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ORIGINAL ARTICLE

Fewer COVID-19-associated strokes and reduced severity during the second COVID-19 wave: The Madrid Stroke Network

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Abstract

Background and purpose: The experience gained during the first COVID-19 wave could have mitigated the negative impact on stroke care in the following waves. Our aims were to analyze the characteristics and outcomes of patients with stroke admitted during the second COVID-19 wave and to evaluate the differences in the stroke care provision compared with the first wave.

Methods: This retrospective multicenter cohort study included consecutive stroke patients admitted to any of the seven hospitals with stroke units (SUs) and endovascular treatment facilities in the Madrid Health Region. The characteristics of the stroke patients with or without a COVID-19 diagnosis were compared and the organizational changes in stroke care between the first wave (25 February to 25 April 2020) and second wave (21 July to 21 November 2020) were analyzed.

Results: A total of 550 and 1191 stroke patients were admitted during the first and second COVID-19 waves, respectively, with an average daily admission rate of nine patients in both waves. During the second wave, there was a decrease in stroke severity (median National Institutes of Health Stroke Scale 5 vs. 6; $p = 0.000$), in-hospital strokes (3% vs. 8.1%) and in-hospital mortality (9.9% vs. 15.9%). Furthermore, fewer patients experienced concurrent COVID-19 (6.8% vs. 19.1%), and they presented milder COVID-19 and less severe strokes. Fewer hospitals reported a reduction in the number of SU beds or deployment of SU personnel to COVID-19 dedicated wards during the second wave.

Conclusions: During the second COVID-19 wave, fewer stroke patients were diagnosed with COVID-19, and they had less stroke severity and milder COVID-19.

KEYWORDS
COVID-19, intracerebral hemorrhage, ischaemic stroke, organized stroke care, outcomes

See commentary by A. H. Katsanos and G. Tsivgoulis on page 3881

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INTRODUCTION

The first coronavirus disease 2019 (COVID-19) pandemic wave challenged stroke care provision worldwide, with reduced stroke admissions and rates of intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) [1,2]. This has been partly attributed to the overload of emergency medical systems (EMS) and hospitals with patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with many of the human and material resources usually dedicated to stroke care reallocated to treat patients with COVID-19 [3].

Several expert-based recommendations on stroke care have been released to provide timely and effective care for stroke whilst ensuring stroke teams' safety and minimizing their risk of infection [4–8]. Therefore, the experience gained during the first COVID-19 wave could have mitigated the negative impact on stroke care in the following pandemic waves. In fact, a recovery in stroke hospitalization volumes was reported in the final period of the first COVID-19 wave [1], and a smaller decline in hospitalizations occurred during the second wave than during the first compared with two pre-pandemic periods in Germany [9]. Moreover, it has been reported that strokes experienced by patients infected with SARS-CoV-2 are more severe and had poorer outcomes [10,11], but it is possible that the treatment protocols for COVID-19, refined thanks to the results of clinical trials and observational studies conducted during the first wave, together with better organization of stroke care for infected patients, might have resulted in better outcomes.

The Madrid Stroke Network provides acute stroke care for approximately 6.5 million inhabitants, and seven hospitals are MT-ready on a weekly rotation basis, ensuring that three hospitals provide full-time coverage every day. During the first wave of the pandemic, some organizational changes to secure stroke care provision were arranged [12,13]. Briefly, they included protocols to ensure access to hospital care; measures for the early recognition of COVID-19-positive patients; the organization of specific pathways for infected and non-infected patients; the avoidance of unnecessary diagnostic procedures that could increase the risk of contagion; and early discharge.

Our aims were to analyze the characteristics and outcomes of patients with acute stroke admitted during the second COVID-19 wave and to evaluate the differences in stroke care provision compared with the first wave of the pandemic in the Madrid Health Region.

METHODS

A retrospective, multicenter cohort study was conducted that included all consecutive acute stroke patients admitted to any of the seven hospitals equipped with stroke units (SUs) and endovascular treatment facilities in the Madrid Health Region [14]. The number and characteristics of stroke patients with or without a diagnosis of SARS-CoV-2 infection were compared and the organizational changes implemented for stroke care between the first (25 February to 25 April 2020) [10] and second (21 July to 21 November 2020) pandemic waves were recorded. The dates defining the two waves were selected considering the beginning of the rise in the incidence and the flattening of the downward slope of the curve according to the official data on the daily incidence of COVID-19 in the Madrid Health Region [15]. No exclusion criteria, other than stroke mimics, were applied, to ensure the complete capture of all patients with acute stroke admitted to the participating hospitals.

Demographic data, risk factors, stroke characteristics and management, workflow metrics (times from onset to arrival, door-to-imaging, door-to-needle if IVT, door-to-puncture if MT) and stroke severity (assessed using the National Institutes of Health Stroke Scale [NIHSS] score) were recorded. The time elapsed between stroke and SARS-CoV-2 infection diagnosis, treatment received, chest computed tomography (CT) and laboratory data were recorded, as well as in-hospital complications and modified Rankin Scale score at discharge.

Confirmed diagnoses of COVID-19 disease were based on detecting SARS-CoV-2 nucleic acid by polymerase chain reaction (PCR) assay from nasopharyngeal/oropharyngeal swabs or detecting immunoglobulin G (IgG) or IgM serum antibodies in selected patients with high level of suspicion of COVID-19 and a negative PCR test [16,17]. Given the deficiency of PCR and immunoglobulin assays during the first wave, some patients might have been classified as suspected COVID-19 cases based on their clinical symptoms, blood assessments and chest CT findings [18]. The clinical severity of COVID-19 was classified as mild (mild symptoms), moderate (evidence of lower respiratory disease during clinical assessment or imaging with oxygen saturation [SpO_2] ≥94% on room air or with low supplemental oxygen requirements) or severe (high oxygen requirements, non-invasive or invasive ventilation or other cause of intensive care unit admission).

