of the entities included in the UMC-19 project, was labeled as the UMC-19 Study 11 (UMC-19-S_{11}) and consisted of a retrospective, case-control, ED-based, multicenter study that reviewed the medical reports of COVID-19 patients diagnosed with stroke during ED assessment and management in Spanish EDs before hospitalization.

Participants

The case group was formed by COVID-19 patients with a diagnosis of stroke based on clinical and radiologic findings. All strokes were confirmed by a neurologist. Patients in whom stroke were diagnosed during hospitalization but not during ED patient care were excluded. Diagnosis of COVID-19 was accepted based on SARS-CoV-2 detection in nasopharyngeal swab by reverse transcriptase–polymerase chain reaction (RT-PCR) and a clinically compatible picture (including at least malaise, fever, and cough) with the presence of the typical lung parenchymal infiltrates in chest X-ray or pulmonary CT in patients with some other clinical symptoms attributable to COVID-19.

We defined two different control groups. One group was formed by COVID-19 patients (without stroke) presenting to the ED during the same period of the COVID-19 outbreak as that used for case inclusion (March 1 to April 30, 2020). This group was formed by selecting two nonstroke COVID-19–positive patients for every COVID-19 stroke case. They were the COVID-19 patients seen immediately before and after the COVID-positive stroke case (case:control ratio of 1:2). This group, named control group A (COVID-19 controls without stroke), was specifically designed to uncover the predictor variables for stroke development in COVID-19 patients.

The other control group was formed by non–COVID-19 patients diagnosed with stroke seen in the ED during the same period as the cases (March 1 to April 30, 2020), which was defined in the same terms as the cases. To avoid some of these control cases eventually having inadvertent infection by SARS-CoV-2, in this group we also included all patients with stroke diagnosed in the ED from March 1 to April 30, 2019, just 1 year before the COVID-19 pandemic. From the complete list of stroke diagnoses performed in the ED during this 4-month period, we randomly selected two non–COVID-19 patients with stroke for every case (case:control ratio of 1:2). This group, named control group B (stroke controls without COVID-19), was specifically designed to uncover the particular distinctive clinical characteristics of stroke developed in COVID-19 patients with respect to stroke developed in the general population.

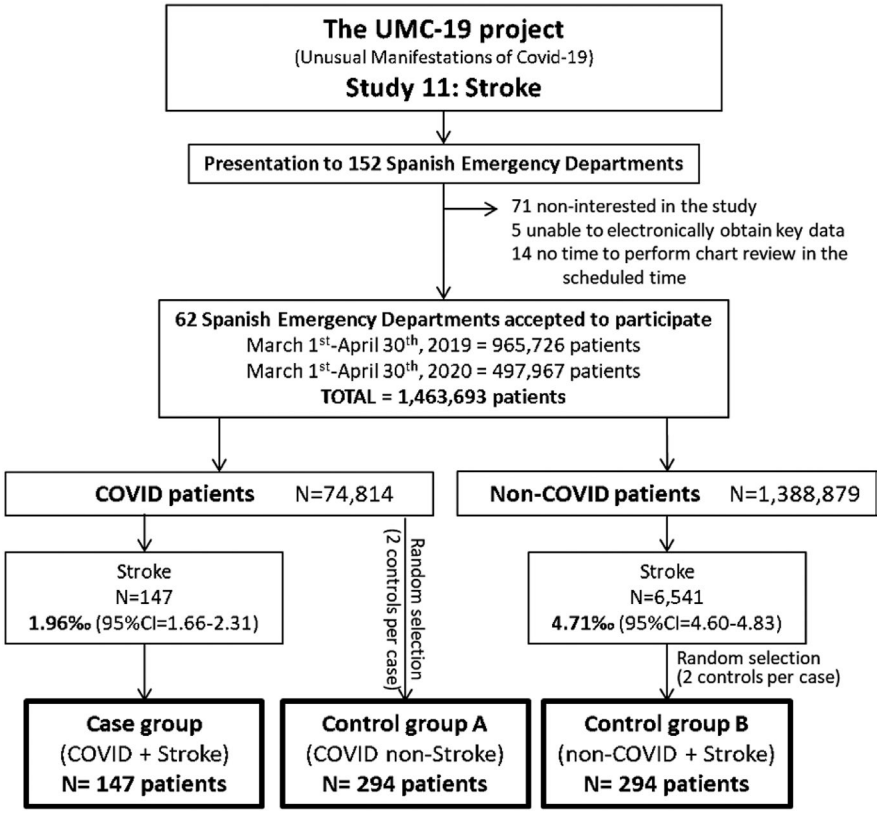

FIGURE 1 Study design and patient inclusion flow chart.

Variables, data sources/measurement

We collected 59 independent variables from the medical reports, which included two demographic data (age, sex), 12 comorbidities (hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, obesity clinically estimated, chronic obstructive pulmonary disease, asthma, active smoker, cerebrovascular disease, chronic kidney disease creatinine > 2 mg/dL, dementia, active cancer), 18 symptoms (time elapsed since symptoms started to ED attendance, fever, rhinorrhea, cough, expectoration, dyspnea, chest pain, syncope, hemoptysis, abdominal pain, vomiting, diarrhea, confusion, low level of consciousness, headache, anosmia, dysgeusia, symptoms associated with a stroke diagnosis upon initial presentation such as focal neurologic deficit), five vitals at ED arrival (temperature, systolic blood pressure [SBP], heart rate, respiratory rate, room air pulse oximetry), 16 laboratory parameters (C-reactive protein [CRP], creatinine, sodium, potassium, aspartate aminotransferase [AST], bilirubin, lactate dehydrogenase [LDH], procalcitonin, ferritin, hemoglobin, leukocytes, platelets, D-dimer, prothrombin time, activated partial thromboplastin time), four radiologic findings in chest X-ray (cardiomegaly, lung interstitial infiltrates, ground-glass opacities, pleural effusion), and two electrocardiogram (ECG) data (rhythm and corrected QT interval). In addition, for cases and control B patients (stroke controls without COVID-19), data from a brain computerized tomography (CT) study was also recorded.

