The impact of COVID-19 pandemic in stroke code activation and time from symptom onset to hospital arrival in a Portuguese comprehensive stroke centre

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Introduction. Coronavirus disease 2019 (COVID-19) impacted emergency services worldwide.

Aim. We aimed to evaluate COVID-19 effect on the number of stroke code activations and timings during the first two months of the pandemic.

Material and methods. We reviewed the stroke code database of a single comprehensive stroke centre in Portugal for the number of activations through 2019-2020. We compared the pathway timings between March and April 2020 (COVID-19 period) and the homologous months of the previous four years (pre-COVID-19 period), whilst using February as a control.

Results. Monthly stroke code activation rates decreased up to 34.2% during COVID-19 pandemic. Compared to the pre-COVID-19 period, we observed an increase in the time from symptom onset to emergency call, with a significant number of patients waiting more than four hours (March 20.8% vs. 6.8%, $p = 0.034$; April 23.8% vs. 6%, $p = 0.01$); as well as an increase in the time from symptom onset to hospital arrival (March: median 136 minutes [IQR 106-410] vs. 100 [IQR 64-175], $p = 0.001$; April: median 188 [IQR 96-394] vs. 98 [IQR 66-168], $p = 0.007$). No difference between both periods was found concerning in-hospital times, patient characteristics, stroke/mimic diagnosis, stroke severity, and mortality.

Conclusion. COVID-19 related factors probably reduced healthcare services utilization, and delayed emergency calls and hospital arrival after stroke onset. These highlight the importance of health education to improve the effectiveness of medical assistance. The preservation of in-hospital times validates the feasibility of the protected stroke code protocol.

Key words. COVID-19. Emergency service. Portugal. Stroke. Stroke code activation. Stroke code timing.

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Neurological manifestations are common in COVID-19 and patients from all ages can develop acute ischemic stroke, intracerebral haemorrhage, and cerebral venous thrombosis as part of the disease spectrum [1]. Since the first reported cases in December 2019, it became an ongoing pandemic, officially declared by the World Health Organisation on March 11, 2020, and has enforced a nearly worldwide lockdown [2]. In Portugal, the first cases were confirmed on March 2, 2020. The number of confirmed cases rose, and the state of emergency was declared on March 18, with 642 confirmed cases at that time [3].

Stroke is the leading cause of mortality in Portugal, having been responsible for 15,820 deaths in 2017 [4]. Located in a district with a reference population of 779,399 inhabitants [5], our hospital is the only comprehensive stroke centre and the main hospital treating COVID-19 patients in this area, including those requiring intensive care treatment.

While concern grew about the risk of stroke in COVID-19 patients, the number of stroke patients admitted worldwide has decreased. Fear of contagion may have kept stroke patients with milder symptoms at home [6]. Moreover, the necessary adoption within hospitals of a protected stroke code pathway [7], as well as other safety measures to limit COVID-19 cross-contamination, may have a negative impact in the time-dependent nature of acute stroke care.

Aim

We aimed to evaluate the impact of COVID-19 pandemic on the number of stroke code activations and

on the performance of the acute stroke pathways during the first months of the outbreak, compared to the homologous period of the previous years.

Material and methods

This is a retrospective, observational, analytic, single-centre study. In our database of stroke code patients, established in 2011, every patient entering this clinical pathway is recorded prospectively. We collect data on gender, age, stroke code activation source, stroke or stroke mimic diagnosis, modalities of acute stroke treatment, and duration of pre and in-hospital phases of the stroke code pathway.

First, we analysed the weekly number of stroke code activations from January 2019 to April 2020. Since the first confirmed case of SARS-CoV-2 infection in our country occurred on March 2, 2020, the length of time from that day onwards, up to the end of April, was established as the COVID-19 period. We then modelled the stroke code calls using linear regression with the week of the year as the independent variable and compared the gradient of linear regression (B parameter) with estimation of goodness-of-fit by the coefficient of determination (R^2) of the model, before and during the COVID-19 period.

