Chapter 8. **Stroke**

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Chapter 8. Stroke

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Introduction

Coronavirus disease 2019 (COVID-19) has been associated with an increased risk of venous and arterial thromboembolic complications, including stroke. Patients affected by the illness may develop clinically significant coagulopathy probably mediated by several factors such as hyperinflammation, endothelial dysfunction, thrombin generation and platelet activation. Since the spread of the outbreak, a series of early reports indicated an association between COVID-19 and cerebrovascular disease, particularly ischemic stroke. In a case series of individuals admitted to a hospital in Wuhan, China, during the emergency, six patients (3%) presented stroke; five out of six strokes were ischemic and only one was hemorrhagic[1]. A series of five cases of severe large-vessel stroke (mean National Institutes of Health Stroke Scale [NIHSS] score: 17) in patients under 50 years of age was described in New York City[2] drawing attention to the potential relationship between large-vessel stroke and COVID-19 in young patients. From then, several studies have been published showing that the COVID-19 outbreak has had a considerable impact on stroke incidence and etiology.

Epidemiology

Incidence of ischemic stroke among COVID-19 admissions in clinical series is approximately 0.9-2.7%[3-7]. A lower incidence has been reported for intracranial hemorrhage (range 0.2-0.9%)[8,9] and for cerebral venous thrombosis (0.08%)[10]. Moreover, there is a higher occurrence of stroke among patients with COVID-19 compared to patients with other viral respiratory infections (SARS-CoV-1 or Influenza)[11]. Although there is evidence to suggest a high rate of cerebrovascular complications in patients with SARS-CoV-2 infection, the actual frequency of stroke among patients with COVID-19 has probably been underestimated because of the phenomenon of missed stroke diagnoses due to possible falling rates of new ischemic stroke admissions. Patients have been less likely to go to hospital

to ask for medical assistance, especially in the presence of mild symptoms. In addition, stroke diagnosis has been missed in those patients with severe respiratory involvement who were not extubated (thus clinical neurological symptoms could not be detected) or who did not survive mechanical ventilation. Finally, the number of stroke cases were probably underestimated due to fewer MRIs being carried out. Stroke generally developed later, after a mean 1-2 weeks from onset of COVID-19 symptoms. In a metanalysis, neurological symptoms related to stroke represented the reason for hospital admission in 37.7% and the median delay of stroke from onset of COVID-19 symptoms was 8.8 days[12]. In a UK study, fever, cough or dyspnea occurred a median 6 days before stroke onset[13]. This delay between stroke onset and COVID-19 infection is probably secondary to the development of the increased hypercoagulable and inflammation state as trigger mechanisms of cerebrovascular complications.

