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Time of Stroke Onset in Coronavirus Disease 2019 Patients Around the Globe: A Systematic Review and Analysis

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Introduction: Coronavirus disease 2019 has been associated with stroke, particular characteristics of these patients are not fully understood. The adequate management of these patients depends on the comprehension of factors such as temporality, clinical presentation and etiology. We hypothesize there is an important temporal relationship between COVID-19 severity and stroke onset. *Methods:* a systematic review of the available literature was conducted using Pubmed and Scopus, studies reporting patients with Coronavirus disease 19 and stroke were included. Clinical, sociodemographic and laboratory characteristics of patients were extracted and analyzed. *Results:* Forty-seven studies and 176 patients were included, with a mean age of 63.1 years (SD= 16 *n*=122), most of them were males (63.2% *n*=171). The most frequent etiology was cryptogenic 40.9% *n*=66), and a mean National Institute of Health Stroke Scale of 14.4 points was found (SD= 8.6 *n*=73). Large vessel occlusion was reported in 65.9% patients (*n*=91) and these patients were younger with greater stroke severity. D-dimer, C-reactive protein, fibrinogen, ferritin and lactate dehydrogenase were elevated in most patients with reported findings. Most patients had severe Coronavirus disease 2019. The mean time from onset of respiratory symptoms to stroke was 9 days (SD=9.9), the shortest time was noted in those with mild and moderate disease. *Conclusions:* There is a trend between the severity of Coronavirus disease 2019 and time to stroke onset. Also, age and stroke severity were found to be related to the development of large vessel occlusion. Inflammation and hypercoagulability markers are elevated in this disease, we propose to not discard hypercoagulability secondary to severe acute respiratory syndrome-coronavirus-2 as an underlying cause of stroke in these patients.
Key Words: Stroke—Coronavirus disease 2019—Temporality—Severity
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Introduction

Coronavirus disease 2019 (COVID-19) rapidly became a pandemic. As of August 29th, 2020, over 24 million cases have been confirmed worldwide.[1] Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection is associated with diverse neurological manifestations involving both the central and peripheral nervous system.[2,3] In fact, reports of ischemic stroke in patients with COVID-19 have increasingly been published, suggesting an association between these conditions. It has been proposed that SARS-CoV-2 infection induces a severe inflammatory response and hypercoagulable state, making patients susceptible to thrombotic complications, especially in those who are critically ill.[4] Furthermore, elevated D-dimer levels have been associated with poor prognosis.[4] Mechanisms in which the virus directly infects the endothelial vascular cells causing direct damage to the vasculature have also been proposed leading to a

potential increased risk of developing stroke.[5] The importance of identifying those patients at risk for developing cerebrovascular manifestations that could end up in disability and a worse overall prognosis, has led to the study of stroke characteristics in association with COVID-19. In addition, the temporal relationship between the infection and the development of neurologic manifestations has recovered interest. There are reported cases, where respiratory disease has occurred a few days prior to the onset of neurological symptoms.[6] On the other hand, cases of asymptomatic COVID-19 patients debuting with stroke have been reported,[7] rising concerns among physicians regarding adequate triage and classification of stroke patients. This raises the need for further investigations on temporality and specifically ischemic stroke events. A detailed analysis of the presentation, patient characteristics, clinical course and outcomes of those presenting with stroke associated with COVID-19 is critical in the context of this pandemic, as we believe these are different from the no-COVID-19 population. Identifying specific factors of these patients will contribute to the timely diagnosis and appropriate treatment, ultimately leading to improving the prognosis and adequate prevention. We hypothesize there is an important temporal relationship between COVID-19 severity and stroke onset. The secondary objectives of this systematic review include to determine if characteristics such as presentation of the stroke, younger age, involvement of large vessel occlusion and pattern of paraclinical markers could be distinct from the no-COVID-19 population.

