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Severe COVID-19 and Stroke—Another Piece in the Puzzle*

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KEY WORDS: coronavirus disease 2019; extracorporeal membrane oxygenation; hemorrhagic stroke; intensive care; ischemic stroke; neurocritical care

Concomitant neurologic manifestations have been described since the early emergence of the coronavirus disease 2019 (COVID-19) pandemic (1). While the range of reported neurologic manifestations is wide (2), occurrence of acute cerebrovascular disease drew specific attention due to the high rate of coagulopathy and thrombotic complications that was observed early on in patients with severe COVID-19 (3–5). Early case series and cohort studies reported an occurrence rate of stroke between 2% and 6% (2), and a meta-analysis of studies published up to June 2020 found the frequency of stroke to be 1.1% among hospitalized COVID-19 patients (6). However, these reports used varying definitions for stroke and other data, limiting accurate estimates across populations. In a recent combined publication of two global consortia formed to specifically address incidence, type, and outcomes of neurologic manifestations among patients hospitalized with COVID-19, the observed overall stroke incidence was 3% (7–9).

How do these data compare to those in general critical illness? Stroke occurs in 1–4% of patients admitted to ICUs for non-neurologic conditions (10–12). As applies for COVID, stroke risk factors in ICU patients are different than for the general population, with systemic infections and coagulopathy (13, 14), other pro-inflammatory states (15), and invasive vascular and cardiac procedures, especially extracorporeal membrane oxygenation (ECMO), playing a major role (14, 16, 17). In ECMO patients, a subpopulation of the critically ill of specific interest in the COVID pandemic due to the common failure of respiratory support with regular mechanical ventilation (18), the overall occurrence of neurologic complications is estimated to be around 13% (19), but also ranges widely, dependent on study and methodology. With specific respect to venoarterial or venovenous ECMO, neurologic complication rates vary between 15% and 18% (venoarterial) and 4–13% (venovenous), respectively (19–22). In a recent single-center analysis of 416 ECMO patients between 2009 and 2017, 13.3% had an imaging-confirmed CNS complication, including 7% ischemic stroke and 3.4% hemorrhagic stroke (20). With respect to COVID-19 and ECMO utilization, the current study by Cho et al (23) sheds further light on these potential complications.

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In their study, published in this issue of *Critical Care Medicine*, Cho et al (23) further examine the frequency of strokes in patients admitted to the ICU with severe COVID-19 and their outcome, with specific attention to the subgroup placed on ECMO. The authors set out specifically to determine the occurrence of stroke in patients admitted with severe COVID-19, in whom ischemic or hemorrhagic strokes had not occurred prior to ICU admission, and the impact of stroke occurrence on outcomes in this group. For their work, they analyzed prospectively collected data from the registry of the COVID-19 Critical Care Consortium—a data registry spanning over 370 international sites from 52 countries. Disease severity was determined through validated severity scores including Acute Physiology and Chronic Health Evaluation II (APACHE II) (24) and Sequential Organ Failure Assessment (SOFA) scores at ICU admission (25). Ischemic and hemorrhagic strokes were differentiated by imaging findings (either CT or MRI), and a documented persistent focal neurologic deficit in the absence of imaging or imaging findings was included as "unspecified stroke." In addition to descriptive analyses, survival models based on five stages (ECMO, no ECMO, stroke, discharge, and death) were employed to assess the impact of stroke on outcomes, with hazard ratios (HRs) and CIs presented as estimates. In the overall cohort of 2,699 COVID-19 patients whose median age was 59 years and 65% were male, 70% required mechanical ventilation, and 10.5% were placed on ECMO. Of the 75 patients who were documented to have a stroke as complication during their hospitalization, 16 were excluded for either unknown timing or stroke occurrence prior to ICU admission, rendering the frequency of stroke as complication 2.2% (59/2,699). Among those 59, hemorrhagic stroke was most common, occurring in 27 patients (46%), while 19 (32%) had ischemic strokes, and 13 (22%) were unspecified. Provided the high degree of baseline critical illness of patients with severe COVID-19 in their cohort (70% requiring mechanical ventilation), specific attention was given to patients receiving ECMO therapy. Of the patients in the ECMO cohort, 266 (94%) received venovenous ECMO support and 17 received venoarterial ECMO support. In the 283 patients on ECMO, 15 (5.3%) suffered a hemorrhagic stroke, 3 (1.1%) had an ischemic stroke, and 4 (1.4%) were classified as unspecified stroke—in contrast to 12 of 2,415 patients (0.4%) with hemorrhagic stroke, 16 of 2,415 (0.6%) with ischemic stroke, and nine of 2,415 (0.3%) with unspecified stroke in the non-ECMO group. In addition to higher occurrence of stroke in the ECMO cohort, patients with stroke were generally more ill, with higher APACHE II and SOFA scores, had higher frequency of mechanical ventilation, and required vasopressor treatment more often. Furthermore, preexisting cardiac disease and hypertension were more prevalent in stroke patients. In analysis of laboratory data, platelet count (94,000/mcL vs 279,000/mcL) was lower among patients with ischemic stroke with no difference observed between hemorrhagic stroke and controls. In reference to outcomes, hemorrhagic stroke (HR, 2.74; CI, 1.42–5.27), older age (HR, 1.45), and ECMO use (HR, 1.78) were significantly associated with mortality, while ischemic stroke was not.