Lastly, a survey amongst the SU coordinators from the participating centers was conducted to analyze the organizational changes implemented for stroke care provision during the first and second COVID-19 waves. Questions were focused on changes in infrastructure and resources, stroke code pathways and rehabilitation, and on the provision of educational and research activities.

Data management and statistical analysis

Study data were collected and managed using Research Electronic Data Capture (REDCap) [19] tools hosted at IdiPAZ Health Research Institute. IBM SPSS Statistics v21 and Stata 12.1 (Stata Corp LP) were used for the statistical analysis. Data are shown as absolute and relative frequencies for categorical variables or median and interquartile ranges (IQRs) for numerical variables. Data were compared using the chi-squared test, Fisher's exact test, Student's *t* test or the Mann–Whitney *U* test, as appropriate.

The data recorded during the first and second COVID-19 waves were compared and the differences between the patients with confirmed SARS-CoV-2 infection in both waves were analyzed. The relationship between the COVID-19 diagnoses and stroke outcomes (death or dependence) during the second wave was analyzed using multivariate logistic regression models to adjust for confounders. Temporal trends in stroke admissions were analyzed by the autoregressive integrated moving average. Statistical significance was considered when p values were <0.05.

This study was approved by the Ethics Committee of La Paz University Hospital. As a retrospective study, the committee exempted it from the need for patient consent.

RESULTS

A total of 550 and 1191 patients with acute stroke were admitted during the first [10] and second COVID-19 waves, with a daily admission rate (median, IQR) of 9 (5) and 9 (4), respectively. Patients admitted during the second wave were more frequently smokers and had a higher frequency of prior stroke, namely prior cerebral infarction (13.7% vs. 8.9%; $p = 0.002$) (Table 1).

COVID-19 was confirmed in 105 (19.1%) and 81 (6.8%) acute stroke patients during the first and second COVID-19 waves ($p < 0.001$). Confirmation was based on PCR in 101 (96.2%) and 78 (96.3%) patients in the first and second waves, respectively. Other diagnostic tests such as antibody tests were less frequently used as the only confirmation test (3.8% and 3.7% in each wave). All patients in the second wave had a confirmed diagnosis, and none was managed based on clinical suspicion, whilst 19 (3.5%) patients were managed as clinically suspected COVID-19 cases during the first wave [11].

Acute stroke management and global outcomes

Figure 1 shows the total number of new PCR-confirmed COVID-19 patients according to the official data in the Madrid Health Region (bottom figure) and the temporal trend in the number of stroke admissions in the participating hospitals in both waves. To note, the incidence of COVID-19 during the first wave might be underestimated since PCR tests were restricted to symptomatic patients, whilst the second wave also included asymptomatic PCR-confirmed COVID-19 patients. Interestingly, in contrast to the first wave [10], the rate of stroke admissions remained stable throughout the second wave.

The prehospital stroke code was activated for 47.9% of patients during the second wave, a rate significantly lower than that of the first wave [10], with a higher proportion of patients arriving at hospital using their own personal transport and no differences in the percentage of secondary transfers. Interestingly, in-hospital strokes significantly decreased during the second wave (Table 1). Figure 2 shows the temporal trends in the transport methods for arriving at the hospital during the second wave. There was a slight increase in transfers to hospitals by the EMS throughout the study period, whilst secondary transfers and arrivals by personal transportation remained stable.

TABLE 1 Comparison of demographics and baseline data of patients with acute stroke admitted during the first and second COVID-19 waves

	First wave $N = 550$	Second wave $N = 1190$	p
Male patients, n (%)	311 (56.5)	650 (54.6)	0.243
Median age, years (IQR)	73 (61;82)	75 (62;84)	0.099
Hypertension, n (%)	169 (69.3)	813 (68.6)	0.413
Diabetes, n (%)	143 (26.5)	317 (26.8)	0.462
Dyslipidemia, n (%)	286 (52)	611 (51.3)	0.413
Ischaemic cardiopathy, n (%)	60 (10.9)	128 (10.8)	0.503
AF, n (%)	114 (20.8)	270 (22.8)	0.192
COPD, n (%)	49 (9)	96 (8.1)	0.303
Tobacco use, n (%)	93 (16.9)	242 (20.6)	0.041
Alcohol abuse, n (%)	43 (7.8)	72 (6.1)	0.111
Prior stroke, n (%)	84 (15.4)	234 (19.9)	0.014
Type of stroke (final diagnosis), n (%)			
TIA	60 (10.9)	158 (13.3)	0.167
Cerebral infarction	406 (73.8)	863 (72.5)	0.553
Intracerebral hemorrhage	77 (14)	145 (12.2)	0.288
Subarachnoid hemorrhage	4 (0.7)	10 (0.8)	1
Cerebral venous thrombosis	3 (0.5)	15 (1.3)	0.20
Type of hospital arrival, n (%)			
Emergency medical services	290 (54.3)	559 (47.9)	0.014
Patient/relative personal transportation	136 (25.5)	396 (33.9)	0.000
In-hospital stroke	43 (8.1)	35 (3.0)	0.000
Transfer from another hospital	65 (12.2)	177 (15.2)	0.101
Stroke severity			
NIHSS, median (IQR)	6 (2–16)	5 (1–13)	0.000
Median metrics in stroke management, min (IQR)			
Stroke onset to hospital arrival[a]	132 (85–295)	149 (85–323)	0.403
DTI time	29 (17–53)	29 (18–60)	0.630
Ward at first admission, n (%)			
Acute stroke unit	397 (72.4)	955 (80.8)	0.000
Neurology ward	23 (4.2)	60 (5.1)	0.426
Non COVID-19 medical ward	4 (0.7)	16 (1.4)	0.337
COVID-19 medical ward	52 (9.5)	11 (0.9)	0.000
ICU	40 (7.3)	114 (9.6)	0.111

(Continues)

TABLE 1 (Continued)

	First wave N = 550	Second wave N = 1190	p
Emergency department wait longer than 24 h	30 (5.5)	17 (1.4)	0.000
Outcomes on discharge (if alive)			
In-hospital mortality, n (%)	87 (15.9)	118 (9.9)	0.000
Death or dependency (mRS 3–6), n (%)	264 (48.2)	491 (41.3)	0.007
Median stay, days (IQR)	5 (3–10)	5 (3–10)	0.246
Destination on discharge (if alive), n (%)			
Home	343 (62.7)	760 (64.3)	0.522
Nursing home	19 (3.5)	33 (2.8)	0.440
Another hospital including rehabilitation facilities	98 (17.9)	271 (22.9)	0.018

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DTI, door-to-imaging; ICU, intensive care unit; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS; National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

[a]Data on 806 patients with known stroke onset date who arrived at the hospital by emergency medical systems or their own transport (255 in the first wave and 601 in the second wave). Data on patients with stroke during the first pandemic wave have been reported previously [10].

