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COVID-19 and stroke: from the cases to the causes

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Abstract: During COVID-19 pandemic, a wide variety of stroke typologies have been described in patients affected by SARS-CoV-2. Investigating the case reports of acute stroke in COVID-19 patients, published since the beginning of the pandemic, we tried to trace the pathogenic mechanisms of stroke during SARS-CoV-2 infection. We conducted a systematic review analyzing demographic data, cerebrovascular risk factors, NIHSS score, vascular territory involvement and laboratory findings of 168 patients described in 89 studies, from a pool of 1243 records. Based on our results, we have identified different stroke profiles: (1) cerebral large vessel disease (CLVD) profile with a low disability, simultaneous onset of COVID-19 and stroke symptoms, good outcome and low serum levels of D-dimer and CRP; (2) intracranial bleeding (IB) profile with high disability, poor outcome and low levels of serum markers of inflammation and coagulopathy; (3) CLVD profile with a short time-lapse between COVID-19 symptoms and stroke onset, high neurological disability and very high systemic inflammatory markers; (4) multiple thrombo-embolic disease (MTED) profile with older patients, many comorbidities, disabling stroke, poor outcome, evident alteration of coagulation tests and high serum levels of both D-dimer and CRP. We therefore summarized these different profiles in a spectrum similar to that of visible light, where the violet–blue band included IB and CSVD with low inflammation and prothrombotic activity, the green–yellow band

included CLVD with high inflammation and moderate prothrombotic activity and the orange–red band for MTED with moderate-high levels of inflammation and very high prothrombotic activity.

Keywords: COVID-19; D-dimer; intracranial bleeding; SARS-CoV-2; small vessel; stroke.

Introduction

In October 2019, an outbreak of pneumonia due to the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), rapidly spread firstly throughout China and then, in few months, all over the world (Li et al. 2020). From then on, coronavirus disease 2019 (COVID-19) pandemic and the resulting lockdown profoundly changed the lives of people everywhere, influenced behaviors and crushed the economic and the healthcare system. The new reorganization of the health network had to face new challenges over an unexpected and severe disease with a multi-organ involvement. Indeed, although COVID-19 mainly causes lung and respiratory tract infections, it often determines a systemic disease involving several organs and systems including central nervous system. Anosmia and ageusia as early indicators of SARS-CoV-2 infection (Lechien et al. 2020) and delirium experienced in COVID-19 hospitalized people (Kotfis et al. 2020) have been the early clues of selective neutropism. Later, the “neurological” list has been further extended to include Parkinsonism (Eldeeb et al. 2020), encephalomyelitis (Ye et al. 2020), Guillain-Barré syndrome (Zhao et al. 2020), memory loss (Cothran et al. 2020) but most of all brain hemorrhage and stroke (Tsivgoulis et al. 2020). Since the beginning of the COVID-19 pandemic, meta-analysis and epidemiological studies have evidenced an increased stroke incidence in patients with SARS-CoV-2 infection. Patients are generally younger and with few comorbidities, while clinical manifestations are more severe (Oxley et al. 2020; Tsivgoulis et al. 2020). On the other hand, case reports and case series published in the same period describe acute stroke patients with heterogeneous clinical, neuroradiological and laboratory features, suggesting different underlying pathogenic mechanisms (Alay et al. 2020; Al-Dalahmah et al. 2020; Alkhaibary et al. 2020; Al-muftay et al. 2020; Al-Olama et al. 2020; Al Saiegh et al. 2020; Ashraf et al. 2020; Avci