We collected the number of COVID-19 cases occurring in the whole country and in the municipalities of the reference population from the Ministry of Health official webpage [3]. We calculated the 14-day cumulative incidence rate per 100,000 inhabitants for each week in the COVID period for Portugal and for our hospital reference population and compared its evolution with the 14-day rate of stroke code activations and COVID-19 hospital admissions.

Pre-hospital stroke code activation begins when patients call the emergency services line (112). Time from symptom onset to 112 call is publicly and readily available on the National Institute of Emergency Service webpage [8], and we compared historical information to COVID-19 period for our district.

To investigate the impact of the pandemic, in terms of potential delays, in our performance during acute stroke management, we studied a) the time from symptom onset/last time seen well-to-hospital arrival, b) door-to-CT time, and c) CT-to-needle or CT-to-groin time, from February to April 2020, and compared the same temporal indicators with the corresponding ones from the homologous months from 2016 to 2019.

Using the software SPSS 25.0 (IBM Corp. SPSS Statistics for Windows, Version 25.0. Armonk, NY. Released 2017) we present patient descriptives and used non-parametric methods to compare differences between groups (Chi square test) and to compare differences in median relevant times between the aforementioned stroke pathway timings (Independent samples Kruskal-Wallis test), with alpha equal to 0.05.

This study was approved by the local Ethics Committee. Waiver of informed consent was obtained in accordance with national research legislation.

Results

A total of 996 stroke code activations were registered between January 2019 and April 2020. Up until the beginning of March 2020, we were experiencing a modest upwards trend in stroke code activations (B = 0.076; 95% CI: 0.012-0.139; R^2 = 0.089). During March and April 2020 this tendency was markedly inversed (B = −1.133, 95% CI: −2.742-0.476, R^2 = 0.284), as can be seen on figure 1. This amounts to a monthly reduction in stroke code activations of around 34.2%.

Concerning the 3-month period of February, March, and April, from 2016 to 2020, we received 730 stroke code patients, 312 (42.7%) of them from pre-hospital notifications. The median age was 73 years old (IQR 61-82), and 369 (50.5%) were male. After evaluation, 472 (64.7%) were diagnosed as ischemic stroke or transient ischemic attack, 69 (9.5%) as haemorrhagic stroke, and 189 (25.9%) were stroke mimics. Revascularization treatments, either intravenous thrombolysis and/or endovascular thrombectomy, were carried out in 270 patients (57.2% of ischemic stroke patients). Compared to the homologous period of the previous years, there was no decline on the rates of thrombolysis (23.5% vs. 30.2%, p = 0.241) or thrombectomy (33.3% vs. 29.5%, p = 0.517) during the COVID-19 period. There were also no significant differences concerning age, sex, marital and work statuses, proportion of pre-notifications, stroke or stroke mimic diagnosis, stroke severity measured by the National Institutes of Health Stroke Severity (NIHSS) scale, and in-hospital mortality, between pre-COVID-19 and COVID-19 periods. Detailed characteristics by month can be found on the table.

Regarding the time elapsed from symptom onset to 112 call we can appreciate on figure 2b and 2c that during March and April 2020 there was a shift

towards delaying the emergency call after symptom onset. The number of patients waiting more than four hours increased in both March (20.8% vs. 6.8%; p = 0.034) and April (23.8% vs. 6%; p = 0.01) 2020 when compared to the pre-COVID-19 period.

Concerning the time from symptom onset/last time known well-to-hospital arrival, during the months of March and April 2020, it was markedly increased when comparing to the same months from 2016 to 2019 –March: median 136 minutes (IQR 106-410) in 2020 vs. 100 (IQR 64-175) in 2016-2019, p = 0.001; April: median 188 minutes (IQR 96-394) in 2020 vs. 98 (IQR 66-168) in 2016-2019, p = 0.007–.