There were no significant differences in the time from stroke onset to hospital arrival, even amongst EMS transfers (median time [IQR] 117 min [76–199.75] vs. 122.5 min [83.25–209.75]; $p = 0.565$) or in other workflow time metrics (Table 1).

During the second wave, significantly fewer patients waited longer than 24 h in the emergency department to be admitted to a hospital ward (1.4% vs. 5.5%), and a higher proportion were first admitted to the SU (80.8% vs. 72.4%). As a result of the decrease in the number of patients with stroke with a COVID-19 diagnosis, fewer patients were admitted to a dedicated COVID-19 ward (Table 1). Significantly fewer chest CTs were performed during the second wave (8% vs. 52.1%; $p = 0.000$).

Figure 3 shows the distribution of NIHSS scores at admission and the modified Rankin Scale scores at discharge by COVID-19 wave. Overall, stroke severity was lower during the second wave in terms of lower NIHSS score, as were in-hospital mortality and the rate of death or dependence at discharge. The proportions of stroke types in the final diagnosis were similar (Table 1).

COVID-19 characteristics

COVID-19 was diagnosed prior to stroke in approximately half of the infected patients, with no differences between the first and second waves (45.2% vs. 54.5%, $p = 0.232$). During the second wave, more patients with COVID-19 and stroke were transferred from another hospital, with the differences in other arrival methods like those of the overall sample (Table 2). Patients with COVID-19 presented less severe strokes and milder COVID-19 during the second wave, with significantly higher oxygen saturation at stroke onset and lower levels of acute phase reactants (Table 2). Of note, fewer patients underwent drug therapies empirically targeted against COVID-19. Forty-two percent and 10% of patients were administered corticosteroids and remdesivir, respectively, during the second wave; unfortunately, these data were not collected in the first wave. A higher proportion of patients were treated with MT alone during the second wave (Table 2). Overall, there was a decrease in in-hospital mortality for patients with stroke and COVID-19 during the second wave. The main cause of death was related to COVID-19 pneumonia, but its proportion was significantly lower in the second wave than in the first (11.1% vs. 26.7%, $p = 0.009$).

Cerebral infarction

A total of 1269 patients were diagnosed with cerebral infarction: 406 in the first and 863 in the second wave, with confirmed COVID-19 in 85 (20.9%) and 60 (7%) patients, respectively ($p < 0.001$). The demographics and comorbidities were similar in the two waves except for a higher proportion of patients with prior stroke in the second wave (19.6% vs. 14.6%; $p = 0.019$).

Cerebral infarction severity was lower in the second wave. The proportion of patients undergoing reperfusion therapy was similar, as were the time metrics. During the second wave, fewer patients developed in-hospital complications (seizures, hemorrhagic transformation, COVID-19-related pneumonia, deep vein thrombosis and urinary tract infections). There were no differences in stroke etiology (Table S1).

Confirmed COVID-19 diagnoses were associated with a greater risk of death or dependence at hospital discharge during both waves, even after adjusting for age, stroke severity and reperfusion treatment (odds ratio 1.87, 95% confidence interval 1.01–3.48, $p = 0.011$, for the first wave [10] and odds ratio 2.08, 95% confidence interval 1.08–3.98, $p = 0.027$, for the second wave).

Intracerebral hemorrhage

A total of 222 patients were diagnosed with intracerebral hemorrhage (77 and 145 in the first and second waves, respectively), 14 (18.2%) and 13 (9%) of whom had a confirmed COVID-19 diagnosis ($p = 0.018$). Overall, the clinical profiles, time metrics and outcomes were similar (Table S2), except for a higher frequency of COVID-19-related pneumonia during the first wave (64.3% vs. 23.1%; $p = 0.038$). Patients with intracerebral hemorrhage and confirmed COVID-19 had higher rates of in-hospital death (50% vs. 30.8%; $p = 0.267$) and of death or dependence at discharge (100% vs. 92.3%; $p = 0.481$) during the first wave than during the second.

