

In Reply: May Cooler Heads Prevail During a Pandemic: Stroke in COVID-19 Patients or COVID-19 in Stroke Patients?

To the Editor:

It is with substantial disappointment that we recently read the “Letter: May Cooler Heads Prevail During a Pandemic: Stroke in COVID-19 Patients or COVID-19 in Stroke Patients?”¹ At a time when continued denial of the reality that is COVID-19 is causing our country to set new records daily for the numbers of new cases and expected death estimates continue to rise, we would hope that Drs Spiotta and Alawieh would seek to pursue a course based on evidence and not assumptions. Our report, as accepted and published in the NEJM, is a factual account of our observation of a higher than usual number of young patients with large vessel stroke presenting during the peak of the COVID-19 in New York City. They even go as far as to accuse our group of providing “misinformation.” They base this conclusion on what can be factually demonstrated as blatantly incorrect and unscientific statements. This is all the more surprising as they are making their assumptions from a position of having essentially zero experience directly dealing with this Pandemic at the time of their writing this letter. South Carolina and Georgia are only just now seeing COVID-19 at any significant rate (though still well below NYC at its peak), and they may now have to learn to take this disease as seriously as it deserves (<https://www.scdhec.gov/infectious-diseases/viruses/coronavirus-disease-2019-covid-19/sc-testing-data-projections-covid-19> and <https://www.ajc.com/news/coronavirus-georgia-covid-dashboard/jvoLBozRtBSVSNQDDAuZxH/>).

To help clarify the scientific and factual inaccuracies as presented by Drs Spiotta and Alawieh, we provide the following brief responses to the statements made in their letter¹:

1) “Systemic inflammation that may occur after *severe* COVID-19 infection promotes a prothrombotic state that may predispose to thrombotic events, including stroke. However, stroke as the presenting complaint of COVID-19 patients with otherwise mild or no systemic disease raises concerns over COVID-19 being a bystander given its high prevalence in reporting regions.” Please note that the italics are Drs Spiotta and Alawieh’s, not ours.

This is a blatantly misleading statement. We addressed in our NEJM publication² how the population reported is not a normal sampling of the NYC population, but one must first question why the authors put forth their uninformed opinion, contrary to data, that procoagulant effects are specific to *severe* COVID-19, implying that there is not an established association with mild COVID-19. There is increasing consensus that increased thrombosis risk occurs early in COVID-19. Supporting this well-established conclusion are large numbers of reports of early COVID-19 presenting with thrombotic events.³⁻¹³ The

references listed are only a limited number of the available studies. In fact, data is also published specifically addressing macrothrombosis in the internal carotid artery in mild COVID patients,^{14,15} with stroke as a presenting symptom of the disease,⁴ newly presenting emergent large vessel occlusions with COVID-19 being a very different population compared to typical ELVO patients¹⁶ and demonstrating that COVID-19 is associated with a 7.6 fold increased odds of suffering stroke as compared to influenza (a similar respiratory virus previously demonstrated to be associated with stroke).¹⁷ Furthermore, all 5 of our reported patients had demonstrable coagulation abnormalities on their presenting labs. It is well accepted that coagulation abnormalities in dDimer and fibrinogen can occur early in COVID-19. Hence, there is ample data demonstrating early laboratory coagulopathy, early COVID-19 patients presenting with thrombotic events, and mild COVID-19 patients presenting with stroke. Why Drs Spiotta and Alawieh would provide wishful thinking, contrary to actual evidence and without evidence of their own, is hard to fathom.

2) “The findings presented remain anecdotal and lack the methodological and statistical rigor to claim that COVID-19 infection increases stroke risk in the youth or that stroke could be the presenting symptom of COVID-19.”

The referenced publication was a letter, expressly because an early experience, during a pandemic, alarming for patients not seeking care in a timely fashion due to fear of the virus, should be reported as soon as possible, and understood with appropriate caveats. However, while not hypothesis driven and observational in nature, we demonstrated in the referenced publication that these patients were highly unlikely to represent an isolated anecdotal experience. We reported that our typical weekly rate of ELVO in <50-yr-old patients was 0.73 over the prior 12 mo. The reported patients represent a 7-fold increase in our standard rate of young patient stroke- a substantial departure from a well-established norm. This fact very clearly allows us to claim that we have seen an increased rate - and to very reasonable posit that it is likely related to the presence of COVID-19 in all of these patients. Our assessment was data driven and met adequate rigor for NEJM, and yet somehow was felt by Drs Spiotta and Alawieh to be lacking.

This observation is supported by additional data from other centers in areas with high COVID-19 prevalence who report, as we have seen, stable or increased ELVO stroke numbers, while mild stroke has decreased due to the effects of quarantine.¹⁸ In addition, the mean patient age in multiple recently published thrombectomy case series of COVID-19 is remarkably similar and younger than the traditional population (Mean age of 52.8 in a separate series from New York,¹⁹ mean age of 59.5 in another series from Paris²⁰ and the same 59.5 in a combined series from New York and Philadelphia.⁴ Our own data confirm

a statistically younger age in ELVO patients diagnosed during the pandemic when COVID positive versus COVID negative,¹⁶ mirroring findings of the Paris group.²⁰

3) “In fact, our Stroke Thrombectomy and Aneurysm Registry reports that 12% of 5000 patients undergoing thrombectomy are younger than 50 yr. Similarly, 8% of patients from the stroke thrombectomy trials were under 50 yr”.