We defined four different outcomes for cases and controls. They consisted of: (1) the need for hospitalization; (2) the need for admission to an ICU; (3) prolonged hospitalization (defined as length of hospitalization greater than 7 days, which is the median length of stay in Spanish hospitals [for the latter, time was dichotomized to detect prolonged hospitalization, that was defined as a length of stay longer than 7 days from the ED arrival to patient discharge home]; and (4) in-hospital all-cause mortality.

Bias

Taking into account the epidemiologic context of the 2 months of the study period, we considered that exclusive analysis of patients with a positive microbiologic test could suppose a selection bias by excluding patients presenting a clear clinical-radiologic diagnosis in an environment with a very high prevalence of COVID-19. For this reason, we included patients with a positive PCR and those who presented clinical and highly suggestive radiology of COVID-19. In addition, a sensitivity analysis was performed considering only cases and patients in group A (COVID-19 controls without stroke) with confirmation of SARS-CoV-2 infection by a PCR nasopharyngeal smear.

On the other hand, there could have been a possible bias in control group B (stroke controls without COVID-19) patients selected from two different periods (pre–COVID-19 and COVID-19). Therefore, we also performed a sensitivity analysis of outcomes by comparing cases with the subgroup of patients in group B (stroke controls without COVID-19) who were included during the pre-COVID period (2019) and by comparing cases with the subgroup of patients in group B included during the COVID period (2020).

TABLE 1 Baseline characteristics of patients with COVID-19 with stroke and comparison with patients with COVID-19 without stroke (control group A) and with patients with stroke without COVID-19 (control group B)

	Cases (COVID-19 and stroke), *n* = 147	Control group A (COVID-19 controls without stroke), *n* = 294	Control group B (stroke controls without COVID-19), *n* = 294	p-value[a]	p-value[b]
Demographics					
Age (years), median (IQR)	76 (66–85)	64 (49,75)	77 (68–84)	<0.001*	0.757
Age > 65 years	117 (79.6)	141 (48.0)	241 (82.0)	<0.001*	0.547
Sex (female)	72 (49.0)	125 (42.5)	121 (41.2)	0.198	0.119
Other comorbidities					
Hypertension	100 (68)	134 (45.6)	215 (73.1)	<0.001*	0.264
Dyslipidemia	68 (46.3)	110 (37.4)	141 (48)	0.074	0.736
Diabetes mellitus	45 (30.6)	56 (19)	90 (30.6)	0.006*	1.000
Coronary artery disease	28 (19.0)	21 (7.1)	40 (13.6)	<0.001*	0.136
Cerebrovascular disease	26 (17.7)	18 (6.1)	80 (27.2)	<0.001*	0.027*
Dementia	19 (12.9)	25 (8.5)	37 (12.6)	0.144	0.919
Active cancer	19 (12.9)	25 (8.5)	50 (17)	0.144	0.266
Obesity (clinically estimated)	19 (12.9)	46 (15.6)	48 (16.3)	0.447	0.348
Chronic obstructive pulmonary disease	14 (9.5)	31 (10.5)	37 (12.6)	0.739	0.343
Chronic kidney disease	13 (8.8)	24 (8.2)	29 (9.9)	0.808	0.731
Active smoker	12 (8.2)	18 (6.1)	47 (16)	0.538	0.023*
Asthma	4 (2.7)	24 (8.2)	5 (1.7)	0.027*	0.489

Note: Data are reported as *n* (%) unless otherwise reported.

Abbreviation: IQR, interquartile range.

[a]Comparison between cases and control A group.

[b]Comparison between cases and control B group.

*Statistical significance ($p < 0.05$).

Study size

We performed a retrospective study that was performed as part of a larger COVID-19 study and, as such, no specific sample size was calculated for the specific outcomes and statistical analysis of this exploratory stroke study.

Quantitative variables and statistical methods

Discrete variables were expressed as absolute values and percentages and continuous variables as median and interquartile range (IQR). Following the strategy in previous studies of the UMC-19 project,[13–21] we calculated the relative frequency of stroke in COVID-19 and non–COVID-19 patients coming to the ED as cases per thousand (‰) with 95% confidence intervals (CI). Additionally, standardized incidences (cases per 100,000 persons per year) were calculated based on the catchment area of the 62 EDs involved in the study. To estimate COVID-19 and non–COVID-19 populations in each ED catchment area, we used the Spanish provincial SARS-CoV-2 seroprevalences determined between April 27 and May 11, 2020.[22] Differences between the case group and controls groups were assessed by the chi-square test (or Fisher exact test if needed) for qualitative variables and the Mann-Whitney nonparametric test for quantitative variables. The magnitude of associations was expressed as unadjusted odds ratio (OR) with 95% CI, and for these estimations the continuous variables were dichotomized using clinically meaningful cutoffs. Because the number of cases expected to be identified was not large, we did not plan to go further in the investigation of the significant relationships identified in the unadjusted analysis using adjusted models. The only exception was the estimation of outcomes, which were adjusted for age and sex. Finally, we performed some sensitivity analyses of outcomes: (1) considering only cases and patients in group A (COVID-19 controls without stroke) with confirmation of SARS-CoV-2 infection by a positive PCR nasopharyngeal smear, (2) comparing cases with the subgroup of patients in group B (stroke controls without COVID-19) included during the pre-COVID period (2019), and (3) comparing cases with the subgroup of patients in group B included during the COVID period (2020). In all comparisons, statistical significance was accepted if the p-value was <0.05 or if 95% CI of the risk estimations excluded the value 1. The analyses were performed with the SPSS (v.24) statistical software package.