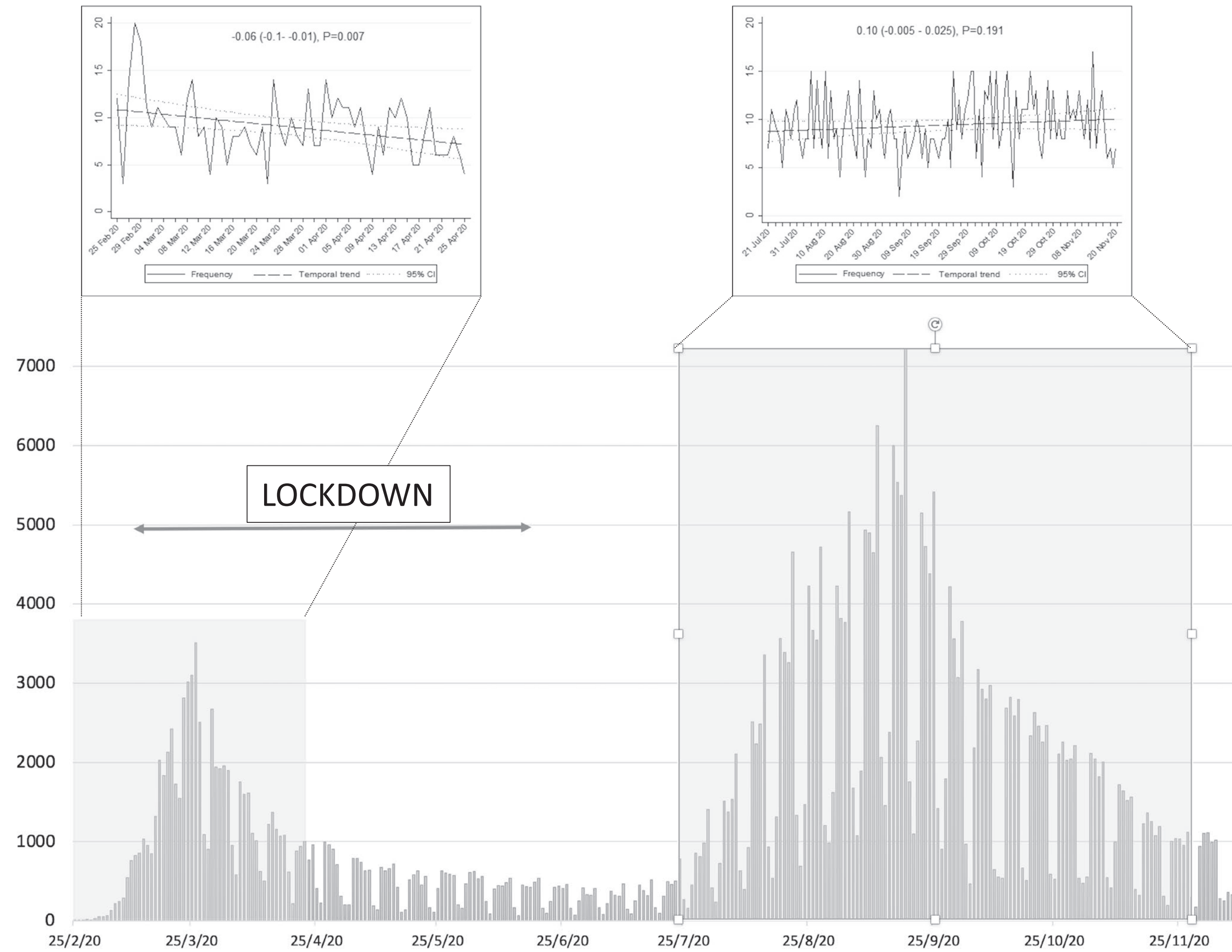

FIGURE 1 Total number of new PCR-confirmed COVID-19 patients according to the official data in the Madrid Health Region (bottom figure) and temporal trends in the number of stroke admissions: upper left box, first COVID-19 wave; upper right box, second COVID-19 wave. Shaded areas represented the study periods. The *y*-axis indicates the number per day

Organizational changes in stroke care provision

During the first COVID-19 wave, there was a reduction in SU beds and neurology ward beds at four and seven hospitals, respectively. The SUs were reallocated to provide semicritical non-stroke care in one hospital, and the neurological ward was moved elsewhere in three hospitals. However, the second wave had a lower impact on stroke care infrastructure, with only one hospital reporting a reduction in SU beds (Figure 4a). Moreover, neurologists and neurology residents were less frequently reallocated to COVID-19 wards (Figure 4b). During the first wave, the availability of 24 h/7 days MT was implemented in all seven hospitals, whilst during the second wave it was not deemed necessary, and the rotatory shift between hospitals was maintained due to reduced EMS overload (Figure 4c).

However, the provision of rehabilitation therapies did not improve from the first to the second wave, with delays in starting physiotherapy in four hospitals and reductions in the number of in-hospital rehabilitation-dedicated beds. Nevertheless, none of the hospitals reported discharging disabled patients to home due to a lack of resources during the second wave, which was a limitation faced by two hospitals during the first wave (Figure 4d). In fact, a significant increase in the proportion of stroke patients discharged to other hospitals including rehabilitation facilities was found during the second wave, with no significant changes in the discharges to nursing homes (Table 1).

The COVID-19 pandemic also affected the educational and research activities during the first wave, with a slight improvement during the second wave, although education for medical students remained restricted in all seven hospitals (Figure 4e). Fewer stroke physicians were on leave due to COVID-19 compared with the first wave (Figure S1).

DISCUSSION

This was a multicenter cohort study aimed at describing the differences in clinical characteristics and outcomes of patients with acute