This is an irrelevant, and also misleading, statement by Drs Spiotta and Alawieh. As mentioned above, we reported that “all 5 patients tested positive for COVID-19. By comparison, every 2 wk over the previous 12 mo, our service has treated, on average, 0.73 patients younger than 50 yr of age with large-vessel stroke.” The authors’ reference to their Stroke Thrombectomy and Aneurysm Registry is simple self-promotion, as that registry is a self-reported un-adjudicated and highly selected collection of data, that while having value in some applications, provides little meaningful insight into public incidence of stroke. This is evidenced by the STAR data having a 50% higher rate of occurrence of young stroke than other stroke trials that the authors then reference, which demonstrate an approximate 8% incidence of young stroke. However, neither of these data provide any evidence against our NEJM correspondence. In fact, our reported rate of 0.73 reported cases every 2 wk correlates to an ~8% incidence of stroke in patients <50 yr old annually as compared to our annual thrombectomy volume. The exact same as seen in the larger stroke trials. And yet, the reason we wrote this correspondence is because the NEJM reported COVID-19 patients represented a 7-fold increase in this rate. Please take a moment to understand this fact. Drs Spiotta and Alawieh use population data to argue that we are misrepresenting reality by reporting our findings, but those data exactly mirror our typical experience and the newly reported data is confirmed to be greatly elevated as compared to both published as well as our own young stroke experience.

4) “the scientific literature lacks evidence providing a causal link between COVID-19 and large vessel stroke.”

This statement is clearly pure conjecture and is demonstrably false. There are already multiple publications examining potential pathophysiological causal links between COVID-19 and large vessel thrombosis.²¹⁻²⁷ These referenced papers are only a small selection. Furthermore, several recent publications have demonstrated neuropathological evidence for viral induced endotheliitis or endotheliopathy potentially leading to angiopathic thrombosis.²⁸⁻³⁰

5) “Therefore, anecdotal reports of small case series of stroke in younger adults with COVID-19 do not reach the threshold, to date, to raise public fear among young adults.”

As demonstrated above, our data, and other confirming data since published (even before Drs Spiotta and Alawieh’s letter¹), all raise this report above the level of anecdote. But the authors then go further to accuse our efforts as being “to raise public fear among young adults”. Firstly, to raise public fear is never one’s intent. Rather it is to appropriately educate both the public and the broader scientific community as to important, scientific

ically credible data that has come to light—particularly when a disease, like COVID-19, is relatively unknown to our community and when we know that stroke treatment is extremely time dependent. We believe it is extremely important that physicians take every measure to get this information to the broader scientific community through whatever means necessary. Since the referenced media communications, we have received countless communications from physicians around the globe who have had similar observations, and who have then provided us with additional insights. These contacts occurred specifically because the story was shared through broader media circles. This communication is good. This communication is necessary. It is hard to fathom why Drs Spiotta and Alawieh would have a problem with such communication. Secondly, it is clear that Drs Spiotta and Alawieh misunderstood not only the science of these communications, but also the intent. We repeatedly stated in multiple interviews with the broader media that this information was not to “raise public fear among young adults” (in Drs Spiotta and Alawieh’s words), but rather to highlight the insights provided by this observation for COVID-19 in general. To that end, we provide actual quotes from one of those public media correspondences (please forgive the grammar as this is an off the cuff interview): “this immediately alerted us that it’s likely the disease has a component that’s causing clots and potentially putting people at increased stroke [risk] but also other diseases caused by clots—renal failure, heart attacks, and other things. So our initial urgent communication to The New England Journal, which has just come out, was more of an alert. It was only 5 patients that were very young. But it was such a stark contrast that it drew our attention. We’ve now analyzed all of the strokes seen over that period, and there’s clearly a strong association identified. In fact, after noticing this trend, we started talking to our colleagues in pulmonology, the lungs or in the kidneys. And they started telling us they’re also seeing blood clots form a lot. And it’s really developed our understanding of the disease. And in fact, there was a paper just published recently last week in Lancet that showed how the virus can directly infect the lining of the blood vessels, the cells that protect the blood from clotting.”³¹

As the reader can see, these meaningful and factual statements are scientifically reasonable and provide critical insight into the broader disease that is COVID-19. Drs Spiotta and Alawieh conclude their letter¹ by stating, “Physicians are encouraged to seek sound medical evidence during care for patients and news appearances.” We would second this statement, and we strongly stand behind the scientific underpinnings of our patient care and news appearances. We would counter that Drs Spiotta and Alawieh are encouraged to use rational science and informed thinking prior to writing editorials, rather than relying on their own wishful thinking, unfounded hypotheses, and relative lack of experience as justification for their ill-informed opinions.

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