The current issue of Stroke journal features 2 retrospective cohort studies investigating characteristics and outcomes of COVID-19 patients suffering a stroke. In the first study, Qin et al report that in a total of 1875 patients with COVID-19 hospitalized at a single-center institution from January 27, 2020, to March 5, 2020, in Wuhan, China, 50 patients had a history of stroke (90% of which were ischemic, and 10% were hemorrhagic). In the second study, Yaghi et al report that in a total 3556 patients with diagnosis of COVID-19 hospitalized between March 15, 2020, and April 19, 2020, within a major health system in New York, 32 (0.9%) experienced an ischemic stroke. Out of the 32 patients in the study by Yaghi et al, the index ischemic stroke was the reason for admission in 14 cases (43.8%), while the remaining 18 patients (56.2%) developed ischemic stroke during their hospitalization for COVID-19 respiratory symptoms.

The two studies give us different and important messages to gain more insights into the complex relationship between COVID-19 and stroke. The study by Qin et al indicates that subjects with a history of stroke are at higher risk of poor outcome if they develop COVID-19, due to increased risk for acute respiratory distress syndrome, need of mechanical ventilation support, and intensive care admission. In-hospital mortality was higher for patients with COVID-19 and history of stroke compared with COVID-19 patients without history of stroke. The study by Yaghi et al provides rates of ischemic stroke occurrence in patients with COVID-19 and gives some insights into the characteristics of the ischemic events. The reported prevalence rate of concurrent COVID-19 infection and ischemic stroke is significantly lower in the study by Yaghi et al compared with those reported by previous cohort studies published to date (Figure).

Differences in the patient populations, consisting of a multiethnic representative sample in the study by Yaghi et al, differences in healthcare system organization, and intensity of screening should also be taken into consideration. In the study by Yaghi et al, screening for COVID-19 was performed at first provider contact only for patients with a history of fever or respiratory symptoms. It has been very well documented that a significant
 proportion of COVID-19 patients may have very mild symptoms or be even asymptomatic\(^2\) and that the sensitivity of COVID-19 screening testing can also vary.\(^9\) Therefore, it becomes evident that the reported ischemic stroke rates in COVID-19 patients should always be interpreted within the setting of the implemented diagnostic protocol for COVID-19 cases.

In the cohort by Yaghi et al, diagnostic workup did not establish the ischemic stroke etiology for a substantial proportion of patients with concurrent COVID-19 infection and ischemic stroke. Cryptogenic stroke diagnosis was twice more prevalent in COVID-19–positive patients (65.6%), compared with both COVID-19–negative contemporary stroke patients (30.4%) and ischemic stroke patients hospitalized in the same hospital system between March 15, 2019, and April 15, 2019 (25.0%).\(^8\) Compared with the historical COVID-19–negative stroke cases mentioned above, COVID-19–positive stroke patients were younger and present with more severe stroke syndromes, which was attributed to higher proximal large vessel occlusion prevalence.\(^8\) These findings are in concordance with a recent case-series publication from another New York stroke center raising concerns for a potential increased risk for severe stroke syndromes in young patients affected by COVID-19.\(^11\)

The laboratory investigations of COVID-19 patients with stroke history in the cohort by Qin et al revealed higher neutrophil count and lower lymphocyte and platelet counts than those without a history of stroke. Interestingly, interleukin-6, D-dimers, troponin, and N-terminal pro-brain natriuretic peptide levels were markedly elevated in patients with COVID-19 infection suffering a stroke compared with contemporary COVID-19 patients without stroke symptoms.\(^7\) Likewise, patients with COVID-19 and ischemic stroke in the study by Yaghi et al\(^8\) had higher D-dimer levels, when compared with contemporary COVID-19 patients without stroke symptoms, but also elevated troponin and erythrocyte sedimentation rate levels, when compared with historical ischemic stroke control patients not infected by COVID-19. A presumptive underlying hypercoagulability disorder,\(^12,13\) coupled with the lack of established stroke etiology, prompted the initiation of anticoagulation in 25 (78.1%) COVID-19 patients suffering from ischemic stroke in the study by Yaghi et al.\(^8\) SARS-CoV-2 infection has been linked to a prothrombotic state, causing venous and arterial thromboembolism and elevated D-dimer levels.\(^14\) As data suggest that SARS-CoV-2 infection can act as a trigger for the development of a prothrombotic state leading to thromboembolic complications, the International Society of Thrombosis and Haemostasis currently recommends for immediate low-dose (prophylactic) anticoagulation with low-molecular-weight heparin for hospitalized COVID-19 patients.\(^15\) However, existing data on the utility of empirical therapeutic anticoagulation, using intermediate or full doses, in COVID-19 patients without evidence of venous thromboembolism are very limited to date.\(^16\)

Finally, in the study by Yaghi et al,\(^8\) 63.6% of the stroke patients with active SARS-CoV-2 infection died during their hospitalization. However, as the vast majority of these patients (81.3%) met the criteria for severe COVID-19 disease, it is particularly challenging to estimate the additional contribution of stroke in the fatal outcome.\(^8\) The findings of both studies by Qin et al\(^7\) and Yaghi et al\(^8\) are in accordance with a very recent meta-analysis suggesting that stroke is associated with a 2.5-fold increase in the likelihood of severe COVID-19, with a trend for increased mortality.\(^17\)

As stroke physicians are struggling to sustain optimal patient care in both the acute and in-hospital setting during COVID-19 pandemic, the need for high-quality data to inform healthcare planning and treatment decisions becomes more compelling than ever. The COVID-19 outbreak is reported to be associated with a decrease in hospital admissions\(^18\) and acute treatments.\(^19\) On the contrary, COVID-19 itself might contribute to the development of vascular events. The prevalence of ischemic stroke in COVID-19 patients is estimated at 1.6% (95% CI, 0.8%–2.5%) in a meta-analysis of available cohort studies (Figure), but there is substantial heterogeneity (I\(^2\)=47%) across the included studies due
to methodological differences in case ascertainment. Even though accruing preliminary evidence suggests an increased stroke risk in COVID-19 patients, the true effect of this association still remains uncertain. Given the disparities in prevalence rates reported to date, the establishment of univocal screening protocols seems to be imperative.

The COVID-19 outbreak had a relevant impact not only on the epidemiology but also on the determined etiology of stroke, as shown by the high proportion of cryptogenic strokes. The hypothesis of inflammation-induced hypercoagulability and occult cardioembolism in COVID-19 stroke patients deserves further investigation. As we wait for evidence-based guidance on the optimal management for COVID-19 patients suffering an ischemic stroke of undetermined etiology, the decision for anticoagulation should be individualized and after carefully weighing the ischemic and bleeding risks for each patient. COVID-19 is a systemic disease requiring the collaboration between different medical disciplines. When navigating in the uncharted waters of a novel virus outbreak, all mariners have to collaborate in the best possible way.

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