Figure 8.1: Pathophysiological processes related to stroke in patients with COVID-19 infection
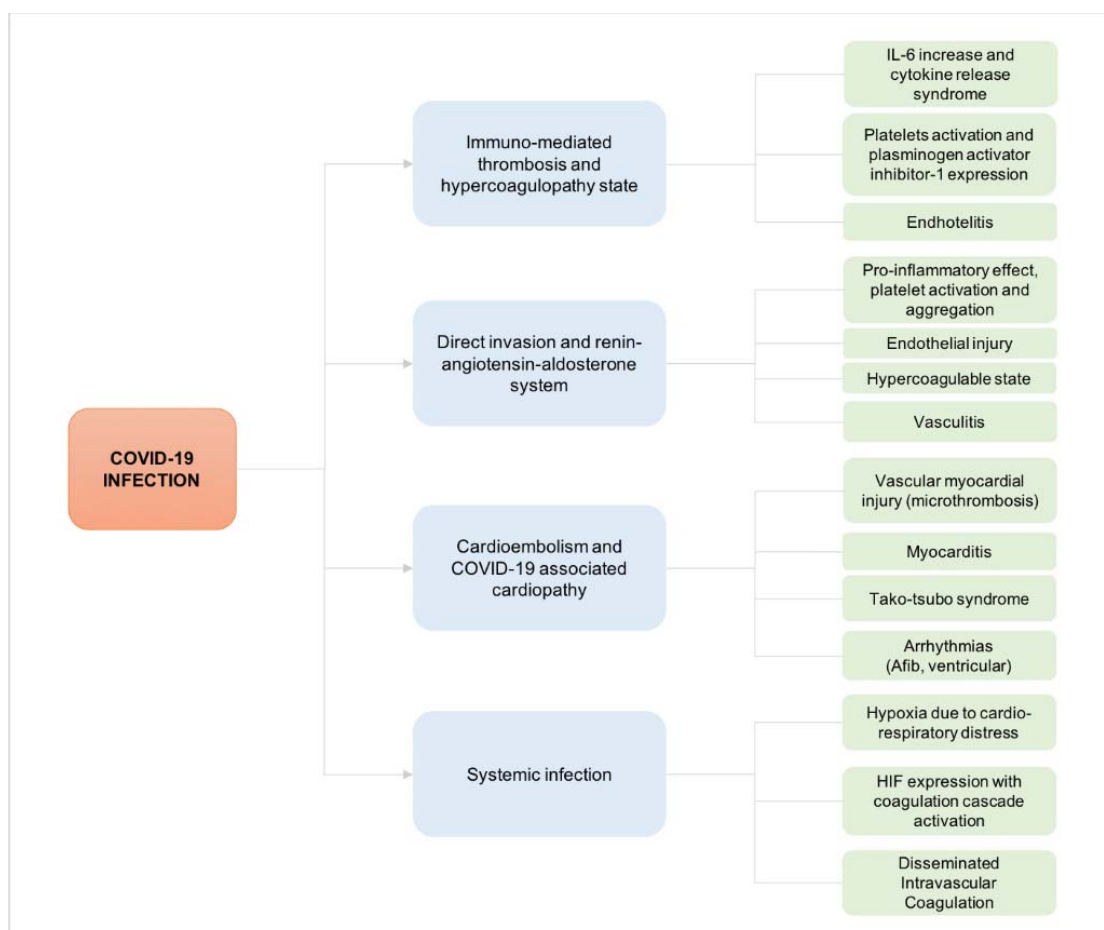
HIF = hypoxia-inducible transcription factor; IL-6 = Interleukin 6.

COVID-19 and cerebral vascular disease: pathophysiological mechanisms

Various mechanisms can lead to involvement of the nervous system in COVID-19[14]. Many reports demonstrated a link between COVID-19 and cerebrovascular disease[1,15], and a recent meta-analysis showed a 5-fold increase in stroke risk for patients with severe COVID-19[12]. COVID-19 patients with ischemic stroke frequently have large vessel occlusion due to either cryptogenic or cardioembolic strokes. However, there is a higher risk even for minor or lacunar strokes. This clinical diversity probably also reflects pathophysiological heterogeneity. Several pathophysiological processes seem to be related to stroke in patients with COVID-19: a) an immunomediated thrombosis and hypercoagulopathy; b) direct invasion of the nervous system; c) heart disease with increased cardioembolic risk; and d) the consequences of systemic infection.

a) Immuno-mediated thrombosis and hypercoagulopathy state

S proteins are expressed on the surface of SARS-CoV-2 that bind the receptor for the enzyme that converts angiotensin (ACE2), also expressed in epithelial alveolar cells and endothelial cells.