We observed no major differences regarding in-hospital stroke pathway times, namely door-to-CT and door-to-needle/groin times, as shown on figure 3, as well as the compound symptom onset/last time know well-to-needle/groin time (not shown).

When observing the evolution of COVID-19 infection rate using the 14-day cumulative incidence, it is noteworthy that the marked decrease in stroke code activations occurred in the first two weeks of Abril, one week after the national COVID-19 notification peak and 2 weeks after the peak in the surrounding municipalities, as illustrated in figure 4.

Figure 1. Weekly counts of stroke code activations from January 2019 to April 2020, before and during the COVID-19 pandemic. The red continuous line shows the regression line calculated from the weekly number of stroke code activations, with 95%CI (95% confidence intervals) depicted in black. The red dotted line shows the estimated progression if COVID-19 pandemic had not happened.

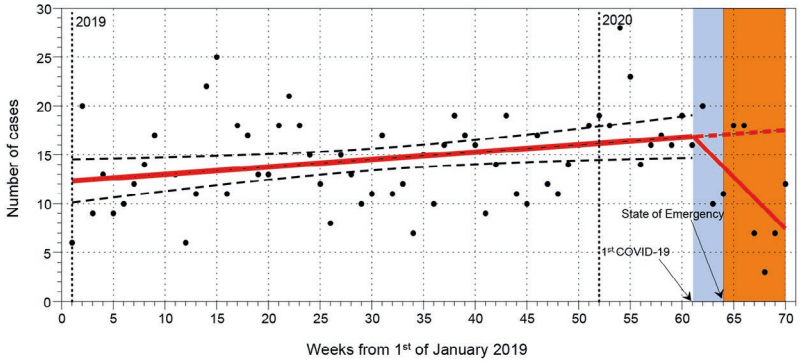
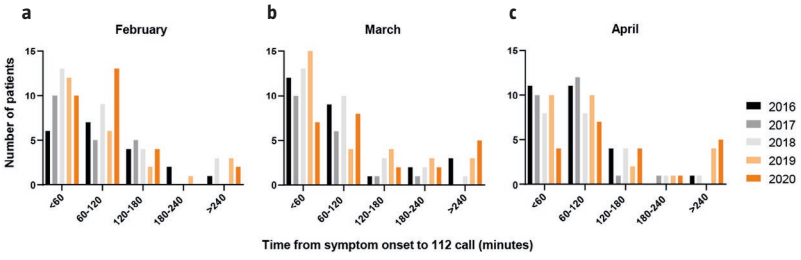


Figure 2. Number of patients calling the emergency line 112 (y axis) distributed by time interval, in minutes, from symptom onset to call (x axis), in the months of February (a), March (b), and April (c), by year.



Discussion

This study shows a major decrease in stroke code activations and a delay in seeking emergent medical care following stroke symptom onset during the COVID-19 period, in comparison to the pre-pandemic years. Nevertheless, when comparing the two periods, there were no major differences in terms of patient and stroke characteristics, the use of reperfusion therapies did not decline, and in-hospital stroke pathway times were kept.

Recent literature suggests that both emergency room (ER) visits and admissions for non-COVID-19 conditions have decreased considerably worldwide, including other cardiovascular diseases such as acute myocardial infarction [9]. Portugal was no exception and a nationwide study revealed a 48% reduction in the number of ER visits in the hospitals of the National Health Service during March 2020 [10]. Accordingly, our hospital saw a reduction of 33% in the first two months of the pandemic [11]. Another Portuguese hospital reported a 57.1% drop in admissions for ST-elevation myocardial infarction in March 2020 [12].