Ethics

The UMC-19 project was approved by the ethics committee of the Hospital Clínic of Barcelona (Spain) that acted as the central

TABLE 2 Clinical, analytical, radiologic, and ECG characteristics of the acute episode of patients with COVID-19 with stroke and comparison with patients with COVID-19 without stroke (control group A) and with patients with stroke without COVID-19 (control group B)

	Cases (COVID-19 and stroke), $n = 147$	Control group A (COVID-19 controls without stroke), $n = 294$	Control group B (Stroke controls without COVID-19), $n = 294$	p-value[a]	p-value[b]
Symptoms at ED arrival					
Length of symptoms (days)	1 (0–4)	7 (4–10)	1 (0–1)	<0.001*	<0.001*
Fever	39 (26.5)	186 (63.3)	7 (2.4)	<0.001*	<0.001*
Rhinorrhea	1 (0.7)	29 (9.9)	1 (0.3)	<0.001*	0.160
Cough	32 (21.8)	175 (49.5)	3 (1)	<0.001*	<0.001*
Expectoration	7 (4.8)	50 (11.3)	3 (1)	<0.001*	0.013*
Dyspnea	36 (24.5)	170 (57.8)	8 (2.7)	<0.001*	<0.001*
Chest pain	8 (5.4)	47 (16)	5 (1.7)	0.002*	0.029*
Syncope	8 (5.4)	6 (2)	22 (7.5)	0.005*	0.422
Hemoptysis	0 (0)	2 (0.7)	1 (0.3)	0.555	0.479
Abdominal pain	6 (4.1)	14 (4.8)	4 (1.4)	0.746	0.070
Vomiting	6 (4.1)	16 (5.4)	13 (4.4)	0.536	0.868
Diarrhea	10 (6.8)	58 (19.7)	2 (0.7)	<0.001*	<0.001*
Confusion	32 (21.8)	18 (6.1)	83 (28.2)	<0.001*	0.145
Low level of consciousness	34 (23.1)	14 (4.8)	60 (20.4)	<0.001*	0.511
Headache	18 (12.2)	31 (10.5)	30 (10.2)	0.592	0.517
Anosmia	3 (2)	21 (7.1)	0 (0)	0.026*	0.014*
Dysgeusia	3 (2)	26 (8.8)	1 (0.3)	0.007*	0.076
Focal neurologic deficit	115 (78.2)	3 (1)	259 (88.1)	<0.001*	0.007*
Signs at ED arrival					
Temperature (°C)	36 (36–36.6)	36.75 (36–37.4)	36 (36–36.5)	<0.001*	0.143
SBP (mm Hg)	142 (124–159)	125.5 (113–142)	150 (131–171)	<0.001*	0.002*
Heart rate (beats/min)	81 (74–92)	89 (78–100)	78 (68–88)	0.001*	0.001*
Respiratory rate (breaths/min)	17 (15–20)	18 (16–22)	16 (15–18)	0.028	0.002*
Room air pulse oximetry (%)	96 (92.75–97)	96 (93–98)	97 (95–98)	0.056	<0.001*
Laboratory findings					
CRP (mg/dl)	4.31 (0.9–10.7)	5.43 (1.92–10.5)	0.9 (0.3–3.69)	0.067	<0.001*
Creatinine (mg/dl)	0.93 (0.7–1.2)	0.90 (0.73–1.16)	0.90 (0.73–1.13)	0.877	0.595
Sodium (mmol/L)	138 (136–140)	138 (136–140)	140 (138–142)	0.050*	<0.001*
Potassium (mmol/L)	4.2 (3.8–4.5)	4.1 (3.8–4.4)	4.1 (3.8–4.45)	0.864	0.969
AST (IU/L)	29 (10–45)	30 (22–41)	21 (17–28)	0.433	<0.001*
Bilirubin (mg/dl)	0.64 (0.42–1.0)	0.5 (0.38–0.78)	0.7 (0.41–0.97)	0.003*	0.894
LDH (IU/L)	284 (200.2–393.7)	269 (208–383)	243 (194.2–318.5)	0.835	0.048
Procalcitonin (ng/ml)	0.08 (0.04–0.16)	0.09 (0.05–0.17)	0.05 (0.04–0.12)	0.350	0.310
Ferritin (ng/ml)	353.5 (193.25–623.25)	471.7 (229–1009)	176.6 (109.2–386)	0.036*	0.020

(Continues)

TABLE 2 (Continued)

	Cases (COVID-19 and stroke), $n = 147$	Control group A (COVID-19 controls without stroke), $n = 294$	Control group B (Stroke controls without COVID-19), $n = 294$	p-value[a]	p-value[b]
Hemoglobin (g/L)	13.4 (11.6–14.5)	13.8 (12.7–15)	13.7 (12.4–14.8)	0.019*	0.081
Leukocyte count ($\times 10^3$ cells/μL)	8.53 (7.07–10.62)	6.46 (4.84–8.83)	8.3 (6.8–10.9)	<0.001*	0.637
Lymphocytes ($\times 10^3$ cells/μL)	1.3 (0.83–2.0)	1.07 (0.7–1.42)	1.69 (18–2.36)	0.001*	<0.001*
Platelets ($\times 10^3$ cells/μL)	240 (183.25–310.75)	203.5 (148.25–259.75)	222 (184–274.5)	<0.001*	0.102
D-dimer (ng/ml)	1737 (799–4077)	570 (330–1154.5)	459 (257–2290)	<0.001*	0.007
Prothrombin time (sec)	13 (11.1–15.55)	12.4 (11.2–14)	12.5 (11,42–14.52)	0.280	0.615
Activated partial thromboplastin time (sec)	30.2 (26.12–34.3)	29.8 (23.65–33.32)	28 (24.25–31.37)	0.274	0.006*
Chest X-ray					
Chest X-ray performed	121 (82.3)	286 (97.3)	190 (64.6)	<0.001*	<0.001*
Cardiomegaly	19 (17.1)	24 (8.7)	40 (23.7)	0.018*	0.189
Interstitial lung infiltrates	50 (42.7)	112 (39.2)	8 (4.3)	0.507	<0.001*
Ground-glass lung opacities	44 (37.6)	176 (61.5)	8 (4.4)	<0.001*	<0.001*
Location of opacities					
Central	6 (4.1)	22 (7.5)	2 (0.7)	0.167	0.012
Peripheral	37 (25.2)	148 (50.3)	6 (2)	<0.001*	<0.001*
Pleura effusion	6 (5.3)	10 (3.6)	6 (3.5)	0.451	0.467
ECG					
ECG performed	126 (85.7)	207 (70.4)	268 (91.2)	<0.001*	0.081
Atrial fibrilation	31 (25.8)	21 (10.3)	63 (25.2)	<0.001*	0.896
Corrected QT interval	0.420 (0.381–0.451)	0.410 (0.390–0.430)	0.420 (0.400–0.450)	0.385	0.714

Note: Data are reported as median (IQR) or *n* (%).

Abbreviations: AST, aspartate aminotransferase; CRP, C-reactive protein; ECG, electrocardiogram; IQR, interquartile range; LDH, lactate dehydrogenase; SBP, systolic blood pressure.

[a]Comparison between cases and control A group.