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et al. 2020; Avula et al. 2020; Ballvè-Martin et al. 2020; Basi et al. 2020; Bessa et al. 2020; Beyrouiti et al. 2020; Bhagat et al. 2020; Bigliardi et al. 2020; Bonardel et al. 2020; Brüggemann et al. 2020; Cerasti et al. 2020; Chibane et al. 2020; Co et al. 2020; De Lorenzo et al. 2020; De Sousa et al. 2020; Deliwala et al. 2020; Díaz-Pérez et al. 2020; Doo et al. 2020; Eschereye and Erdinc 2020; Fara et al. 2020; Flores et al. 2020; Ford et al. 2020; Fraiman et al. 2020; Frisullo et al. 2020; Garg et al. 2020; Gemcioglu et al. 2020; Gill et al. 2020; Goette et al. 2020; Gogia et al. 2020; Goldberg et al. 2020; Gonçalves et al. 2020; González-Pinto et al. 2020; Gunasekaran et al. 2020; Hanafi et al. 2020; Hosseini et al. 2020; Hossri et al. 2020; Kariyanna et al. 2020; Khan et al. 2020; Kohli et al. 2021; Kwon et al. 2020; Mahboob et al. 2020; Malentacchi et al. 2020; Mansour et al. 2020; Mohamed et al. 2020; Morassi et al. 2020; Muhammad et al. 2020; Najjar et al. 2020; Oxley et al. 2020; Panico et al. 2020; Papi et al. 2020; Patel et al. 2020a, b, c; Pavlov et al. 2020; Pisano et al. 2020; Priftis et al. 2020; Rajdev et al. 2020; Ranard et al. 2020; Reddy et al. 2020; Rudilosso et al. 2020; Saggese et al. 2020; Sangalli et al. 2020; Sattar et al. 2020; Sharifi-Razavi et al. 2020; Shoukry and Kite 2020; Singhal et al. 2020; Sparr and Bieri 2020; Trifan et al. 2020; Tunç et al. 2020; Umemura et al. 2021; Valderrama et al. 2020; Viguier et al. 2020; Vu et al. 2020; Wang et al. 2020a, b; Wijeratne et al. 2020; Yang et al. 2020; Zayet et al. 2020; Zhai et al. 2020; Zhang et al. 2020a, b, c; Zheng et al. 2020).

The aim of the present study was to select COVID patients from case reports and case series reported in literature, and to perform a systematic review on this cohort in order to identify specific risk factors for COVID-19-related stroke, looking for possible clues able to trace the pathogenetic mechanisms of stroke in COVID-19 patients.

Methods

Search strategy

We conducted a systematic review of articles in Medline/PubMed, data published between January 1st, 2020 and December 31st, 2020. We performed search strategies using keywords and Mesh terms of “stroke”, “cerebrovascular diseases”, “cerebral infarction”, “brain ischemia”, “stroke alert”, “intracranial bleeding”, “intracranial hemorrhage”, and “COVID-19” or “coronavirus disease 2019” or “SARS-CoV-2”. The initial search was performed by three independent researchers and the resulting discrepancies were solved by discussion. In addition, reference lists of eligible articles were screened for further relevant studies and systematic reviews scanned for appropriate references. Inclusion and exclusion criteria were then applied to the retrieved records. This protocol follows the recommendations established by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.

Inclusion and exclusion criteria

The inclusion criteria have been applied to the selected systematic review case series, case report, research letters, short reports, and original articles containing detailed data of individual patients. The data of interest were age, gender, and vascular territory involvement. The latter was classified as follows based on neuroimaging data: cerebral large vessel disease (CLVD), cerebral small vessel disease (CSVD), multiple thrombo-embolic disease (MTED) or intracranial bleeding (IB). CLVD was defined as an occlusion of internal carotid artery (ICA), first and second segments of the middle cerebral artery (MCA M1, M2), the first segments of anterior cerebral artery (ACA A1), vertebral artery, basilar artery, or the proximal posterior cerebral artery (PCA P1) or ischemia of the corresponding vascular territory (Lima et al. 2016). MTED was defined as the presence of multiple (two or more) ischemic lesions involving two different vascular territories. Stroke etiology was determined using available data and according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria for ischemic stroke (Adams et al. 1993). Review articles, opinion articles and letters not presenting original data were excluded, as well as studies reporting cases with incomplete information or non-English language articles.

Data collection

Age, gender, antiplatelet therapy, cerebrovascular risk factors (hypertension, diabetes mellitus, congestive heart failure, hyperlipidemia, smoking status, history of transient ischemic attack, stroke or coronary heart disease, alcohol consumption, atrial fibrillation, peripheral artery disease, carotid stenosis, obesity, cancer, thrombophilia, heart valve prosthesis, endocarditis), National Institutes of Health Stroke Scale (NIHSS) score on admission, outcome (death, discharge at home, discharge to rehabilitation), vascular territory involvement, laboratory findings (white cell count, lymphocytes, C reactive protein (CRP), D-dimer, activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR), ferritin, fibrinogen), time between COVID-19 related symptoms and stroke onset, stroke symptoms, COVID-19 symptoms, specific acute stroke treatments (thrombolysis, mechanical thrombectomy), NIHSS and mRS scores at last follow-up were collected.