Regarding stroke code activations we observed a 34.2% reduction, therefore inverting the slow but steady increase that we had been registering thus far. These results are consistent with data from other hospitals in regions of Spain (Barcelona, 18% [13]; North-West Spain, 28.3% [14]), France (Alsace, 39.6%) [15], and China (pooled analysis of stroke centres from 280 hospitals, around 40%) [16]. A reduction of the same magnitude was reported in imaging demand for evaluation of acute stroke treatment candidates in the United States of America (39%) [17], and in the number of stroke diagnoses in Spain (Aragon, 56%) [18], which corroborate this finding. Furthermore, data from national and regional stroke networks also described a reduction in minor stroke and transient ischemic attack patients of around 30% in Italy and 45% in Germany, and of acute stroke treatments of about 50% in Italy, demonstrating that the reduction in stroke admissions covered the whole spectrum of stroke severities [19].

Table. Comparison of characteristics of stroke code activation patients between February, March, and April 2020 and the homologous periods of the previous four years.

	February 2016-2019 (*n* = 153)	February de 2020 (*n* = 74)	*p* value	March 2016-2019 (*n* = 191)	March 2020 (*n* = 65)	*p* value	April 2016-2019 (*n* = 206)	April 2020 (*n* = 41)	*p* value
Baseline characteristics									
Age, in years (median, IQR)	72 (61-81)	68.5 (59-82)	0.573	72 (57-81)	72 (65.5-82)	0.308	74 (63-82)	79 (61-85)	0.332
Female (*n*, %)	78 (51)	40 (54.1)	0.664	84 (44)	25 (38.5)	0.437	111 (53.9)	23 (56.1)	0.795
Married (*n*, %)	81 (60)	42 (62.7)	0.713	104 (64.2)	37 (69.8)	0.455	107 (62.6)	18 (51.4)	0.219
Employed (*n*, %)	27 (19.1)	18 (28.1)	0.15	39 (23.4)	11 (18.6)	0.454	37 (21.4)	3 (9.4)	0.115
Stroke code activation									
Pre-notification (*n*, %)	48 (31.4)	24 (32.4)	0.999	61 (31.9)	19 (29.2)	0.989	60 (29.1)	10 (24.4)	0.549
Ischemic stroke (*n*, %)	100 (65.4)	48 (64.9)	0.913	114 (59.7)	43 (66.2)	0.328	138 (67)	29 (70.7)	0.705
Haemorrhagic stroke (*n*, %)	12 (7.8)	7 (9.5)		21 (11)	9 (13.8)		16 (7.8)	4 (9.8)	
Stroke mimic (*n*, %)	41 (26.8)	19 (25.7)		56 (29.3)	13 (20)		52 (25.2)	8 (19.5)	
Ischemic stroke patients									
Baseline NIHSS (median, IQR)	10 (3-19)	10 (5-17)	0.592	9 (2.75-19.25)	12 (4.25-18)	0.691	10 (4-18)	9.5 (6-18)	0.717
Intravenous thrombolysis(*n*, %)	31 (31)	9 (18.8)	0.116	34 (29.8)	8 (18.6)	0.157	45 (32.6)	11 (37.9)	0.581
Endovascular treatment (*n*, %)	16 (16)	11 (22.9)	0.308	36 (31.6)	12 (27.9)	0.656	42 (30.4)	15 (51.7)	0.028
24-hour NIHSS (median, IQR)	5 (1-17)	7 (1-13)	0.895	6 (1.75-16)	9 (4.5-17.5)	0.176	6 (2-16)	8 (3-18)	0.558
Discharge NIHSS (median, IQR)	2 (0-10)	5 (1-11)	0.184	3 (0-9)	6 (1-13.5)	0.286	4 (1-10.5)	9 (1-20.25)	0.167
Length of stay, in days (median, IQR)	9 (3-15)	10 (2.25-16)	0.584	6.5 (1-13)	6 (2-10)	0.752	7 (1-14.25)	7 (1.5-10.5)	0.539
Mortality (*n*, %)	9 (9)	4 (8.3)	0.893	8 (7)	6 (14)	0.174	11 (8)	1 (3.4)	0.391