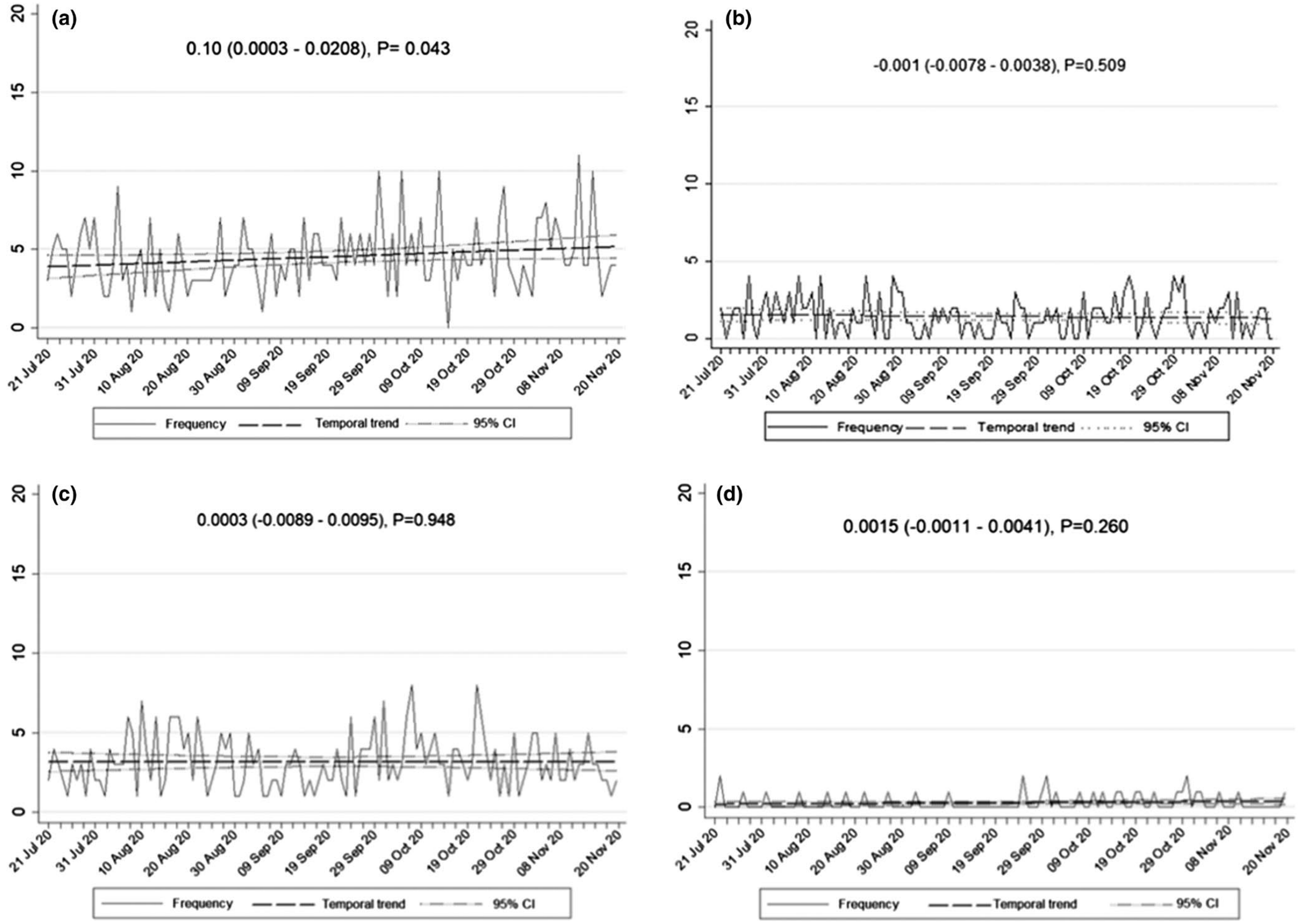

FIGURE 2 Temporal trends. (a) Stroke admissions transferred by EMS. (b) Stroke admissions transferred from other hospitals. (c) Stroke admissions arriving at the hospital by their own transport. (d) In-hospital strokes. The *y*-axis indicates the number per day

stroke and COVID-19 as well as in the impact of the COVID-19 pandemic on acute stroke care provision between the first two waves. A decrease was found in not only concomitant COVID-19 and stroke but also in-hospital strokes, mainly in the COVID-19 group, during the second wave. Furthermore, acute stroke patients with concomitant COVID-19 experienced less severe strokes and milder COVID-19 disease and were more frequently treated with MT alone whilst undergoing fewer drug therapies empirically targeted against COVID-19.

The COVID-19 pandemic changed the clinical profile of patients with acute stroke, with an increased prevalence of younger patients and more severe strokes attributed to large vessel occlusions and higher in-hospital mortality compared with pre-COVID controls [20]. Our study shows no changes in the demographic and risk factor profile between the first two waves, but lower stroke severity and in-hospital mortality in the second wave. Similarly, the characteristics of COVID-19 have changed throughout the pandemic. As previously reported, patients admitted during the second wave presented milder COVID-19 symptoms, less inflammatory analytical profiles and a lower mortality rate, even for COVID-19 pneumonia-related death [21,22]. These differences could be related to the increased awareness of patients who consulted before presenting severe symptoms, as well as to a more prepared and experienced health system. Also, there was a change in the therapeutic approach towards more targeted treatment with a more extensive use of corticosteroids, which helped improve outcomes for patients with COVID-19 [23].

One important concern related to the COVID-19 outbreak was its negative impact on acute stroke care, with reported reductions in ischaemic and hemorrhagic stroke hospitalizations, as well as in IVT and MT rates compared with historical controls [1,2]. A prior report from the Madrid Stroke Network analyzing the first COVID-19 pandemic wave showed a reduction in stroke admissions but a high rate of reperfusion therapies in patients with ischaemic stroke (43.3%), with no differences depending on COVID-19 diagnoses [10]. This finding, together with the maintenance of door-to-imaging, door-to-needle and door-to-puncture times within the recommended range, suggest that the solid organized framework helped address the COVID-19 pandemic without a major impact on acute stroke care [10]. In this new analysis, a number of the organizational changes implemented in our network during the first two waves of the COVID-19 pandemic are described. During the second wave, it