Methods

Literature review and study selection

This systematic review follows PRISMA guidelines and recommendations. From June 17 to July 13th, a systematic search in two databases (PubMed and Scopus) was performed using MeSH terms: "Stroke AND (COVID 19 OR SARS-COV2)", additionally studies from different sources of gray literature were reviewed, no language or publication date limit was set. The review was registered on the International Prospective Register of Systematic reviews (PROSPERO) with the registration number CRD42020198432. Duplicates were removed and publications were revised by four researchers (M.O, M.Z, N.V, L.E). The inclusion criteria were as follows: observational studies including cohort studies, case-control studies, case report and case series, 18 years of age or older, diagnosis of ischemic stroke by imaging, diagnosis of COVID-19, and published or in press publications. The exclusion criteria were: studies with insufficient data on patient's demographic and clinical data, studies focused on hemorrhagic lesions and cerebral venous sinus thrombosis, no English or Spanish translation. Conflicts between the reviewers were solved by the senior author (H.B). Rayyan QCRI web application was used for the study selection.

Data extraction

The following data was extracted and tabulated:

-Sociodemographic and clinical variables: age, sex, comorbidities, country, NIHSS (National Institutes of Health Stroke Scale), time of stroke onset from initial COVID 19 symptoms, evidence of large vessel occlusion (LVO), presence of COVID 19 symptoms and the severity of the disease including mortality outcome, stroke imaging features such as vascular territories, stroke etiology based on TOAST criteria, and treatment for stroke.

-Laboratory variables: c-reactive protein (CRP), fibrinogen, lactate dehydrogenase (LDH), ferritin, and D-dimer.

Quality assessment and risk of bias

We critically appraised the quality and susceptibility to bias using the methodological quality assessment for case series and case reports, consisting of four domains, as well as the Newcastle-Ottawa Scale for the cohort studies.[8] For Fig. 2 elaboration RevMan 5 was used.

Data analysis

Measures of central tendency and dispersion used to describe continuous data were mean, standard deviation and range. For categorical data, frequencies and percentages were used. Individual case data was separately pooled with patient demographics, stroke characteristics, COVID-19 disease severity, treatment, inflammatory markers, hypercoagulability markers and outcome. The values of the inflammatory and hypercoagulability markers were categorized as low-normal or high according to the reference range reported on literature. Mann Whitney U test and Kruskall−Wallis one way analysis of variance were used to find differences of dependent continuous variables when grouped by independent categorical variables with 2 groups or more than 2 groups, respectively. Odds Ratios with two-sided Fisher's exact tests were calculated to evaluate the relationship between categorical variables. All data analysis was conducted using STATA 16.1.