IQR: interquartile range; NIHSS: *National Institute of Health Stroke Scale.*

Several studies have questioned whether these findings represent a true decrease in stroke incidence. We do not believe this to be the case, as our patients were similar in their demographic and clinical characteristics, in the COVID-19 and pre-COVID-19 periods. Neither the fear of contagion which could prevent patients with milder symptoms from seeking medical assistance, nor the social isolation among the elderly which could cause symptom onset to remain inconspicuous to the family members [6] appear to explain our cohort, which has a similar baseline NIHSS and median age across periods. However, as we found out from our pre-hospital data, both patients and bystanders took longer to call the emergency services after stroke symptom onset. Some may have waited so long, that they no longer met the criteria for stroke code activation and are thus unaccounted for in our study. Another plausible explanation for such findings is that, in line with an excess in mortality during the COVID-19 pandemic, also reported in Portugal [20], and not likely explained just by the infection itself, some stroke patients may have died before seeking medical assistance and amount to these fatalities. Either way, we cannot fully exclude that stroke incidence did indeed reduce. Quaran-

tine measures forced people to behavioural changes, some of them leading to healthier lifestyles. For instance, reduced levels of pollution and decreased levels of physical and emotional stress could lower stroke risk [6].

In line with longer times from symptom onset to emergency call, we found a significantly longer time from symptom onset to hospital arrival. Although this could have been due to emergency ambulance transport capacity being exceeded with COVID-19 patients, this appears unlikely, since both the total number of ER admissions by all causes, and the average daily activation of emergency vehicles, decreased in March 2020 [11], and thus timely primary transport must have been available. For this analysis we used the month of February, which was prior to the COVID-19 period, as a control group. We noticed that the median time from symptom onset to hospital arrival in February 2020 was in line with the February times of the last three years, making it a typical month in stroke code activity and a good control. For March and April 2020, compared to the homologous months from 2016 to 2019, the median time from symptom onset to hospital arrival is consistently higher in all performed analysis, and may therefore represent a true consequence of COVID-19 pandemic on acute stroke care. As the most important decline in stroke code activation occurred one to two weeks after the peak of national and regional COVID-19 notification rates, it is possible that fear of infection might best explain the delay on seeking hospital care, therefore being responsible for missed opportunities of timely revascularization treatment.

Considering the in-hospital times, we did not find significant differences on door-to-CT, door-to-needle, or door-to-groin times between the COVID-19 period and the previous years. This observation agrees with the experience from other centres, namely the ones in Barcelona, Alsace, and New Jersey [13, 15, 21]. One could expect cautionary measures to negatively impact these times, as our hospital timely adopted a protected stroke code protocol [7], use of adequate personal protective equipment became mandatory to evaluate all stroke suspects, and strict safety and hygiene measures were enforced to limit cross-contamination, leading to prolonged waiting times for imaging and in-hospital transfers. However, acute care to neurologic emergencies, including stroke code activations, was delegated on experienced neurologists, well-trained on the protocols, and acute stroke treatments were primarily delivered in the ER, while, before the pandemic, patients not undergoing thrombectomy would be admitted to the stroke unit prior to receiving thrombolysis. Though these considerations can help explain how we managed to keep the same times from previous years, it is important to note that CT scan-to-treatment times had a higher standard deviation in the COVID-19 period (Fig. 3, graphics g-i). This implies that, in some situations, these times were in fact delayed but also that, due to our sample size, they were not found to be significant. Still, we demonstrated that keeping time from symptom onset-to-treatment in line with pre-COVID-19 period is feasible, if one has an optimized protected stroke code pathway. We also note that none of the professionals involved in the stroke code pathway were infected during this period, ascertaining the safety of the protocol measures.