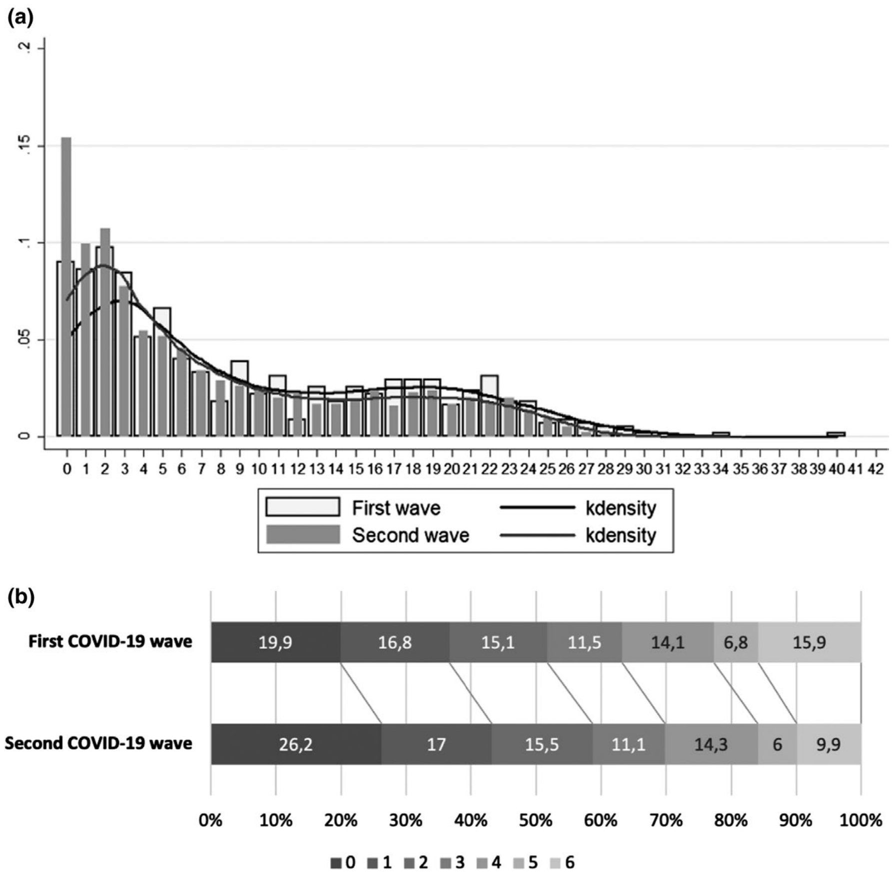

FIGURE 3 Stroke severity and stroke outcomes during the first and second COVID-19 waves. (a) Histogram and kernel density estimates of the NIHSS scores at admission. (b) Distribution of the modified Rankin Scale scores at discharge; $p = 0.006$

was possible to maintain better stroke care organization by creating COVID-19 SU beds and avoiding the reduction in non-COVID SU beds, as well as reallocating SU infrastructure and personnel to COVID-19-dedicated wards. These efforts might have contributed to maintaining stroke care quality and metrics. However, the provision of rehabilitation therapies has not improved from the first to second wave.

One of the challenges in providing acute stroke care was to ensure protection of stroke care workers against SARS-CoV-2 contagion, and specific recommendations from scientific societies and expert-based consensus on this topic were released [13,24–27]. Earlier studies have shown that front-line healthcare workers had a three-fold higher risk of a positive COVID-19 test compared with the general population, even after accounting for other risk factors [28]. This finding might have been associated with the scarcity and reuse of personal protective equipment during the first wave of the pandemic [28]. In our setting, a study from the Stroke Group of the Spanish Society of Neurology reported an 18% rate of medical leaves affecting staff neurologists and 23% of the neurology residents [29]. During the second wave, when protection measures were clearly improved, five of the seven hospitals participating in this study reported a reduction in the proportion of neurologists infected, and only one hospital showed a higher contagion rate compared with the first wave. The limitations of this analysis were that data were not collected on the serological prevalence or infection rates amongst other members of the stroke teams (stroke nurses, neurointerventionalists, rehabilitation physicians and neurology residents). It is not possible to specify whether the stroke neurologists were infected during stroke care, because of their redeployment to attend COVID-19 patients, or due to transmission from coworkers before the universal use of masks [28,30,31].

Stroke education for medical students and neurology trainees in our network were negatively impacted by the COVID-19 pandemic in line with other reports [29], and certain modifications to neurology residence training have been proposed to promote resident safety such as virtual education activities. Also, different approaches have been implemented to rapidly adapt to redeployment, service needs and trainee illness [32].

The number or the extent of the clinical trials or academic studies whose recruitment was delayed or stopped or those that could not be started because of the delayed regulatory or funding approval during the national lockdown was not specifically addressed. However, the negative impact on stroke research has been highlighted as collateral damage of the COVID-19 pandemic [33]. Our results suggest a slight but encouraging improvement in research activities in our setting during the second wave.

Our study has several strengths. First, the study was based on a multicenter hospital registry covering all the hospitals with SU and endovascular facilities in the Madrid Health Region. Secondly, it included consecutive patients with acute stroke without selection

TABLE 2 Characteristics of patients with confirmed COVID-19 diagnosis

	First wave $N = 105$	Second wave $N = 81$	p
Demographic data, risk factors and comorbidities			
Male patients, *n* (%)	66 (62.9)	49 (60.5)	0.429
Median age, years (IQR)	74 (63; 81.5)	71 (59.5; 84)	0.526
Hypertension, *n* (%)	78 (74.3)	51 (63.8)	0.083
Diabetes, *n* (%)	28 (28.3)	25 (32.1)	0.352
Dyslipidemia, *n* (%)	52 (49.5)	36 (44.4)	0.295
Ischaemic cardiopathy, *n* (%)	10 (9.5)	10 (12.3)	0.351
AF, *n* (%)	21 (20)	22 (27.2)	0.165
COPD, *n* (%)	17 (16.3)	8 (9.9)	0.144
Tobacco use, *n* (%)	12 (11,4)	10 (12.5)	0.499
Alcohol abuse, *n* (%)	10 (9.5)	4 (4.9)	0.186
Prior stroke, *n* (%)	10 (9.6)	9 (11.1)	0.462
Type of hospital arrival, *n* (%)			
Emergency medical services	51 (49.5)	28 (35)	0.049
Patient/relative personal transportation	15 (14.6)	26 (32.5)	0.004
In-hospital stroke	29 (28.2)	9 (11.2)	0.005
Transfer from another hospital	8 (7.8)	17 (21.2)	0.008
Stroke and COVID-19 clinical severity			
NIHSS, median (IQR)	11.5 (4 – 18.75)	5 (2 – 15)	0.004
Mild COVID-19, *n* (%)	34 (32.7)	43 (56.6)	0.001
Moderate COVID-19, *n* (%)	35 (33.7)	15 (19.7)	0.039
Severe COVID-19, *n* (%)	35 (33.7)	18 (23.7)	0.147
Baseline vital signs and laboratory findings, median (IQR)			
Body temperature, °C	36.6 (36.1–37.1)	36.6 (36.3–36.9)	0.963
O_2 saturation, %	95 (92–97)	96 (95–98)	0.004
Platelet count	257,000 (180,000–345,500)	224,000 (178,000–265,000)	0.010
Fibrinogen	599 (492.2–740)	490 (349.7–571.7)	<0.001
D-dimer	1973 (850–4294)	760 (280–1538)	<0.001
C-reactive protein	18.7 (4–86)	5.8 (1.1–19.9)	0.001
Type of stroke, *n* (%)			
TIA	3 (2.9)	6 (7.4)	0.181
Cerebral infarction	85 (81)	60 (74.1)	0.262
Intracerebral hemorrhage	14 (13.3)	13 (16)	0.602
Subarachnoid hemorrhage	2 (1.9)	0 (0)	0.506
Cerebral venous thrombosis	1 (1.0)	2 (2.5)	0.581
Treatments for COVID-19, *n* (%)			
None	16 (15.2)	36 (44.4)	<0.001
Hydroxychloroquine	82 (78.1)	1 (1.2)	<0.001
Azithromycin	42 (40)	7 (8.6)	<0.001
Lopinavir/ritonavir	29 (27.6)	0 (0)	<0.001
Remdesivir[a]	ND	8 (9.9)	–
Interferon-beta	10 (9.5)	0 (0)	<0.001
Tocilizumab	10 (9.5)	8 (9.9)	0.564
Corticosteroids[a]	ND	34 (42)	–