Statistics

Categorical variables were presented as percentages and continuous variables as mean with SD or median with IQR. Comparison of baseline variables among four categories: CLVD, CSVD, IB, MTED were performed using χ^2 test for categorical variables and one-way analysis of variance or Kruskal–Wallis test for continuous variables. A value of $p < 0.05$ was considered significant. Statistical analyses were performed using Statistical Package for Social Science (SPSS) software version 20.

Results

A total of 1243 records were retrieved from database or other sources using the search strategy, of which 1229

remained after removal of duplicates. A total of 821 records were then removed after assessing whether the inclusion criteria were met. After the full texts were screened for eligibility, we excluded 319 more articles because detailed data on the involved cerebral territory of individual patients were not present. We included 89 studies for our qualitative and quantitative analyses. PRISMA flow diagram summarizes the study selection criteria (Figure 1) (Supplementary Table 1).

In this systematic review, we included 168 patients, 144 (85.7%) with ischemic stroke and 24 (14.3%) with IB (Table 1). The median age of the patients was 53 (IQR: 30), ranging from 25 to 89 years, with a male prevalence (58.9%). One-hundred-twenty-nine (76.8%) patients showed at least one cerebrovascular risk factor. The most common risk factor was arterial hypertension (47.6%) followed by diabetes mellitus (32.1%), vascular disease (peripheral artery, myocardial infarction, aortic plaque) (13.1%), hyperlipidemia (11.9%), previous stroke (7.7%), atrial fibrillation (7.7%), smoking or alcohol consumption (7.7%), obesity (6.5%), cancer (5.3%), thrombophilia (4.1%), congestive heart failure (4.1%), carotid stenosis (0.6%), heart valve prosthesis (0.6%), endocarditis (0.6%) and CADASIL (0.6%). The median NIHSS score was 14 (IQR = 12), ranging between 1 and 36. Considering the recanalization procedures performed in ischemic stroke patients, 22/144 (15.3%) patients received

intravenous thrombolysis, 16/144 (11.1%) direct mechanical thrombectomy and 11/144 (7.6%) both procedures. The median time between the onset of COVID-19 symptoms and stroke was 5 days (IQR = 10.5). In-hospital mortality was 32.1%.

Considering vascular territory, CLVD was observed in 62/168 (36.9%) patients, CSVD in 52/168 (30.9%) patients, MTED in 30/168 (17.9%). The patients affected by MTED and CSVD were significantly older (mean age = 64.4 and 61.8 years, respectively) than IB patients (mean age = 52 years; $p = 0.015$ and $p = 0.036$, respectively). The time between the onset of COVID-19 symptoms and the onset of stroke was significantly longer in the MTED group (mean time = 11.1 days) than in CLVD (mean time = 5.2 days; $p = 0.041$) and CSVD (mean time = 4.8 days; $p = 0.018$) (Figure 2A).

Female gender was more frequent in the CSVD group (53.9%), while almost all MTED patients (86.7%) had at least one cerebrovascular risk factor. Considering the risk factors individually, arterial hypertension was the most frequent (61.5%) in patients with CSVD. Unexpectedly, atrial fibrillation was not a prevalent risk factor in the CLVD group, involving only 8.1% of patients. The prevalence of thrombophilia was significantly higher in MTED patients (13.8%; Pearson's chi-squared, $p = 0.028$) compared to the other patient groups. The survival of patients with IB and MTED was lower (42.6% and 45.0, respectively) than that