Results

We obtained 561 publications from the search. After the removal of duplicates and applying inclusion and exclusion criteria, 47 publications were eligible and 176 patients were included in the final analysis (Fig. 1). Risk of bias and quality assessment were made as shown in Fig. 2. Patients from 13 countries were included, most of them were from the United States (95 patients, 54.3%), followed by China (20 patients, 11.4%) (Fig. 3). The mean age was 63.1 years (SD = 16, range 29−91) and most patients were males (63.2%, 108/171). Regarding comorbidities (n=151), 56.3% had hypertension, 43.1% diabetes mellitus and 27.2% dyslipidemia. Only 10.2% had a history of previous stroke (n=147), and 27.3% had a history of cardiovascular
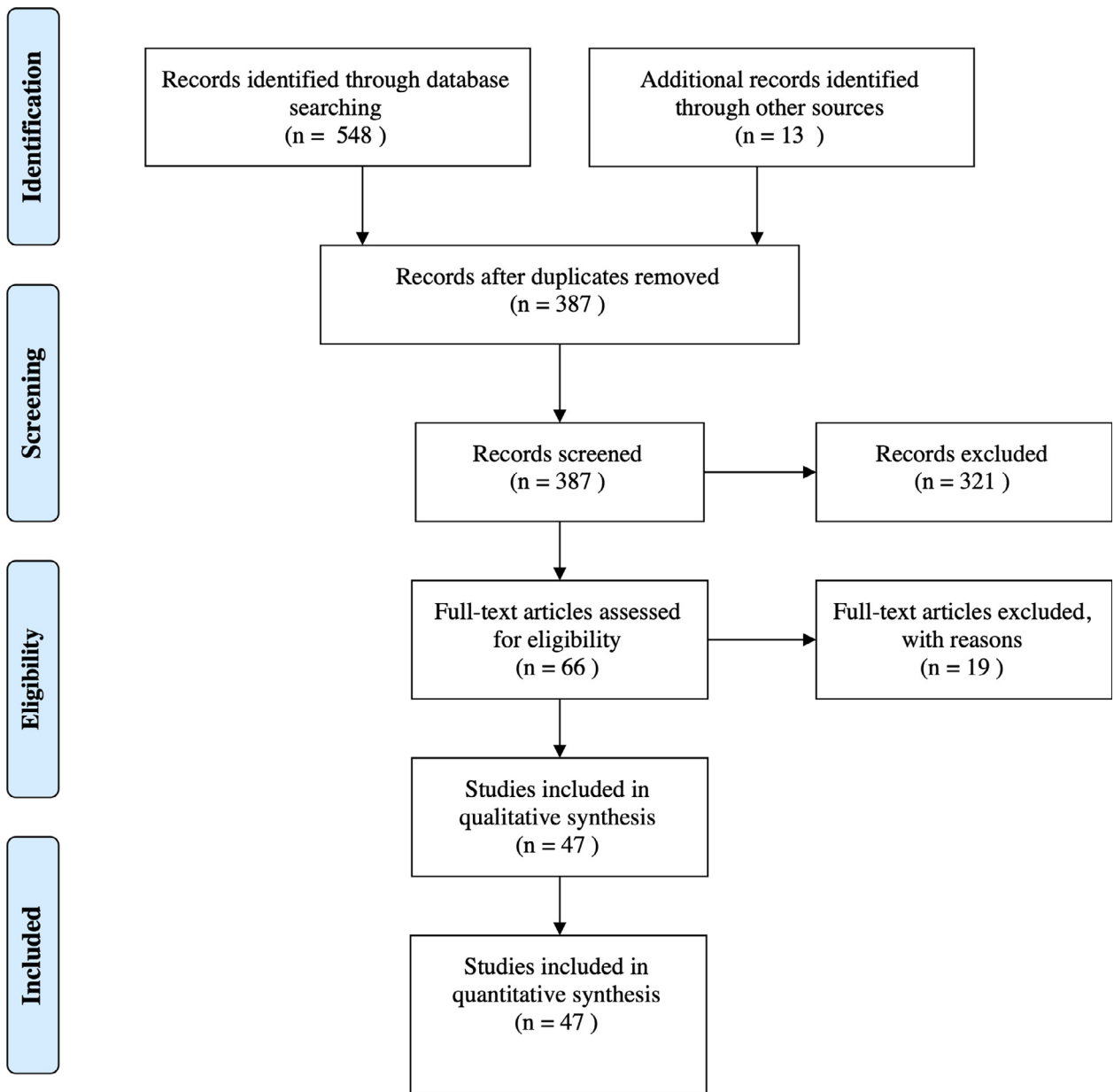
Fig. 1. *PRISMA flowchart of the selection of the studies for this systematic review.*
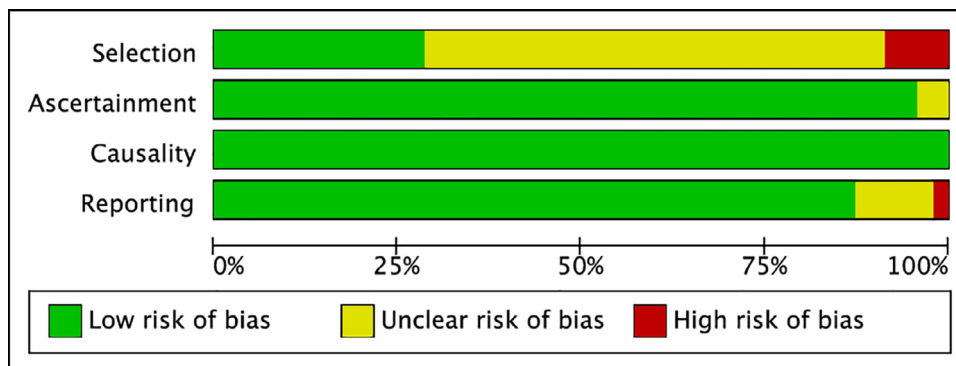