The strengths of the study by Cho et al (23) include data generation through prospective collection of an international multicenter consortium (26) and its focus on critically ill patients admitted with symptomatic COVID-19—as opposed to intermixing a priori neurologic manifestations with those acquired during the critical course of COVID-19—and a specific focus on neurologic complications in severe COVID-19 patients on ECMO. The overall frequency of stroke among hospitalized critically ill COVID-19 patients of 2.2% falls within the previously reported ranges (6, 9). In contrast to most prior studies, hemorrhagic stroke was more common than ischemic stroke, especially in patients on ECMO. The overall frequency of complications on ECMO was lower than most previously reported ones.

However, although the study by Cho et al (23) was overall conceptualized carefully, several important limitations have to be considered when interpreting the presented results. The focus of this registry on neurologic manifestations remains basic (26). As such, no details are available on imaging findings; hence, some hemorrhagic strokes may in fact have been hemorrhagic transformations of ischemic strokes, a consideration questioning the meaning of the reversed ratio of hemorrhagic: ischemic strokes. This finding is further weakened by the significant proportion (22%) of patients with unspecified stroke, which could add to the ischemic burden or further question alternate diagnoses relevant in COVID-19 patients including hypoxic-ischemic brain injury and multifactorial encephalopathy. Additionally, as is common in observational studies, brain imaging was obtained at the discretion of the treating clinician. This phenomenon likely underestimates the true frequency especially of ischemic strokes in a population similar to other facets of critical care populations, where a diagnosis of stroke may be missed due to decreased levels of consciousness (27); higher rates of intracerebral hemorrhage may also be detected with systematic imaging of ECMO patients (28). Lastly, when quantifying hemorrhagic stroke risk, it should not be understated that the presence of cerebral microbleeds (usually identified via MRI) are separate, known independent risk factors of critical illness and ECMO and may have contributed to the data set (29–31). Such pathology is not unique to COVID-19, however, details about the imaging findings were not presented and this entity was not discussed in Cho et al (23).

When looking at outcomes, especially mortality: the impact of withdrawal of life-sustaining therapies (WOLST) on death rates was, while acknowledged as a limitation, not evaluated by Cho et al (23). WOLST has been found to have a significant impact on outcome data in acute brain injury and specifically in patients with intracerebral hemorrhage (32, 33), hence, limiting the outcome interpretation of the study by Cho et al (23) and the ability to draw conclusions for clinical practice. This limitation, although, is equally applicable to many other previous reports of higher mortality in patients with neurologic complications including those for patients on ECMO (19, 20).

Additionally, Cho et al (23) explore a variety of laboratory values for patients who suffered a stroke versus those who did not. The aforementioned association of lower platelet counts in patients with ischemic strokes are in line with previous reports (1). Higher median Pao_2 levels in patients with hemorrhagic stroke are likely reflective of higher degree of critical illness, as the authors point out, as all patients with hemorrhagic stroke were mechanically ventilated compared with the overall ventilation rate of 70%, inferring lower Pao_2 values in native airways with COVID-19. The presented data on anticoagulation, suggesting absence of association of anticoagulation with increased risk for either type of stroke, are largely limited by the degree of missing data, although systemic anticoagulation was far more common than prophylactic use in the hemorrhagic stroke subpopulation.