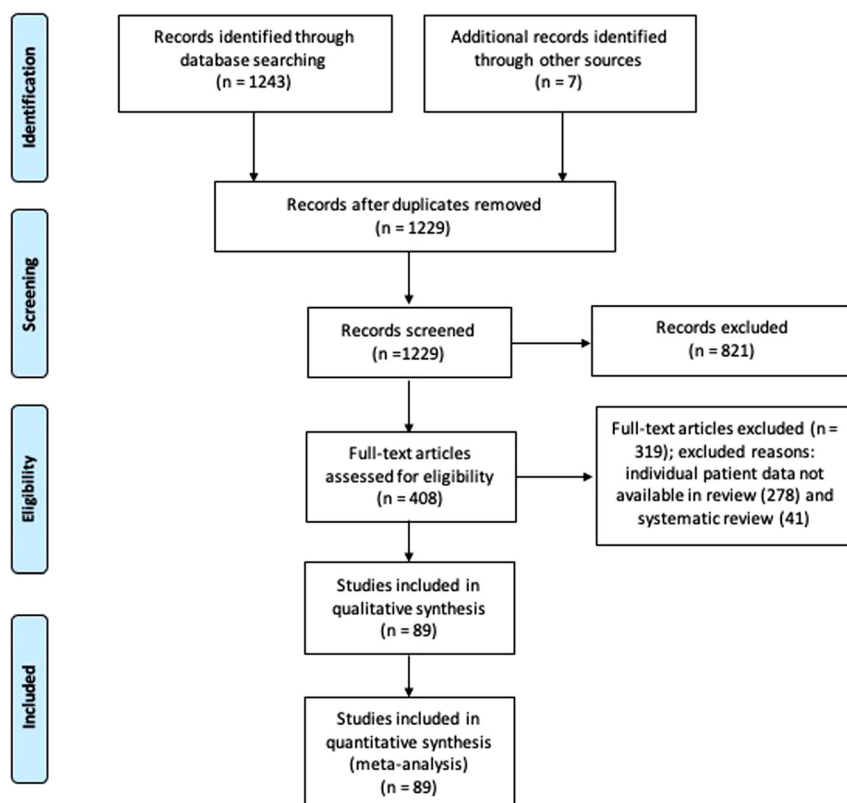


Figure 1: PRISMA flow diagram.

Table 1: Clinical features and laboratory parameters of stroke patients divided according to the type of stroke (hemorrhagic or ischemic) and the vascular territory involvement.

Percentage	CLVD	CSVD	IB	MTED	p value
Gender (male)	62.0	46.1	60.9	63.3	0.757
Risk factors (all)	74.2	20.8	62.5	86.7	0.165
Hypertension	41.9	61.5	41.7	40.0	0.118
Congestive heart failure	4.8	1.9	0.0	10.0	0.228
Diabetes	24.2	23.1	25.0	40.0	0.185
Previous stroke	6.4	13.5	37.5	6.7	0.204
Hyperlipidemia	14.5	15.4	8.3	3.3	0.334
Vascular disease	11.3	9.7	4.1	20.0	0.340
Atrial fibrillation	8.1	7.7	0.0	13.3	0.342
Smoking or alcohol	6.4	5.8	12.5	10.0	0.705
Carotid stenosis	1.6	0.0	0.0	0.0	0.633
Obesity	8.1	5.8	12.5	0.0	0.287
Cancer*	1.3	8.3	0.0	16.7	0.014
Thrombophilia*	3.2	0.0	4.1	13.8	0.028
Heart valve prosthesis	0.0	0.0	0.0	3.3	0.310
Outcome (alive)	67.9	74.4	42.6	45.0	0.046
White cell count*					0.010
H	25.0	20.6	52.9	47.6	
L	17.8	5.9	0.0	4.8	
N	57.1	73.5	47.1	47.6	
Platelet count*					0.039
H	7.4	6.1	0.0	0.0	
L	11.1	12.1	11.8	40.0	
N	81.5	81.8	88.2	60.0	
Prothrombin time*					0.018
H	38.1	4.8	0.0	34.9	
L	4.8	0.0	0.0	7.7	
N	57.1	93.7	100	38.5	
aPTT*					0.011
H	36.4	4.8	18.7	55.6	
L	4.5	9.5	6.2	0.0	
N	59.1	85.7	75	44.4	
Ferritin					0.410
H	70.0	50.0	57.1	93.3	
L	5.0	0.0	0.0	0.0	
N	25.0	50.0	42.9	6.7	
Fibrinogen					0.004
H	55.6	41.7	16.7	50.0	
N	44.4	58.3	83.3	50.0	
D-dimer*					0.019
H	77.8	61.1	75.0	96.5	
N	22.2	38.9	25.0	3.4	
CRP					0.017
H	97.3	64.5	66.7	92.2	
N	14.7	35.5	33.3	4.8	

CLVD, cerebral large vessel disease; CSVD, cerebral small vessel disease; MTED, multiple thrombo-embolic disease; IB, intracranial bleeding; H, high levels; L, Low levels; N, normal levels; aPTT, activated partial thromboplastin time; CRP, C reactive protein. *Statistical significance - p value < 0.05.