Fig. 2. *Risk of bias graph. Caption: Risk of bias assessment using methodological quality assessment for case series and case reports. Excluding the cohort by Yaghi et al. For individual assessment and cohort evaluation see appendix.*
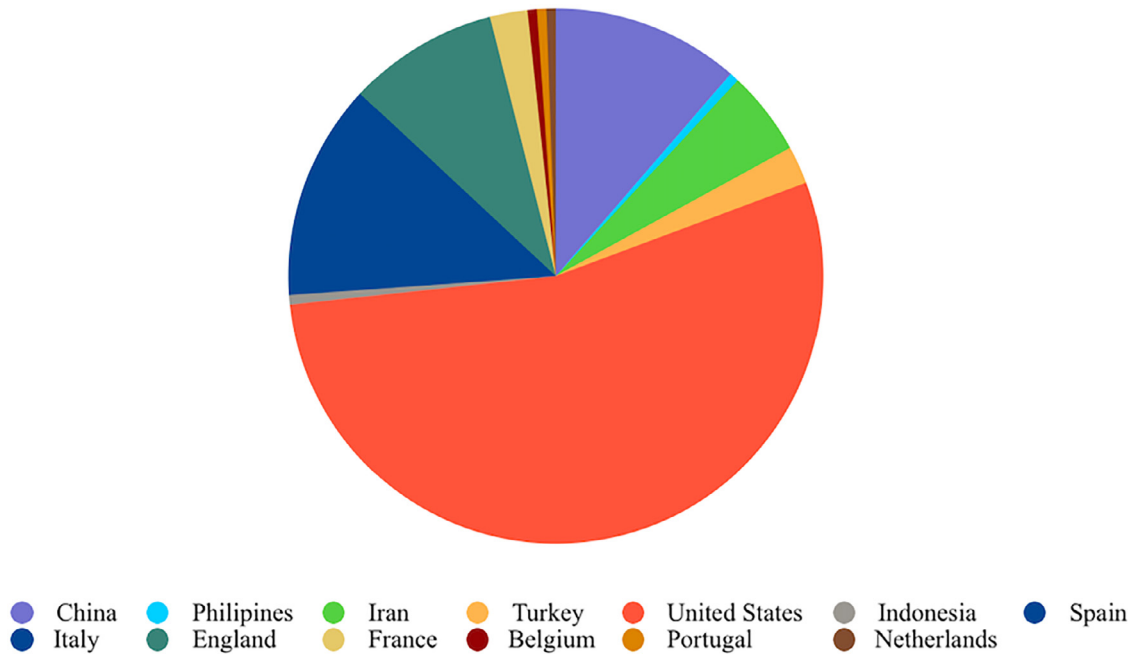
Fig. 3. *Distribution of cases by country.*

disease (*n*=150) (Table 1). Most patients had one vascular territory involved (66.4%, *n*=122) and LVO was documented in 60 patients (65.9%, *n*=91) (Table 2). The National Institutes of Health Stroke Score (NIHSS) was reported in 73 patients and the mean was 14.4 points (SD = 8.6, range 0−36). The mean NIHSS of those presenting with LVO was 17.9 points and 8.4 in those without LVO, this difference was statistically significant (*p*=0.0006, *n*=36). Furthermore, the mean age in patients who presented with LVO was 62.1 years and 69.2 for those who did not, with a statistically significant difference (*p*=0.04). The mean time to development of stroke did not differ among those with LVO and non-LVO ischemic stroke (7 vs 7.4 days, *p* = 0.83, *n* = 68) (Table 3).

Reperfusion therapy was administered to 43 patients and 99 patients received medical management (Table 2). The most frequent etiology by the TOAST criteria was cryptogenic (40.9%) (Table 2). Fifty-one patients had

information on both medical management and etiology. Of these 76.9% (20/26) patients with cryptogenic stroke received anticoagulants, while 5 of them received antiplatelets.

Table 2. *Stroke characteristics.*

TOAST *n* (%)		
n= 66	Large artery atherosclerosis	7 (10.6)
	Cardioembolic	18 (27.3)
	Small vessel	3 (4.6)
	Other etiology	11 (16.7)
	Cryptogenic	27(40.9)
Large vessel occlusion *n* (%)		
n=91	Yes	60(65.9)
	No	31(34.1)
Reperfusion therapy *n* (%)		
n=152	Thrombolysis	14 (9.2)
	Endovascular treatment	11 (7.2)
	Thrombolysis + Endovascular treatment	18 (11.8)
	None	109(71.7)
Medical management *n* (%)		
n=115	Anticoagulation	51 (44.4)
	Antiplatelet	30 (26.1)
	Dual antiplatelet therapy	16 (13.9)
	Anticoagulation + antiplatelet	2 (1.7)
	None	16 (13.9)

TOAST Trial of ORG 10172 in Acute Stroke Treatment Criteria.