[b]Comparison between cases and control B group.

*Statistical significance ($p < 0.05$).

ethical committee (reference number HCB/2020/0534). Due to the exceptional circumstances generated by the COVID-19 pandemic, the urgent need to obtain feasible data related to this new disease, and the noninterventional and retrospective nature of the project, the requirement of written patient consent was waived. Each investigator of the participating centers took responsibility for following the central instructions on collecting data from the medical record and coding it into a general deidentified database. Patient identity remained anonymous to investigators who analyzed the database. The UMC-19-S_{11} was carried out in strict compliance with the Declaration of Helsinki principles. The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish.

RESULTS

During the COVID-19 phase, EDs delivered care to 497,967 patients (average of 133 patients/day/ED) and 74,814 (15%) were diagnosed as having COVID-19. We identified 147 strokes in COVID-19 patients (frequency = 1.96‰ of COVID-19 patients arriving to the ED, 95% CI = 1.66‰ to 2.31‰) and constituted the case group (Figure 1). Control group A (COVID-19 controls without stroke) was formed

TABLE 3 Magnitude of statistically significant associations found in the unadjusted analysis

	OR	95% CI
Risk factors for developing stroke in COVID-19 patients (compared to COVID-19 patients not developing stroke)		
Symptoms associated with a stroke diagnosis upon initial presentation	9.837	7.071–13.685
Age > 65 years	2.766	1.942–3.940
Low level of consciousness	2.463	1.940–3.129
Confusion	2.176	1.680–2.818
D-dimer > 1,000 ng/ml	2.151	1.674–2.765
SBP > 140 mm Hg	2.065	1.595–2.674
Cerebrovascular disease	1.939	1.455–2.584
Hypertension	1.882	1.406–2.520
Coronary artery disease	1.882	1.415–2.503
Leukocytes > 10 ($\times 10^3$ cell/μl)	1.875	1.449–2.427
Atrial fibrilation	1.815	1.370–2.405
Syncope	1.755	1.093–2.819
Hemoglobin < 12 g/dl	1.704	1.310–2.217
Bilirubin > 1.2 mg/dl	1.670	1.180–2.364
Cardiomegaly (X-ray)	1.647	1.128–2.406
Diabetes mellitus	1.485	1.132–1.948
Rhinorrhea	0.940	0.140–0.647
LDH > 480 IU/L	0.712	0.545–0.930
Heart rate at ED arrival > 100 beats/min	0.607	0.395–0.935
Platelets < 150 ($\times 10^3$ cell/μl)	0.576	0.373–0.888
Ground-glass lung opacities	0.501	0.365–0.689
Temperature at ED arrival > 38°C	0.440	0.220–0.880
Chest pain	0.404	0.210–0.777
Diarrhea	0.400	0.222–0.721
Dyspnea	0.370	0.267–0.513
Fever	0.347	0.253–0.475
Expectoration	0.337	0.166–0.683
Cough	0.315	0.223–0.444
Characteristics of stroke in COVID-19 patients (compared to stroke in non–COVID-19 patients)		
D-dimer > 1,000 ng/ml	3.980	3.203–4.946
LDH > 480 IU/L	3.372	2.553–4.453
Cough	3.228	2.683–3.884
AST > 50 IU/L	3.183	2.297–4.411
Interstitial lung infiltrates	3.127	2.488–3.928
Fever	3.101	2.534–3.795
Anosmia	3.042	2.661–3.477
Dyspnea	2.926	2.371–3.610
Ground-glass lung opacities	2.863	2.287–3.584
Left ventricle dysfunction	2.737	1.613–4.643
Ferritin	2.736	2.173–3.445
Diarrhea	2.609	1.950–3.481
CRP > 5 mg/dl	2.294	1.801–2.921
Expectoration	2.155	1.405–3.306
Temperature at ED arrival >38°C	2.155	1.405–3.306

(Continues)

TABLE 3 (Continued)

	OR	95% CI
Room air pulsioxymetry <95%	2.032	1.584–2.607
Respiratory rate > 20 breaths/min	1.990	1.523–2.600
Chest pain	1.895	1.207–2.975
Bilirubin > 1.2 mg/dl	1.845	1.325–2.571
Lymphocytes < 1 ($\times 10^3$ cells/μl)	1.759	1.356–2.282
Activated partial thromboplastin time > 40 sec	1.671	1.172–2.384
Hemoglobin < 12 g/dl	1.514	1.156–1.982
SBP > 140 mm Hg	0.737	0.567–0.957
Symptoms associated with a diagnosis of stroke upon initial presentation	0.644	0.480–0.863
Active smoker	0.576	0.341–0.971
Cerebrovascular disease	0.575	0.350–0.943
Dysgeusia	0.296	0.101–0.871

Abbreviations: AST, aspartate aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase; SBP, systolic blood pressure.

by 294 COVID-19 patients without stroke during the same period. Confirmation of COVID-19 infection by RT-PCR was performed in 83% and 80.6% of patients, respectively.

During the non–COVID-19 period, EDs delivered care to 965,726 patients (average of 255 patients/day/ED). Among the non–COVID-19 patients seen in EDs during both periods, 6,541 were diagnosed with stroke (3,957 during the non-COVID period in 2019 and 2,584 during the COVID period in 2020). The total frequency was 4.71‰ of non–COVID-19 patients seen in the ED (95% CI = 4.60‰ to 4.83‰) while the frequency during the non-COVID period was 4.10‰ (95% CI = 3.97‰ to 4.23‰) and 6.11‰ (95% CI = 5.87‰ to 6.35‰) during the COVID period. Of these, 294 selected patients with stroke from among these non–COVID-19 patients formed control group B (stroke controls without COVID-19). No patient in group B included in the COVID-19 period (2020) had a positive RT-PCR. The frequency of stroke was lower in COVID-19 than in non–COVID-19 patients seen in the ED (OR = 0.42, 95% CI = 0.35 to 0.49; OR = 0.48, 95% CI = 0.41 to 0.56, when compared only with the non–COVID period, and OR = 0.33, 95% CI = 0.28 to 0.39, when compared only with the COVID period). The overall standardized incidences of stroke were 124 per 100,000 COVID-19 individuals per year (95% CI = 116 to 132) and 133 per 100,000 non–COVID-19 individuals per year (95% CI = 131 to 135, with partial standard incidences of 158 in the non–COVID-19 period and 108 in the COVID-19 period). Accordingly, the OR for stroke in COVID-19 patients compared to non–COVID-19 patients was 0.93 (95% CI = 0.87 to 0.99; OR = 0.79 compared to the non–COVID-19 period, 95% CI = 0.74 to 0.84; OR = 1.15 compared to the COVID-19 period, 95% CI = 1.07 to 1.23).