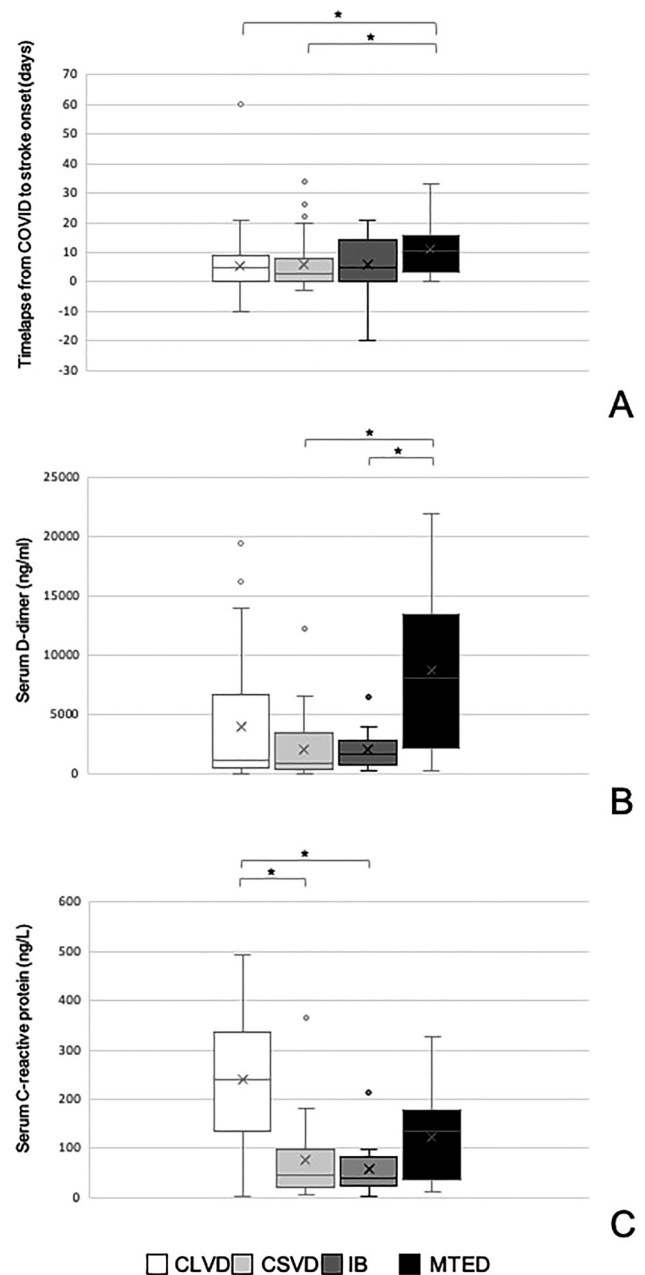


Figure 2: Timelapse between onset of COVID-19 symptoms and stroke onset, D-dimer and C-reactive protein. (A) Time in days from the onset of COVID-19 symptoms and the stroke onset. (B) D-dimer serum levels. (C) C-reactive-protein serum level. Box plots express the first (Q1) and third (Q3) quartiles within a given dataset by the upper and lower horizontal lines in a rectangular box, in which the horizontal line shows the median. The whiskers extend upwards and downwards to the highest or lowest observation within the upper ($Q3 + 1.5 \times \text{interquartile range}$) and lower ($Q1 - 1.5 \times \text{interquartile range}$) limits. * p -values indicate statistical significances (<0.05) between the different groups.

observed among CLVD (67.9%) or CSVD (74.4%) patients. A more detailed distribution of risk factors is reported in Table 1. As expected, NIHSS was significantly lower in CSVD patients (mean NIHSS = 9.4) compared to NIHSS observed in MTED patients (mean NIHSS = 16.2; $p = 0.039$) and in CLVD (mean NIHSS = 17.2; $p = 0.018$). Evaluating the etiology of ischemic stroke, according to the TOAST classification, most strokes were cryptogenic (55%), followed by stroke due to large-artery atherosclerosis (16%), cardioembolic stroke (12%), lacunar stroke (10%) and stroke of other determined etiology (7%). Subdividing stroke of undetermined etiology according to vascular territory involvement, 54/92 (58.7%) were consistent with CLVD, 23/92 (25.0%) with CSVD and 15/92 (16.3%) with MTED.