Table 1. *Sociodemographic characteristics and comorbidities.*

Age mean (SD, range)		
n=122		63.1 (16, 29−91)
Sex *n* (%)		
n= 171	Male	108 (63.2)
	Female	63 (36.8)
Comorbidities *n* (%)		
n= 151	Hypertension	85(56.3)
	Diabetes mellitus	65(43.1)
	Dyslipidemia	41(27.2)
n=150	Cardiac disease	41(27.3)
n=147	Previous stroke	15(10.2)

SD Standard deviation.

Table 3. *Characteristics of stroke in patients with large vessel occlusion.*

	Large vessel occlusion		
	Yes	No	*p*-value
Age mean (SD)	62.1 (15.1)	69.2 (12.4)	0.04
NIHSS mean (SD)	17.9 (8.2)	8.4 (8.1)	<0.001
Days to stroke mean (SD)	7 (6.7)	7.4 (7.3)	0.83

NIHSS National Institutes of Health Stroke Scale, SD standard deviation.

Regarding COVID-19, most patients were symptomatic (91.8%, *n*=170). Severity of the disease was reported in 74 patients most of whom were classified with severe disease (41.9%) (Table 4). Time from presentation of COVID-19 symptoms to the development of stroke was reported in 131 patients, the mean being 9 days (SD = 9.9, range 0−65). Sixty-seven patients had information on both: time from COVID-19 symptoms onset to stroke development and disease severity. In this subgroup, we found that the time since the onset of symptoms until stroke presentation

Table 4. *Clinical and laboratory characteristics of COVID-19.*

Severity *n*(%)		
n=74	Mild	13(17.6)
	Moderate	14 (18.9)
	Severe	31 (41.9)
	Critical	16 (21.6)
Days to stroke mean (SD)		
	Overall (*n*=131)	9 (9.9)
By disease severity		
n=67	Mild	5.1 (6)
	Moderate	4.6 (5.2)
	Severe	9 (7)
	Critical	23.2 (18.9)
		P<0.001
D-dimer *n* (%)		
n= 117	High	107 (91.5)
	Normal	10 (8.6)
C-reactive protein *n* (%)		
n=92	High	89(96.7)
	Normal	3 (3.3)
Fibrinogen *n* (%)		
n=52	High	39 (75)
	Normal or Low	13 (25)
Ferritin *n* (%)		
n=48	High	33(68.8)
	Normal or Low	15(31.3)
Lactate dehydrogenase *n* (%)		
n=49	High	44(89.8)
	Normal or low	5(10.2)

SD standard deviation.

was longest in those with critical disease and shortest in those with mild and moderate disease (Table 4). This difference in the timing of presentation of stroke in relation to the severity of COVID-19 was statistically significant (*p*=0.0006).

The included markers of inflammation and hypercoagulability, CRP (c-reactive protein), D-dimer, fibrinogen, ferritin and LDH (lactate dehydrogenase) were elevated in most patients with reported data on these (Table 3). Of the patients that presented with LVO, 67.3% of them had elevated D-dimer values (33/49, OR = 0.92, *p*=1), 56.4% elevated CRP (22/39, OR = 3.14, *p*=0.56) and 57.6% increased fibrinogen levels (19/33, OR = 1.18, *p* = 1). Of the 159 patients with information on mortality outcome, 34.6% died and 65.4% survived. These markers were elevated in symptomatic patients for the infection as well as in asymptomatic individuals. D-dimer was high in 97/106 and 9/10 patients, CRP in 80/82 and 8/9, fibrinogen in 37/46 and 2/6, ferritin in 29/42 and 4/6 and LDH in 39/44 and 5/5, respectively.