The median age of the cases was 76 years (IQR = 66–85 years), and 49% were female. The most frequent baseline comorbidities were hypertension in 100 (68%) patients, dyslipidemia in 68 (46.3%) patients, diabetes mellitus in 45 (30.6%) patients, coronary artery disease in 28 (19%) patients, and cerebrovascular disease in 26 (17.7%) patients (Table 1). The signs and symptoms most frequently observed were fever, cough, dyspnea, confusion, low level of consciousness, and symptoms, such as focal neurologic deficit, associated with a diagnosis of stroke upon initial presentation. The median time from symptom onset to ED consultation was 1 day (IQR = 0–4 days). The remaining clinical characteristics and laboratory, chest X-ray, and ECG findings are presented in Table 2. Atrial fibrillation was detected in 25.8% of ECGs. On the other hand, interstitial lung infiltrates and ground-glass opacities were the most frequent chest X-ray abnormalities observed, and cardiomegaly was more frequent in patients with stroke. Most patients with stroke underwent a brain CT during ED stay, but it was more frequently performed in non–COVID-19 patients (97%) than in COVID-19 (88%) patients. However, there were no differences in the type of stroke defined by the brain CT, with ischemic stroke being the predominant type (74.8% and 72.1%, respectively; see Table S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14389/full) Table 4

When cases were compared with controls, some statistically significant differences were found (Tables 1 and 2). The magnitudes of these associations are shown in Table 4. When COVID-19 patients with stroke were compared with the COVID-19 controls without stroke, we observed that symptoms associated with a stroke diagnosis (such as focal neurologic deficit); low level of consciousness and confusion were associated with stroke (OR = 9.83, 95% CI = 7.07 to 13.68; OR = 2.46, 95% CI = 1.94 to 3.13; and OR = 2.17, 95% CI = 1.68 to 2.82, respectively). Additionally, stroke was also found to be associated with higher levels of D-dimer, SBP, leukocytes, and cardiomegaly but lower hemoglobin values. Other predictor variables for developing stroke in COVID-19 patients were cerebrovascular and coronary artery disease, hypertension, atrial fibrillation, syncope, and diabetes mellitus. On the other hand, and in comparison, with non–COVID-19 patients presenting to the ED, COVID-19 patients with stroke exhibited a significantly higher frequency of cough, fever, anosmia, dyspnea, expectoration, and chest

TABLE 4 Sensitivity analysis for outcomes (adjusted for age and sex) in COVID patients with stroke (case group) compared with COVID-19 controls without stroke (control group A) and stroke controls without COVID-19 (control group B)

	OR (95% CI) for COVID-stroke (Cases) versus COVID-19 controls without stroke (Group A)	OR (95% CI) for COVID-stroke (Cases) versus Stroke controls without COVID-19 (Group B)
Hospitalization		
Main analysis	3.41 (1.27–9.16)*	1.47 (0.88–2.45)
Sensitivity analysis A[a]	3.19 (1.06–9.63)*	2.21 (0.72–6.75)
Sensitivity analysis B[b]	—	1.94 (0.60–6.27)
Sensitivity analysis C[c]	—	2.54 (0.85–7.59)
Admission to ICU		
Main analysis	3.79 (1.69–8.50)*	1.22 (0.88–1.68)
Sensitivity analysis A[a]	3.22 (1.47–7.07)*	1.70 (0.88–3.29)
Sensitivity analysis B[b]	—	1.16 (0.55–2.43)
Sensitivity analysis C[c]	—	1.96 (0.85–4.53)
Prolonged hospitalization		
Main analysis	1.47 (0.93–2.31)	1.55 (1.24–1.94)*
Sensitivity analysis A[a]	1.58 (0.97–2.60)	2.62 (1.62–4.24)*
Sensitivity analysis B[b]	—	1.96 (1.18–3.26)*
Sensitivity analysis C[c]	—	2.15 (1.29–3.59)*
In-hospital all-cause death		
Main analysis	1.58 (0.93–2.66)	1.77 (1.37–2.30)*
Sensitivity analysis A[a]	1.41 (0.81–2.46)	3.17 (1.84–5.49)*
Sensitivity analysis B[b]	—	3.47 (1.84–6.54)*
Sensitivity analysis C[c]	—	2.77 (1.51–5.09)*

[a] Sensitivity analysis A consisted of considering, for cases and group A, only patients with microbiologic confirmation of SARS-CoV-2 infection by PCR (122 cases, 237 patients in group A).

[b] Sensitivity analysis B consisted of considering, for group B, only patients included during the pre-COVID period (2019; 150 patients in group B).

[c] Sensitivity analysis C consisted of considering, for group B, only patients included during the COVID period (2020; 144 patients in group B).

* denotes statistical significance ($p < 0.05$).

pain. In addition, higher levels of D-dimer, LDH, AST, bilirubin, ferritin, and CRP but lower hemoglobin values and lymphocyte counts were found in the case group. Chest X-ray findings such as interstitial lung infiltrate and ground-glass lung opacities were more frequent in COVID-19 patients with stroke. These patients had a higher temperature and respiratory rate and lower room air pulse oximetry as vital signs at ED arrival. No differences were detected in brain CT findings (ischemic and hemorrhagic signs) between COVID-19 and non–COVID-19 patients.

With respect to outcomes, COVID-19 patients with stroke (case group) had higher percentages of hospitalization, ICU admission, prolonged stay, and in-hospital mortality than control groups A and B. However, after adjustment for age and sex, the case group only maintained significantly higher rates than control group A (COVID-19 controls without stroke) for hospitalization (OR = 3.41, 95% CI = 1.27 to 9.16) and ICU admission (OR = 3.79, 95% CI = 1.69 to 8.50) as well as compared to control group B (stroke controls without COVID-19) for prolonged hospitalization (OR = 1.55, 95% CI = 1.24 to 1.94) and in-hospital mortality (OR = 1.77, 95% CI = 1.37 to 2.30; Figure 2). Sensitivity analyses of outcomes supported all these results (Table 4).