Considering the blood examinations performed when the patients were admitted to the emergency department, white blood cell and platelet counts and blood coagulation parameters, such as prothrombin time and aPTT, were frequently normal in patients with CSVD or IB. Conversely, prothrombin time and aPTT were significantly increased in about half of the patients with CLVD and MTED.

Although elevated serum levels of D-dimer and CRP were detected in all four patient groups, almost all MTED patients (96.5%) showed high serum levels of D-dimer, while high levels of CRP were found in almost all patients with CLVD (97.3%). The prevalence of patients with increased fibrinogen serum levels was significantly higher in CSVD (41.7%), CLVD (55%) and MTED (50%) than in IB patients. The serum concentration of D-dimer and CRP, whose values have been regularly reported on published papers, was significantly higher in MTED patients (mean D-dimer = 8921 ng/ml) compared to CSVD (mean D-dimer = 2461 ng/ml; $p = 0.011$)

and to IB (2108 ng/ml; $p = 0.009$) (Figure 2B). CRP, on the other hand, was significantly higher in patients with CLVD (mean CRP = 241.5 mg/l) than in IB (mean CRP = 77 mg/l, $p = 0.019$) (Figure 2C).

Discussion

Growing evidence is mounting on the increased risk of stroke in COVID-19 patients, even in comparison with the other seasonal infectious diseases or influenza, with a reported incidence that ranges from 1 to 6% (Merkler et al. 2020). Clinical pictures of stroke can be extremely variable, although generally more severe than in non-COVID patients, and with a poor prognosis (Yaghi et al. 2020; Ying-Kiat et al. 2020). In this systematic review, we have grouped the clinical cases reported in the literature according to the type of stroke (ischemic or hemorrhagic) and to the vascular district involved (large vessels, small vessels, multiple districts involvement). Then we have compared the demographic features, risk factors, outcome, treatments and laboratory parameters in order to trace a possible pathogenic profile by which SARS-CoV-2 determines cerebrovascular disease.

As a result of this work, we have summarized the possible pathogenic profile in a color-coded spectrum similar to visible light, that ranges from direct virus damage to the endothelium of small and medium-caliber vessels (violet–blue band) through immune-mediated or inflammatory damage (green–yellow band), up to a thrombophilic mechanism that determines a state of diffuse hypercoagulability (orange–red band) (Figure 3).

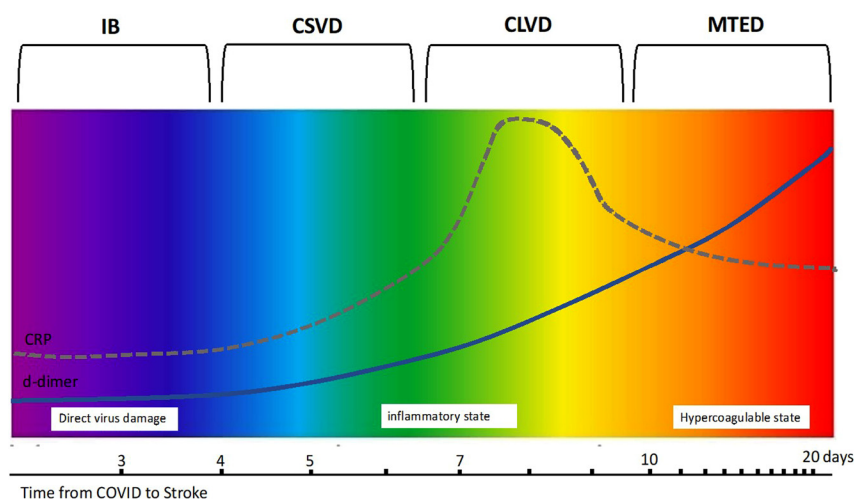


Figure 3: The “spectrum” of cerebrovascular disease in COVID-19 patients.