Figure 3. Evolution of relevant stroke code pathway times, in minutes (median, IQR), by month. Time from symptom onset/last time known well to hospital arrival (a, b and c), time from hospital arrival to CT scan (d, e and f) and time from CT scan to initiation of thrombolysis or thrombectomy (g, h, and i), for the months of February (a, d and g), March (b, e and h), and April (c, f and i). * $p < 0.05$, ** $p < 0.01$

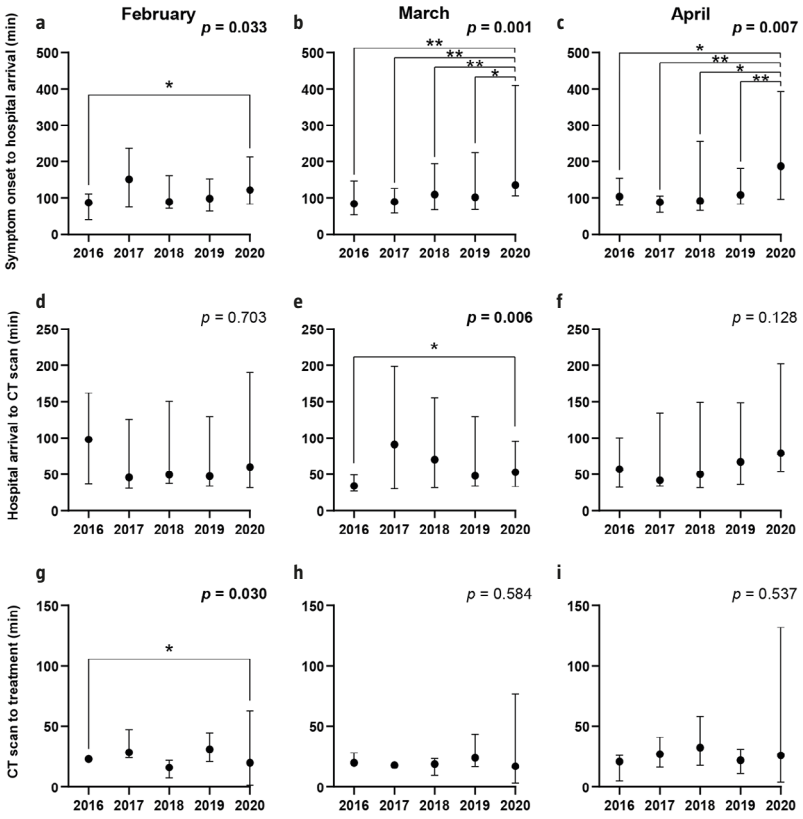
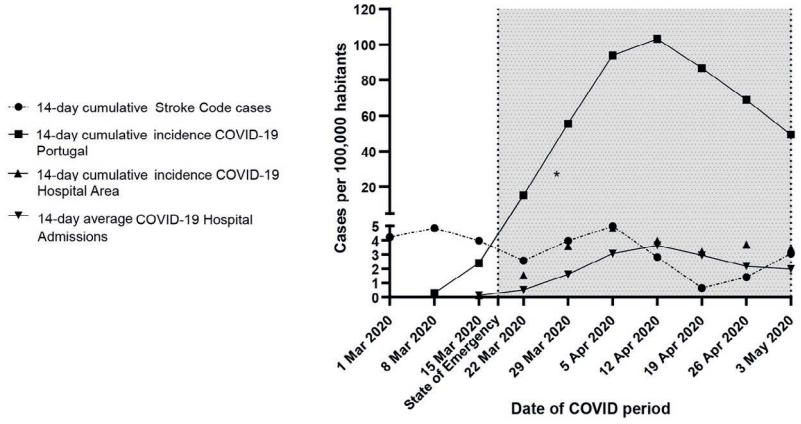


Figure 4. Evolution of the 14-day cumulative incidence of COVID-19 in Portugal, in the hospital reference municipalities, alongside the 14-day evolution of stroke code episodes and hospital admissions by COVID-19 in our centre.