(Continues)

TABLE 2 (Continued)

	First wave *N* = 105	Second wave *N* = 81	*p*
Supplemental oxygen requirements	30 (28.6)	16 (19.8)	0.113
Mechanical ventilation	6 (5.7)	6 (7.4)	0.430
Non-invasive ventilation	3 (2.9)	4 (4.9)	0.359
Palliative care	12 (11.4)	5 (6.2)	0.165
Recanalization therapies (if ischaemic stroke), *n* (%)			
Any recanalization therapy	30 (35.7)	27 (45)	0.171
IVT	13 (15.5)	6 (10)	0.338
MT	5 (6)	15 (25)	0.001
IVT + MT	12 (14.3)	6 (10)	0.443
Median metrics in stroke management, min (IQR)			
Stroke onset to hospital arrival[b]	130 (86; 176)	154 (75.75; 434.5)	0.190
DTI time	31.5 (19.75; 57.75)	32 (18.5; 66.25)	0.757
DTN (if IVT)	55 (27; 100)	40 (19; 92)	0.564
DTP (if MT)	110 (82; 165.75)	73 (52.75; 137.25)	0.121
Outcomes on discharge (if alive)			
In-hospital mortality, *n* (%)	44 (42.3)	13 (16)	<0.001
Death or dependency (mRS 3–6), *n* (%)	75 (72.1)	48 (60)	0.084
Median stay, days (IQR)	12 (5; 21)	12 (6; 20.5)	0.197
Cause of death			
Related to COVID-19 pneumonia	28 (26.7)	9 (11.1)	0.009
Related to stroke	14 (13.3)	2 (2.5)	0.008
Destination on discharge (if alive), *n* (%)			
Home	37 (35.6)	45 (56.2)	0.005
Nursing home	7 (6.7)	3 (3.8)	0.518
Another hospital including rehabilitation facilities	16 (15.4)	19 (23.8)	0.152

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DTI, door-to-imaging; DTN, door-to-needle; DTP, door-to-puncture; ICU, intensive care unit; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS; National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

[a]Not included in the first wave database.

[b]Data on 64 patients with known stroke onset date who arrived at the hospital by emergency medical services or their own transport (34 in the first wave and 30 in the second wave). Data on patients with stroke during the first pandemic wave have been reported previously [10].

based on type of stroke; therefore, ischaemic and hemorrhagic strokes were included. Thirdly, the outcomes of patients with COVID-19 were compared with concurrent patients with acute stroke but without COVID-19 who were treated using the same management protocols.

The study's main limitations were as follows. (i) There was a lack of information regarding stroke admissions to hospitals without SUs or those with SUs but without endovascular treatment facilities in the Madrid Health Region. This limitation reduces the external validity of our results, given that it is possible that some patients arrived at those hospitals on their own and without activating the stroke code. Therefore, the characteristics and impact on stroke care of the first and second COVID-19 waves might be different in hospitals without those facilities. (ii) The time periods considered for the first and second waves differed (2 vs. 4 months) due to the different temporal profile of the two waves in our region. The strict lockdown might have contributed to a fast reduction in the total duration of the first wave, whilst no lockdown was imposed during the second wave. (iii) The underdiagnosis of COVID-19 during the first wave due to the shortage of PCR tests, which were mainly restricted to patients with COVID-19-suggestive respiratory symptoms, could explain the paradox of the lower COVID-19 incidence at the first wave compared with the second wave, in which PCR was performed for any patient arriving at the hospitals. A higher seroprevalence was detected during the first compared with the second wave in Madrid (12.6% vs. 7.7%) [34], and a national seroprevalence study highlighted the undertesting of COVID-19 during the first wave of COVID-19 in Spain [35]. (iv) It was not possible to evaluate the potential impact of