In the lung, the virus is recognized by Toll like receptor (TLR) and upregulates pro-interleukin-1β expression of macrophages[16]. Macrophages cause the release of pro-inflammatory acute-response cytokines (tumor necrosis factor and IL-1β) and a sustained increase in IL-6. In turn, IL-6 supports the inflammatory process, similar to what happens in cytokine release syndrome[17]. During this hyper-inflammatory state, activated platelets induce the extrinsic coagulation cascade, leading to thrombin formation. The cytokine storm also promotes expression of plasminogen activator inhibitor-1 from the endothelium, thus inhibiting the formation of plasmin inhibiting fibrinolysis[18]. Simultaneously, circulating viruses, binding endothelial cells, facilitate endothelial and vascular inflammation (endothelitis)[19]. In turn, damaged endothelial cells also release Von Willebrand factor, causing platelet hyperactivation. The pro-inflammatory state, platelet and coagulation activation, and endothelitis result in hypercoagulability and microvascular immune-mediated thrombosis[20]. In some patients, hypercoagulopathy is also determined by the presence of antiphospholipid antibodies or lupus anticoagulant[21]. High D-dimer levels and elevated fibrinogen without hypofibrinogenemia characterize COVID-19 hypercoagulopathy. Furthermore, prolonged inflammation determines oxidative stress with the production of reactive oxygen species (ROS) which in turn enhance the inflammatory response[22].

b) Direct invasion and renin-angiotensin-aldosterone system

As mentioned above, S proteins on the surface of SARS-CoV-2 bind ACE2, which is expressed not only in the lung and endothelium but also in the Central

Nervous System (CNS), especially in the olfactory bulb, in the cingulate cortex, the temporo-mesial lobe, the substantia nigra, in cerebral capillaries, smooth muscle cells, and microglia. Direct CNS invasion by a virus probably occurs in several ways, but mainly through the olfactory nerve and olfactory bulb[23]. The hematogenous spread of a virus by crossing the blood-brain barrier could also cause direct damage. ACE2 counteracts the renin–angiotensin–aldosterone system by degrading angiotensin I and II and promoting vasodilating and an-inflammatory effects. By binding ACE2, SARS-CoV-2 downregulates ACE2 expression and higher formation of angiotensin II causes the migration of leukocytes into the tissues with a pro-inflammatory effect, promoting platelet aggregation[24]. These effects, together with endothelitis, cytokine storm, complement, platelet and neutrophil activation, may affect both the stability of already vulnerable atherosclerotic plaques and contribute to a hypercoagulable state and arterial embolism[25]. In addition, direct infection of the cerebrovascular endothelium and immune dysregulation could cause a viral cerebral vasculitis in the brain[26]. Direct (viral invasion) or indirect (inflammatory cytokine, prothrombotic factors, activation of coagulation cascades) endothelial damage increases not only the thrombotic risk, but also contributes to vascular fragility. This, associated with blood brain barrier dysfunction, can result in a cerebral hemorrhage[27].

c) Cardioembolism and COVID-19-associated cardiopathy

Pro-inflammatory pattern and cytokine storm may lead to myocardial injury, elevating microthrombi genesis[28]. In addition to vascular myocardial damage, several studies report an increased incidence of myocarditis and Tako-tsubo syndrome in COVID-19 patients[29,30]. Myocardial damage, whether vascular or non-vascular, causes left ventricular dysfunction, which is a well-known cause of embolic stroke. Furthermore, myocardial damage associated with a systemic infection can result in atrial fibrillation or in malignant ventricular arrhythmias, which in turn can be a potential cause of cardioembolism.

d) Systemic infection

COVID-19 is known to be a systemic disease. Therefore, disease-related brain damage is also closely linked to the systemic alterations caused by the disease. Hypoxia due to cardio-respiratory distress increases the risk of ischemic stroke. Furthermore, systemic hypoxia promotes the expression of Hypoxia Inducible Factor (HIF), which in turn activates the coagulation cascade via extrinsic coagulation pathway, maintaining hypercoagulability in hypoxic regions[18]. Sepsis with high D-dimer levels can result in sepsis-induced Disseminated Intravascular Coagulation. Furthermore, co-pathologies play an important role: severe disease is usually seen in older patients who often have comorbidities

that increase their risk of stroke (diabetes, hypertension, obesity, smoking habit), and these have a significant negative effect on prognosis.