DISCUSSION

We found that around 2‰ of COVID-19 patients coming to the ED presented with stroke. This frequency, found during a 2-month period of the COVID-19 outbreak, should be considered as high, but it is lower than the incidence in non–COVID-19 patients (4.71‰ ED comers). The reported global crude incidence of stroke in the population ranges from 234 to 284 per 100,000 person-years, but varies greatly between countries, and stroke incidence rates in high-income countries are usually lower than in middle-low income countries.[23] In the current report, estimation of the overall standardized incidences of stroke in our cohorts showed 124 per 100,000 COVID-19 individuals per year and of 133 per 100,000 non–COVID-19 individuals per year, with an OR for stroke in COVID-19 patients compared to non–COVID-19 patients of 0.93 (95% CI = 0.87 to 0.99), being closer to figures reported in Spain in 2006 (220 per 100,000 persons/year).[24] Differences with our incidence could be partly related to the time elapsed (15 years) between the previous data and that found in our study, and to the fact that during the COVID-19 pandemic, many countries reported a sharp reduction in admissions of patients with stroke, suggesting that patients with mild symptoms

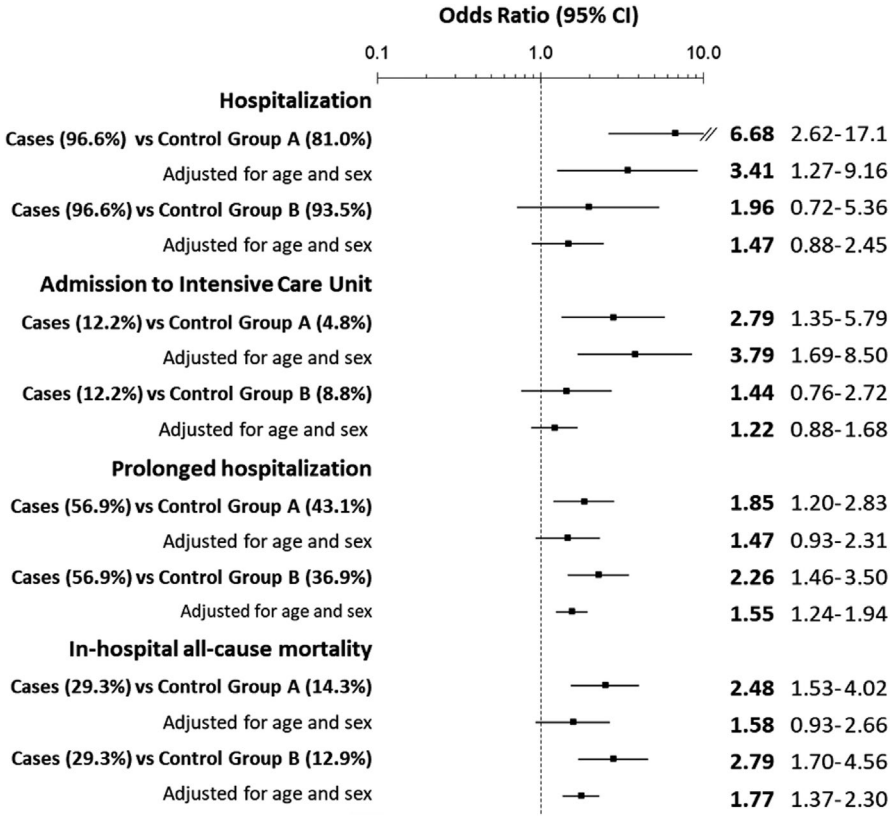

FIGURE 2 Outcomes of patients with COVID-19 and stroke compared with COVID-19 controls without stroke (control group A) and with stroke controls without COVID-19 (control group B).

were not referred to hospital[25–27] or they spontaneously preferred to stay home and not contact medical assistance during population lockdown due to fear of COVID-19 contagion.[28] Nevertheless, this potential bias is probably less than expected due to the alarm caused by stroke. Besides, a recent study in Barcelona reported that initial stroke severity was not different between patients with stroke admitted to hospital in March 2019 and March 2020.[29]

Our figures suggest a very weak relationship, if existent, between SARS-CoV-2 infection and the development of stroke, which is in contrast with previous reports. In this sense, we found a slight but statistically significant OR of 1.15 only when COVID patients were compared with non-COVID patients that were seen in the ED during the same COVID period. A single health system identified five cases of acute ischemic stroke associated with COVID-19 over a 2-week period, with symptoms suggesting large-vessel occlusion; all patients were under 50 years of age, an incidence overpassing that expected before the pandemic.[30] In case series of patients with COVID-19 admitted to the ICU, ischemic stroke was observed in three of 184 patients,[31] and cerebral ischemia was seen in three of 150,[32] while in another case series of COVID-19 patients hospitalized in general wards (not in ICUs), six of 314 patients had ischemic strokes.[33] However, the ED-based approach of the UMC-19-S_{11} study is substantially different from that of these previous studies. Taking into account only stroke cases in COVID-19 patients diagnosed at ED arrival, we evaluated the risk of stroke when developing COVID-19 during the initial phases of the disease. Strokes developed during hospital stay can include other factors aside from the effects of the viral infection itself, as hospitalization usually increases complications in bedridden patients with multidrug treatment or in very poor condition and could even be the result of inadequate antiplatelet therapy and/or anticoagulation management. Focusing on patients with COVID-19 at ED arrival, before hospital admission, probably surpasses some of these limitations and could help to answer this question.