Diagram that exemplifies possible pathogenic mechanisms of stroke in patients with COVID-19. Violet–blue band for IB and CSVD: low levels of inflammation and low prothrombotic activity; green–yellow band for CLVD: high levels of inflammation with moderate prothrombotic activity; orange–red band for MTED: moderate-high levels of inflammation and very high prothrombotic activity.

Violet–blue band

The clinical profile of IB in the violet–blue band identifies a patient with high disability, with few cerebrovascular risk factors and poor outcome in almost two out of three cases. From a laboratory point of view, the serum markers of inflammation and of systemic coagulopathy are likely to be normal. The profile of CSVD is characterized by a pre-dominant female gender, with a low degree of disability and simultaneous onset of stroke and COVID-19 symptoms. Two out of three patients suffer from hypertension and their outcome tends to be good with a survival of three out of four. Serum inflammatory or pro-thrombotic markers are low.

SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed on the epithelium of lung and small intestine, thus providing possible routes of entry for the SARS-CoV-2 (Hamming et al. 2004, Iadecola et al. 2020; Natoli et al. 2020). The attack to the endothelium by SARS-CoV-2, however, does not seem to end exclusively through the ACE2 receptor, as it possibly mediated also by other receptors/facilitators, including transmembrane serine protease 2, sialic acid and extracellular matrix metalloproteinase inducer, that are more common in arterial and venous endothelial cells, also in the central nervous system (Matsuyama et al. 2020; Tortorici et al. 2019). Signs of endothe-itis with the presence of viral elements within endothelial cells and inflammatory cell death has been recently described in a post-mortem analysis of patients infected by SARS-CoV-2 (Varga et al. 2020). Morphological alterations and disappearance of endothelial cells in arterioles, capillaries and venules, secondary to caspase-3 mediated apoptosis, leukoencephalopathy and intracerebral hemorrhages are more common neuropathological findings confirming the SARS-CoV-2-induced endothelial dysfunction (Hernández-Fernández et al. 2020; Kremer et al. 2020). On the other hand, the viral attack can also induce endothelial activation at the microcirculation level in response to the release of cytokines and poor cleavage of von Willebrand factor (VWF), thus resulting in bleeding (Crawley et al. 2011).

Hemorrhagic or ischemic damage is worsened in the presence of pre-existing endothelial dysfunction, as observed in patients with smoking habits, hypertension, diabetes, obesity, and cardiovascular disease. Accordingly, these latter conditions are associated with poor outcomes in COVID-19. The SARS-CoV-2 related microangiopathic damage, secondary to either direct virus damage or local immune response, usually is not associated to an increase of systemic inflammatory or prothrombotic serum markers that remain silent.

Green–yellow band

The CLVD profile of the green–yellow band identifies patients that develop neurological symptoms shortly after COVID-19 onset with high neurological disability. The presence of very high systemic inflammation without evident signs of hyper-coagulopathy is a typical feature of this profile.

SARS-CoV-2 infection polarizes the immune response into T-helper type 1 (Th1) profile, triggering the production of pro-inflammatory cytokines, such as interleukin (IL)-2, IL-12, interferon- γ and tumor necrosis factor- α , and the induction of nitric oxide free radicals. On the contrary, T-helper type 2 (Th2) response or T regulatory response (Treg) has a compensatory function, regulating the Th1 response against the virus. An erroneous balance among the Th1, Th2 and Treg responses may result in a systemic post-infectious immune-mediated disease. The term “cytokine storm” associated with COVID-19 infection has been already linked to the avian H5N1 influenza virus infection and correlated directly with tissue injury and an unfavorable prognosis of severe influenza (Yuen and Wong 2005). In patients with SARS-CoV-2 infection, an increased secretion of both pro-inflammatory Th1 (Huang et al. 2020) and Th2-immune-oriented cytokine (Zhang et al. 2020a, b, c) induce a diffuse inflammatory state (Ellul et al. 2020), which in turn causes ARDS, acute stroke, multiple organ failure, and, at least in the most severe cases of SARS-CoV-2 infection, death (Xu et al. 2020). IL-6 plays a crucial role in mediating inflammation of SARS-CoV-2 infection and is increased in more than one half of patients with COVID-19 (Zhang et al. 2020a, b, c). Moreover, IL-6 induces the hepatic synthesis of CRP, a known proinflammatory marker of atherothrombotic vascular disease, that is significantly increased in patients with severe COVID-19 (Ali et al. 2020; Wang et al. 2020a, b). In this inflammatory phase of the disease, CRP amplifies immune damage by activating the classical complement pathway of the immune system and modulating the phagocytic activity (Young et al. 1991).

