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Risk of Acute Ischemic Stroke in Patients 65 and Older is Early After COVID-19 Diagnosis

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Associated acute and long-term medical complications of the SARS-CoV-2 infection COVID-19 beyond respiratory illness include acute ischemic stroke (AIS).¹⁻⁵ Hypercoagulability, inflammation, cardiac dysfunction, and endothelial inflammation can occur during the infectious phase lead to thrombotic events and thus cerebral ischemia.⁶ Reported risks of stroke in COVID-19 varied substantially across studies.⁷ Most studies have focused on AIS incidence in patients diagnosed during or upon hospitalization. Unlike any other infectious disease in modern times and as a result of the need to trace and monitor for outbreaks to prevent the spread of COVID-19, a very large number of patients have been screened for COVID-19 at the time of hospital admission. This screening has identified both asymptomatic and symptomatic individuals with COVID-19 thus making it more difficult to determine if and in whom COVID-19 may increase the risk of AIS and if the association is true or incidental. In this issue of NEUROLOGY, Yang et al.⁸ evaluated the estimated incidence rate ratio of AIS after COVID-19 infection in a known high-risk group, patients greater than the age of 65, and determined the time frame of highest risk of AIS associated with COVID-19 within this population.⁸

The authors used inpatient and outpatient Fee-For-Service Medicare claims to identify 37,379 patients with COVID-19 and AIS between January 2019 and February 2021.⁸ A pre-COVID diagnosis phase was used to account for unknown possible inoculation times, and the time frame from COVID-19 billing diagnosis to stroke billing diagnosis code of up to 28 days was evaluated.⁸ Applying the self-controlled case series method, they found that the incident rate ratios (IRR) were highest within three days of diagnosis of COVID-19, with an odds ratio of 10.3 (95% confidence interval 9.86–10.8), and that the estimated IRR was higher in those between the age of 65-74 without a prior history of stroke.⁸ By contrast, the association between stroke

and COVID-19 was weaker 15-28 days after the initial diagnosis, suggesting that AIS rarely manifests as a long-term COVID-19 sequela in elderly patients.⁸ Major strengths of the current study are the inclusion of COVID-19 cases diagnosed both in the outpatient and the inpatient settings, the inclusion of a large number of patients from minority groups, and the use of robust statistical methods, such as the self-case-controlled case study, which has the advantage of implicit control for all fixed confounding effects. The authors made a great effort to verify that all assumptions were not violated, albeit with some modifications. They further solidified the findings of their study by performing a number of sensitivity analyses.

Interpretation of the current study results should, however, consider potential limitations, which were amply described by Yang et al.⁸ These limitations stem primarily from the retrospective nature of the analysis and the use of administrative claims to identify cases of COVID-19 and AIS. As the Medicare data is updated monthly, cases of COVID-19 and deaths could have been missed. Also, rapid changes in the entire healthcare system during the COVID-19 pandemic, including access to preventative care, patient presentation to healthcare facilities for evaluation of stroke-like symptoms, availability of testing and procedures, and acute stroke care, could have affected the results and the applicability of the self-case-controlled case study.⁹

The current study has important clinical implications. The authors identified both a group of patients (65-74 years without a prior history of stroke) and a critical period (first three days) for which the risk of AIS after COVID-19 diagnosis is highest. These raise important questions: Should patients aged 65-74 years of age be treated more preemptively and aggressively to

prevent ischemic stroke? Also, what would be the ideal duration of such specific interventions?

Well designed clinical trials will be needed to answer these questions.

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