The comorbidities for stroke development in COVID-19 patients were age > 65 years, cerebrovascular and coronary artery disease, hypertension, atrial fibrillation in the ECG examination, and diabetes mellitus. All of these are well-known risk factors associated with stroke in the general population.[34–37] Other signs and symptoms associated with a diagnosis of stroke, such as focal neurologic deficit, low level of consciousness, confusion, and syncope, were associated with the development of stroke in COVID-19 patients; however, they are frequent findings in the clinical context of stroke.[38,39] In our study leukocyte counts were significantly higher in COVID-19 patients with stroke. This may be due to a reactive increase in comparison with COVID-19 patients without stroke who usually present a lower leukocyte count,[40,41] although we found no differences in lymphocyte counts between patients with or without stroke. With respect to D-dimer levels, they were also higher in COVID-19 patients with stroke, which can be related to an increased risk of thrombotic events.[42]

In relation to other publications, some authors suggest that COVID-19 patients with stroke evaluated during the COVID-19 period could present a more severe illness.[43] Ntaios et al.[44] performed an analysis of patients with COVID-19 with stroke versus non–COVID-19 patients with stroke and suggested that

COVID-19–associated ischemic strokes are more severe with worse functional outcomes and present a higher mortality than non–COVID-19 ischemic strokes. However, these authors pooled hospitalized patients with stroke who may have been assessed in the EDs or may have developed stroke during hospitalization. With the aim of evaluating the risk of stroke in the initial phases of COVID-19, our study did not include patients who developed stroke during hospitalization because it may have been related to other confounding factors. Thus, we performed an additional analysis of a group of patients with COVID-19 without stroke that was designed to discover predictor variables for developing stroke in COVID-19 patients. On the other hand, Qureshi et al.[45] also included patients diagnosed with stroke at discharge from hospital who may have been assessed during hospitalization. They concluded that acute ischemic stroke was infrequent in patients with COVID-19 and usually developed in the presence of other cardiovascular risk factors and the risk of discharge to a destination other than home or death increased with the occurrence of acute ischemic stroke twofold in patients with COVID-19. In our study, we also observed a lower incidence of stroke in COVID-19 patients, although we evaluated other outcomes such as ICU admission, need for hospitalization, prolonged hospitalization, and in-hospital death. These are fundamental aspects from the perspective of the ED, especially in a period of work overload during which the availability of hospital beds was at a premium. On the other hand, the profile of COVID-19 patients with stroke in our study was somewhat different from that observed in the general population, although an overlapping of risk factors may be shared by the two groups.[46]

In our study, COVID-19 patients with stroke had higher percentages of hospitalization, ICU admission, prolonged stay, and in-hospital mortality than control groups A and B. However, after adjustment for age and sex, the case group only maintained significantly higher rates for hospitalization and ICU admission than control group A (COVID-19 controls without stroke) and for prolonged hospitalization and in-hospital mortality than control group B (stroke controls without COVID-19). This means that age seems to generate some confusion in the interpretation of outcomes, because the cases were older than patients of either of the control groups. This is in contrast with a recent meta-analysis that concluded that previous cerebrovascular and cardiovascular diseases were associated with increased poor outcomes in COVID-19, but this association was not influenced by gender, age, hypertension, diabetes, and respiratory comorbidities.[7]

LIMITATIONS

This study has several limitations. First, in about one in six COVID-19 patients with stroke, SARS-CoV-2 infection was not demonstrated by RT-PCR, although this proportion was very similar to the general COVID-19 population seen in the ED during the pandemic. Second, although stroke is a serious disease that can be well identified by the patient, it is possible that stroke with a very mild neurologic deficit or without deficit at the first assessment in the ED (transitory ischemic attack) may have been underestimated by the patient or the physician within the context of the pandemic. In addition, the predominance of respiratory symptoms in COVID-19 patients may have contributed to the lack of recognition of stroke. Furthermore, we did not include clinical aspects related to the severity of the stroke upon arrival at the ED, taking into account that patients with minor symptoms might have gone unnoticed. Third, we could not assess the characteristics of the whole COVID-19 and stroke population; only patients who came to hospital EDs were analyzed (registry of ED visits), and therefore, patients could have potentially been eligible. Fourth, a decrease in ED census during the COVID-19 period could have modified the profile of non–COVID-19 patients with stroke coming to the ED. We tried to address this limitation by including non-COVID patients seen during a pre–COVID-19 period. Fifth, we did not adjust the incidence of stroke in COVID-19 patients by patient-related or disease-related factors that could have accounted for the increased risk of stroke diagnosis. Sixth, as a retrospective study, although the case record form was standardized, there was no monitoring of data collection methods. Seventh, despite this being the largest series of COVID-19 patients developing stroke, the sample size is quite limited and, accordingly, a type II error could be present in some of our estimations.

CONCLUSIONS

Despite these limitations, we conclude that in our sample the incidence of stroke in COVID-19 patients presenting to EDs was lower than that of the non–COVID-19 population. COVID-19 patients with focal neurologic deficit, low level of consciousness, confusion, or syncope should be assessed to rule out stroke, particularly in those who have concomitant cardiovascular comorbidities. In our sample, stroke in COVID-19 patients was associated with a higher in-hospital mortality than that of the general non–COVID-19 population.

CONFLICT OF INTEREST

The authors have no potential conflicts to disclose.

AUTHOR CONTRIBUTIONS

All authors discussed the idea and design of study and provided patients. Data analysis and first draft writing—Eric Jorge García-Lamberechts, Òscar Miró, and Marcos Fragiel. All authors read this draft and provided insight for the final version. Eric Jorge García-Lamberechts is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to publication.

ORCID

Eric Jorge García-Lamberechts https://orcid.org/0000-0001-6826-9194
Pere Llorens https://orcid.org/0000-0002-9291-7179
Sònia Jiménez https://orcid.org/0000-0002-8332-7492
Alfonso Martín https://orcid.org/0000-0003-3874-7401
Francisco Javier Martín-Sánchez https://orcid.org/0000-0002-5970-725X

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX

The SIESTA network is formed by the following researchers and centers (all from Spain)

Steering Committee

Òscar Miró, Sònia Jiménez (Hospital Clínic, Barcelona), Juan González del Castillo, Francisco Javier Martín-Sánchez (Hospital Clínico San Carlos, Madrid), Pere Llorens (Hospital General de Alicante), Guillermo Burillo-Putze (Hospital Universitario de Canarias, Tenerife), Alfonso Martín (Hospital Universitario Severo Ochoa de Leganés, Madrid), Pascual Piñera Salmerón (Hospital General Universitario Reina Sofía, Murcia), E. Jorge García Lamberechts (Hospital Clínico San Carlos, Madrid), Javier Jacob (Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona), Aitor Alquézar-Arbé (Hospital de la Santa Creu i Sant Pau, Barcelona).