Risk factor of stroke in COVID-19 patients

Some early reports observed that ischemic stroke frequently occurred in young patients with COVID-19. In a retrospective cohort study of consecutive patients with ischemic stroke who were hospitalized within a major health system in New York, among the 32 patients with COVID-19 and stroke, the median age was 62.5 years[2,4]. In a systematic review and metanalysis, patients with COVID-19 and stroke were younger than patients with stroke without infection with a pooled median difference for age of 6.0 years[12]. In the largest study, comprehensively reporting the characteristics and subtypes of stroke in SARS-CoV-2–infected patients from the Multinational COVID-19 Stroke Study Group, in a population of 323 patients with acute ischemic stroke, 36.2% were <55 years of age[31]. However, these data have not been confirmed by subsequent studies and systematic analysis which have shown a higher mean age of COVID-19 patients with stroke of over 65 years[7,32]. In the Global COVID-19 Stroke Registry study[33], median age was 71.2 years.

Male sex is more frequently associated with stroke and COVID-19 infection[34] and in several studies the proportion of Black people was higher[32,35,36]. Earlier observations from smaller case series also suggested that patients with COVID-19 who developed acute ischemic stroke did not have pre-existing cardiovascular risk factors[4].

However, subsequent studies and metanalysis showed stroke risk in Covid-19 was higher in patients with cardiovascular risk factors, with patients developing cerebrovascular diseases having greater likelihood of a smoking habit, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, coronary artery disease, and congestive heart failure[12,32].

Stroke in COVID-19 patients seems to be associated with more severe infectious disease. In a retrospective study in patients admitted to the intensive care unit (ICU), incidence of stroke was 5.7% compared to 0.8% of patients with a non-severe disease course. Siepmann et al.[37] conducted a meta-analysis of 741 patients showing severe COVID-19 infection was associated with an increased risk of acute stroke. In a recent systematic review and meta-analysis of 5,266 patients, according to the severity of the disease, patients with severe COVID-19 had an increased risk of acute ischemic stroke compared with patients with non-severe disease: total stroke rate 3.37% and 0.61%, respectively[38]. Moreover, patients with severe manifestations of COVID-19 have significantly more frequent ischemic strokes with multivascular territorial distribution, hemorrhagic transformation, and simultaneous infarction and intracranial hemorrhage[36]. Stroke in severe COVID-19 is also associated with significantly higher

C-reactive protein and ferritin levels, elevated D-dimer levels, and more frequent lymphopenia and renal and hepatic injury, supporting the proposed pathogenic mechanisms of hyperinflammation activating a prothrombotic state, particularly in those with severe disease[36].

COVID-19 and stroke characteristics

Patients with COVID-19 and stroke have a higher prevalence of moderate-severe stroke with higher admission NIHSS score. In an early report from a hospital in New York, median NIHSS score was 19 in COVID-19 patients compared to 8 in patients not infected[4]. Sahajouel et al.[31] reported that, in a population of 323 acute ischemic strokes, up to 74% of patients had a NIHSS score ≥5. The high prevalence of more severe strokes can be explained by a greater prevalence of large vessel occlusions (LVO) that is twice as frequent as previously reported (up to 47%), with higher prevalence across all age groups, even in the absence of risk factors or comorbidities[7,31]. Up to 68.8% of young patients present a LVO[7]. Considering published data, young patients probably represent only a small proportion of the entire population of COVID-19 stroke patients and show specific features with respect to older individuals, such as lower prevalence of traditional vascular risk factors and higher incidence of LVO.

In COVID-19 patients, strokes usually present cortical and lobar location and multiterritorial involvement, and associated brain hemorrhage (hemorrhagic transformation or simultaneous hemorrhage and infarction) is common[39]. With regards to stroke etiology, cryptogenic subtype is the most frequently reported from several studies with a prevalence of 50-63%[4,40,41]. Around 50% have no identifiable source and are categorized as embolic stroke of unknown source (ESUS)[42]. In a recent metanalysis, patients infected by SARS-CoV-2 appear to have increased odds of cryptogenic stroke when compared to contemporary or historical non-infected controls[43]. The higher incidence of cryptogenic strokes and ESUS is probably due to blood hyperviscosity and a hypercoagulable state; these have been linked to an immune-mediated response following SARS-CoV-2 infection. In fact, high levels of biomarkers of inflammatory response (neutrophils, C-reactive protein, IL-6) and coagulation defects (high level of D-Dimer, low platelet count, elevated PT and aPTT) were found in patients with cryptogenic strokes[3,4,41], and significantly higher levels of CRP and D-dimer were found in patients with more severe infection, suggestive of an acquired thrombophilia[36]. Moreover, a temporal correlation has been identified between stroke onset and the peak of acute phase reactants, including C-reactive protein, ferritin, and D-dimer, supporting the hypothesis that ischemic stroke is due to an underlying endotheliopathy and thrombosis[44]. An association with newly