In addition to CRP and IL-6, other proinflammatory cytokines such as IL-1 β , IL-2, tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor upregulate procoagulants such as tissue factor, P-selectin, factor VIII, fibrinogen, and VWF. Moreover, these molecules also downregulate anticoagulants such as thrombomodulin and endothelial protein C receptor contributing to a condition of hypercoagulability (Al-Samkari et al. 2020).

There is growing evidence that systemic inflammation is involved in multiple aspects of stroke etiology and pathology since it compromises normal endothelial function. Indeed, co-morbidities, such as atherosclerosis,

hypertension, diabetes or infection, that increase systemic inflammatory status, are the same poor prognostic factors in severe COVID-19 disease (Varga et al. 2020).

Systemic inflammation, endothelial dysregulation, and an increase of inflammatory markers as CRP are associated with overall ischemic stroke and the large-vessel disease subtype (Ladenvall et al. 2006). In our review we confirmed the relationship of high CRP serum levels and the development of CLVD, supporting a general link between systemic inflammation and stroke susceptibility. Systemic inflammatory response in patients with SARS-CoV-2 infection can result in endothelial damage, with a consequent increase in thrombin generation and a reduction in endogenous fibrinolysis (Shorr et al. 1999). Accordingly, in patients with CLVD it has been observed a parallel increase in inflammatory markers leading to elevated D-dimer levels via cytokine activation of the coagulation cascade and corresponding inhibition of fibrinolysis.

Orange–red band

The profile of the MTED patient belonging to the orange–red band is generally characterized by older age, with a more disabling stroke, many comorbidities, and a poor outcome in about half of the cases. These patients show clear signs of hypercoagulability with thrombocytopenia in one out of three patients, an increase of aPTT in more than half of the cases and high levels of D-dimer.

The SAR-CoV-2 related hypercoagulability seems to go beyond its relationship with the pro-inflammatory profile. It should be related to a specific SARS-CoV-2 interaction with coagulation cascade or to the effect of persistency of pro-inflammatory status producing multiple thrombo-embolism phenomena. The question is not yet cleared up. Despite the absence of robust evidence, interim guidelines recommend regularly monitoring of hemostatic markers, namely D-dimers, prothrombin time, and platelet count, in all patients presenting with COVID-19 and prophylactic use of low molecular weight heparin in all hospitalized patients, unless there are contraindications. Moreover, antiphospholipid antibodies (anticardiolipin and anti- β -glycoprotein I antibodies) and lupus anticoagulant have been reported in COVID-19 patients with multiple hemispheric infarcts and with concomitant elevation of D-dimer and CRP (Bowles et al. 2020; Harzallah et al. 2020; Zhang et al. 2020a, b, c).

The longer time-lapse that we observed between the onset of COVID-19 symptoms and the development of MTED could be in favor of a prolonged permanence of a

pro-inflammatory micro-environment as the cause of the state of hypercoagulability. In this scenario, early interventions aimed at reducing inflammation might help prevent thrombosis. The alternative hypothesis of the virus directly or indirectly interfering with coagulation pathways and causing systemic thrombosis, would require early prophylaxis to manage the coagulopathy. The hypoxia and immobility in hospitalized patients with COVID-19 are potent triggers and “amplifiers” of thrombosis.

Conclusions

With this systematic review, we have drawn different profiles of patients with COVID-19 developing an acute cerebrovascular event. In particular, based on common serum markers such as CRP and D-dimer, we postulated clinical parameters and vascular territory as well as different possible pathogenic mechanisms associated with SARS-CoV-2 infection: direct virus damage to the endothelium of small and medium-caliber vessels, immune-mediated or inflammatory damage and prothrombotic mechanism that determines a state of diffuse hypercoagulability. Further studies are necessary to confirm our data and better define the relationship between stroke types and the pathogenic mechanism/s activated by SARS-CoV-2 infection.

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