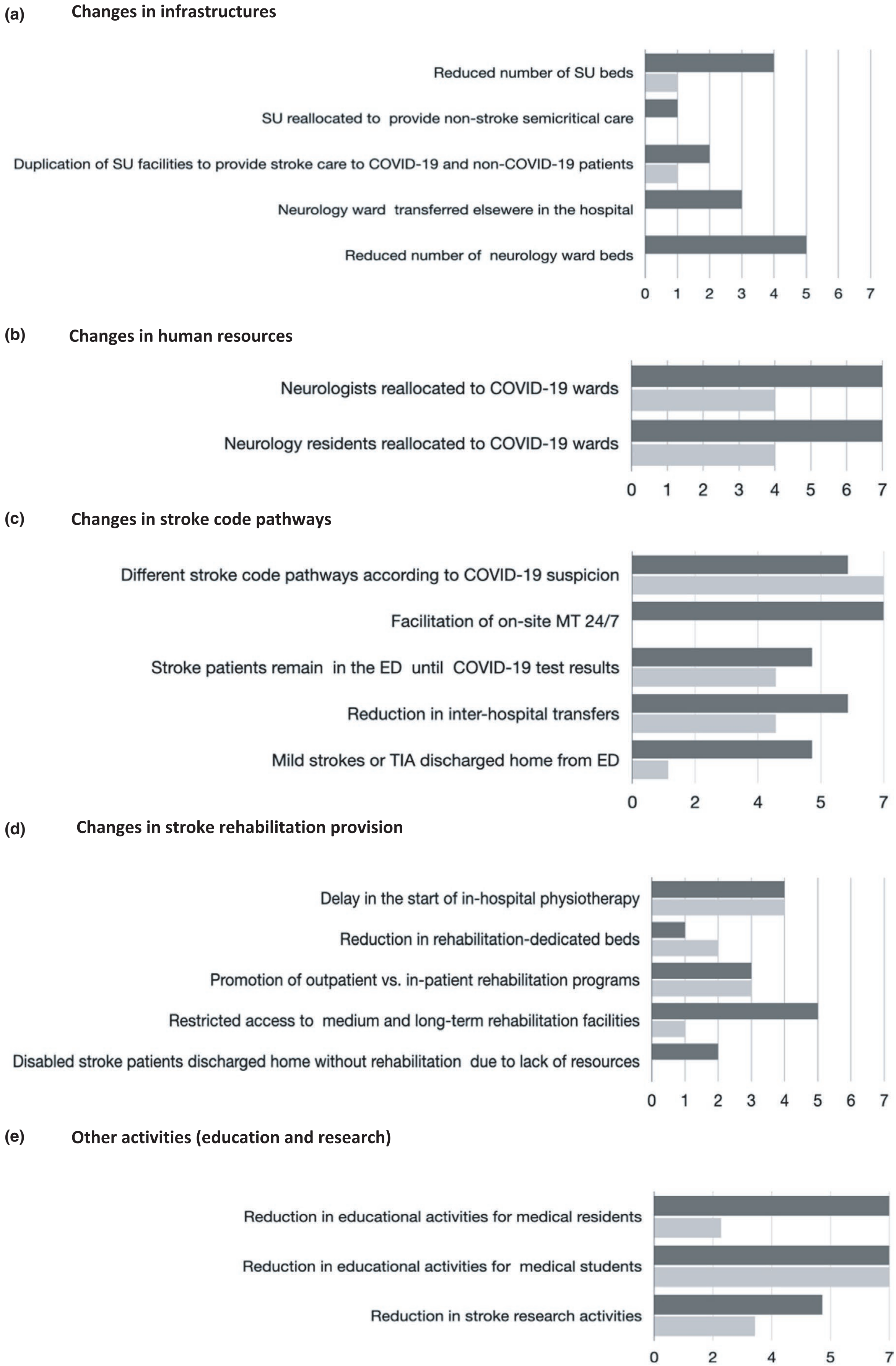

FIGURE 4 Organizational changes in stroke care provision. (a) Changes in infrastructures. (b) Changes in human resources. (c) Changes in stroke code pathways. (d) Changes in stroke rehabilitation provision. (e) Other activities (education and research)

vaccines against COVID-19 on the stroke incidence or stroke severity since they were not yet available in Spain during either of the two COVID-19 waves analyzed.

In conclusion, during the second COVID-19 wave, fewer patients with stroke were diagnosed with COVID-19, and those that were showed milder stroke and COVID-19 severity. Despite a reduction in in-hospital mortality of patients with COVID-19 and stroke in the second wave, COVID-19 remained significantly associated with poorer stroke outcomes. Learning from experience has helped us maintain a strong stroke care organization, avoiding a reduction in SU beds and reduced reallocation of the SU infrastructure and personnel to COVID-19-dedicated wards.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Blanca Fuentes: Conceptualization (lead); formal analysis (lead); investigation (equal); methodology (lead); writing—original draft (lead); writing—review and editing (equal). María Alonso de Leciñana: Conceptualization (lead); formal analysis (lead); investigation (equal); methodology (lead); writing—original draft (lead); writing—review and editing (equal). Ricardo Rigual: Investigation (equal); writing—review and editing (equal). Sebastián García-Madrona: Investigation (equal); writing—review and editing. Fernando Díaz-Otero: Investigation (equal); writing—review and editing (equal). Clara Aguirre: Investigation (equal); writing—review and editing (equal). Patricia Calleja: Investigation (equal); writing—review and editing (equal). José A. Egido: Investigation (equal); writing—review and editing (equal). Joaquín Carneado-Ruiz: Investigation (equal); writing—review and editing (equal). Gerardo Ruiz-Ares: Investigation (equal); writing—review and editing (equal). Jorge Rodríguez-Pardo: Investigation (equal); writing—review and editing (equal). Angela Rodríguez-López: Investigation (equal); writing—review and editing (equal). Álvaro Ximénez-Carrillo: Investigation (equal); writing—review and editing (equal). Alicia De Felipe: Investigation (equal); writing—review and editing (equal). Fernando Ostos-Moliz: Investigation (equal); writing—review and editing (equal). Guillermo González-Ortega: Investigation (equal); writing—review and editing. Patricia Simal: Investigation (equal); writing—review and editing. Carlos I Gómez-Escalonilla: Investigation (equal); writing—review and editing. Pablo Gomez-Porro: Investigation (equal); writing—review and editing (equal). Borja Cabal-Paz: Investigation (equal); writing—review and editing. Gemma Reig: Investigation (equal); writing—review and editing. Antonio Gil-Nuñez: Investigation (equal); writing—review and editing. Jaime Masjuan: Investigation (equal); writing—review and editing. Exuperio Diez-Tejedor: Conceptualization (lead); methodology (lead); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

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

Supplementary Material

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