positive antiphospholipid antibodies has also been observed although the cause of this is uncertain[21,35].

Other possible embolic sources are probably related to cardiac dysfunction associated with critical illness and prolonged stay in the ICU; hypotension and inadequate cerebral perfusion, septic embolization, atrial fibrillation, cardiac dysfunction, stress cardiomyopathy, myocarditis are sometimes underdiagnosed in severely compromised patients. Compared to SARS-CoV-2-negative patients, patients with COVID-19 infection more often have cardioembolism, especially related to atrial fibrillation, as the likely cause of brain ischemia[34]. In fact, atrial arrhythmias have been associated with severe COVID-19 infection[45]. Patients with ischemic stroke under 50 years of age frequently have elevated cardiac troponin, a marker of acute or chronic myocardial injury strongly associated with the risk of stroke and usually secondary to underlying heart disease at baseline or to a myocardial ischemia. In a cohort of young stroke patients with COVID-19, 80% had high troponin. Considering that 44.8% of them had no prior risk factors, these high levels are probably the consequence of acute myocardial injury, which could play a role in the pathophysiology of acute ischemic stroke in young patients with COVID-19[7].

Among other stroke etiologies, cardioembolism represented the second most frequent subtype, while large vessel atherosclerosis and small artery stroke were less frequently reported[12]. In one study, no difference was found in the prevalence of large-artery and lacunar stroke between patients with and those without COVID-19[33].

However, any discussion of the distribution of stroke etiologies during the Covid-19 outbreak has to take into account some epidemiological bias. A high prevalence of cryptogenic strokes is probably related to an underestimation of the frequency of other subtypes. This could partly be explained by some confounding factors such as a relatively low number of diagnostic studies performed during the outbreak and an underestimation of mild stroke (often due to small vessel disease) because individuals with only mild symptoms would avoid going to hospital because of fear of contagion.

Stroke therapy in COVID-19 patients

Acute reperfusion therapies

Safety issues related to thrombolysis have not been specifically studied in the setting of COVID-19 infection. A reduction in the total number of patients treated with Alteplase has been observed, likely related to the lockdown in Milan, which made it difficult for stroke patients to access medical assistance. A study from Italy on treated patients with thrombolysis or bridging therapy, reported higher rates of unfavorable outcomes at 1-month compared to previous

data from the pre-COVID-19 literature. However, there was no increase in risk of symptomatic intracerebral hemorrhage[46]. Therefore, intravenous thrombolytic therapy should be evaluated, as for any patient with acute ischemic stroke, according to current guidelines. A similar approach should be adopted for mechanical thrombectomy. However, as for thrombolysis, the number of unfavorable outcomes after endovascular therapies was also higher compared to previous data. A French study showed an increased risk of reocclusion after initial endovascular recanalization in patients with COVID-19 that could have been related to hypercoagulability associated with the infection[47]. A European study investigated the efficacy and safety of mechanical thrombectomy in patients with acute ischemic stroke and LVO associated with COVID-19 infection and observed a 29% rate of 30-day mortality after treatment; in more than 50%, the primary cause of mortality was neurological associated with ICH or malignant cerebral infarction/edema[48].

Antithrombotic therapy

Up to now, no clear guidelines on antithrombotic therapy in patients with COVID-19 and stroke have been published. Strokes, particularly those resulting from large vessel occlusion, are associated with certain prothrombotic states in COVID-19 infection. On the other hand, anticoagulation is associated with an increased risk of hemorrhagic transformation in COVID-19 patients[49].