Participating centers

1. Hospital Universitario Doctor Peset Aleixandre de Valencia: María Luisa López Grima, Mª Ángeles Juan Gómez.

2. Hospital Universitario y Politécnico La Fe de Valencia: Javier Millán, Leticia Serrano Lázaro.

3. Hospital Universitario General de Alicante: Begoña Espinosa, Tamara García.

4. Hospital Clínico Universitario de Valencia: José Noceda.

5. Hospital Arnau de Vilanova de Valencia: María José Cano Cano, Rosa Sorando Serra.

6. Hospital Francesc de Borja de Gandía, Valencia: María José Fortuny Bayarri, Francisco José Salvador Suárez.

7. Hospital General Universitario de Elche, Alicante: Matilde González Tejera.

8. Hospital Marina Baixa de Villajoyosa de Alicante: Ana María Romero Romero, Liced Aguilar Herera.

9. Hospital Virgen de los Lirios, Alcoy Alicante: Napoleón Meléndez, Patricia Borrás Albero.

10. Hospital Universitario Vinalopó de Elche (Alicante): Marta Ivars Ferrer, Encarna Valero Burgos.

11. Hospital Universitario de Torrevieja de Alicante: Guendolina Fernandez Fernandez, Guillermo Moreno Montes.

12. Hospital Lluis Alcanys de Xativa: Carles Pérez García, Pilar Sánchez Amador.

13. Hospital Universitario de La Ribera de Valencia: José Vicente Brasó Aznar, José Luis Ruiz López.

14. Hospital de la Vega Baja Orihuela de Alicante: María Carmen Ponce.

15. Hospital Universitario Sant Joan Alicante: Elena Díaz Fernández.

16. Hospital General de Requena de Valencia: Luis Martinez Gimenez, Marisa de Reynoso Rodriguez.

17. Hospital de Lliria de Valencia: Ana Peiró Gómez, Elena Gonzalo Bellver.

18. Hospital de la Santa Creu i Sant Pau (Barcelona): Bruno Cabrera Perez, Dunia Bel Verge.

19. Hospital Clinic (Barcelona): Carlos Cardozo.

20. Hospital Universitari de Bellvitge de Hospitalet de Llobregat (Barcelona): Irene Cabello-Zamora, Alejandro Roset-Rigat.

21. Hospital Universitari Germans Trias i Pujol de Badalona (Barcelona): Neus Robert Boter, Marta Alujas Rovira.

22. Hospital de Terrassa (Barcelona): Josep Tost.

23. Hospital del Mar (Barcelona): Alfons Aguirre Tejedo, Silvia Mínguez Masó.

24. Hospital Universitari Joan XXIII (Tarragona): Anna Palau, Ruth Gaya Tur.

25. Hospital Universitari de Girona Dr. Josep Trueta (Girona): Maria Adroher Muñoz, Ester Soy Ferrer.

26. Hospital Universitari de Vic (Barcelona): Lluís LLauger García.

27. Hospital de Sant Pau i Santa Tecla (Tarragona): Brigitte Silvana Alarcón Jiménez, Silvia Flores Quesada.

28. Clinica Sagrada Familia (Barcelona): Arturo Huerta García.

29. Hospital Clínico San Carlos (Madrid): Marcos Fragiel.

30. Hospital Universitario La Paz (Madrid): Alejandro Martín Quiros, Charbel Maroun Eid.

31. Hospital Universitario de la Princesa (Madrid): Carmen del Arco Galán, Guillermo Fernández Jiménez.

32. Hospital Universitario Severo Ochoa de Leganés (Madrid): Davis Martín-Posada Crespo, Belen Sanchez Lopez.

33. Hospital Universitario Rey Juan Carlos (Madrid): Alejandra Sánchez Arias, Verónica Prieto Cabezas.

34. Hospital Universitario del Henares (Madrid): Laura Mao Martín, María Aranzazu Galindo Martín.

35. Hospital Universitario de Fuenlabrada (Madrid): Maria Eugenia Barrero Ramos, Marta Alvarez Alonso.

36. Hospital Universitario Infanta Cristina de Parla (Madrid): Angel Ivan Diaz Salado, Saul Pampa-Saico.

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38. Clínica Universidad Navarra de Madrid: María García-Uría, Raquel Piñero Panadero.

39. Hospital Universitario de Salamanca: AnMarta Fuentes de Frutos, Manuel Angel Palomero Martín.

40. Complejo Asistencial Universitario de León: Alberto Alvarez Madrigal, Ana Barrientos Castañeda.

41. Hospital Universitario de Burgos: María Pilar López Díez.

42. Hospital Universitario Rio Hortega (Valladolid): Monserrat Alvarez Rabanal, Silvia Fernandez Calderon, Ramiro Alonso del Busto.

43. Complejo Asistencial de Soria: Fadh Beddar Chaib, Jorge Pablo Viscarra Gambarte.

44. Hospital Universitario Regional de Málaga: Miguel Moreno Fernandez, Enrique Lagares Santana.

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46. Hospital Costa del Sol de Marbella: Elisa Delgado Padial, Ana Belen Garcia Soto.

47. Hospital Valle de los Pedroches de Pozoblanco (Córdoba): Jorge Pedraza García.

48. Hospital Virgen del Rocío de Sevilla: Amparo Fernández de Simón Almela.

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52. Hospital Universitario General de Albacete: Francisco Javier Lucas-Imbernón, María Ruiperez Moreno.

53. Hospital Virgen de la Luz (Cuenca): Félix González Martínez, Diana Moya Olmeda.

54. Hospital Nuestra Señora del Prado de Talavera de la Reina (Toledo): Ricardo Juárez.

55. Hospital Universitario de Canarias (Tenerife): Marcos Exposito Rodriguez, Patricia Eiroa Hernandez.

56. Hospital Universitario de Gran Canaria Dr. Negrín: José Pavón Monzo, Nayra Cabrera González.

57. Hospital Universitario Central Asturias: Pablo Herrero Puente, Beatriz María Martínez Bautista.

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59. Hospital Clínico Universitario Virgen de la Arrixaca: Eva Quero Motto, Nuria Tomas García.

60. Hospital General Universitario Reina Sofía de Murcia: María Paz Ortega, María Encarnación Sánchez Cánovas.

61. Hospital San Pedro de Logroño: Noemí Ruiz de Lobera.

62. Hospital Clínico Universitario Lozano Blesa: José María Ferreras Amez, Belén Arribas Entrala.