# **EDITORIAL**

# Ischemic Stroke Epidemiology During the COVID-19 Pandemic

# Navigating Uncharted Waters With Changing Tides

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n December 2019, a novel coronavirus causing pneumonia and severe acute respiratory syndrome emerged in Wuhan, China.<sup>1</sup> The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly spread worldwide, and pandemic outbreak of coronavirus disease 2019 (COVID-19) was declared by the World Health Organization on March 11, 2020.<sup>1</sup> During this pandemic, stroke care delivery is relentlessly facing critical challenges, while physicians continue to struggle in uncharted territory.<sup>2</sup> Emerging cohort studies suggest for a potential increased risk for cerebrovascular diseases in patients with COVID-19, while also raise concerns for increased morbidity and mortality for patients experiencing both COVID-19 infection and stroke.<sup>3-6</sup>

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The current issue of *Stroke* journal features 2 retrospective cohort studies investigating characteristics and outcomes of COVID-19 patients suffering a stroke.<sup>7,8</sup> In the first study, Qin et al<sup>7</sup> 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<sup>8</sup> 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,<sup>8</sup> 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<sup>78</sup> 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<sup>7</sup> 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.<sup>7</sup>

The study by Yaghi et al<sup>8</sup> 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<sup>8</sup> 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,<sup>8</sup> differences in healthcare system organization, and intensity of screening should also be taken into consideration. In the study by Yaghi et al,<sup>8</sup> 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

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Figure. Rates of ischemic stroke reported in available to date cohort studies of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Case reports and case series were not included. Pooled rate was estimated under the random effects model. AIS indicates acute ischemic stroke; and COVID-19, coronavirus disease 19.

proportion of COVID-19 patients may have very mild symptoms or be even asymptomatic<sup>9</sup> and that the sensitivity of COVID-19 screening testing can also vary.<sup>10</sup> 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,<sup>8</sup> 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%).<sup>8</sup> 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.<sup>8</sup> 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<sup>7</sup> 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<sup>8</sup> 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,<sup>12,13</sup>

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.<sup>15</sup> 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.<sup>16</sup>

Finally, in the study by Yaghi et al,<sup>8</sup> 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.<sup>8</sup> The findings of both studies by Qin et al<sup>7</sup> and Yaghi et al<sup>8</sup> are in accordance with a very recent metaanalysis suggesting that stroke is associated with a 2.5-fold increase in the likelihood of severe COVID-19, with a trend for increased mortality.<sup>17</sup>

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<sup>18</sup> and acute treatments.<sup>19</sup> 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.<sup>8</sup> The hypothesis of inflammationinduced 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 weighting 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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