Lastly, the authors state that over 80% of the included data were derived from a core group of nine countries but did not specify this further (23). While the consortium clearly expands our knowledge from single-center analyses, it would be helpful to understand this core of data generating centers, in order to understand how to embed the data into the larger, global body of literature.

Undeniably, the rapidly accumulating data and knowledge on COVID-19 and complications pose a scientific challenge: analyses comparing findings across cohorts become more complex as divergent definitions are used in studies and may also change with increasing gain of knowledge. Hence, the development of a coordinated and consistent data set across the international community is imperative to allow for unambiguous and reproducible information that is translatable to clinical practice. For neurologic manifestations, such datasets have to include organized collection of neuroimaging (34).

Importantly, the impact of severe COVID-19 and stroke on functional outcome and quality-of-life remains a large societal concern. Solely relying on short-term outcomes yields an incomplete and potentially narrow picture, especially if mortality data are derived with incomplete details. This can lead to therapeutic nihilism—while such approach might be appropriate in individual cases, significant longitudinal improvement and regaining of neurologic function in the subsequent months following discharge frequently occurs, and it is upon us to find out whether this also applies to patients with neurologic complications recovering from COVID-19.

Thus, the value of the study by Cho et al (23) may be the addition of another two small pieces in the puzzle of COVID-19: first, the overall estimate of symptomatic stroke in COVID-19 is in line with previously described cohorts and seems to settle out in the range of less than or equal to 3% in cumulative data, and thus also similar to the occurrence of stroke in all comers critical care; second, the frequency of complications while on ECMO similarly seem to not surpass those for ECMO for the general critical care population. As such, while we are yet to learn and understand the many new facets and different nuances

COVID-19 poses when compared with other critical illness, there are also parallels. The study additionally shows us that we need to "continue to develop" even carefully crafted global datasets to better include relevant details. Thus, common data elements for stroke, especially for neuroimaging, are necessary to define neurologic phenotypes prospectively, acquire the ability to predict them and, eventually, develop strategies to avoid them. This will aid in systematically filling the frame of the puzzle that COVID-19 with all its complications has given us to solve, one additional piece of knowledge at a time.

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Bronchiolitis and Noninvasive Ventilation. Once Again Time to Review…*

KEY WORDS: administrative database; bronchiolitis; cardiac arrest; children; noninvasive ventilation

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Bronchiolitis (most commonly related to respiratory syncytial viral [RSV] infection) is one of the most common reasons for hospital and PICU admission of infants and young children in the United States and across the world (1). Although bronchiolitis has a low mortality rate, there are substantial numbers of related deaths (predominantly in low-resource settings) (2); there is substantial short-term morbidity (and related costs), and there have been concerns for many years about the long-term effects on respiratory function (3).

Although most infants who suffer from bronchiolitis were previously well, RSV—the most common viral etiology—has a predilection for infants at risk (4) including those who were born prematurely, those with congenital cardiac disease, those with some chromosomal anomalies (5), and those with underlying chronic lung disease (6) or immunodeficiency. The impact of RSV is not limited to children (7, 8).

The use of noninvasive ventilation (NIV) (including high-flow humidified nasal oxygen [HFHNO], nasal continuous positive airways pressure [CPAP], CPAP, and intermittent positive pressure without endotracheal intubation—all using a variety of interfaces) for the management of bronchiolitis has expanded dramatically across the world over the last decade. There is a strong impression that NIV reduces the number of children receiving mechanical ventilation (9) and has economic and clinical benefits, but there is ongoing concern that interventions such as NIV may not improve the outcomes from bronchiolitis (10).

Shanahan et al (11), in their article published in this issue of *Critical Care Medicine*, have presented data from a large administrative database regarding the outcomes of infants with bronchiolitis in the United States. They documented an overall increase in the number of patients diagnosed with bronchiolitis; a

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