Discussion

Stroke has been found to be relevant among patients with COVID-19, with incidences ranging from 0.9% to 6% in some of the largest studied cohorts up to now.[9,10] In our pooled analysis we present 122 patients from 13 different countries. Previous coronavirus outbreaks, SARS-Cov and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) have been compared to COVID 19 proving that the number of cases and complications including deaths from COVID-19 exceed previous viruses. In fact, the literature attributes fewer neurological associations were made in past coronavirus epidemics.[11] In addition, studies have compared stroke patients with influenza as a control group vs COVID-19 stroke patients, demonstrating that the likelihood of stroke is higher in COVID-19 patients with an OR of 7.6.[12] Furthermore, COVID-19 was identified as an independent risk factor for stroke after adjusting by sex, age and vascular risk factors with an OR of 3.9 (95% CI:1.7−8.9).[13]

Although there are studies published suggesting an association of young age and stroke as a manifestation of COVID-19.[9,14] In the reviewed cases, we found a median age of 63.1, an age not far from what the current prevalence is among stroke itself.[15] Stroke risk factors were present in a significant proportion of patients, hypertension being the most common comorbidity followed by diabetes, as described in the literature for stroke in no COVID-19 patients.[16]

Since the pandemic began, there have been concerns regarding the development of LVO in patients with COVID-19, as patients with this presentation have high rates of morbidity and mortality.[17] In the population without COVID-19, LVO has been reported to account for around 24−38% of strokes and the age of these patients is

around 65–70 years.[18] Interestingly, we noted that the incidence of LVO was 65.9% (*n*=91) in this group of patients and those who presented with LVO were younger than those who did not (Table 3). Age is also an important finding presented by a recent Spanish study, where age was an independent predictive factor of poor prognosis with a cut off point of 63 years old.[19] This leads to the idea that an age cutoff needs to be established in order to predict which patients presenting with LVO are potentially developing a stroke as a consequence of COVID-19 disease, even in the absence of typical respiratory symptoms, in order to do an integral approach and give them specific appropriate treatment and establishing a protected stroke code.

The literature has described that neurologic manifestations occur in patients with severe COVID-19[2,20] and has explored a possibility of causality between both entities.[6,13] In the present analysis we observe a trend between the severity of the disease and time of ischemic stroke onset; in those who had severe or critical disease, stroke presented late (mean days 23.2 and 9 respectively), while in those with mild or moderate COVID-19 disease, stroke developed early (median days 5.1 and 4.6 days respectively); this difference was statistically significant (*p* = 0.0006). This suggests that stroke associated with the infection can either be a late complication or an initial manifestation of the disease. Of interest, we noted that the presence of LVO is not a factor that influences the mean time to the development of stroke (Table 3). Therefore, further studies are needed to determine particular factors that can potentially lead to this difference in the temporality of stroke.

The literature has reported associations of NIHSS scores and the presence and location of the vessel occlusion.[21] Although there are no scores with high sensitivity and specificity for LVO, the literature has proposed cortical symptoms to be a reliable indicator.[21] Although, in the presence of COVID-19 disease this might be even more challenging to predict, in our pooled analysis the mean NIHSS was statistically significantly higher in those presenting with LVO (Table 3). In fact, a higher NIHSS was found in patients with COVID-19 compared through a matching analysis with individuals without the infection.[22] These findings are in alignment with our results and can help physicians suspect a COVID-19 infection in severe stroke cases with LVO. Furthermore, another significant finding described by Ntaios et al. was a severe stroke disability in those patients with COVID-19.[22] In brief, this supports the need to identify those patients early to prevent fatal outcomes.

Studies in patients with SARS-CoV-2 have proclaimed an association of the infection with hyperinflammation including cytokine storm and hypercoagulability states.[23,24] In our analysis, the over activation of these two systems is evident, having most patients elevated concentrations of D-Dimer, fibrinogen, CRP, ferritin and LDH. It has also been demonstrated that an exaggerated inflammatory response has negative repercussions in the long-term recovery from stroke.[25,26] In fact, D-dimer and CRP have been reported as markers of poor prognosis in COVID-19.[23] However, it is necessary to determine if this exaggerated inflammatory response has a causal role in the development of stroke in this population. There is also a tendency between the incidence of LVO and these markers. For instance, patients with LVO were more likely to present higher values than those without LVO, however in this study, the difference was not statistically significant. This supports the idea that thrombotic events in patients with COVID-19 could be linked to the derangements occurring in these two systems.[27]