* Data only published after 23 March 2020. Cases per 100,000 inhabitants

14-day cumulative Stroke Code Cases	4.2	4.8	3.9	2.5	3.9	5.0	2.8	0.6	1.4	3.1
14-day cumulative incidence COVID-19 Portugal		0.3	2.4	15.3	55.5	93.9	103.2	86.7	68.9	49.3
14-day cumulative incidence COVID-19 Hospital Area *					32.9	51.7	39.9	24.6	20.5	20.1
14-day average COVID-19 Hospital Admissions			0.1	1.5	3.6	4.8	3.9	3.2	3.8	3.7

This study is the first to report the influence of the COVID-19 pandemic in the stroke code pathways tiemes in the Portuguese setting, by comparing the outcomes in this period with the homologous months from the four years prior to COVID-19. Its strength lies on an experienced team and rigorous recording of all stroke code activations in the last 10 years. Our population and its healthcare seeking behaviour remained steady across the years and we do not expect the fluctuations observed to be attributable to chance. Albeit being the experience from a single centre, the measures adopted were in line with national and international recommendations for this period, and we believe them to be representative of comprehensive stroke centres with a similar population. However, a national-based study would help confirming and strengthening our findings.

The COVID-19 pandemic has brought a reduction in the number of stroke code activations and a delay in both the symptom onset to emergency call and to hospital arrival times. The latter is a well-known and long-standing fragility of the stroke code pathway [16] and is largely dependent on general population education.

In conclusion, this study hopes to emphasize the importance of public health education programmes to improve the effectiveness of medical assistance and thereby help to optimize those timings. Though in-hospital pathway times appear not to have been affected in our hospital, it may not be sustainable in the long run if the COVID-19 infection rates rise. In fact, we believe that the ongoing effort to reinstate several social, economic and healthcare services should include campaigns to educate the public and reinforce patients' trust on emergency services. Furthermore, effort should be made not to neglect or unevenly assist patients with acute non-infectious diseases, regardless of the pandemic pressure on health services.

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El impacto de la pandemia de COVID-19 en la activación del Código Ictus y en el tiempo desde el inicio de los síntomas hasta la llegada al hospital en un centro de ictus portugués

Introducción. La enfermedad por coronavirus 2019 (COVID-19) provocó un considerable impacto mundial en los servicios de emergencia.

Objetivo. Se pretende evaluar el efecto de la COVID-19 sobre el número y los tiempos de activaciones del Código Ictus en el comienzo de la pandemia.

Material y métodos. Se revisó la base de datos del Código Ictus de un centro de ictus de Portugal entre 2016 y 2020. Se compararon los tiempos de activación entre marzo y abril de 2020 (período COVID-19) y los meses homólogos de los cuatro años anteriores, mientras que se utilizó febrero como control.

Resultados. Las tasas mensuales de activación disminuyeron hasta el 34,2% durante la pandemia. En comparación con el período previo, se observó un aumento del tiempo desde los síntomas hasta la llamada de emergencia, con un aumento de pacientes que esperaron más de cuatro horas (marzo: 20,8 frente a 6,8%, $p = 0,034$; abril: 23,8 frente a 6%, $p = 0,01$) y del tiempo desde los síntomas hasta la llegada al hospital –marzo: mediana de 136 minutos (rango intercuartílico [RIC]: 106-410) frente a 100 (RIC: 64-175), $p = 0,001$; abril: mediana de 188 (RIC: 96-394) frente a 98 (RIC: 66-168), $p = 0,007$–. No hubo diferencias en los tiempos de internamiento, las características de los pacientes, el diagnóstico de ictus/*stroke mimics*, la gravedad del ictus o la mortalidad.

Conclusión. Los factores relacionados con la COVID-19 redujeron la utilización de los servicios sanitarios y retrasaron las llamadas de emergencia y el tiempo de llegada al hospital. Esto demuestra la importancia de la educación sanitaria para mejorar la eficacia de la asistencia médica.

Palabras clave. Activación del Código Ictus. COVID-19. Ictus. Portugal. Servicio de urgencias. Tiempo del Código Ictus.