Pharmacological venous thromboembolism prophylaxis is strongly advised for all COVID-19 patients[50]. For patients with ischemic stroke with a strong indication for full-dose anticoagulation (atrial fibrillation, severe heart failure, intraventricular thrombus), early initiation is probably reasonable given the high thrombotic risk seen in patients with COVID-19, to be weighed up with the bleeding risk according to the size of the ischemic lesion.

For other patients with cryptogenic stroke, involvement of multiple vascular territories (suggesting an embolic phenomenon), presence of other potential thrombotic events, an assessment of the severity of systemic illness assessed by measurement of coagulation (fibrinogen and D-dimer) and inflammation markers, should all be considered when deciding between antiplatelet therapy or anticoagulation, always bearing in mind the higher bleeding risk in these patients.

Outcome

The prognosis for COVID-19-associated ischemic strokes is extremely poor. Patients often had severe illness requiring ICU admission and mechanical ventilation[3,4]. The prognosis was particularly bleak in those patients with high levels of D-dimer[5]. Patients have a longer hospital stay with a greater rate of neurological worsening during admission because of a higher rate of neurological

and cardiovascular events during hospitalization including cerebral edema, intracerebral hemorrhage, myocardial infarction, or multisystem involvement[32]. In one study, up to 51% of patients with COVID-19 had severe disability at discharge (median mRS 4 vs. 2) compared with patients without COVID-19[33], and more COVID-19-positive patients suffer in-hospital death[3,40,51]. Friedman et al.[7] reported that a clinical phenotype characterized by older age, a higher burden of comorbid conditions, and severe COVID-19 respiratory symptoms was associated with the highest in-hospital mortality (58.6%) and a 3 times higher risk of death than the rest of the cohort.

COVID-19 and hemorrhagic stroke

COVID-19-related hemorrhagic strokes are much less common than ischemic strokes. In a recent analysis from the COVID-19 cardiovascular disease registry of 21,483 patients, only 48 (0.2%) had had an intraparenchymal hemorrhage[9]. Most were elderly male patients with comorbidities and more vascular risk factors, the most common being systemic hypertension[9,52]. Intraparenchymal hemorrhage was the most common variety[52]. A significant proportion of patients with intracerebral hemorrhage were on some form (therapeutic or prophylactic dose) of anticoagulation therapy, which could have predisposed them to the development of the hemorrhage[40,53,54]. In one study, anticoagulation was associated with a 5-fold increase of intracerebral hemorrhage in COVID-19 patients[54]. Patients with intracerebral hemorrhage are more likely to require ICU admission, mechanical ventilation, extracorporeal membranous oxygenation, and have a higher mortality[9,31]. Higher hemorrhagic risk in COVID-19 patients could be explained by several hypotheses: invasion and direct damage of cerebral blood vessels by SARS-CoV-2, hypertensive effect induced by marked reduction in ACE-2 levels, or systemic hyperinflammatory syndrome characterized by fulminant hypercytokinemia which may mediate vascular damage[26,27].

Niguarda Hospital, Milan: the COVID-19 experience

A retrospective analysis was performed on 901 COVID-19 patients who attended the Niguarda Hospital in Milan[55]. In this case series, 53 patients (5.9%) had a stroke. As expected, our patients with stroke were older and with more comorbidities, and these factors could partially explain the observed higher fatality rate. It should also be noted that a mortality of 37.7% is considerably higher that that reported in the literature, where it ranges from 11% to 19%, and it is higher than previous mortality rates reported at our center (7.7% in 2019). Our data agree with the literature in that there is a substantially higher

mortality in individuals with both COVID-19 and stroke than that observed in patients with stroke without SARS-CoV-2 infection.

Stroke care and assisting patients with COVID-19 infection

Despite the association of SARS-CoV-2 infection with an increased risk of ischemic stroke, in Spring 2020, numbers of inpatient stroke decreased. A decline in acute stroke code activations (Figure 8.1), stroke hospitalizations, and mechanical thrombectomy volumes have been reported in a paper by Friedlich et al.[56] at local, regional, and national levels compared with most reports from comprehensive stroke centers (CSC) in high income countries (*paper has been recently retracted because of lack of written consent from the American Heart Association to use the 'Get with the Guidelines' dataset*).