Description of the potential pathophysiological mechanisms that lead to development of stroke in this population have included the description of COVID-19-associated coagulopathy. The former is presumed to be induced by the acute systemic inflammatory response to the virus and its products, and is characterized by concomitant elevation of the inflammatory and blood coagulation markers previously described.[28] Furthermore, it is mediated by increased production of cytokines and chemokines such as IL-1, IL-6, IL-10, IFN gamma and macrophage inflammatory proteins 1-alpha and 1-beta.[24,28] In particular, this coagulopathy is concerning in those patients with additional predisposing factors that could result in development of stroke.[12] In this line of thoughts, the elevation of these markers is an epiphenomenon of a more profound metabolic derangement, meaning the coagulopathy is a necessary but not sufficient cause in the development of stroke. This is comparable with patients with cancer, in whom, despite all having the procoagulant state, only some finally develop a stroke. It has been described in autopsy cohorts that 15% of cancer patients have strokes, of whom not all are symptomatic. Also an occult malignancy is detected in up to 5.3% of patients diagnosed with cryptogenic stroke.[29]

In line with our results recent findings in other studies agree hypercoagulability could explain the increased number of patients with diagnosis of stroke of undetermined source.[19] According to Yaghi et al., anticoagulation is now included as an early intervention in their protected stroke protocol, considering the association of COVID-19 and hypercoagulability.[9] Also 77% of patients with cryptogenic stroke included in this systematic review received therapeutic anticoagulation as part of their medical management, suggesting that even though physicians are not classifying strokes as "other cause", acute hypercoagulability due to COVID-19 in these patients is a concern that must be addressed. Due to the pandemic, diagnostic assessments done to determine the etiology of stroke are being withheld. However, in the context of SARS-CoV-2 infection, along with the evidence of increased inflammatory response and elevated procoagulant markers, it is

rational to propose that the etiology of the stroke in these patients is hypercoagulability, rather than cryptogenic.

There is limited information on the literature regarding inflammatory response in infected asymptomatic individuals however, it is known that during the course of the COVID 19 infection the immune response is dynamic and can result in different outcomes.[30] Even though in our analysis a minority of patients did not have COVID-19 specific symptoms before the stroke, this population was also noted to have elevated inflammatory and hypercoagulability markers supporting the idea that these derangements present as consequence of COVID-19 and can be associated with the development of cerebrovascular events.

Limitations

This is a pooled analysis of patients reported in case series, case reports and small cohorts up to date, with a total of 176 patients. The information is scarce and there is a need for bigger cohort studies. One limitation is that data is reported with measures of central tendency rather than information per patient, which makes it difficult to analyze potential associations. This information must be interpreted cautiously as the number of consultations of patients with stroke have decreased, mostly due to fear of infection by SARS-CoV-2.[9, 31] Thus, sampling bias is a possibility in that we are only observing patients that consult. Besides, minor strokes and deficits accompanied by negligence can go unnoticed as people are more often alone due to social restrictions.[32] Finally, the difficulties particular to diagnosing stroke in a patient that requires ICU care is meaningful. Also, as noted in our risk of bias analysis, selection bias may be prevalent among the case series and case reports as authors usually try to show the most outstanding cases and may not be a reliable observation of this population as a whole.

Conclusions

Uniquely, we present a trend between COVID-19 severity and temporality of stroke, in which mild disease is associated with early stroke and severe disease with late onset. Age, stroke severity and inflammatory markers were related to the development of LVO. Although stroke is associated with SARS-CoV-2, there is scarce evidence to clearly establish causal relationships between both diseases. However, it has been studied and reported the implications that SARS-CoV-2 has on the immune system causing rapid and aggressive inflammatory responses. The pattern that is proposed in this review is to consider the possibility of hypercoagulability secondary to SARS-CoV-2 as an underlying cause of the development of stroke in these patients. We recognize that data sharing is fundamental to facilitate clinicians in decision making particularly during a pandemic time. Which is why we encourage further studies with appropriate controls in order to identify the exact features that could help

physicians have a high suspicion of COVID-19 in certain stroke patients.

Declaration of Competing Interest

None.

Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2020.105325.

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