Primary stroke centers and centers with higher COVID-19 inpatient volumes experienced steeper declines. The reasons for this decrease are not completely understood but may relate to patients with stroke symptoms not seeking care due to fear of contracting SARS-CoV-2 in the emergency room, lack of recognition of stroke symptoms due to isolation from social distancing, misdiagnosis of stroke in the setting of SARS-CoV-2 encephalopathy, or other factors[56,57].

Since the outbreak began, specific measures have been taken to contain the spread of the disease, including lockdown, converting general medical wards to quarantine wards, and reorganizing in-hospital clinical activities for the emergency management and treatment of acute conditions. One such measure has been to concentrate a large proportion of acute stroke patients in a restricted number of hospitals.

The initial lull in stroke volume allowed centers to develop and implement new processes and protocols to care for stroke patients with SARS-CoV-2 infection with the goal of reducing the duration and frequency with which the staff directly interacted with infectious patients. These changes have the dual benefits of not only reducing staff exposure to potential infection, but also helped to conserve personal protective equipment[58]. Recovery of stroke hospitalization but not intravenous thrombolysis volume was noted in the later phase of the initial pandemic wave and was associated with lower COVID-19 hospital burden, high volume, and higher use of comprehensive stroke centers[59-61]. Furthermore, Rinkel et al.[62] show that there was no change in the proportion of stroke patients treated with intravenous thrombolysis (28% vs. 30%, $p = 0.58$) or endovascular thrombectomy (11% vs. 12%, $p = 0.82$) or associated treatment times, confirming that there is no evidence for a decrease in the quality of acute stroke care. In contrast, Siegler et al.[63] report that evaluation for acute ischemic stroke during the COVID-19 period in pooled clinical data of consecutive adult stroke patients from 14 US comprehensive stroke centers was associated with a small but significant delay in intravenous thrombolysis but no significant delay

in thrombectomy time metrics. The analysis in a prospective multicenter cohort study used data from the Thrombolysis in Ischemic Stroke Patients (TRISP) registry of patients with acute ischemic stroke treated with reperfusion therapies indicates the solid stability of key quality performance measures between 2019 and 2020 that may confirm the resilience of acute stroke care services during the lockdown, at least in well-established European stroke centers[64].

Several studies confirm that patients with COVID-19 have more severe strokes and poorer outcomes despite similar acute management to other stroke patients. A well-established stroke care network helps to diminish the impact of such an outbreak in stroke care, reducing secondary transfers and allowing maintenance of reperfusion therapies, with a minor impact on door-to-puncture times, which were longer in patients who underwent chest computed tomography. The findings of these studies can inform medical preparedness and local policies in the event of a new COVID-19 surge or future pandemic.

Take-Home message

- Patients with COVID-19 have higher prevalence of moderate-severe stroke with large vessel occlusions, cortical and lobar location, multiterritorial involvement and associated brain hemorrhage (hemorrhagic transformation or simultaneous hemorrhage and infarction).
- Cryptogenic stroke is the most frequent subtype, probably related to a hypercoagulable state with high levels of inflammatory and coagulation biomarkers (neutrophils, C-reactive protein, IL-6, D-dimer, PT and aPTT).
- The acute management of ischemic or hemorrhagic stroke in COVID-19 patients should follow the same standards of care as for non-COVID-19 patients, adopting the necessary precautions related to infection control.
- Pharmacological venous thromboembolism prophylaxis should be strongly considered for all COVID-19 patients.
- In patients with cryptogenic stroke, involvement of multiple vascular territories (suggesting an embolic phenomenon), presence of other arterial or venous thrombotic events, elevated coagulation markers should be taken into consideration when deciding whether to initiate anticoagulation therapy, always bearing in mind the higher bleeding risk in these patients.

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